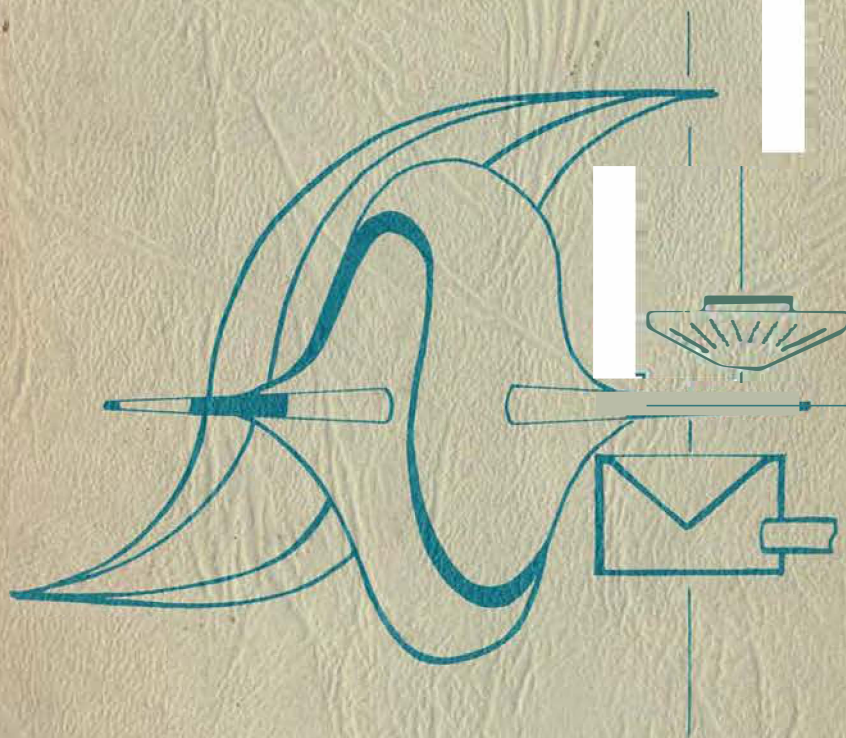


scientists and rotors

the development of biochemical ultracentrifuges

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boelie elzen

SCIENTISTS AND ROTORS

THE DEVELOPMENT OF BIOCHEMICAL ULTRACENTRIFUGES

PROEFSCHRIFT

ter verkrijging van
de graad van doctor aan de Universiteit Twente,
op gezag van de rector magnificus
prof.dr.ir. H.H. van den Kroonenberg
volgens besluit van het College van Dekanen
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CONTENTS

Chapter 1: INTRODUCTION	1
1.1 History of Ultracentrifuges	1
1.2 Technology Studies	3
<i>The Systems Approach</i>	5
<i>The Network Approach</i>	6
<i>The Social Constructivist Approach</i>	7
<i>Conclusion</i>	8
1.3 Approach used in this Study	9
Notes	11
Chapter 2: THEODOR SVEDBERG	13
<i>Education</i>	13
<i>Dissertation - Docent - Professor</i>	16
<i>Distribution of Sizes - Sedimentation Balance</i>	19
<i>Wisconsin - Optical Centrifuge</i>	22
<i>The Ultracentrifuge</i>	28
<i>Diffusion - Sedimentation Equilibrium</i>	38
<i>Proteins</i>	40
<i>The Quest for Higher Values of g - The Oil-Turbine Ultracentrifuge</i>	46
<i>Technique of Measurement</i>	56
<i>Theory of Measurement</i>	58
<i>Problems</i>	60
<i>Application to Proteins</i>	64
<i>Recognition by Colleagues - Nobel Prize</i>	66
<i>Protein Studies - Reception of Svedberg's Claims</i>	73
<i>Further Development of Ultracentrifuges: 1928-1933</i>	79
- <i>Equilibrium Ultracentrifuge</i>	80
- <i>Oil-Turbine Ultracentrifuge</i>	82
<i>Increasing Resolving Power</i>	88
<i>Further Protein Studies</i>	92
<i>Rockefeller Foundation Grants</i>	99
<i>Development of Ultracentrifuges after 1933</i>	107
<i>Further Protein Studies - Inquiries by Other Researchers</i>	118
<i>Proteins as a Driving Force behind the Ultracentrifuge Development</i>	124
<i>Research at Upsala in the 1930s</i>	125
<i>Further Support by the Rockefeller Foundation</i>	128
<i>Svedberg's Activities after 1940</i>	131
Notes	133
Chapter 3: JESSE WAKEFIELD BEAMS	143
<i>Education - UVa School of Physics</i>	143
<i>After Graduation - Spinning Tops</i>	147
<i>Ultracentrifuges</i>	153
<i>Pickels - Sedimentation Ultracentrifuge</i>	155
<i>The Problem of Convection</i>	161

<i>The Vacuum Ultracentrifuge</i>	162
<i>Rockefeller Foundation - Steam and Electrical Drives</i>	173
<i>Other Types of Research</i>	181
<i>Further Development of Ultracentrifuges</i>	183
<i>Separation of Gases and Vapors - Isotope Separation</i>	189
<i>Quantity Heads</i>	197
<i>Electrically Driven, Magnetically Suspended Ultracentrifuge</i>	200
<i>Applications of Ultracentrifuges</i>	208
<i>Uranium Enrichment</i>	212
<i>Better Times for Physics - Committee on Growth</i>	218
<i>Highest Rotational Speeds - Further Development of Ultracentrifuges</i>	221
<i>Coaster</i>	225
<i>Beams' Later Years - Broad Interest in Science</i>	229
Notes	230
 Chapter 4: JAMES WILLIAM McBAIN	 237
<i>Education - Colloid Chemist</i>	237
<i>Ultracentrifuges - Pilgrimage to Upsala</i>	239
<i>McBain's Approach</i>	242
<i>The Periscope Ultracentrifuge</i>	246
<i>Relation with the Rockefeller Foundation</i>	255
<i>'The World' turning against McBain</i>	259
<i>Further Development of Ultracentrifuges</i>	267
<i>The Death of the McBain Ultracentrifuges</i>	274
Notes	276
 Chapter 5: EDWARD GREYDON PICKELS	 281
<i>The IHD Laboratories</i>	281
<i>Viruses - Quantity Ultracentrifuge</i>	284
<i>Analytical Ultracentrifuges - Wyckoff</i>	290
<i>Analytical Ultracentrifuges - Bauer and Pickels</i>	297
Notes	307
 Chapter 6: WIDER USE OF OF ULTRACENTRIFUGES	 311
6.1 Svedberg Ultracentrifuges	311
<i>James Burton Nichols - DuPont Experimental Station</i>	311
<i>Various Scientists</i>	322
<i>Arthur Sproul McFarlane - Lister Institute of Preventive Medicine</i>	324
<i>John Philpot - Oxford University</i>	326
<i>John Warren Williams - University of Wisconsin</i>	329
<i>LKB Produkter AB</i>	336
6.2 Beams/Pickels Ultracentrifuges	340
<i>Beams - Spinning Tops</i>	340
<i>Beams - Vacuum Ultracentrifuges</i>	345
<i>Sharples Specialty Company</i>	347
<i>Edwin J. Cohn - Harvard Medical School</i>	364
<i>Pickels - Spinco Ultracentrifuges</i>	367
6.3 Use and Further Development of Ultracentrifuges	374
Notes	380

Chapter 7: THE DEVELOPMENT OF ARTEFACTS: PATTERNS AND ANALYTICAL MODELS	387
7.1 Summary of the Development of Ultracentrifuges	387
7.2 Patterns of Development	394
7.2.1 Actors and Artefacts	395
<i>Relations between Actors and Artefacts</i>	395
<i>Hard Characteristics of Artefacts</i>	399
<i>The Role of Artefacts in the Relations between Actors</i>	403
<i>Combining SCOT and Networks</i>	407
7.2.2 Patterns of Change	409
<i>Defining Problems - Developing Solutions</i>	409
<i>Interaction Processes</i>	411
<i>Detours and Stabilization</i>	415
7.3 Dynamics of the Development of Artefacts	418
<i>Search Processes of Actors</i>	418
<i>Stable Patterns of Interaction</i>	422
<i>Artefacts embedded in Networks</i>	423
7.4 Discussion and Conclusion	426
Notes	429
 SAMENVATTING: WETENSCHAPPERS EN ROTOREN	
De ontwikkeling van Biochemische Ultracentrifuges	431
 BIBLIOGRAPHY	439

Chapter 1

INTRODUCTION

In this study I will present a historical reconstruction of a number of artefacts called ultracentrifuges. Nowadays there are two important fields of application of ultracentrifuges. One is in the commercial production of enriched uranium which is big business with an annual turnover of hundreds of millions of dollars. The other application is for scientific research on numerous bio-chemical substances. Although these applications have little in common the name of the artefact used suggests that these applications may have some common roots. The development of ultracentrifuges therefore presents an interesting case in the history of technology. The first aim of this study is to present this history.

The other aim of the study is gain a better insight in the development of technological artefacts by identifying some characteristic phenomena and general patterns in these developments. This will be done by making a comparison of the various cases that are described in the following chapters. Developing a better understanding of technological development is also the object of a number of analysts from different backgrounds who, in recent years, have developed some new approaches that aim at developing sociological insights in processes of technological change. I will briefly discuss some of these approaches because they have inspired me to be sensitive for certain aspects of technological development which is reflected in the way I have analyzed and described the development of ultracentrifuges.

1.1 HISTORY OF ULTRACENTRIFUGES

The historical part of this study describes the development of a number of ultracentrifuges. Ultracentrifuges for the enrichment of uranium are now used in a number of countries, notably in the Federal Republic of Germany, the Netherlands, the UK and Japan. Enriched uranium is subsequently used as a fuel for nuclear

power plants. Although the development of these ultracentrifuges would present a very interesting case in the history of technology it will only briefly be mentioned here. This study focusses on the use of ultracentrifuges in the field of biological, biochemical and biomedical investigation. The main reason for focussing on one of these applications is that I want to describe the developments in much detail. Doing both would then simply be beyond the scope of one single study. Nevertheless, I will show that both developments have common roots and I will indicate where the two lines of development became two separate branches on the same trunk. Subsequently, only one of those two main branches will be described further.

In this study, the development of ultracentrifuges is described in five chapters, four of which focus on four different individuals who were engaged in the development of ultracentrifuges. This implies that I have chosen a specific approach in describing the history, notably one which focusses on individual actors. This is done because the historical material was most suited to such kind of a description. To a large extent these actors went 'their own way' although some of them were partly inspired by each other's work. The different approaches of the different actors led to the development a number of different artefacts, some of which were recognised by all as an ultracentrifuge while others were not recognised as such. The Swedish chemist Theodor Svedberg was the man who constructed the first ultracentrifuge and coined its name in 1924. He is now remembered by biochemists as the 'father of the ultracentrifuge'. Although from the outset many recognised this as an important apparatus it lasted some 40 years before it became widely used. But the machine, that became widely used later, had little resemblance with Svedberg's ultracentrifuge and had a history quite distinct from his. The cases will describe how this came about.

Chapter two will describe the development of ultracentrifuges by Svedberg who worked with them from 1924 until his retirement in 1949. Chapter three will follow the paths of the American physicist Jesse Beams who worked on ultracentrifuges from 1930 until his death in 1977. The development of ultracentrifuges by James McBain is described in chapter four. McBain only worked with them for about ten years, from 1930 until 1940. Edward Pickels was a student of Beams who started working on ultracentrifuges in 1933. For some years after his graduation he developed them further for a medical research institute. These developments are described in chapter five. In the early 1940s Pickels hardly worked on ultracentrifuges anymore but in 1946 he established, together with some others, a company for their manufacture. He quit the company again in the mid-1950s. Chapter six describes how some of the ultracentrifuges became used by others. Three were eventually marketed commercially but two of them became a commercial failure. Only one finally became widely used and thanks to this one

Svedberg can now be remembered as the father of the ultracentrifuge although it was not his that finally made it.

In chapter seven, the final chapter, I will start with a historical summary of the development of ultracentrifuges. This will underline the historical aspect of this study. But, as indicated before, I am not only interested in giving a description of the developments but also aim at identifying general patterns in the development of artefacts. In the historical reconstruction, I have made a selective use of recent approaches in the sociology of technology as a 'sensitiser' for analysing the historical material. These approaches have been used primarily as an inspiration for posing certain questions to the historical material and for suggesting the type of patterns that could be looked for. In order to position this historical study in the recent technology studies and in order to make clear which sociological sensitisers I have used for analysing the historical material, I will now describe some recent developments in this field and indicate how and why I have used these approaches in this study.

1.2 TECHNOLOGY STUDIES

Technological development has been and is being studied by scholars from different backgrounds, for instance economists, sociologists and historians. Until recently the situation in the general field of 'technology studies' could be characterised as follows. Economists and sociologists that studied technological development used to deal with technology as a *black box*: the focus of analysis was on input and output, boundary conditions, organizational phenomena, etc. The content of the technology itself, or the content of the black box, was not analyzed in detail. By contrast, the historians of technology have given numerous accounts of the development of technological artefacts in which the artefacts themselves are described in much detail. But in general, the historians were not much interested in theoretical or methodological questions. This has resulted in studies of a very heterogeneous nature which makes it hard to compare the various cases in order to identify general patterns in technological development. The situation in the study of technology could be characterised by stating that sociologists and economists stayed outside the black box and did not look in while the historians went inside the black box and did not look out.¹

In the past decade an increasing number of studies has appeared that try to bridge the gap between the two sets of approaches mentioned above. Also, within the different disciplines developments are taking place that try to overcome the limitations indicated. A number of economists and sociologists have become more interested in the content of technology whereas some historians have become more

interested in theoretical and methodological issues. Some workshops and symposiums have been organised in which historians and sociologists of technology joined forces in the search for better understanding of technological development.² Some new approaches are being developed in which notions and insights are sometimes used that have been developed in the field of *science studies*.³ The new approaches in the field of technology studies are still young and, as can be expected, are quite heterogeneous in nature. But there are also some shared insights behind these approaches which often contrast with the traditional approaches in the study of technological development. A first insight is that the investigations should break away from professed as well as implicit *technological determinism*. Technological determinism characterises a view on technology in which technology is seen as an autonomous, independent factor, a factor outside of society that impinges upon society. Changes in technology are seen as the cause of social changes and in their strongest version theories based on technological determinism claim that change in technology is the most important cause of change in society. The new approaches in technology studies stress that technology should not be seen as an independent factor but should itself be studied as the result of a variety of factors, among which are social and economic factors.⁴ A second shared insight is that technological development should not be seen as an isolated factor among others, like economic, social, or political factors, but that all of these factors are closely interlinked and can in principle influence one another at any time. The American historian Thomas P. Hughes has coined the phrase *seamless web* to account for this interrelationship.⁵ Hughes argues that those concerned with the development of technology, do not only try to influence technological factors; they also influence social, economic, political and scientific factors. A third insight is that technological development should not be seen as the work of one man or woman (the technological hero) but rather as a process in which many persons play a role. Each of those contributes to the process as a whole and that process cannot be understood by only analysing the actions of one single individual. For instance, as this study will show, Svedberg is now remembered as the father of the ultracentrifuge. But if it had not been for one of the other actors, who started producing ultracentrifuges commercially, nobody nowadays might remember Svedberg's name in this respect.

These insights have implications for the type of studies that should follow. First, seeing technology as the (temporary) outcome of a process rather than only seeing it as the starting point for subsequent social developments, implies that the content of technology should also be analyzed - the black box should be opened up. In this respect, the approach of the historian of technology should be followed in order to give a 'thick description' of the events. This thick description will result in a wealth of detailed information on the various aspects of the

development under study. But, besides giving thick descriptions, the field of technology studies has also more theoretical aims. In order to make the complexity of the details amenable to such type of analysis, some simplifying and structuring concepts should be used. Over the recent years, three typical approaches have been developed which, each in their own way, try to reduce this complexity. These three approaches will be discussed briefly below.

The Systems Approach

The systems approach has been developed by Thomas P. Hughes and focusses attention on the analysis of the development of 'technological systems'.⁶ These technological systems contain a very heterogeneous set of elements like physical artefacts, social organizations, scientific 'knowledge', political elements, etc. A technological artefact (and, for that matter, any other component of the system) is in continuous interaction with other components of the system. If something happens to one component, this will have effects for the others as well. Furthermore, systembuilders, like Thomas A. Edison working on the development of electric power systems, try to reach their goals by modifying technical components as well as by trying to change other components of the system.

In order to characterise patterns of development Hughes often uses the concept of *reverse salient*. A reverse salient is an aspect of the development that lags in the development of the system as a whole and is seen by the systembuilder as a component that might hamper further development. Systembuilders tend to focus their attention to such reverse salients and translate it into a *critical problem*. A critical problem gives the reverse salient in a form that facilitates its possible solution. For instance, in 1878 Edison had reached the conclusion that his plans for a system of distribution of electricity were not feasible. The reverse salient was constituted by the maximum length of copper wires: the high price of copper made it impossible for the system to function economically. Put in this form, the problem could not be solved by Edison. However, he was able to translate the reverse salient into a problem that he could solve. Edison realised that copper wires could be made cheaper by making them thinner. According to Ohm's law this implied that the electric current transmitted through them should be made lower; and this could only be done by making a light bulb with a high electrical resistance. So, Edison's critical problem became: develop a light bulb with a high resistance filament. After one year a lightbulb with the required resistance had been developed which was in later historical descriptions transformed to 'the invention of the incandescent lamp'. However, in Hughes vocabulary there is no such thing as the invention at a certain point of time. The light bulb is part of a

system in which many other components also play a role and these other components, like the price of copper, are partially reflected in the light bulb. This example also shows that a reverse salient does not have to be of a technical nature, nor need the critical problem be. The concepts therefore facilitates the study and understanding of various aspects of the development of a technological system from one and the same perspective.

Another important concept in Hughes' approach is that of *technological momentum*. Technological systems are not autonomous but only appear to be so because they have gained momentum: they have a 'mass' because of their components, a direction because of their goals and a 'speed' because of their growth. In Hughes view, this momentum is caused by people and organizations that have interests in the development of the system. The concept of momentum makes it possible to analyze not only the growth but also the decrease of the so-called 'autonomy' of technological development.

The Network Approach

The network approach has been developed by the French school in the new field of technology studies. It has been developed by Michel Callon in his study of the French electric vehicle (VEL - véhicule électrique) which describes how engineers of Electricité de France (EDF) tried to develop plans for an electric vehicle as an alternative to present cars driven by internal combustion engines.⁷ As in the systems approach, elements of a different nature are described as equivalent components in a network: accumulators, catalysts, engineers, electrons, ministerial departments, research institutes, lead, gasoline ... All of these components are called actors. These, and many other actors interact through networks to create a coherent actor world. Callon does not, therefore, distinguish the animate from the inanimate, individuals from organizations. The actor world shapes and supports the technical object, an electric vehicle in the case Callon presents. Like Hughes' systembuilders, Callon's engineers continuously used technical, social, economical and political resources in order to pursue their case. By doing so, EDF tried to build up a network in which all of the actors, they tried to combine, had a place. Callon shows in much detail how these networks are built up in such processes and may also eventually be deconstructed again.

A central concept in the network approach is that of *translation*.⁸ The actors in the network are no fixed, unchangeable entities. They change continuously under the influence of changes in the other actors in the network. This transforms the network as a whole and so on. For instance, the other elements in the VEL network would not simply accept the role EDF had in store for them. Each

component has to be designed to interact harmoniously with the characteristics of the other. Callon stresses that, once the translation has been made, it is very difficult to fix or stabilise it. The heterogeneous actors tend to revert to their former roles in other networks and take on other actors so the network may break down. In the network-approach, Hughes' systembuilder becomes an *heterogeneous engineer*,⁹ a phrase coined by John Law. The heterogeneous engineer must perform translations continuously in order to prevent his network from collapsing. The concept of translation is used to study the dynamics of the development of networks and of technology as well as technologies are embedded in these networks. Callon tries to use the concept in order to understand the actions taken by technicians, manufacturers, politicians, consumers, and other related groups.

The Social Constructivist Approach

The social constructivist approach has been developed by Trevor Pinch and Wiebe Bijker. The approach is usually referred to as SCOT which is an acronym for 'Social Construction of Technology'.¹⁰ As the name indicates, technological objects are seen by them as social constructions. Borrowing and adapting from the sociology of knowledge, Pinch and Bijker argue that the social groups that constitute the social environment of a technological development play a critical role in the development of the artefact. These groups are called *Relevant Social Groups* (RSG). For Pinch and Bijker, technological artefacts do not exist as such. What exists are the various meanings given to an artefact by various RSG's. In the case of the bicycle, they showed that for some RSG's the air tyre was a means to move faster, while others saw an 'ugly looking way of making th low-wheeler yet more unsafe ... than it already was'.¹¹ Pinch and Bijker talk of *interpretative flexibility* to denote the differences in giving meaning to a technological artefact, differences which represent a range of potential lines of development of the artefact, and can thus be said to constitute different artefacts. It is the existence of interpretative flexibility which leads Pinch an Bijker to claim that technological artefacts are 'socially constructed'.

After having identified the relevant social groups for a certain artefact, Pinch and Bijker suggest that we should look for the *problems* each group has with respect to the artefact. Often, around each problem, several variants of *solutions* can be identified. Describing the developmental process in terms of problems and solutions will bring out various kinds of conflicts: conflicting technical requirements; conflicting solutions to the same problem; moral conflicts; and so on.¹² Thus, in the SCOT approach, like in the network and systems approaches, no a priori distinction is made between the influence of, for instance, technical,

natural or social factors.

Although the name might suggest otherwise SCOT does not emphasize 'sociological' factors in favour of 'technological' factors. Pinch and Bijker only stress that the technological content of artefacts should be described through the eyes of the actors rather than through the eyes of an historian looking back in retrospect. The idea in the background is that the analyst should prevent to use 'nature' or the 'technological functioning' of an artefact as an explanatory category of technological development. 'Functioning' is not an objective category, independent of social circumstances. It is exactly the fact that a certain group sees an artefact as 'functioning' (or not) that should be explained. Bodewitz, Buurma and De Vries give a nice example from medical technology: in the Spanish *Pharmacopoeia*, a pharmaceutical compendium, estrogen-progesterone combinations (the contraceptive pill) are described as effective in regulating menstrual cycles, but as having the serious side effect of preventing pregnancy.¹³

The interpretative flexibility of an artefact is not usually so easily to demonstrate as in the case of the contraceptive pill. Moreover, an important consequence of scientific and technological developments is that the interpretative flexibility disappears: after a certain time different actors tend to see an artefact in the same way which Pinch and Bijker describe by stating that *closure* has taken place. In SCOT, an important question then becomes why a specific meaning of the artefact has become dominant and why other artefacts have not been able to make it. These failures should, Pinch and Bijker believe, be of as much interest to historians and sociologists of technology as the success stories. In saying this they are borrowing from the 'Strong Programme' in the sociology of scientific knowledge that calls for sociologists to be impartial to the truth or falsity of beliefs so that they can be explained symmetrically.¹⁴

Conclusion

At this stage, these three models should be primarily seen as an analytical tool: they suggest the analyst what to look for in the development of technological artefacts. All three approaches have also explanatory goals which I will not discuss here. At this point it suffices to observe that the three models do not give any contradictory suggestions to the analyst on what to look for. All stress the integration of technological, economical, political and social elements. All refuse to see technological development as an independent process and stress the need for thick descriptions of the development of technological artefacts. They only put different emphases on what the analyst should look for and, therefore, can also be seen as an reinforcement of one another. For instance, McKenzie has argued that

Hughes' reverse salient can be looked upon as being constructed socially by the actors themselves, rather than being a problem identified in retrospect by the historian. In the same way the SCOT-inspired analyst leaves it up to the actors studied to decide whether an artefact is 'working' or 'not working', the systems-inspired analyst could study the development of reverse salients through the meanings attributed by the actors.¹⁵

1.3 APPROACH USED IN THIS STUDY

In this study I will use the three approaches mentioned above in a sensitising way. First, I will describe the developments as much as possible through the eyes of the actors involved. I will 'follow the actors' as Bruno Latour would say. I will analyze the development of artefacts by focussing on *problems* and *solutions* (as is emphasized in the SCOT approach). Whenever an actor does something with respect to the artefact, like modifying it, I will see this as an attempt to solve a problem. I will then try to analyze what, *for the actor*, the problem looked like and why this was a problem. I am aware that in many cases the historical sources will make such an analysis problematic, especially if we go further back in history. But in the case of ultracentrifuges sufficient published and unpublished material was available that made it possible to follow this route. The question why something was a problem for the actor can be answered in a number of ways and will largely depend upon the perspective of the analyst. Answers may include psychological, social, economical, etc., factors. My goal here is not to provide a direct answer to the question but rather to identify possible patterns in the way something becomes a problem for the actor and the way the actor tries to solve the problem. Such patterns might be found by noticing the meaning an artefact has for a specific actor. Such a meaning usually remains unaltered for longer periods of time but it can, as this study will show, also change rather drastically. Because artefacts can have different meanings for different actors (as is stressed in the SCOT approach) different actors can consider different characteristics of the artefact as being problematic. This can subsequently lead the actors to develop the artefact in quite different directions as will be shown. On the other hand meanings can also be shared with other actors which makes it possible to see an individual actor's problem partly as a characteristic of a larger group. This makes it possible to ask for social influences on the way actors deal with artefacts. These considerations have made me ask the historical material questions like: Is the meaning, the actor gives to the artefact, characteristic of more actors and, if so, which? What do they usually do with the artefact? Is the meaning specific for the artefact under study or does it relate to more artefacts? How do they usually try to solve their

problems? These questions may help to trace patterns in the way actors deal with artefacts and in the way they try to develop them.

Focussing on problems and solutions I want to stress that I am not only interested in technological problems and solutions. The problem that an artefact does not sell may be just as important for its further development as the problem that the rotor of an ultracentrifuge exploded. Furthermore, problems do not determine what type of solutions will be sought. For a manufacturer the problem that an artefact does not sell can in principle be solved in many ways. For instance by choosing a different marketing strategy or by modifying the artefact. This illustrates that actors can choose from a very heterogeneous set of possibilities in order to solve their problems (as is emphasised in the systems and network approaches). Seeing the actor as a *heterogeneous engineer*, as John Law would say, or a *systembuilder* as in Tom Hughes' vocabulary, may make the analyst aware of the heterogeneous nature of the development of artefacts. The heterogeneous possibilities for solving problems illustrate that artefacts play a role in relations between actors. Trying to understand the development of artefacts then implies that we also have to study these relations. The relations can be the result of the development of the artefact up to a certain point in time but they are also a starting point for subsequent development of both the artefact and the relations. Seeking to understand the role of artefacts in these relations and their implications for further development then implies that we should ask questions like: what relations does the actor have with other actors in which the artefact plays a role? What role does the artefact play or is it intended to play? How are these relations affected by the development of the artefact or how do they affect the development? Studying the development of artefacts with these questions in mind will give us a better picture of the heterogeneous nature of developmental processes of artefacts.

The questions mentioned in the section above have been used as sensitisers in studying the historical material and have accordingly structured the descriptions given in the following chapters. Having used the same approach for describing the development of the various ultracentrifuges in Chapters 2-6 will then enable me to make a comparison of the various case studies in order to identify a number of patterns in the development of these artefacts. These patterns, which are described in Chapter 7, suggest making a distinction between situations in which artefacts have primarily meaning for single actors only and situations in which the artefacts have become embedded in relations between actors and shared meanings have developed. It is argued that these different situations should be analyzed using different analytical tools. In the latter type of situations the three approaches mentioned above can enhance our insight in technological development.

For cases where individual actors play a primary role a new analytical tool has been developed that I have called the *definition-artefact spiral*. This model is supported by the patterns identified and fits and can be seen as an addition to the new approaches in technology studies.

Notes

1. Bijker (1987c). For a review and a discussion of the limitations of the various approaches see: Pinch and Bijker (1984), pp.400-408; McKenzie and Wajcman (1985), pp.2-25.
2. In the summer of 1984 a workshop was held at the University of Twente, Enschede, the Netherlands, on 'New Directions in the Sociology and History of Technology'. The papers presented at this workshop were published: Bijker, Hughes and Pinch (1987). In the summer of 1987 another workshop was held at Twente on the 'Integration of Social and Historical Studies of Technology'. The papers presented at this workshop will also be published as an edited volume. The closing of the gap between historical and sociological studies of technology is also apparent from a joint session that was organised by members of the Society for Social Studies of Science (4S) and the Society for History of Technology (SHOT) at the 'Four Society Meeting' at Pittsburgh, Pa. in November 1986. Furthermore, in its 1987 meeting, held at Raleigh, NC, SHOT had organised a session on 'Social Construction of Technology'.
3. For a review of the relevance of models of scientific change for understanding technological change see Laudan (1984), pp.1-18. A concrete example is the SCOT approach in technology studies (briefly discussed below) which is inspired by the 'Empirical Programme of Relativism' in the sociology of science.
4. For a criticism of technological determinism and a discussion of alternative approaches see: McKenzie and Wajcman (1985), pp.2-25.
5. Hughes (1986).
6. Hughes (1983 and 1987).
7. Callon (1980 and 1987). This type of network approach is also used by Bruno Latour and John Law. See e.g. Latour (1987) and Law (1987).
8. See e.g. Callon (1980b and 1986) and Latour (1983).
9. Law (1987).
10. Pinch and Bijker (1984 and 1987). The SCOT approach has also been used by Boelie Elzen. See Elzen (1985 and 1986). Based on the SCOT approach, Wiebe Bijker has developed some theoretical concepts whereby the development process of technological artefacts can be understood. See Bijker (1987a).
11. Pinch and Bijker (1984), p.422. Some methodological problems related to the identification of relevant social groups are discussed in Bijker (1987b).
12. Pinch and Bijker (1984), p.415-416.
13. Bodewitz, Buurma and De Vries (1987), p.250.
14. See e.g. Bloor (1973).
15. McKenzie (1987). That these approaches reinforce each other is also implicit in the argument in Bijker, Hughes and Pinch (1987), pp.9-15 (introduction to Part I) and pp.107-110 (introduction to Part II).

Chapter 2

THEODOR SVEDBERG

Education

The (Theodor) Svedberg was born 30 August 1884 at Flerång in the parish of Valbo near Gävle, Sweden. He was the only child of Elias Svedberg and Augusta Alstermark. His father was manager at different iron works in Sweden and Norway, and the family lived at various places in Scandinavia. Since his boyhood Svedberg had been deeply interested in chemistry, physics, and botany. From his father, who often took him on excursions, he inherited his love for nature and his deep interest in botany. He spent the years 1900-1903 at a grammar school in Örebro, where he had some teachers who allowed him to study by himself in the physical and chemical laboratories of the school in the afternoons after the ordinary lessons. He built a Marconi-transmitter and a Tesla-transformer and arranged some public demonstrations including wireless telegraphy between the two buildings of the school. Later this experience became useful in his first experiments to prepare colloids by oscillating discharges. He was thrilled by many of the new findings in physics and chemistry which made him finally decide to study chemistry and not biology, especially botany, although this subject also had his intense interest.¹

In January 1904 Svedberg matriculated at the University of Upsala.² When he came to Upsala, the old institute from 1859 was still in use, but by September 1904 the new building, planned by the organic chemist Oskar Widman, was inaugurated. The Institute was mainly adapted to the form of organic chemistry which was prevalent in Germany during the last decade of the 19th century. Some rooms had been reserved for physical chemistry although equipment was lacking and had to be constructed and made by the students themselves.³ During the latter part of the 19th century the effectivity and versatility of various physical methods in the investigations of chemical problems was gradually realized and an increasing number of chemists started to utilize them. Also in Upsala number of researchers started doing research that would later be classified as physical

chemistry. In 1887 Wilhelm Ostwald in Leipzig and Van 't Hoff in Amsterdam jointly started the publication of the first periodical in the new field - the *Zeitschrift für Physikalische Chemie*. Around 1905, when Svedberg started in Upsala, Nernst in Berlin was a great name in the field of Physical Chemistry; he was engaged in the same research fields which Svante Arrhenius, at Upsala, had pioneered only some fifteen years earlier. Svedberg did not follow this 'traditional' line. Instead he selected the newly emerging science of colloids and with this a new trend was brought to physical chemistry at Upsala. A contributing reason for his choice was that he felt convinced that the study of colloidal systems would help to explain the processes in living matter which reflected his deep interest in biology.⁴

Colloid chemistry generally is regarded as having been founded by Thomas Graham in the 1860s when he divided all substances known into two classes, depending on their diffusion properties: 'crystalloids' and 'colloids'. Graham studied both free diffusion and diffusion through membranes and found that crystalloids diffuse readily through a membrane and move rapidly in free diffusion while colloids (derived from the Greek word for 'glue') do not penetrate a membrane such as parchment paper and move extremely slowly in free diffusion. Graham had formulated a central problem - 'whether the colloid molecule may not be constituted by the grouping together of a number of smaller crystalloid molecules, and whether the basis of colloidalilty may not really be this composite character of the molecules.'⁵ He introduced the names 'sol' for a colloid solution and 'gel' for the product formed by setting of the solution. At the turn of the century many of the best known colloids were known to be constituted by small particles. In these reversibly dissociable systems the colloiddally dispersed phase was considered to be an aggregate of smaller units held together by secondary forces. Many chemists spoke of a 'colloidal state of matter', and a belief developed that any substance, under appropriate conditions, could be converted to a 'colloidal state'. An extension of this view was the converse notion that all colloids were aggregated clusters of molecules.⁶

Svedberg studied intensely, and in record time he passed the necessary courses and examinations and got his Fil.kand (B.Sc.) in September 1905. During his studies he literally lived in the laboratory.⁷ He was fascinated by the new colloid chemistry; the transition between crystalloid and colloid systems appeared to him significant at a time when there was considerable debate about whether molecules existed as particles or not. In his spare time he had read the 1903 edition of Nernst's *Theoretische Chemie*, and had been especially interested in the part dealing with colloids. He also read Zsigmondy's *Zur Erkenntnis der Kolloide* Bredig's *Anorganische Fermente*. Especially Zsigmondy's book impressed him and it

was mainly through Zsigmondy's influence that he became interested in colloids.⁸ After his candidate-studies Svedberg started doing research work by preparing organosols of various metals by a modification of Bredig's method. He improved this method considerably by, instead of using a direct current, introducing alternating current discharges from an old Ruhmkorff inductorium which he found in the museum of the institute.⁹ He undertook a careful investigation of the optimal conditions for the production of stable colloids, and performed a large number of experiments in organic solvents. His first publication, on metal colloids, came in 1905.¹⁰ In the following month he studied the preparation process in some detail, and in a second publication he described organosols from more than 30 different metals, some of them very stable, others stable only for one day or less. He learned how to prepare a number of stable metal sols in a reproducible way, and next started quantitative studies on the physico-chemical properties of these metal sols, especially with regard to particle size, one of his main interests for the following fifteen years.¹¹ Svedberg's work meant the beginning of a new era in chemical research at Upsala University, which until that time had been largely descriptive, preparative, and analytical. Svedberg had no major professor to teach and guide him and, on his own, developed new methods to prepare colloids in organic liquids using electrical discharge; he introduced physical measurements to study the size, size distribution, electrical charge and random motion of the colloidal particles; he applied mathematical theory to describe and interpret the results.¹²

Together with Carl Benedicks who was a new docent (assistant professor) in physical chemistry, Svedberg succeeded in obtaining the necessary parts to build a Zsigmondy-Siedentopf ultramicroscope.¹³ In 1903 the German chemist Richard Adolf Zsigmondy, together with H. Siedentopf, an optician with the firm of Zeiss, had developed the ultramicroscope which made it possible to study various aspects of colloidal behaviour directly.¹⁴ Thereupon the ultramicroscope had become a powerful instrument in colloid chemistry research. One of the important aspects of colloidal behaviour, as revealed by the ultramicroscope, was that colloids exhibited Brownian movement. The theory of Brownian movement was developed in 1905/1906 by Albert Einstein. He showed that the same principles were applicable to the random thermal motion of small molecules and of much larger, visible particles.¹⁵ The theory subsequently played an important role in assimilating the chemistry of colloids to the general concepts of physical chemistry.¹⁶ With his new ultramicroscope instrument Svedberg could study the Brownian movements of the particles in the metal sols and could determine the influence of the solvent, viscosity, temperature and so on. He was able to interpret his experimental results by the new theories of Einstein and of von Smoluchowski.¹⁷

Because of the almost complete lack of physical equipment in the chemical

laboratories in the early nineteenthundreds the researchers had to make most of their instruments themselves. For a lot of work at Upsala in those days another problem was that there were no electric mains. E.g. for the ultramicroscope an intensive light source was necessary, viz. an electric arc lamp. The necessary electricity for the lamp had to be obtained from a generator in the basement, which was driven by a hot air engine with a heavy balance wheel and which had to be started by hand and not without risk. And to provide resistances Svedberg bought large quantities of iron wire which he coiled into spirals which were hanging on the ceiling all over the place. Because of the extensive use of apparatuses physical chemistry in those days was often referred to as that part of chemistry which used physical instruments.¹⁸

Dissertation - Docent - Professor

In December 1907 Svedberg defended his thesis *Studien zur Lehre von den kolloiden Lösungen* for the degree of doctor of philosophy. It was divided into three main sections, where the previously mentioned problems of synthesis, stability and Brownian movements of colloids were discussed. He also studied the effect of particle size upon optical absorption as well as the coagulation of hydrosols upon the addition of electrolyte, particularly the influence of temperature.¹⁹ A few weeks after the completion of his thesis he was appointed 'docent' in physical chemistry at the university, obtained better laboratory facilities and could have his own students. Within a few years he succeeded in getting together a small group of research students, all of them enthusiastically occupied with the investigation of colloids, like Harald Nordenson, Sven Odén, Arne Westgren, Nils Pihlblad and Ivar Nordlund. Their chief experimental tool was the ultramicroscope and the objects of their investigations were mostly the inorganic colloid solutions such as gold sols, mercury sols, sulphur sols. One of their leading ideas was to try to synthesize colloid systems of high purity and simplicity with the object to find out the general laws governing the behaviour of colloids. Between 1905 and 1912 Svedberg published over 40 papers dealing with various aspects of colloidal behaviour and Upsala became known as a centre for quantitative work on inorganic sols.²⁰ His modification of Bredig's technique made possible the preparation of a large number of new colloids and already in his thesis Svedberg described the preparation of sols of more than 30 metals in organic solvents, mainly isobutanol and ethyl ether. The preparative work was expanded in the following five to ten years, and in 1909 a large and detailed monograph on the preparation of colloids was published entitled *Die Methoden zur Herstellung Kolloider Lösungen anorganischer Stoffe*²¹ which was very well received. Another interest of Svedberg were the discoveries

connected with radioactive substances which had fascinated him ever since his school days and continued to interest him all through his life. Shortly after having become docent, he started an investigation on isomorphic coprecipitation of radioactive compounds. These experiments were carried out together with Strömholm, newly appointed Professor of Inorganic Chemistry at Upsala University.²²

In the summer of 1908 he made his first trip abroad. He went to Germany where he visited Zsigmondy and Siedentopf among others. In Zsigmondy's laboratory some experiments with colloidal sulphur especially attracted his attention. He came to the conclusion that different particle sizes were present in the sulphur sols and had many speculations about a possible relationship between the size of the particles and the properties of the sols. A few experiments with colloidal sulphur were made by him before suggesting to one of his students, Odén, that he should study the problem in detail. This eventually led to Odén's dissertation 1913: *Der kolloide Schwefel*.²³

By 1910 Svedberg had become a quite well known and respected experimentalist in his field but nevertheless his position at the university was insecure. At the time there were only few permanent academic positions in Sweden and 'docents' such as Svedberg only held their posts for six or, exceptionally, seven years. In order to keep Svedberg at Upsala University, in September 1911 two Professors of Chemistry, Strömholm and Widman, proposed that he be offered a personal chair. Their proposal was strongly supported by Svante Arrhenius and was also backed by the Chancellor for the Swedish Universities. These efforts were successful and on 29 June 1912 Svedberg was appointed to the first Chair of Physical Chemistry in Sweden. His inauguration lecture took place on 1 February 1913 and had the title: *Atomic research in modern physics and chemistry*.²⁴

In the same year Svedberg was appointed professor, Wilhelm Ostwald received the Chemistry Nobel Prize for his work on catalysis and his investigations into conditions for chemical equilibrium and velocities of reaction. About the same time Svedberg published his book *Die Existenz der Moleküle* in which he defended their existence against those scientists which, like Wilhelm Ostwald, held the opinion that molecular theoretical considerations had become obsolete.²⁵ In their view, many laws of nature could just as well be formulated and systematized without any theory of molecules, especially by the use of thermodynamics. Ostwald believed that all phenomena could be understood by using energy as a central category. Svedberg, however, was convinced that molecules were more than a mere construct and that their existence could really be demonstrated. The investigation of colloids would provide a way of showing this. Some years later 'grand old man' Ostwald became convinced of Svedberg's view and stated that he had been wrong on this matter. In a letter he wrote:

"Ich habe mich von der Richtigkeit der Svedbergschen Anschauungen überzeugt. Sie bilden tatsächlich einen Beweis für die molekularkinetische Theorie. Ich zögere nicht, zuzugeben, dass, nachdem nun ein befriedigender Beweis erbracht ist, ich nicht mehr das Recht habe, noch länger die Molekulartheorie abzulehnen. Die Ablehnung beruhte ja nur auf dem bisher nicht erbrachten Beweis. Ich vermute, dass in der Zukunft noch grosse Erfolge zu erwarten sind von diesem jungen, begabten und energische Mann."²⁶

During the next 10 years research work by Svedberg and his collaborators was devoted mainly to the study of the physico-chemical properties of colloidal systems, particularly the size distribution of their particles. These activities resulted in some important general findings which were published in several dissertations by his students: a work on Brownian movement by Westgren in 1913 led to a well-founded value for Avogadro's number (a basic unit in chemistry); Nordenson in 1914 described the effect of light on colloidal systems; in 1918 Nordlund produced a study on mercury sols; an investigation into the relationships between light absorption and particle size was published by Pihlblad in 1918, and in 1921 Börjeson produced a study on the electric synthesis of colloids.²⁷ Toward the end of this period photochemical problems connected with the formation and growth of the latent image in a photographic emulsion also aroused Svedberg's interest.²⁸

In the view of many colloid chemists, including Svedberg, one of their main tools, the ultramicroscope, had two serious limitations. In the first place, it could only make visible particles of which the index of refraction differed greatly from that of the solvent (or dispersion medium as the 'solvent' of colloids was usually called). Only in especially favorable cases, such as gold, platinum and silver particles, it was possible to penetrate down to sizes of the order of 5 micron. (One micron is one-thousandth of a millimetre). The wide and important domain of lyophilic colloids, such as sulphur, ferric oxide, silicic acid, proteins, starch, cellulose, rubber, could only to a very limited extent be explored by means of the ultramicroscope. In the second place, even in the favorable case of, say, a gold colloid, ultramicroscopic observation could only give rather incomplete information with regard to the statistical distribution of the various particle sizes present in the colloid solution. The applicability of the ultramicroscope was therefore limited, especially in view of the investigation of substances Svedberg was interested in. Thereupon, Svedberg engaged himself in a search for some other means of attack in cases where the ultramicroscope failed. Perrin's work (1908) on Brownian movement and the sedimentation of small particles suggested some method built on diffusion, osmotic pressure and sedimentation. Svedberg thought it should be possible to combine these properties so as to dispense with the necessity of making the particles visible.²⁹

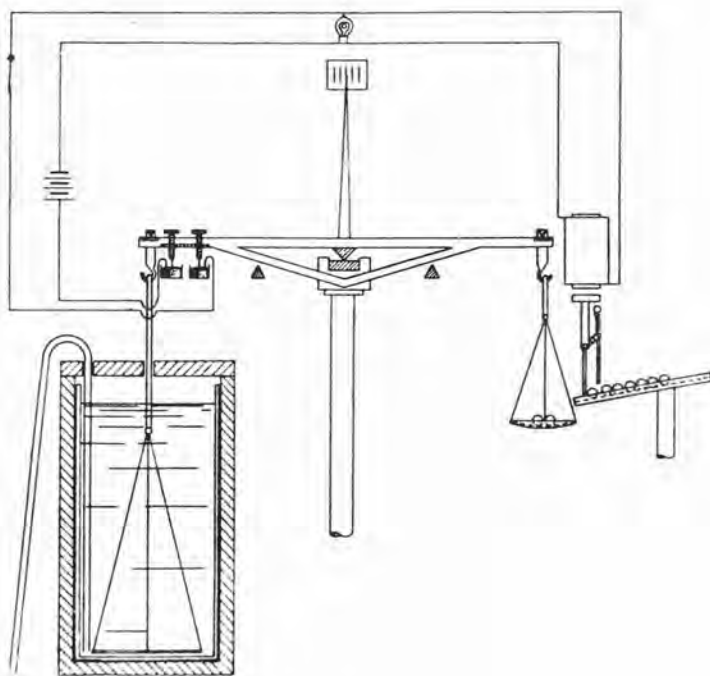
Distribution of sizes - Sedimentation balance

An important topic in colloid chemistry was the determination of particle sizes in sols. In the Svedberg's view, especially the determination of the *distribution* of sizes should be considered an important problem. Before 1910 most investigations had only resulted in a *mean* particle size. In 1911 Svedberg pointed out that use of the ultramicroscope would unquestionably allow to obtain the distribution curve for the particles but the work would be very tedious. Two possible methods were outlined: for coarser colloids and suspensions the rate of sedimentation could be measured; for finer colloids displacement due to the Brownian movement could be measured. If this were done for a sufficiently large number of particles, a distribution curve would be obtained.³⁰ Some series of measurement illustrating the use of the first method were given. The fall of a statistically sufficient number of particles was measured with the aid of a microscope provided with a dark-field condenser and the frequency curves of the size of particles were drawn. A preliminary attempt to utilize the second procedure was made by Svedberg and Nordlund, but the rather large number of determinations necessary for sufficiently reliable statistics discouraged them from pursuing the work.³¹

In 1915 Sven Odén, one of Svedberg's collaborators worked out a method in which one scale of a balance was hung in a colloidal solution. Sedimentation under the influence of gravity caused that scale to become heavier as a function of time. The balance was kept in equilibrium by putting weights on the other scale (figure 2.1). Thus the sedimentation as a function of time could be registered. Subsequently, the theoretical relation between particle size and sinking speed made it possible to determine the distribution of particle sizes.³² Odén's apparatus was originally devised for the study of rather coarse systems such as clays, and required comparatively large quantities of particles, namely, about 1 gramme. This method was improved by Börjeson using a method of 'direct weighing of sediment' which made it possible to extend Odén's method to quantities of 0.1-0.2 gramme.³³ This work lay dormant for a number of years but was picked up again in the early 1920s by Svedberg and Herman Rinde, one of his students:

"The importance of size-frequency curves in colloid chemistry is constantly increasing and we have, therefore, again taken up the problem of the determination of such curves. On the one hand, we have tried to introduce such improvements in Odén's procedure as to make it meet the requirements of the colloid chemist better than in its original form, and on the other hand, we have tried to find some other variation (...), capable of being extended to particles of such smallness as occur in fine-grained disperse systems, that is, in true colloid solutions.

For our purpose we desired if possible to be able to use only 0.02 g. and to have the deposition of such small quantities recorded automatically. In such a case Odén's procedure of adding automatically small counterweights was not practicable."³⁴

*Figure 2.1*

Sedimentation Balance (Odén, 1916, p.226).

As a solution they devised a method of compensating automatically for the disturbance of equilibrium of the balance by means of a coil acting on a tube of iron suspended on the arm of the balance, and by recording the current in the coil by means of a selfregistering milliammeter (figure 2.2). In this way they obtained a diagram showing the variation of compensating current with time; this curve could be easily transformed into a curve giving the variation of weight of sediment with time. They applied this new method to the determination of particle curves in gold and mercury hydrosols. Regarding the results they remarked:

"We do not intend to discuss here the character of these distribution curves. We should like, however, to call attention to the fact borne out by these measurements that even in sols that have been looked upon as consisting of particles of fairly equal size, as for instance in the case of the gold hydrosols prepared by the nuclear method, there can actually be present groups of particles of sizes varying over a considerable range in radius."

This new registering method made the procedure ten times more accurate than the old method. Particles with sizes down to approximately 150 nm. (one nm is one millionth of a millimetre) could now be measured.

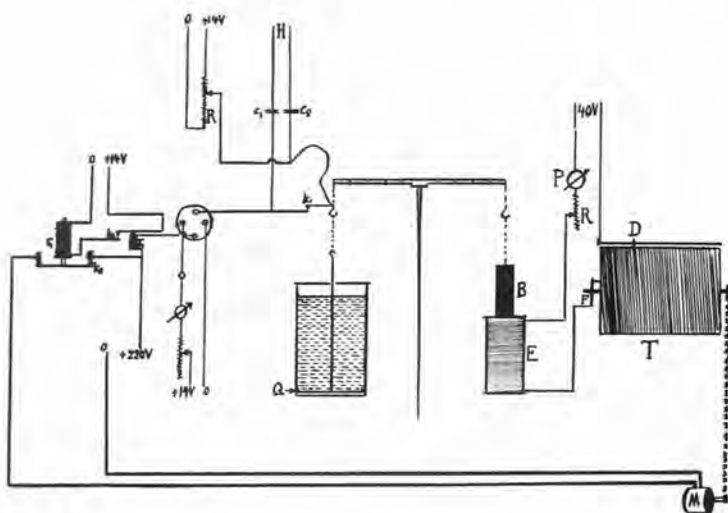


Figure 2.2

Selfregistering sedimentation balance. The particles settle on a plate that is suspended on one arm of the balance which is immersed in the sedimentation vessel. On the other arm of the balance is suspended an iron tube B with its end reaching into the coil E. The latter is connected with the regulation resistance R, the precision self-registering milliammeter P, an accumulator battery and the drum resistance T. At the beginning of an experiment the resistance R is adjusted so as to give equilibrium. When the weight of the plate increases, because of the particles settling on it, the contact k_1 is closed and by means of a very sensitive system of relays the motor M is set in motion revolving the drum T. By this means the sliding contact D is carried toward the left, a certain portion of the resistance wire is cut out and thus the equilibrium re-established. (Svedberg and Rinde, 1923, p.945).

The method was not considered accurate enough to register the sedimentation of the 'true colloid solutions'. In order to be able to do so Svedberg thought that a further improvement in the registering method would not help him out. Increasing the accuracy would only be possible by adopting 'a procedure which will give us high values of g , that is we must be able to expose the system to a centrifugal force'.³⁵ The use of centrifuges, however, apart from solving a problem, also presented new problems. Thus, Svedberg figured it would be virtually impossible to register sedimentation as a function of time. Better results would, he thought, be obtained by determining particle concentration as a function of the height of the column of sediment. To do this, an optical method would have to be developed to make external observations without disturbing the sedimentation process.

"An ideal method would be to measure the absorption of X-rays of a suitable wave length, a procedure which would give the mass concentration directly and be independent of the various sizes of the particles. In such cases where the relation between size of the particles and absorption of ordinary light is known or in cases where the light absorption does not vary much with the sizes of particles, a determination of the variation of light absorption with height can be used."³⁶

Svedberg developed such a method himself, using a mercury quartz lamp as a light source. He tested the method by registering the concentration gradient of a colloidal solution in a beaker, using gold sols of the same kind as the one recorded with the balance method. The distribution of particle sizes thus registered turned out to correspond roughly with the distribution found with the 'old' method for measuring the sediment. Svedberg's conclusion was that the optical method produced reliable results.³⁷

In July 1922 Svedberg made a first draft of a system for following the sedimentation in a centrifuge. It was based on ultramicroscopic observation during centrifugation. The idea remained on paper and so did other proposals drafted during the fall of 1922. When he spoke to his students about this possibility they were not very enthusiastic about it.³⁸

Wisconsin - Optical Centrifuge

According to Claesson and Pedersen, after World War I in Sweden it was very difficult to obtain funds for research. It was therefore a great encouragement to Svedberg, when James Howard Mathews extended an invitation to him to give lectures and organize research in colloid chemistry at the University of Wisconsin in Madison, USA.³⁹ At that time in the US, research in colloid chemistry was just starting. The first book dealing with colloid chemistry to be authored in the US was that of Wilder D. Bancroft, published in 1921. People like Mathews, who gave the early lectures in the subject had to lean heavily on European publications, such as Freundlich's *Kapillarchemie* (1909), Ostwald's *Handbook of Colloid Chemistry*, and on journal articles. Mathews became more and more interested in the subject of 'the chemistry of the neglected dimensions' as Ostwald christened it. In 1919 Mathews became Chairman of the Chemistry Department of the University of Wisconsin, Madison (WI). A year later C.S. Slichter was made Dean of the Graduate School; he was much interested in improving graduate work and in stimulating research at Wisconsin. One day in 1922 he approached Mathews with a plan for stimulating research and suggested to organize a symposium on colloid chemistry. Mathews thought this was a great idea and shortly thereafter suggested that, in order to insure its success and to give it the needed publicity they should have a foreign guest who was distinguished in the field of colloid chemistry. The best candidate would be Svedberg who, in Mathews' opinion, was the world's most distinguished experimentalist in the field. Furthermore, Mathews suggested that in order to make the symposium a real success, to stimulate research in colloid chemistry and to make the deal more attractive to Svedberg they ought to bring him to Wisconsin for two semesters of research bracketing the symposium and that

he should also give a course of lectures for the benefit of their students, and to arouse campus interest in the subject. This would be a great attraction for the summer session. The dean agreed and Svedberg accepted the invitation with enthusiasm.⁴⁰ Svedberg suggested the following topics for research:⁴¹

- size of particles by centrifugal method
- electric synthesis of colloids
- cataphoresis of proteins
- distribution of size of particles
- percentage developable grains in photographic process
- photographic action of slow cathode rays
- heat of wetting of powders
- density of protein solutions

Svedberg had written what type of special equipment would be needed for these researches and by the time of his arrival most of the equipment had been constructed and a group of eight eager young men was ready to begin research under his direction. One of them, James Burton Nichols, chose the first topic as a research project. Nichols had already met Svedberg when the latter, on his way to Wisconsin, had stopped at the Eastman Kodak Co. in Rochester, N.Y. to give a general lecture on his work in Sweden. Svedberg was invited for this lecture because he had also done some work on photographic emulsions. At the time, Nichols was just finishing his undergraduate work at Cornell University with Wilder D. Bancroft as his major professor. When he went to Rochester to meet Svedberg he expected to see a 'plump, middle-aged bewhiskered European professor with grey hair'. To his complete surprise he saw a boyish, slight man with flashing eyes and very black hair', 38 years of age.⁴²

In about two weeks Nichols was at Wisconsin and had selected the optical centrifuge as his research project. Svedberg told Nichols later that the other men had avoided it for more promising projects. For example, Elmer O. Kraemer worked on the formation of MnArsenate gels under the kinoultramicroscope while John W. Williams worked on specific heats of organic liquids.⁴³ In the spring of 1923 Nichols developed a centrifuge where the sedimentation could be followed optically while the centrifuge was running. Nichols had had a little mechanical training during his studies which helped him somewhat in judging the mechanical problems involved. The centrifuge was built by the mechanic of the College of Engineering. Svedberg gave Nichols pretty much of a free hand in the development. Nichols had placed sandbags around the apparatus as a safety arrangement in the case of an explosion. They planned to go to ten or twenty thousand r.p.m. (revolutions per minute) but with their arrangement, using a readily available grinding motor on which they put a relatively heavy head, they never reached more than a few thousand r.p.m.⁴⁴ The results were presented at the 'First National Symposium On Colloid Chemistry', held at Madison in June 1923. The

symposium was attended by representatives from both industrial and academic science. The industrial chemists came from such diverse laboratories as those of rubber, oil, glass, soap, adhesives, forest products, leather, paper, and photographic materials. Most of the university representatives were physical or chemical scientists, but there were a number from the biological, medical, and some related agricultural sciences. In the announcement of the symposium it was also stated that Svedberg would give a series of about twenty-four lectures in colloid chemistry during the summer session of the university.⁴⁵ Svedberg's presentation at the symposium was entitled 'Colloid Chemistry Technique' in which he stated:

"The ordinary methods of chemistry and physics have only a limited bearing upon the colloid systems, because these methods have been developed without taking into account the particular properties, the peculiar structure, of colloids. Almost every advance in colloid chemistry can therefore be traced back to some new technical means especially designed for the study of colloids. Colloid chemistry has been neglected, it has not yet got the experimental equipment that its sister sciences have had at their disposal for quite a while. This undoubtedly is to some extent due to the fact that it has not until recently been fully understood that colloid chemistry requires its own technical facilities, different from the ordinary equipment of a physico-chemical laboratory. We have to contemplate the properties of colloids, as far as we know them, and ask ourselves: what kinds of instruments would one like to have at one's disposal to study such systems? I think that such a method would pay much better in the long run than just to take the instruments one might happen to come across in the field of ordinary physics and chemistry and try to study colloids by means of those instruments. In my opinion it would save a lot of work, time and money if the colloid chemist would stop a moment in his investigations of colloid systems and take a look at his equipment. He would find then that all the technical means we use in colloid chemistry are not rational, that, perhaps, we had better devote some of our time and attention to the development of colloid chemistry technique before we try to proceed any further in our investigations of the colloid systems."⁴⁶

Svedberg outlined the various colloid chemistry techniques which were developed at the time together with a few suggestions for new methods. About the centrifugal method he stated:

"Most sols have particles too small to allow determinations of size of particles by utilizing the force of gravity. Recently the writer has suggested the use of a centrifugal force in such cases where setting under the influence of gravity is too slow. (...)

Nichols and the writer (in this laboratory) have carried out measurements of size of particles in fine grained sols by using a special centrifuge which allowed determinations of the movement of the boundary between the sol and the clear dispersion medium during centrifuge. This method is now being worked out in more detail and seems to be rather promising. In some cases we have already been able to measure the size of particles which could not be counted in the ultramicroscope. In cases where both the centrifugal and the ultramicroscopic method could be applied the values found by the different methods agreed very well.

The centrifugal method can also be used for recording the distribution curve of fine grained sols. The experimental details are now being worked out by Nichols and the writer."⁴⁷

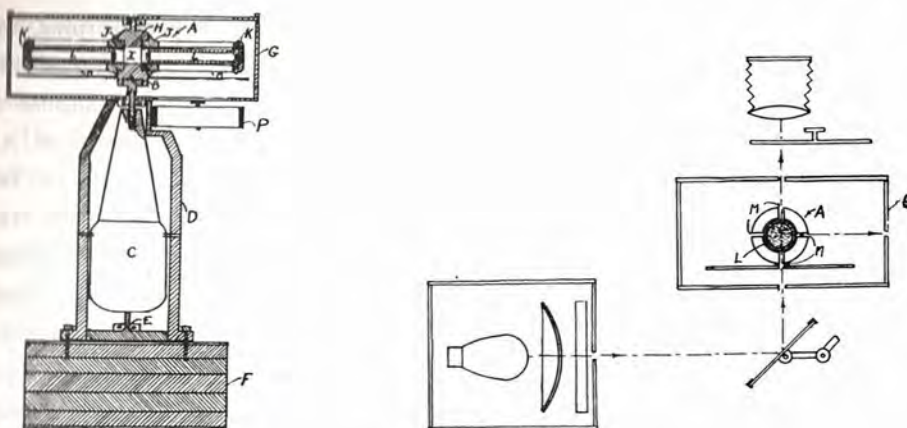


Figure 2.3

Optical centrifuge. Explanation: see text. (Svedberg and Nichols, 1923, p.2912).

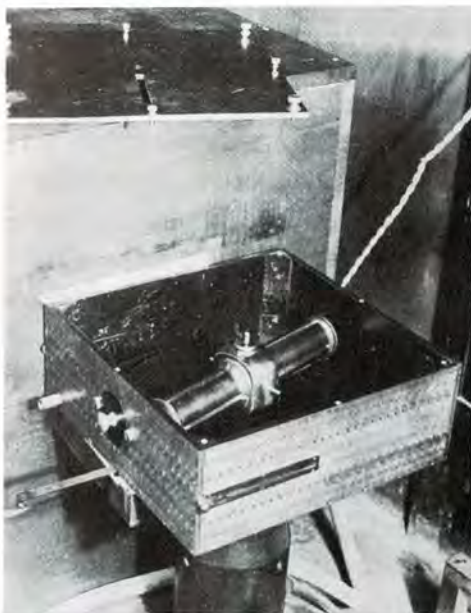


Figure 2.4

Svedberg and Nichols' Optical Centrifuge (Pedersen, 1976, p.4).

Late 1923 Svedberg and Nichols published their first article on the centrifuge method in the *Journal of the American Chemical Society*. Figure 2.3 gives a diagram of this centrifuge which is also shown photographically in figure 2.4. The rotor A was directly connected at B to a Dumore special 20,000 r.p.m. motor C suspended in the heavy metal casing D and supported by a pivot bearing E. The

machine was mounted on a large wooden base F, laminated to prevent warping, and several thicknesses of linoleum were glued on the top and bottom to absorb vibration. The rotor was enclosed in a square metal box G for the purpose of protecting the tube from air currents and resulting temperature differences. Air might be blown through the box also in order to obtain constant temperature. The top was made removable so that the rotor might be adjusted when necessary. The rotor consisted of the central head H, horizontally cored I, to which were screwed the two arms J, also cored to correspond to the core of the head. These arms were closed at the outer end by screw caps K to provide a means for changing the tubes L contained. In order to obtain vertical or horizontal illumination of the tubes, the arms were slotted M, on top and bottom and on both sides. Proper balancing appeared essential because otherwise vibrations tended to mix the colloid and vitiate the effect of the force applied. A special adjustment arrangement was developed which was sensitive enough for their needs.⁴⁸

Experiments with uniform gold sols showed that the particle sizes as determined with the centrifuge method differed about 5 % from the values obtained with the ultramicroscope. Experiments with barium sulfate in the centrifuge showed that a certain range of particle sizes was present. The particle sizes obtained differed considerably from the ones obtained with the ultramicroscope which they ascribed to the fact that the latter method only gave information on the average size of the particles. The procedure adopted was only usable for uniform sols, i.e. sols in which only a narrow range of particles was present. For non-uniform sols, i.e. most colloids, a rather complicated procedure would have to be followed. First, a picture was taken of the contents of the centrifuge tube when the rotor has just come up to speed and practically no sedimentation had taken place. Then a photograph was taken on the same plate after a given length of time of running and a third photograph was taken of a wedge cell of the material. All three pictures had to be given the same intensity of illumination and length of exposure. Then by comparing the second and the third strips in a photometer, they obtained the density on the wedge cell strip corresponding to the density of the sol representing its original concentration. Beer's law could then be used to determine the concentration at each layer of the wedge cell and the values obtained put in the form of a scale parallel to the photograph strip of the wedge cell. The density of this strip was next determined throughout the whole height which gave concentration in terms of density. However, if the material under observation contained a wide range of sizes of particles, the variation of the light absorption constant with radius should be considered. Finally, the density of each layer of the sedimenting sol could be obtained from the photograph taken of the contents of the tube after the

centrifuge had been running for some time, and when it was known what each density represented in terms of concentration, the change in concentration with distance could be determined for the material.⁴⁹

The first experiences with the centrifuge method indicated that this road would not be an easy one to travel. First, it was evident that all measurements had to be done while the sample was rotating at constant speed. Accordingly only optical methods could be used for recording the sedimentation. Second, the centrifuging had to be conducted at constant or only slightly and uniformly varying temperature. These two conditions had to be fulfilled in order to obtain convection-free sedimentation. In the third place, the centrifugal field created within the solution to be studied should be of high intensity and homogeneity.⁵⁰ Another problem with respect to the first optical centrifuge was that the centrifugal force caused the particles to move outward along a radius through the central point of rotation. With a tube-shaped cell this implied that particles would collide against the side walls of the cell which made their behaviour unpredictable. No simple and exact calculation of the rate of sedimentation as a function of particle size was possible.⁵¹ Yet, Svedberg was convinced that this problem of convection currents was solvable, and on the boat back to Sweden he drew the first sketches of a new type of centrifuge (figure 2.5).⁵²

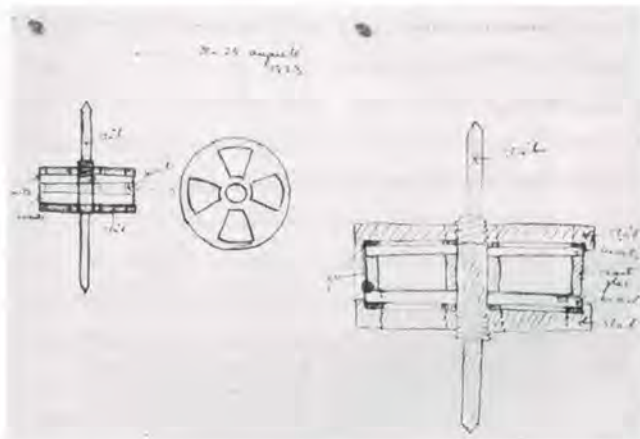


Figure 2.5

Sketch of a new rotor for the Optical Centrifuge. (Pedersen, 1976, p.4).

The eight months at the University of Wisconsin had been extremely stimulating for him and meant a turning point in his scientific career. He returned to Upsala loaded with new ideas and enthusiasm. The period in the US meant not only recognition, it also stimulated him to carry out ideas and plans on a much larger scale than was possible at that time in Upsala. He started to think in terms of 'big

science'.⁵³ In Upsala the head of the Institute of Chemistry was shocked when Svedberg said he needed a new physical chemistry laboratory. It seemed impossible to ask the Parliament for funds for such a purpose. But Svedberg argued that this was just what should be done.⁵⁴

The Ultracentrifuge

Back at Upsala he and Rinde worked during the autumn on the construction of a new centrifuge. They also enquired with a number of companies what type of centrifuges could be supplied from stock. The Dutch 'Giro' company informed him that they could supply a centrifuge with a rotor of 13 cm diameter which rotated 20,000 r.p.m. It would cost about Dfl. 5000 (about \$ 2000,- at the time) including some accessories. It would also be possible to construct a similar centrifuge for 30,000 r.p.m. but that would probably require a rotor spinning in a chamber which would be first evacuated and next be filled with hydrogen in a way similar to a special type of compass supplied by the same company. This would cost an additional Dfl. 2000,-.⁵⁵

Because there did not seem to exist a centrifuge which directly suited their needs Svedberg and Rinde started with an existing cream separator supplied by the 'Upsala Separator Fabrik' and tried to adapt it to their research. Late 1923 they were ready to start experiments with a centrifuge running at 10,000 r.p.m. while at the same time designing a centrifuge for 30,000 r.p.m. In order to be able to determine the gradient of the blackening of the photographs recorded with the centrifuge they developed a special microphotometer which cost about \$ 500,-.⁵⁶ Svedberg corresponded on their progress with Nichols in Madison who continued to develop the original design further. Nichols found it very difficult to prevent mixing of the substance centrifuged because of non-uniform temperature, varying speed and vibrations due to imbalance. It also appeared that his source of light was not very constant which made interpretation of the photographic plates more difficult.⁵⁷ During their development work Svedberg and Rinde also encountered a number of problems. First, it was hard to take into account that it would take some time before the motion of the particles had become constant. On theoretical grounds, however, Svedberg believed that they could always keep the velocity so low that this effect would be negligible.⁵⁸ They also found that it was essential to keep the temperature as constant as possible as well as the rotation of the rotor. They determined the amount of heat produced in the different bearings of the machine and arranged it so that this heat could be carried away from the centrifuge. In order to secure constant rotation Svedberg collected a lot of information on 'self-balancing' centrifuges which could seek their own axis of

rotation because they had a flexible shaft - the so-called spinning top principle. In order to be able to use this principle it was not possible to use the type of fixed bearings Nichols was still using so new bearings would have to be designed.⁵⁹

On 23 november 1923 Svedberg drew a rough sketch of a centrifuge on a sheet of paper marked 'centrifugal analysis of proteins'. Their aim was to construct a centrifuge that could be used for sedimentation studies on metal sols.⁶⁰ On 15 February 1924, the centrifuge was for the first time called the *ultra-centrifuge* in Svedberg's laboratory record. Then followed a period of adjustments and tests. After 5 to 6 weeks, the first sedimentation measurements on a colloid were noted in the record and here the name *ultracentrifuge* (without a hyphen) appeared for the first time.⁶¹ Sedimentation in the new ultracentrifuge occurred in a sector-shaped cell. As the gravitational forces generated were directed from the centre to the periphery, the particles in a sector-shaped cell did not experience forces directed towards the side-walls of the cell. Thus, they expected, there were to be no unpredictable movements along the walls of the cell anymore. The cell was placed in a heavy rotor which was fastened to the axis of a modified milk separator centrifuge. However, convection currents still occurred. According to the researchers this was either due to vibrations in the apparatus or to the heating of the rotor. If the latter were the case, the problem could be solved by making use of the heat-conducting properties of hydrogen. And indeed, when the rotor was spun in a hydrogen atmosphere, convection-free sedimentation was obtained.⁶²

In the beginning of 1924, Svedberg and Rinde used the centrifuge to carry out experiments with gold sols, and in July 1924 the first paper dealing with ultracentrifuge experiments was sent to the *Journal of the American Chemical Society*. In the introduction they stressed the importance of the new apparatus:

"(...) every possible measure should be taken in order to develop this procedure to the point of greatest reliability for the determination of size and distribution of size of particles in very fine-grained sols. (...) The new centrifuge constructed by us allows the determination of particles that cannot be made visible in the ultramicroscope. In analogy with the naming of the ultramicroscope and ultrafiltration apparatus, we propose the name *ultra-centrifuge* for this apparatus."⁶³ (emphasis in original)

Figures 2.6 and 2.7 show a sketch of this ultracentrifuge and the surrounding equipment. The apparatus was built by Svedberg and Rinde themselves in cooperation with Ing. A.G. Bergström.⁶⁴ The centrifuge was constructed according to the self-balancing principle which was generally used commercially in the construction of separators. A modified milk separator centrifuge of de Laval's design was used as the drive unit and the cell was placed in a heavy rotor. A vertical shaft (figure 2.6; 15) whose base was a specially tempered steel hemisphere rested on an equally well tempered steel plate and was enclosed by a pivot bearing.

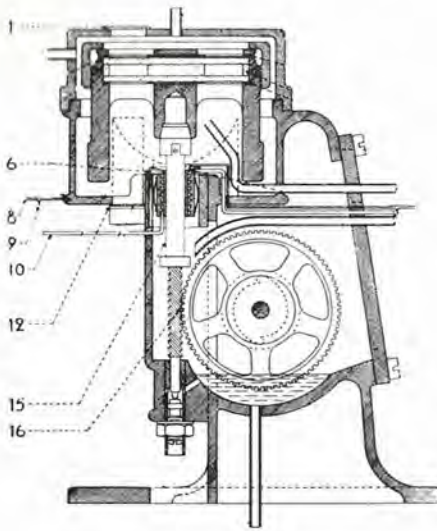


Figure 2.6

Self-balancing Ultracentrifuge. Explanation: see text. (Svedberg and Rinde, 1924, p.2678).

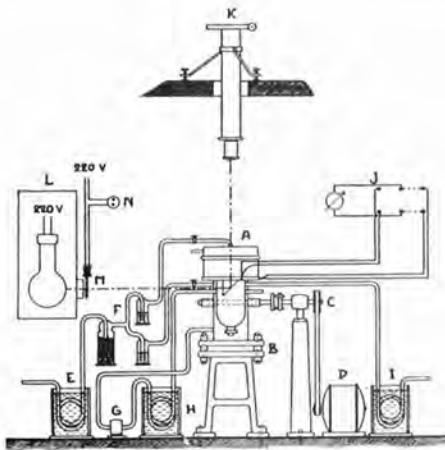


Figure 2.7

Ultracentrifuge and surrounding equipment. A, Centrifuge; B, Stand; C, Pulley; D, Motor; E, Cooling Spiral for hydrogen current; F, Valves; G, Oil circulation pump; H, Cooling spiral for oil current; J, Galvanometer and key; K, Camera; L, Lamp; M, Shutter; N, Switch for shutter. (Svedberg and Rinde, 1924, p.2679).

An upper bearing (figure 2.6; 6) which was surrounded by a spring arrangement to give flexibility in the horizontal plane held this shaft in position. The shaft was rotated by the slant-toothed wheel (figure 2.6; 16) which acted upon an endless screw thread on the shaft. A clutch was inserted between this gear and its shaft to enable the wheel to run freely when the motor was switched off. The rotor

rested on the top of the shaft and was brought into motion with it by means of a special frictional device and the centre of gravity of the rotor lay underneath its suspension point. The rotor first used was so constructed that the circular glass cuvette, whose diameter was slightly less than that of the rotor, was placed above the top of the shaft. The rotor consequently became rather heavy (8,660 grammes) but it was supposed that this would counterbalance the variation in speed of the electric motor. Later experiments indicated, however, that a lighter rotor vibrated less than the heavy one. In the beginning the pulley was fixed on the same shaft as the gear. This arrangement appeared to be very problematic as vibrations occurred on account of unevenness in the belt, and also vibrations from the electric motor were directly transferred to the rotor. It proved necessary, therefore, to mount the pulley on a separate stand (figure 2.7; C) and transfer the rotation by means of a special coupling to the shaft carrying the gear.

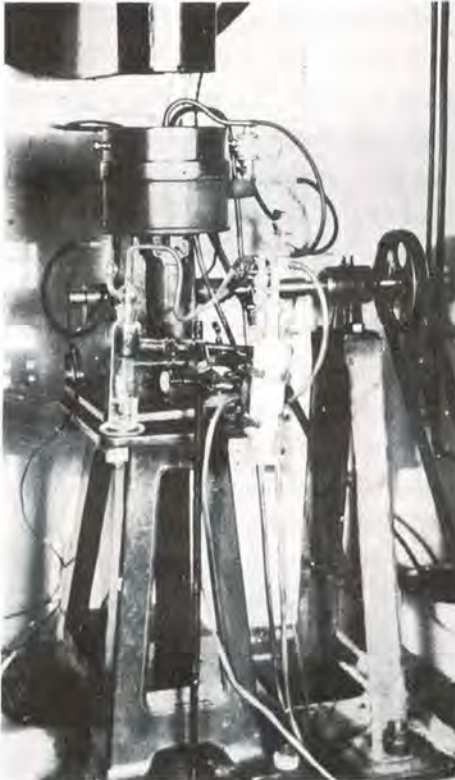


Figure 2.8

Svedberg and Rinde's first ultracentrifuge (Pedersen, 1976, p.6)

The rotor, the vertical shaft, and the gear were enclosed in a metal casing at the bottom of which was a reservoir for oil from which the lower bearing and the

endless screw were lubricated. The metal casing was fixed to the cast iron support (figure 2.7; B) which in turn was bolted down to a heavy concrete base. Between the cast iron stand and the concrete base were inserted thick rubber plates to absorb vibrations, and between the centrifuge casing and the metal stand were placed wooden plates. The metal casing was provided with two windows (figure 2.6; 1 and 12) to permit a beam of light to pass through the centrifuge. In order to prevent oil droplets from collecting on the lower window during long centrifugings a metal shutter was placed above it, and opened only during the exposures. The speed of the rotor was varied partly using different pulleys and partly by changing the speed of the electric motor, the rotor of which was shunted and provided with variable resistances. A photograph of the apparatus is shown in figure 2.8.

Concerning the sector-shaped sedimentation chambers they had tried several designs. The cuvette first used was made of three circular glass plates 12.4 cm in diameter and cemented together with de Khotinsky cement (figure 2.9). The thickness of the upper and lower plates was 5 mm, and of the middle one was 10 mm. In this plate two sector-shaped openings were cut out, and through a hole in the upper plate these could be filled with a colloidal suspension. With such a construction the two halves A and B of the middle glass plate tended to separate from each other during rotation on account of the centrifugal force, and at high speeds a crack occurred in this plate along the line CD (figure 2.9). A smaller cell in the shape of a wedge the apex of which had been cut off was therefore constructed. This cell was also made of three glass plates cemented together and of the same thickness as in the cuvette described above. In the middle plate a sectorial aperture was cut. These cells were placed in opposite pairs in a special circular cell holder of brass (figure 2.10, left). With cells of this type the construction of the rotor also could be altered. It was built as shown in figure 2.10, right. It could be made considerably lighter, its weight with cells and cell holder being 5,840 grammes. Under this rotor, however, it was necessary to fasten a metal disc for the purpose of preventing an oil fog from forming on the lower surface of the cell. These cells proved to be very resistant to the high pressure within the cell during rotation. In later constructions the cells had been made circular and enclosed in special metal collars. On the bottom of the cell holder a thin ebonite plate was placed provided with one sectoral aperture of exactly the same size as that of the cell. One cell was thus covered and the beam of light was permitted to pass through only one of the cells.

Concerning the sector shaped cell it appeared difficult to get the various component parts solidly united. Trying to solve this problem he approached Adam Hilger Ltd. in London, instrument makers of optical equipment, whether they could construct a cell for him according to the specifications he included.⁶⁵ Hilger

replied that such would not cause much trouble but that it seemed to them that it would be very much simpler to make the aperture of the cell larger, and to cut it down to the required sectorial aperture by means of a metal mask. Such a cell would cost about £ 10.⁶⁶ Thereupon Svedberg ordered four cells but stressed that it was essential that the cell should *'be of sectorial shape itself, i.e. it is not only a sectorial aperture but also a sector-shaped volume of liquid that is required'*.⁶⁷ (emphasis in original).

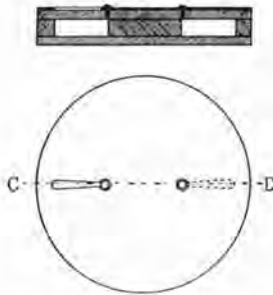


Figure 2.9

Positioning of cells in rotor (Svedberg and Rinde, 1924, p.2680).

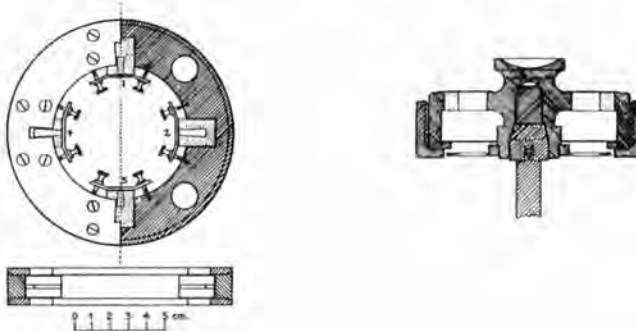


Figure 2.10

New cell and rotor construction (Rinde, 1928, p.85 and 86).

During the centrifuging, vibrations sometimes occurred, and at certain speeds of rotation they became large on account of resonance phenomena. The heavy rotor was first balanced by adding bits of solder. It was then always possible to find a position of the cell holder where the vibrations disappeared or were small at a given speed of rotation. The vibrations were always slow compared with the number of revolutions per minute which probably explained the fact that the vibrations never had any effect on the progress of the sedimentation. On the other hand, the image of the cell was blurred because of this movement. In their experiments the amplitude of vibration of the cell, and consequently the resulting

indistinctness of the image, never exceeded 0.1 mm. As a rule, no vibration occurred in the experiments.

The absence of rapid and large vibrations was a necessary condition for obtaining reliable results, but it was of equal importance that constancy of temperature would be maintained in the cell during the run. With any variation of temperature in the cell convection currents would arise. These were noticeable through the fact that the boundary between colloid and dispersion medium, which for 'normal' sedimentation would be diffuse, became sharp. At the same time the clear dispersion medium beneath the meniscus became colored by colloid, and also the colloid between the boundary and the bottom of the cell got darker through acquisition of particles already settled to the bottom. It seemed as if there were generally two convection currents: one in the dispersion medium beneath the meniscus and the other in the colloid. That the boundary between colloid and dispersion medium also formed a boundary between the two convection currents could possibly be explained by the difference in specific gravity between colloid and dispersion medium.

The points where disturbances in the constancy of the temperature could arise were the following:

- 1) At the point of friction between the vertical shaft (figure 2.6; 16) and the gear and in the lower bearing. Through the thorough oiling and the fact that the heat generated was transmitted to the heavy surrounding metal casing this source was made to have a negligible effect on the temperature of the cell. The cooling of the oil used in the first experiments was therefore omitted as not necessary.

- 2) Through the friction in the upper bearing a considerable amount of heat was produced. In one experiment the temperature rose 10° in fifteen minutes of centrifuging. For the purpose of keeping the temperature of the bearing constant a spiral channel was bored in the material through which cooling water was passed (figure 2.6; 6). For the temperature control a thermocouple was placed about 0.5 mm from the rotating shaft. By regulating the speed of the water the temperature of the bearing could be kept constant. In order to prevent radiation of heat from the bearing to the rotor a screen of copper was inserted. This screen, moreover, had the function of preventing droplets of oil, thrown out from the bearing, from entering the rotor chamber and impinging on the walls of the cell and the windows of the metal casing.

- 3) Considerable production of heat arose also through the friction between the rotor and the surrounding gas. In order to reduce the formation of heat to a minimum the centrifuge was filled with hydrogen, and during the centrifuging a fairly rapid stream of gas was passed through it. A study of the consumption of electric energy in the motor when the rotor of the centrifuge was running in air and in hydrogen at a speed of 5600 r.p.m. showed that the friction in air generated

5.7 calories per second while the friction in hydrogen only gave 1.4 calories per second. Moreover, the heat conductivity of hydrogen was about six times the heat conductivity of air. On account of the friction between rotor and hydrogen the temperature increased slowly (about 1° per hour at 10,000 r.p.m.). An attempt was made to keep the temperature of the centrifuge constant by cooling the hydrogen in passing it through a three-meter copper spiral immersed in ice water before entering the centrifuge. Such a procedure, however, gave rise to convection currents in the cell while a slow increase in temperature during the centrifuging showed no effect on the sedimentation.

4) Through evaporation from the liquid surface the temperature decreased in a layer immediately below it. The water in this layer became higher in specific gravity and was centrifuged down. In this way convection currents were formed. The simplest way to prevent this evaporation was to cover the colloid with a layer of oil of low vapour pressure. When using gold colloids it was difficult to find an oil which would not coagulate the sol. It was necessary to close the cell with an ebonite cover tightened with rubber packing and firmly pressed against the cell by screws in the cell holder. Later they found that a special American oil for vacuum pumps did not coagulate gold sols.

The distribution of the concentrations in the cell was determined from measurements of the absorption of light. Figure 2.7 shows the experimental arrangement. A horizontal beam of light from a 500 watt Argenta lamp (L) passed through a photographic shutter (M) controlled by an electromagnet, through a water filter to remove the heat radiation, and then through a suitable light filter. The light was totally reflected by a prism passed through the centrifuge and the cell, and entered the camera (K) placed in a room above that in which the centrifuge stood. From this upper room (control room) the centrifuge could be started, the speed varied, the temperatures of the centrifuge and the bearing read, the flow of water regulated, and exposures taken. The run could, therefore, be completely conducted from the control room, and only the determinations of the speed of rotation were made in the centrifuge room itself. The camera was focused to give a sharp image of actual size of the cell and was provided with a Voigtländer Euryscope lens with a focal length of 54.5 cm. In all experiments it was stopped down to F:22.5. The observation end of the camera was covered with a metal plate in which was cut a rectangular opening of 7.5 x 34 mm, and the plate holder with the photographic plate was movable on slides on this metal plate. By means of this arrangement twenty exposures could be taken on the same plate.

The first application of the ultracentrifuge was for the study of gold sols. Figure 2.11 shows a reproduction of a plate recording the sedimentation of a gold sol. The interval between successive exposures was in this case 5 minutes and the

speed of rotation 5,700 r.p.m. In general, the time of exposure varied from 5 to 30 seconds but was, as a rule, 20 seconds. During the centrifuging about ten exposures of the sol were taken.⁶⁸ The photographs of the sol at various intervals of time and at various concentrations at the time zero as well as the prints of the wedge on the plates were recorded by means of a 'Siegbahn self-registering microphotometer' which was built in the workshop of the Department of Physics at Upsala University by Professor Siegbahn's mechanics and under his supervision.⁶⁹ Siegbahn had originally constructed the apparatus for accurate measurements of distances but it appeared as very suitable for the measurement of blackening.⁷⁰ Reading the photographic plate with the microphotometer gave the amount of blackening of a photographic recording as a function of distance (figure 2.12). Following this procedure for each of the recordings taken after each interval, gave a series of concentration curves (two are shown in figure 2.12).



Figure 2.11

Successive photographs of a sedimenting gold sol (Svedberg and Rinde, 1924, p.2686).

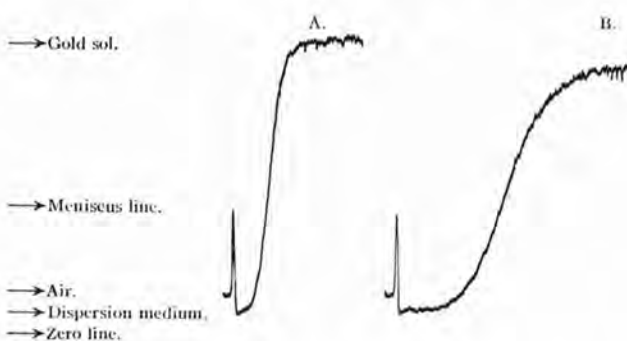


Figure 2.12

Microphotometer recordings of sedimenting sol (Svedberg and Rinde, 1924, p.2686).

A problem was that the absorption of light was not only a function of the number of particles at various depths in the cell but also a function of the size of

these particles. This effect was neglected, however, in cases where the distribution of size of particle was measured only over a small range. Then, the light absorption of the sol was regarded as practically independent of size, while in cases where the distribution was measured over a wide range of size of particle a correction for the variation of light absorption with size had to be introduced. This would necessitate special experiments in order to determine this influence.

In their first experiment published they had not yet calculated the distribution curve (it involved rather tedious calculation). They only determined the radius of particle corresponding to the maximum of the distribution curve from the position of the inflection point of the concentration curves. The average size of particle was also calculated from the decrease in concentration in the sol during centrifuging. For the sake of comparison they also determined the average size by means of Zsigmondy's nuclear method and found differences ranging from 10% to 40%.⁷¹ In his next article, Svedberg described an experiment showing differences of only a few per cent.⁷² They also described another method for registering the rate of sedimentation which consisted in directly observing the rate of movement of the boundary between pure dispersion medium and sol by means of a telescope provided with a scale in the ocular. This method of observation gave tolerably accurate results in the case of sols of rather large particles of comparatively equal sizes, that is, in cases where the boundary remained comparatively sharp during the time of centrifuging. The method was less laborious than the more accurate procedure of measuring the variation of concentration with distance from the axis of rotation.⁷³

There remained a number of errors which could influence the determination of the sedimentation and the distribution curves. In his doctoral dissertation Rinde listed the following. (1) A constant or variable fog on the photographic plate. The sensitivity might be different at different points on the plate; (2) The lack of exactly the same time of exposure for each field; (3) An imperfect sectorial aperture in the cell used; (4) A variation in the intensity of light from the illuminating lamp; (5) A variation in the intensity of the photometer light; (6) Irregularities in the photometric curve emanating from the thermopile; (7) Halation; (8) A variation in the thickness of the photographic plate and the gelatin film; (9) An inaccuracy in the determination of the sedimentation time; (10) A variation in the speed of rotation.⁷⁴

To summarize, we may conclude that Svedberg, after his decision to develop the centrifuge method further, started by using generally available technology. But he used it in a specific way. Working from the perspective of a colloid chemist, for him the key problem of the centrifuge method was to avoid disturbing

sedimentation of the substances under observation. After leading him to the special design of the cells, this perspective focussed his attention on the heating and vibration problems. The meaning he attributed to the ultracentrifuge, is also reflected in the prefix 'ultra' he adds to the word 'centrifuge': the only thing the three apparatuses, he mentions, had in common was that they were used in the same scientific field for comparable experiments. The problem of vibrations led him to the self-balancing principle and the use of an indirect drive. Convection led to sector-shaped cells and the necessity of temperature control. The latter led to the hydrogen atmosphere. The breaking of cells led to the smaller types and the necessity of optical observations led to a special camera arrangement. High values of g were not an issue at this point but would become so later on. At that time, however, he expected that the speed could be kept to low as not to cause problems in the initial stages when the particles would not have a constant motion. Thus, the development was an answer to concrete problems, problems that were defined from the perspective of colloid chemistry and these problems were dealt with in a way that was characteristic for colloid chemists in general: either do it yourself or go to a workshop in town.

Diffusion - Sedimentation Equilibrium

For very small particles there was still another problem to be solved. In the case of prolonged centrifuging of very fine-grained sols the influence of diffusion had to be taken into account. The effect was a more or less pronounced blurring of the boundary. If the centrifuging would be fast enough to permit a zone of clear liquid to be formed close to the meniscus of the sol, that is, if the reflection of the particles against the meniscus could be neglected and if the boundary was far enough from the bottom of the cell so that reflection of particles from the bottom could also be neglected, a simplified solution of the diffusion equation could be used to express the diffusion of the particles. This implied that measurements had to be made before any notable reflection of particles at the bottom of the cell would have reached the region where the measurements of concentration were made, that is, before sedimentation equilibrium had begun to be manifest.⁷⁵ In most cases, however, it was very difficult to account for the influence of diffusion, both experimentally and theoretically. As he put it himself: 'The exact mathematical analysis of this phenomenon has not been worked out (...) but an approximate solution of the problem can be arrived at (...) if the sol to be studied is comparatively uniform (...)'.⁷⁶ At first then, the idea was to choose the experimental conditions in such a way that diffusion should play a negligible role. However, already in Wisconsin he had pointed out (although not in connection with

centrifuges) that after some time, in a sedimenting colloid, an equilibrium would develop between sedimentation and diffusion. Furthermore:

"The sedimentation equilibrium can, of course, be used for determination of size of particles. (...) Westgren (one of Svedberg's students; BE) has actually made an attempt to determine the distribution curve for gold sols by means of the sedimentation equilibrium. In the original sol containing particles of different sizes, it was found to be very difficult to get accurate values of the distribution from measurements of the sedimentation equilibrium. If, however, we could by some means make a separation of the particles of different sizes and then study sedimentation equilibrium, we could get some idea of the distribution of the sizes."⁷⁷

Westgren had worked out such a method in principle which, however, would need a great number of determinations for sufficiently reliable statistics. Therefore, the method was not worked out in detail.⁷⁸ However, now that the success of the ultracentrifuge method largely depended on the solution of the same problem, Svedberg tackled it again. The mathematical approach appeared to be too complicated and Svedberg, therefore, chose to determine the diffusion constants experimentally by constructing a special diffusion apparatus for this purpose.⁷⁹ Now that he could determine the effect of diffusion Svedberg could make use of the fact that after a certain period an equilibrium developed between sedimentation and diffusion. After this equilibrium had formed (which in Svedberg's experiments would often take some days) the particle concentrations at various heights would no longer change. In the case of uniform sols or molecular solutions the particle size or molecular weight could then be determined on the basis of a single photographic recording of this state of equilibrium.⁸⁰ Svedberg worked out this idea into a practicable experimental procedure and subsequently often made use of this 'sedimentation equilibrium method'.

Svedberg could now use his ultracentrifuge for two different experimental methods, viz. the 'old' sedimentation velocity method and the 'new' sedimentation equilibrium method. For him, the ultracentrifuge thus had gained two different meanings. As we shall see later on, these two artefacts have followed quite different routes of development indeed and have resulted in very different machines.

In 1924, Svedberg was the only person in his field with an experimental method suitable for determining the size distribution of very tiny particles (down to sizes of only a few nm) in colloids. His first observations showed - surprisingly - that particles were much less uniformly sized than he had expected. His new method enabled Svedberg to investigate a whole new field of problems concerning the relationship between various physico-chemical properties of colloids and the

distribution of their particle sizes. In the ultracentrifuge he had a powerful tool that did a good job for him. Thus, there was not much reason to develop it further. His principal problems were solved and he could now devote himself to performing scientific experiments with it. Soon, however, his scientific results would get him into trouble again.

Proteins

By the end of 1924 the ultracentrifuge enabled Svedberg to study the size distribution of a variety of sols. He was interested in studying the usual inorganic colloids as well as organic substances like proteins. Parallel to the work with the ultracentrifuge, he had started to study the diffusion of proteins and amino acids making use of fluorescence and of light absorption to follow the blurring of the boundary between solution and solvent in diffusion experiments.⁸¹ That an inorganic chemist like Svedberg wanted to study proteins is not as surprising as it may seem to us now because in those days proteins were considered to be colloids. In proceedings of the colloid symposiums often papers can be found describing protein studies. Svedberg himself had also published some work on proteins⁸². In a lecture at the First Colloid Symposium held in June 1923 at Madison, he had said:

"It is possible to build up a method for recording distribution curves from observations of diffusion (...). Experiments of this kind are planned in my laboratory. They are of importance because we are here dealing with one of the few possible means for studying the distribution of sizes in protein sols".⁸³

In Svedberg's view, very little was known about the physical chemistry of proteins. Nothing was known with respect to their size, whether they were homogeneous in size or not although Svedberg believed, on the basis of his experience with inorganic colloids, that they would be heterogeneous. Early 1923 he had therefore already indicated that one of the most important things to do in protein chemistry was to determine their distribution curves.⁸⁴ From his laboratory records and notes it is evident that his mind was working on determining distribution curves from diffusion and from sedimentation measurements. Svedberg developed a new diffusion apparatus for the study of proteins which was completed early 1924⁸⁵ and he also planned to use his new centrifuge for similar studies. A rough sketch, dated 23 November 1923, of a centrifuge rotor with cells was marked 'centrifugal-analysis of proteins'.⁸⁶

When Svedberg started studying proteins most chemists held the opinion that they were aggregates of smaller molecules. But some chemists, by end of the 19th

century, had expressed the opinion that proteins were large molecules with a definite structure. They thought that there was clear evidence from analytical determinations, particularly in the case of the haemoglobins (proteins found in blood), and considerably less certain evidence from physical measurements, such as osmotic pressure, that proteins were truly large molecules. The fact that so many of them could also be obtained in crystalline form indicated that they were molecules of definite structure - though not necessarily homogeneous in any given preparation - not merely random aggregates. According to a monograph published by F.N. Schulz in 1901 many chemists had 'made' crystalline proteins.⁸⁷ A second monograph by Schulz published in 1903 portrayed the problem of the molecular weight of proteins as it appeared at the turn of the century. The general situation was confused and uncertain because the methods of physical chemistry used for studying proteins were considered inadequate and unreliable. As Schulz summarized: 'Im Ganzen ist das Bild ein wenig erfreuliches'.⁸⁸ Molecular weight data discussed in Schulz' monograph came from a variety of sources: There was the method of so-called 'freezing point depression' which gave a definite, though unreliable, figure for the molecular weight; or a method where a minimum molecular weight was calculated from the total sulfur, iron, cystine or tyrosine content. About this time the first studies of the osmotic pressure of protein solutions began, which led for example to a molecular weight near 48,000 for dog haemoglobin, three times greater than that calculated from an empirical formula for haemoglobin.⁸⁹ For a variety of reasons none of the figures obtained were widely acknowledged: because of inaccuracy of the experiments; because many experiments proved to be irreproducible; and because of the idea, prevailing in chemistry at the time, that such large molecules simply did not exist. Before the work of Hermann Staudinger, who introduced the concept of macromolecule in 1924, nearly all organic chemists were very reluctant to think of large molecules as true chemical entities and to seriously consider to their possible existence.⁹⁰ Furthermore, most colloid chemists held that 'solutions' of colloids (and thus of proteins because proteins were considered to be colloids as well) actually were 'suspensions' and that, hence, the physical-chemical laws of solutions were essentially inapplicable to them.⁹¹

Whether a particle was called a molecule depended on whether the particle was held together by chemical, so-called covalent bindings or by 'secondary', inter-molecular (often called physical) forces. In the latter case the particle was considered to be an aggregation of smaller molecules. A particle in the 'colloidal state' was considered to be an aggregation of smaller molecules. The colloidal state of matter was to be distinguished physically from the crystalline state and the idea developed that every material could in principle be obtained in the colloidal state. A logical extension of this view was the converse notion that all colloids were aggregated clusters of small molecules. Colloidal 'solutions', whether proteins or

iron oxide sols, were considered biphasic systems to which the solution laws of van 't Hoff were thought inapplicable.⁹²

The idea of a colloidal state of matter as an aggregation of smaller particles was strongly adhered to by Wilder D. Bancroft and Wolfgang Ostwald. Not only were they considered to be important physical chemists but they were also editors of journals like the *Journal of Physical Chemistry* and the *Kolloid Zeitschrift* respectively. This implied that scientists who thought differently faced some serious problems in getting their results published in those 'leading' journals. Until 1925 few scientists held a molecular viewpoint in biology.⁹³

At that time many different proteins had been prepared mainly by salting out or by other fractional precipitation methods. As, however, the starting materials usually contained a mixture of different proteins together with other chemical substances, the composition of the protein salted out varied with the experimental conditions. In order to improve the purity of the protein, it was often reprecipitated a few times to remove foreign material and in the hope of obtaining a pure protein. However, the great problem was that there hardly existed any criteria of purity for proteins. They were characterized mainly by their origin, solubility, optical rotation, and elementary composition. In a few cases, an approximate amino acid composition had been determined after many months' work.⁹⁴

As noted previously, the theory of Brownian movement as developed by Einstein in 1905/1906 did much to break down the distinction between colloids and crystalloids and indirectly gave encouragement to those investigators who were attempting to describe the behaviour of proteins in terms of the general laws of physical chemistry.⁹⁵ Following this line of thought, S.P.L. Sørensen argued in 1917 that ovalbumin in aqueous salt should be thought of as a true solution because it obeyed a general law of physical chemistry.⁹⁶ Indispensable to this work was the definition of the pH-scale (a measure for the acidity of solutions), and the development of a means of measuring it, which Sørensen himself had worked out some years before. Solubility studies on proteins could not be made reproducibly until the necessity of specifying the pH, as well as the salt concentration and temperature, was fully appreciated. Sørensen's work was published during the First World War and it took several years before it became known more widely. The conclusions Sørensen drew, however, were not easily accepted by many of the colloid chemists⁹⁷ and when Svedberg started studying proteins in the mid 1920s, the general idea was that proteins were aggregates of smaller molecules and that molecules with a mass over approximately 5,000 did not exist. The proteins were considered to be polypeptides of some twenty amino acid residues, aggregated to form reversibly dissociable component systems.⁹⁸

On the basis of the figures given for the size of proteins Svedberg hardly expected 'more than indications' with the centrifuge he possessed in 1924.⁹⁹ They were still working on the plans for a centrifuge of 30,000 r.p.m. Although he did not expect to see much Svedberg did apply the existing centrifuge to the study of proteins in collaboration with Nichols who had come over from Wisconsin with a grant from the 'American Scandinavian Foundation'. They took egg albumin which, according to the textbooks in biochemistry, should have an average molecular weight of 34,000. However, before they were able to investigate this protein they had to solve the problem that certain proteins, like egg albumin, did not absorb light from the visible part of the spectrum. In order to overcome this problem Svedberg developed an optical arrangement that used ultraviolet light. This created a new problem as the glass used for the cells did not let through ultra-violet light so he had to use more expensive and more vulnerable crystal quartz windows.¹⁰⁰ Such an arrangement was developed and subsequently they could run the egg albumin in the ultracentrifuge. As he expected no sedimentation of the egg albumin could be observed.

About this time Svedberg got acquainted with Robin Fåhræus, Mrs. Svedberg and Mrs. Fåhræus being old friends. Fåhræus was Assistant Professor of Pathology at the Caroline Institute (the Medical School of Stockholm). His dissertation had been on 'The suspension stability of the blood' and he was profoundly interested in proteins. In the fall of 1924 he came to Upsala to study some months with Svedberg. After the unsuccessful experiments with egg albumin Svedberg and Fåhræus started to run bovine milk in the ultracentrifuge on 12 September 1924. The light absorption method showed that the casein sedimented. From exposures taken at different times during the run they could calculate the particle size distribution. From a series of experiments they came to the conclusion that the casein particles had a very broad frequency distribution with coarse particles of the order of 10 to 70 nm.¹⁰¹ This was just what Svedberg had expected of a protein. After these first successful experiments Fåhræus suggested Svedberg to centrifuge a solution of haemoglobin. Svedberg had not much faith in this as haemoglobin should only have a molecular weight of about 17,000 according to its iron content, and egg albumin with the double molecular weight did not sediment in the ultracentrifuge. Nevertheless he agreed to try and they started to prepare CO-haemoglobin from horse blood. As soon as the preparation was ready, late in the evening of 16 October 1924, the experiment was started. As Svedberg did not expect to observe anything before the next day, he went home and let Fåhræus watch the centrifuge. In the middle of the night, Svedberg was woken by a telephone call from Fåhræus saying: 'The, I see a dawn'.¹⁰² Svedberg rushed to the Institute where he found that the upper part of the cell was clearing up indeed - the haemoglobin had actually started to sediment. Shortly afterwards a

crack developed at the bottom of the cell and the solution leaked out. Some weeks later the cell had been repaired and in the middle of November some successful sedimentation equilibrium experiments were made. The bottom of the cell was separated from the top by a sharp boundary. This was remarkable, since in earlier experiments, sedimentation became visible as a gradually increasing or decreasing colour intensity, caused by particles with different molecular masses settling at different speeds. Now all particles seemed to be settling at the same speed, which indicated that they might all be the same size. Their calculations indicated that the molecular weight was four times 16,700 and that it was constant from the meniscus to the bottom of the cell. Early 1927 a number of sedimentation equilibrium experiments were carried out under different experimental conditions. They all showed that haemoglobin was a monodisperse protein with molecular weight of about 67,000.¹⁰³ However, such a conclusion was completely contrary to Svedberg's expectations. E.g. in Madison he had spoken of a 'distribution of sizes'. As he wrote himself a few years later:

"When the author, after some series of measurements carried out in cooperation with J.B. Nichols (...) and H. Rinde (...) on inorganic colloids, in particular on goldhydrosols, set to the task of studying the dispersity of proteins, he was fully convinced that these, like the gold hydrosols, would prove to be polydispers. He therefore set himself the task of determining the distribution curves of protein particle sizes under various experimental conditions."¹⁰⁴

July 1925 Svedberg and Fåhræus submitted an article on their experiments to the *Journal of the American Chemical Society*. In the article, published in February 1926, they referred to 'preliminary measurements'. In the introduction they wrote:

"The lack of a reliable method for the determination of the molecular weights of substances possessing a very complicated structure has been a serious obstacle in the progress of our knowledge of the chemistry of the proteins. In the present paper such a method will be proposed and its use will be illustrated by a few preliminary measurements on haemoglobin."¹⁰⁵

They discussed the theory of sedimentation and derived a formula for the molecular weight. The formula held only for dilute solutions and when the solute was electrolytically dissociated the formula would also have to be modified. They also discussed the new type of cell which was now made up of three circular glass or quartz plates 2.0 cm in diameter cemented together with de Khotinsky cement and surrounded by a brass ring. In the middle plate a sectorial aperture of 50° angle and 5.2 cm radius had been cut out and in this cavity the solution was placed. In most of the experiments on haemoglobin the thickness of the layer of solution was 0.145 cm, but in some cases it was 0.98 cm. Evaporation from the solution was one of the most serious sources of error in experiments of this kind

because of the eddy currents in the solution to which it gave rise. It was found that the best means of completely preventing evaporation was to cover the solution with a layer of liquid paraffin. The time of centrifuging necessary for reaching sedimentation equilibrium was found to be about six hours per 0.1 cm length of column of solution in the case of haemoglobin. Usually a length of about 0.5 cm was chosen which required 30 hours of centrifuging. The magnification of the microphotometer was 10 and the photographs of the column of solution were taken in the scale 1:1 so that an abscissa of 0.1 cm in the photograph corresponded to 1.0 cm in the microphotometric curve. For the study of proteins which had absorption in the visible spectrum, such as haemoglobin and phytoerythrin, a suitable incandescent lamp eventually combined with light filters was used as light source. The lamp had to be fed by accumulators and the voltage should be carefully controlled. In the case of substances possessing absorption only in the short-wave ultraviolet region, such as serum albumin, egg albumin, etc., a quartz mercury lamp with filters of gaseous chlorine and bromine was used. In the latter case the optical parts of the centrifuge had to be made of quartz and fluorite.¹⁰⁶

A number of determinations with the solution of carbonmonoxide-haemoglobin were carried out in order to show whether or not the values of the molecular weight found were dependent on the experimental conditions. Measurements were made on solutions containing 0.5, 1.0, 2.0, 3.0 g. of carbonmonoxide-haemoglobin per 100cc. of solution. The values of the molecular weight were constant within the limits of experimental error. The length of the column of solution was varied from 0.25 to 0.8 cm without any marked influence upon the molecular weight. The same molecular weight was found when the speed of the centrifuge was 7200, 8700, and 10,000 r.p.m. It was further found that practically the same equilibrium was arrived at when the speed was raised from zero to 7200 r.p.m. and when it was lowered from 10,000 to 7200 r.p.m. In the latter case the comparatively high fall of concentration with distance from the centre of rotation decreased by virtue of diffusion until the same state was reached as by direct centrifuging at 7200 r.p.m. In some of these experiments the centrifuging of a sample of solution was carried on for a week without interruption, but there was always some danger of changes taking place in the substance studied during so long a time. Therefore as a rule experiments longer than 40 hours were avoided. Svedberg and Nichols described four series of determinations, two on carbonmonoxide-haemoglobin solutions and two on met-haemoglobin.¹⁰⁷ In a footnote they wrote:

"These experiments should be regarded more as an illustration of the method than as a precise determination of the molecular weight of haemoglobin. A more refined technique of measurement will, we hope, enable us to communicate such determinations later on".¹⁰⁸

The scientist Svedberg was reluctant to make a strong claim of a result that ran counter to his own expectations and counter to the beliefs of the majority of other scientists in the field. But there was the result of the experiment, which created a problem - a scientific problem. In terms of his scientific method the problem was that the sedimentation equilibrium method was not very sensitive to small differences in particle sizes. A more sensitive method would be the sedimentation velocity method. In this method the shape of the sedimenting boundary in a dilute monodisperse solution would be determined solely by the diffusion coefficient of the sedimenting substance. A larger spreading of the boundary than that corresponding to the diffusion of the substance, or to the appearance of separate boundaries, would indicate inhomogeneity of the material. But the sedimentation velocity was too low to be measured with the desired accuracy. With the sedimentation equilibrium method one never could tell whether or not a few percent of differently sized particles would be present.¹⁰⁹ From the results obtained with haemoglobin it was evident that, in order to introduce the sedimentation velocity method, it would be necessary to use a centrifugal field of 70,000 to 100,000 g, corresponding to a 15-20 fold increase of the centrifugal field available in the first ultracentrifuge. But Svedberg saw no way to increase the speed of his ultracentrifuge to that extent himself. The only way he saw was to ask the assistance of technical experts but such an approach was bound to cost a lot of money. Money for research was very scarce in Sweden at that time, and it was almost impossible to finance such a comparatively big project. Fåhræus advised him to send an application to a new private foundation for medical research. Svedberg applied for 25,000 Swedish crowns (almost \$ 7,000), a huge sum at that time. In spite of much opposition he got this grant as well as another one from the chemistry section of the Nobel Foundation. According to Svedberg's own interpretation it was the suggestion that haemoglobin could be monodisperse which stimulated the interest of the new foundation.¹¹⁰

The Quest for Higher Values of g - The Oil-Turbine Ultracentrifuge

Having found finances, Svedberg contacted Fredrik Ljungström of the Ljungström Steam Turbine Company in Stockholm. Svedberg considered different kinds of drive like a high frequency electric motor, air turbines, and hydraulic turbines. Ljungström, however, suggested the use of oil-turbines, because they simplified lubrication of the bearings.¹¹¹ He also made a number of other suggestions and let one of his young engineers, Alf Lysholm, assist Svedberg in the construction and testing of the ultracentrifuge. Svedberg expected much of this new apparatus and was willing to invest a considerable sum of money in it, the

expected costs of its development being \$ 3,500.¹¹² The ultracentrifuge was built at the workshop of the Ljungström Company during the spring and summer of 1925. Auxiliary equipment, such as pumps and measuring instruments, were obtained partly from Sweden, partly from abroad. The installation of the new ultracentrifuge at Upsala started in the fall, but not until January 1926 could the first test run be started. The result of the test was very disappointing; instead of the 40,000 r.p.m. only 19,000 r.p.m. were reached. Many unexpected difficulties had to be solved. The turbines were drastically modified, the bearings reconstructed, the oil system changed. They had a lot of trouble with vibrations and built a special balancing machine in order to detect very small imbalances in the rotor. Heat convection currents in the solution during sedimentation together with the very marked gas friction around the rotor at high speed also created a lot of trouble. These problems were minimized by making the rotor spin in a hydrogen atmosphere at low pressure (10 to 20 mm Hg). The introduction of these various modifications resulted in a gradual increase in the speed obtained (10-15%). The turbines also caused trouble but this difficulty was eventually overcome, partly due to the skill and interest of the first instrument mechanic at the laboratory, Ivar Eriksson.¹¹³

In the early 1920s chemical laboratories at the universities in Sweden rarely had mechanical workshops, nor mechanically skilled personnel; even smaller construction work usually had to be given to workshops in the city. Ready-made instruments could be bought only occasionally due to shortage of funds. Furthermore, the fields of investigation were in most cases so new and different that suitable instruments were not commercially available but had to be designed and developed as part of the research projects.¹¹⁴ Researchers also sometimes made part of their apparatus themselves, like glass viscometers. Glass blowing constituted an important part of the education of a chemist. In the work on the ultracentrifuge Svedberg found it necessary to have more easy access to mechanically skilled assistance. Ivar Eriksson, who held a position at the workshop of a bicycle factory at Upsala, used to help Svedberg in his spare hours. One day early in 1924, Svedberg was astonished to meet him at the laboratory already in the morning. Eriksson then told Svedberg that he had left his job at the factory to come and work full time on the centrifuge. He thought that Svedberg needed his help. When Svedberg, who had not been notified in advance, worried about the salary, Eriksson replied that such matters would probably take care of themselves, which turned out to be true. From that time onwards, hand in hand with the development of new methods of investigation, the workshop was extended in order to manufacture all the apparatus used in a variety of chemical experiments. It became customary at the institute for the researchers to go down to the workshop in order to get an indication of how things might be done.¹¹⁵ Concerning the first oil-turbine ultracentrifuge Eriksson never believed in the design of the oil inlets

and the turbine blades according to the engineering drawings, and he started to experiment on his own. One morning he told Svedberg about his new model which was already finished and ready to be put into the centrifuge. Against the reluctant opinion of Svedberg he got it tested. As soon as the new parts were installed, the speed went up markedly. On 2 March 27,400 r.p.m. was reached and finally, on 7 April 1926, a rotor speed of 40,000 r.p.m. achieved, corresponding to a centrifugal field of about 100,000 g in the cell. Afterwards Eriksson's ideas for further modifications were always followed immediately.¹¹⁶

After it became possible, in April 1926, to run the new high-speed ultracentrifuge at the speed aimed at, viz. 40,000 r.p.m., a number of tests and adjustments were carried out. Svedberg considered it important to minimize the risk of getting convection in the centrifuge cell. He therefore began a systematic study of how the convection currents started and how they developed. Thermoelements were placed at various places in the casing to make it possible to follow the temperature variation near the rotor and at the bearings. Resistance thermometers were inserted in the pipes carrying the turbine oil and the lubricating oil for the bearings, as well as into the oil coolers and the pipes for the cooling water. The sedimentation was followed by studying the sedimentation of dilute solutions of haemoglobin. All the early experiments were carried out with coloured solutions, first with the gold sols in the first low-speed ultracentrifuge and later with coloured proteins in the high-speed ultracentrifuge. In this way convection could be discovered as soon as they started, and the development could be followed in detail and could be referred to the temperature distribution in the system and the cooling of the turbine oil. The effect of a change in temperature of the turbine oil could immediately be observed in an otherwise worthless experiment. In June 1926 Svedberg made some melting-point observations with azoxybenzene in the cell in order to see if the cell temperature would be much different from the temperature on the rotor casing just outside the periphery of the rotor. He came to the conclusion that the cell temperature was 1.5 °C higher than the inside temperature of the casing.

In 1927 Svedberg and his colleagues published a number of articles on the oil-turbine ultracentrifuge. Svedberg and Nichols published an article in the *Journal of the American Chemical Society*.¹¹⁷ With Lysholm, Svedberg described the apparatus in a series called *Nova Acta Regiae Societatis Scientiarum Upsaliensis*¹¹⁸ and he also described it in the German *Zeitschrift für Physikalische Chemie*.¹¹⁹ According to these publications, the most important conditions which the centrifuge had to fulfill were: a centrifugal force in the cells of 80,000-100,000 times the force of gravity, temperature in the cells not higher than 35°, amplitude of vibration small enough so that sharp photographs could be taken during centrifuging at high speed,

and optical parts inside the centrifuge remaining free from oil dust.¹²⁰

Svedberg distinguished the following main parts with respect to the apparatus: the centrifuge proper, the oil circulation system, the vacuum and hydrogen system, the temperature measurement instruments, the optical system, the tachometer, and the balancing machine.¹²¹ Figure 2.13 gives a diagram of the centrifuge, showing to the left an axial section and to the right a section at right angles to the axis of rotation. The main parts of the centrifuge were the rotor, the top and bottom casing, and the two end brackets. The rotor was cylindrically shaped having a diameter of 150 mm and a thickness of 60 mm. It was made of a solid chrome nickel steel forging without a centre bore in order to reduce the centrifugal stresses. The dimensions of the journals and bearings were 19.74 and 19.80 mm respectively, leaving a diametrical clearance of 0.06 mm. The turbines which were screwed in at the ends of the shaft, were 20 mm in diameter and carried 8 blades each. The ends of the turbines were fitted with hardened steel points serving as parts of pivot thrust bearings. Between the shaft and the rotor proper was a system of oil rings of special shape which together with a corresponding system of oil catchers in the end brackets constituted a centrifugal oil seal preventing the oil that was pumped through the bearings from reaching the disc of the rotor. In the rotor there were 4 holes taking 4 cells for the solution to be studied. Of these only three could be used at the same time for measurement, the fourth served only as counterweight. Figure 2.14 shows the rotor alone with one of the four steel shells for the cells and the guard ring removed which served to fix it in the rotor.

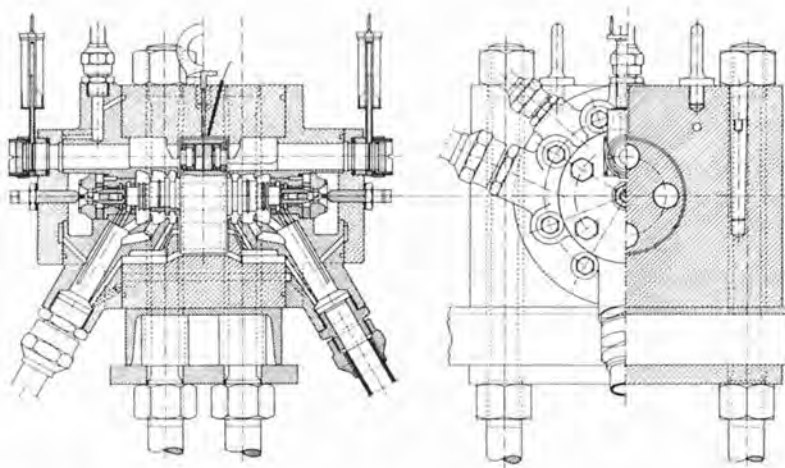


Figure 2.13

Oil-Turbine Ultracentrifuge. (Svedberg and Lysholm, 1927, p.6).



Figure 2.14

Rotor and Cell. (Svedberg and Lysholm, 1927, p.7).

In the top and bottom casings a system of channels was drilled through which oil could be pumped in order to regulate the temperature of the centrifuge. This precaution, however, proved unnecessary and was later abandoned. The casings were made of steel. The top casing had an inlet for hydrogen and also carried a thermocouple for the measurement of the temperature of the interior of the centrifuge. The end brackets were made of brass and contained the turbine chambers carrying inlets and outlets for the oil to the turbines and also outlets for the oil that had been pumped through the bearings. In the end brackets were further mounted the main shaft bearings and the steel plates that formed parts of the pivot thrust bearings. Two thermocouples were mounted so that the temperature in the main bearings could be ascertained. In order to maintain a vacuum in the centrifuge a system of oil grooves was cut in the end brackets, top and bottom casings. The inlet for this oil was fixed to one of the end brackets. An observation channel 34 mm in diameter was drilled through the end brackets and the top casing and closed by round glass or quartz windows 10 mm in thickness which could be fixed in the end brackets. Special electromagnetic shutters protected the inner sides of the windows from oil dust when no observations were being made. The top and bottom casing, and the end brackets were held together by heavy screws, and the whole centrifuge was fixed to a system of girder irons and anchor bolts which were fastened to a concrete foundation. Figure 2.15 shows the centrifuge assembled.

The cells for the solution to be studied were built in the following way. Two round glass or quartz plates, 30 mm in diameter and 10 mm thick, were cemented to another glass plate, 30 mm in diameter, 1.85 mm thick, and having a sectorial aperture. The cells were cemented with so-called 'De Khotinsky Cement' which was prepared in a specific way. The angle of the sector in the middle plate was 50° and its apex, which should coincide with the centre of the rotor, was situated 52.2 mm from the centre of the round plates of the cell. The cell was cemented in a steel collar which had an opening coincident with the opening of the sector so as to

permit liquid to be introduced into the cell. The steel collar with the cell was then put into the steel shell and supported at both ends by a system of sectorial discs and diaphragms (figure 2.16). If we proceed from the cell outward we have first, a 0.5 mm thick ebonite plate with a sectorial aperture of 6° , then a brass plate with a sectorial aperture of 3° , and finally a hollow cylinder of brass with a sectorial aperture of 6° . Special keys and grooves kept the different parts in position. The steel shell was then put into the rotor and fixed by means of a guard ring. If more than one cell was used at a time the depth of the sectorial apertures in the cells had to be different and the brass sector plates accordingly adjusted so that the image of the solution in the different cells would appear one above the other when the rotor was in motion.

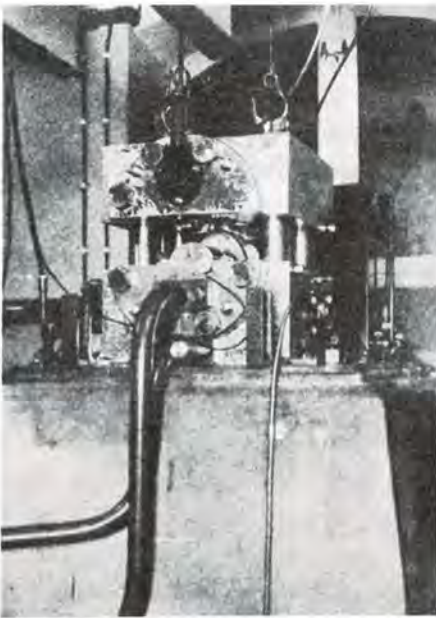


Figure 2.15

The Oil-turbine ultracentrifuge on its pier with the upper part of the casing raised, laying bare the rotor and the turbine and bearing chambers. (Boestad, Pedersen and Svedberg, 1938, p.349).



Figure 2.16

Ultracentrifuge cell disassembled (Svedberg and Lysholm, 1927, p.9).

The rotor of the centrifuge was kept in motion by means of two small turbines, one at each end of the shaft of the rotor, and driven by high pressure oil. The two bearings carrying the rotor shaft were lubricated and cooled by means of a rapid current of oil pressed through the bearing clearances and oil grooves. The oil employed had to have low vapour pressure and low viscosity. In figure 2.17 the oil circulation system is shown diagrammatically. The centrifugal pump B directly coupled to a 20 h.p. three-phase electric motor A sucked the oil from the container C and forced it through the oil-cooler D to the centrifuge E. From the turbines the oil passed through the pipes FF (only one of them shown in figure 2.17) and back to the container C. The oil flow through the turbines corresponded to about 230 litres of oil per minute of a maximal pressure of 11 kg/cm^2 . At the same time 7 litres of oil were driven through the bearings per minute in order to lubricate and cool them. This oil current was drained from the centrifuge through the pipes GG (only one of them shown in figure 2.17) and was collected in the lower container H. From there it was raised to the upper container by means of the pump J. On its way up it passed through the filter K. Thus during centrifuging part of the oil was continually purified. Before starting a run the oil flow was directed through the filter for about one hour by means of the three way valve N in order to get the oil dirt-free. The filtering was considered essential because if the oil contained too much suspended material the bearings and the shaft would rapidly wear. By changing the speed of the big motor the oil pressure could be varied, and in this way the speed of the centrifuge could be regulated.

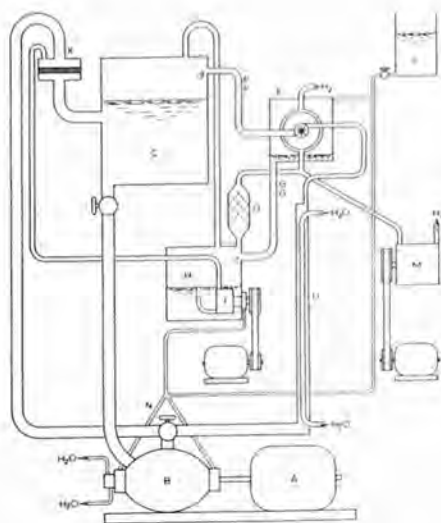


Figure 2.17

Oil circulation system. Explanation: see text. (Svedberg, 1927b, p.73).

In hydrogen as well as in air at atmospheric pressure the rotor warmed up more than 10° in a few minutes. Even a 0.5 mm air vacuum did not prevent injurious heating because the heat generated in the residual air could not be conducted away rapidly enough. However, the heat conductivity of hydrogen was very high and was independent of pressure down to about 20 mm Hg whereas the heating up of the rotor decreased rapidly with the hydrogen pressure. Combining these two effects they found an optimum pressure for the hydrogen of 20 mm Hg at which the heating up of the rotor had its minimal value. Still, at this minimum the rotor heated up 1.5° during a run. In order to surround the rotor with sufficiently pure hydrogen of the required pressure the following arrangements were made. A very efficient oil vacuum pump (M in figure 2.17) driven by an electric motor enabled them to pump out the air from the centrifuge and the whole oil circulation system in a few minutes to a pressure of 0.5 mm Hg. Hydrogen was let in from a container of compressed gas at the periphery of the rotor, and the system was kept air free by continuous pumping with the vacuum pump during centrifuging and allowing hydrogen to leak in so as to maintain the pressure. The trap O served to catch the oil spray. The joints in the centrifuge and the bearings of the pumps B and J were kept vacuum tight by oil seals. The tightening oil was supplied from the tank L.

For their purposes the temperature of the solution in the cell had to be known, and also for the control of the machinery the temperature of the bearings and the temperature of the oil and water at different points was followed during centrifuging. The temperature observations were made with the aid of six resistance thermometers and three thermocouples. The thermocouples were introduced in the two main bearings of the centrifuge and in the lid of the centrifuge. They could be read off by means of a galvanometer and a scale. To get the temperature in the cells one had to know the difference in temperature between the top casing of the centrifuge and the cells. This difference was ascertained by observing the melting of a substance of known melting point under the conditions with regard to speed, hydrogen pressure, oil temperature, etc. which one actually had in a centrifuging experiment. By mixing azoxybenzol and piperonal one could get a suitable temperature region in the vicinity of 30° . In most of their runs the temperature difference was about 1.5° . By adding this figure to the temperature of the centrifuge top casing as read off by means of the thermocouple the temperature in the cell was determined. When equilibrium was reached the top casing was usually about 5° warmer than the oil in the turbines, and the bearings were about 0.5° warmer than the lid.

Figure 2.18 gives a diagram of the optical system in the case when diffuse visible light was used. The white Philips Argenta lamp B was surrounded by a double-walled water-cooled house A that was mounted movably on rails. C was a

water cell to remove the infra-red radiation. D was a light filter, E a photographic shutter, and F the centrifuge. When diffused ultra-violet light was wanted the white lamp was replaced by a quartz mercury arc lamp. The lens H of the camera G was in the same room as the centrifuge (figure 2.19, left) and the camera extended through the wall into the instrument room (figure 2.19, right). For visible and long wave ultra violet light an anastigmatic lens of aperture $f:12.5$ and focal length 99 cm specially built by Zeiss was used. Pictures in the short wave ultra violet could be taken by means of a quartz lens of aperture $f:40$ and focal length of 100 cm. Various filters could be inserted in order to obtain light of well-defined wave lengths. All optical parts, the lamps and lenses of the illumination system as well as the parts of the camera, were mounted on optical benches.

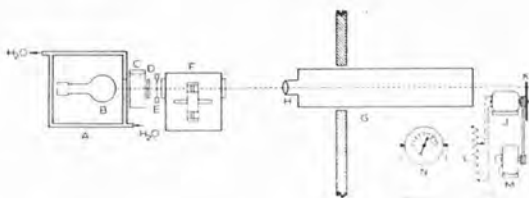


Figure 2.18

Optical system. Explanation: see text. (Svedberg, 1927b, p.74).

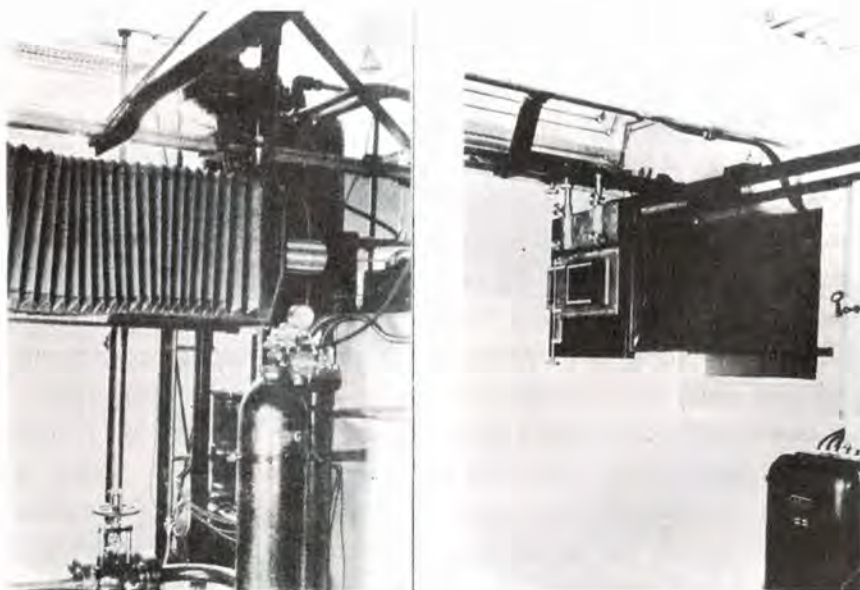


Figure 2.19

Camera arrangement. (Svedberg and Lysholm, 1927, p.15).

In order to reach the highest possible speeds the rotor should run free of any gearing arrangement for speed measurement. The speed was therefore determined by means of a stroboscopic tachometer which made no physical contact with the rotor. At the back of the camera was mounted a motor (J, figure 2.18) carrying a disc K with a suitable number of holes. The stroboscope motor was connected to a small generator M which acted on a hot-wire ammeter N with a scale calibrated to give directly the number of revolutions per minute of the centrifuge. To measure its speed the plate holder of the camera was taken out and the motor of the stroboscope was started and its speed regulated by means of the resistance L until when observing the rotor of the centrifuge through the holes in the stroboscopic disc one saw the image of the cell come to a stop. In order to eliminate vibrations it was essential that the rotor with the cells in it should be carefully balanced. For this purpose a special balancing machine was built similar to the so-called 'Lawaczeck-Heyman' apparatus. By systematic trial with small lead pieces put into the steel shells which held the cells, the amplitude of vibrations could gradually be depressed and the unbalance brought down to a value of a few milligrams. Experience had shown that an unbalance of even a few centigrams was without injurious effect; it should not, however, exceed a decigram.¹²² Figure 2.20 gives a photographic view of the whole apparatus.

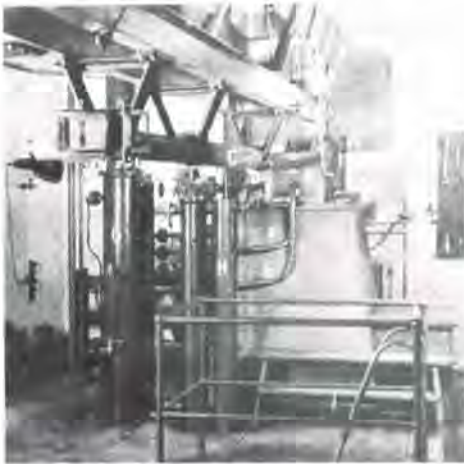


Figure 2.20

Oil-turbine ultracentrifuge with adjoining arrangements. A, Lamp holder; B, Centrifuge; C, Camera; D, Turbine oil inlet; E, Turbine oil outlet; F, Bearing oil inlet and outlet; G, Main oil reservoir; H, Oil cooler; J, Steps to compressor room. (Svedberg and Pedersen, 1940, p.164).

A number of people had made contributions in constructing the oil-turbine ultracentrifuge. It was built in the workshops of the Ljungström Steamturbine Co. by the courtesy of Fredrik Ljungström. Alf Lysholm had contributed in a variety of

ways during the actual development. G. Nordgren and G. Johansson had given assistance in carrying out the detailed calculations of the machine and in making the working drawings. The alterations and improvements found necessary during the testing of the apparatus were made in the workshop of the laboratory, by Ivar Eriksson. Svedberg credited Eriksson for rendering valuable service in suggesting several important improvements of the machinery. With regard to the other parts of the apparatus they were obtained from a variety of sources. The centrifugal oil pump with motor was delivered by Zander and Ingeström, Stockholm, the oil cooler by Stål, Finspong, the vacuum pump by Pfeiffer, Wetzlar, most of the electrical instruments by Hartmann and Braun, Frankfurt am Main, and by Siemens-Schuckert, Berlin. The optical parts were made by Zeiss, Jena, and by Steeg and Reuter, Homburg. The oil containers and the oil pipes were made by the Tullgarn Works, Upsala. The turbines, the camera, the cells, the stroboscope tachometer, as well as numerous minor parts were made in the workshop of the laboratory.¹²³

Technique of Measurement

The cell or cells were filled with solution (one of them, if desired, with a standard solution for comparison) and a few drops of vacuum oil were added so as to form a layer about 2 mm thick on top of the solution. The oil served two functions: the pressure of the layer of oil prevented boiling (caused by the vacuum of the centrifuge) and it offered a very efficient thermal protection. In the earlier ultracentrifuge, when the rotor was run in an atmosphere of hydrogen, convection currents sometimes occurred, especially if the dissolved substance was not greatly different in density from the solvent. A slight evaporation from the surface of the solution into the air space of the cell was found to be the agent. Therefore, when the meniscus was covered with a thin layer of vacuum oil, temperature uniformity could be maintained for days if necessary.¹²⁴ The centrifuge was always started at atmospheric pressure, the vacuum pump not being put into action before an oil pressure in the turbines of about 3 atmospheres had been reached. This corresponded to a speed of 14,000 r.p.m. However, already at 10,000 r.p.m. the 2 mm of oil in the cells exerted a pressure of one atmosphere, thus preventing the solutions from boiling. The cells were introduced in the steel shells and these were put in position in the rotor. The contact surfaces of the top casing of the centrifuge were rubbed with wool fat to make the centrifuge vacuum tight, and the lid was put on and screwed tight. The windows with their electromagnetic shutters were introduced in the holes in the ends of the centrifuge.

After removing air bubbles from the centrifugal oil pump the big motor was gradually put in action. When about 3 kg/cm² oil pressure had been reached the

vacuum pump was switched on, and at the same time the pump in the lower oil container was put into action. In about five minutes an air vacuum of 0.5 mm Hg was attained. Hydrogen was next introduced through the opening in the lid of the centrifuge close to the periphery of the rotor and regulated until a total pressure of about 15 mm Hg was reached. Under these conditions the centrifuge consumed $\frac{1}{4}$ cubic meter of hydrogen of atmospheric pressure per hour. The oil pressure was next raised until the desired speed of the rotor was reached. At the same time that the speed was increased the water for the oil cooler was turned on and regulated until the oil that entered the turbines had a temperature of 25°C.

During the centrifuging photographs of double natural size were taken at suitable intervals of time - e.g. every 30 minutes. For a substance possessing a molecular weight of the order of 67,000 the centrifuging should be continued for about 3 hours if a speed of 39,000 r.p.m. - corresponding to a centrifugal force of 80,000 times the force of gravity - was used. The length of the column of solution was 15 mm. As a rule, seven exposures were taken. After stopping the centrifuge a suitable number of different concentrations of the same solution were pipetted into the cell one after the other and photographed on the same plate. For the photographing of the concentrations the centrifuge was run at low speed (about 8,000 r.p.m) and without the heavy lid screwed on: A light wooden lid served as optical protection during the exposures. After developing the plate the photographs of the solution at different times of centrifuging as well as the scale of solutions of different concentrations were recorded by means of a self-registering microphotometer. From the records thus obtained the curves giving the relation between concentration of the solution and distance from the centre of rotation at different times were then constructed.

The temperature of the inner wall of the lid of the centrifuge was measured from time to time during centrifuging. From these data and from the known temperature difference between the lid and the rotor, the temperature of the latter could be found. The speed of the rotor was measured from time to time by means of the stroboscopic tachometer. For the calculation of the molecular weight one further needed the partial specific volume and the diffusion constant of the solute. These constants were obtained by means of widely used physico-chemical methods. Usually, the diffusion constant could be calculated from the photographs of the solution during centrifuging. This method was preferred because the diffusion value might decrease by the pressure developed at the high centrifugal forces used.¹²⁵ One of the problems with the optical arrangement was, that especially at very low concentrations, the light absorption of many proteins was very low. In order to overcome this problem Svedberg tried to use high intensity cadmium sparks which might enable him to use concentrations 8 times lower than before. For this he had special equipment ordered by Nichols in the US.¹²⁶ The use of these sparks indeed

enabled him to use very low concentrations but it appeared unpleasant to use the lamp because the pictures taken with it were banded owing to the oscillatory nature of the spark and the rotation of the rotor.¹²⁷

Theory of Measurement

According to theory the particles sedimented outward due to the centrifugal force that acted upon them. This was not a free movement as, during sedimentation, the particles experienced friction from the substance in which they were dissolved (usually water). The centrifugal force per mol was given by:

$$F_c = M(1-Vp)(2\pi f)^2x$$

The frictional force per mol was:

$$F_f = f_c \, dx/dt, \text{ where:}$$

In these formulae the symbols used had the following meaning:

M = molecular weight

V = partial specific volume of solute

p = density of solution

f = number of revolutions per second of the rotating centrifuge

x = distance from centre of rotation

f_c = frictional coefficient per Mol

t = time.

When the motion of the molecules had become steady, in general after a very short time, the two forces were equal, thus:

$$M(1-Vp)(2\pi f)^2x = f_c \, dx/dt.$$

For dilute solutions this formula was reworked, giving:

$$M = R T s / \{D(1-Vp)\} \quad (1)$$

In this formula s was defined as $\{dx/dt\}/\{(2\pi f)^2x\}$, the sedimentation velocity under the influence of unit force.

In most cases the diffusion which took place during centrifuging caused such a

blurring of the boundary between solvent and solution that x-values could not be read off directly. Under certain assumptions it could be deduced that the position of the boundary was given as the distance at which the concentration in the solutions was half that of the constant part. The distribution of the different kinds of molecules in a mixture could be found from sedimentation velocity data provided the molecular weights of the various forms possible and their diffusion constants were known. As a rule only the diffusion constant of the most common form was known, but the diffusion constants of the other forms could be approximately calculated from theory.¹²⁸

Figure 2.21 gives a series of microphotometer curves for a 9% haemoglobin solution centrifuged at 94,000 g. The curves were taken at successive intervals of time and give the concentration of the material as a function of the location in the cell, expressed as the distance from the meniscus. For monomolecular substances, under certain assumptions, one such curve could already yield the sedimentation velocity and thus, using formula (1), the molecular weight. In the graph shown the various curves give different values for the sedimentation constant which varied a few per cent. The average of these was then used to give the molecular weight. The dotted curves in figure 2.21 represent the distribution of concentration which was expected if all molecules in the solution had the same weight. Although the deviation from the experimentally determined distribution was small it might nevertheless exceed the limits of experimental error. In this case the assumption of a mixture of 10% molecules of weight 33,400, 80% of weight 66,800 and 10 % of weight 100,200 explained the results better than the assumption of a single molecular weight of 68,340 as calculated from the average sedimentation velocity.¹²⁹

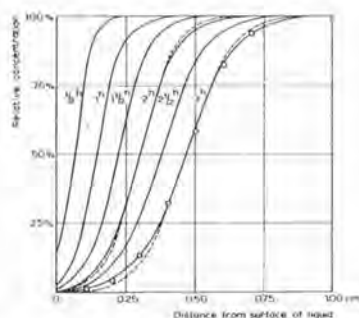


Figure 2.21

Microphotometer curves (Svedberg and Lysholm, 1927, p.23).

The interpretation of the experimental results was far from straightforward. The effect of diffusion had to be taken into account which, only under certain

conditions and assumptions could be done using a relatively simple formula. In other cases very complicated formulae were used. With respect to arriving at the molecular weight(s) it had to be assumed in advance whether one or several molecular sizes were present and then theoretically calculate the curves that could be expected under these assumptions. Next, the 'theoretical' curves were compared with the 'experimental' ones. This procedure involved a lot of computation and also the comparison between the two sets of curves was not trivial as the experimental curves obtained in practice were not as smooth as the ones shown in figure 2.21. This is evident when they are compared with the ones in figure 2.12.

Problems

Nichols' Dissertation was entirely devoted to his ultracentrifuge work. His studies on CO-haemoglobin were performed as a Fellow of the International Education Board.¹³⁰ He also presented a paper on the ultracentrifuge at the sixth American Colloid Symposium.¹³¹ In his dissertation Nichols also discussed the uncertainties of the method. One of the greatest uncertainties was due to the use of photographic plates. It was commonly assumed that a photographic method introduced an error of five per cent. Photographing a standard solution together with a solution being centrifuged somewhat reduced the errors inherent in the photographic method but since in the determination of the diffusion constant from sedimentation velocity data the observed quantity had to be squared, the error was still much larger than the probable error in the centrifuging under favorable conditions. Fairly accurate results might be obtained if the average was taken from a sufficient number of plates to eliminate effects arising from non-uniform distribution of fog over the plate, different exposure times, unequal depression of density by soluble developer products, and many other factors influencing plate characteristics. Eventually a direct method of recording, such as the employment of a photoelectric cell or a thermopile, might prove more satisfactory. It was a question of obtaining an arrangement with a sufficiently small period of inertia and yet sensitive enough to react to a very low intensity of the light transmitted through the centrifuge cell. The reaction of the photoelectric cell would be practically instantaneous, but the amplifying device which would be required to give the cell the desired sensitivity introduced a time lag which probably would render its use inapplicable to the determination of sedimentation data. If strict constancy could be obtained it might, however, be applied to the measurement of sedimentation equilibria. The best existing thermopile required about two seconds to attain equilibrium, so even though this proved sufficiently sensitive the time element would prevent its use in the study of sedimentation phenomena.

Another group of errors - those arising in the photometering of the photographic record - was of lesser importance if a photometer of the Siegbahn type was employed. Appreciable errors might arise, however, if the photometer voltage was not kept constant and the proper care would not be taken to control the adjustments. If, for example, the plate bearing the photographic record of the centrifuging should be placed in the carriage of the photometer not quite at right angles to the beam of light passing through the exposure strip from the photometer lamp to the thermopile, the photometer diagram obtained would be rotated through a slight angle and thus give erroneous results. In the original type of the Siegbahn microphotometer there was a certain amount of play and vibration, thus broadening the photometer diagram somewhat more than the irregularities produced by the individual grains in the emulsion of the original photographic record. In 1927 Erich Bäcklin developed a new type in the Siegbahn laboratory which was much sturdier and more compact than its predecessor.¹³² This should reduce the photometer errors to a minimum.

At that time it was not possible to study the phenomena occurring during the initial period of sedimentation while the centrifuge was attaining its final speed. Aside from the uncertainty introduced into the value of the diffusion constant by the incomplete knowledge of the starting conditions, it was possible to obtain information on such questions as whether for colloids or proteins of low electrolyte content there existed a certain 'time of relaxation' which was required to adjust the double layer of the particle for a state of motion. Here, a good speed recorder would prove invaluable.¹³³

The ultracentrifuge still presented Svedberg with many problems. In the first years all measurements in the rotating cell were based upon light absorption. But some substances he wanted to investigate did not have sufficient light absorption, neither in the visible spectrum, nor in the ultraviolet range. Among Svedberg's notes from this time there are paper sheets dated 14-16 December 1925, where he referred to a paper by O. Wiener which dealt with the deflection a beam of light would undergo when passing through a concentration gradient.¹³⁴ Svedberg sought to apply this phenomenon to the measurement of concentration gradients in a centrifuge cell. He also indicated the equation for calculating the molecular weight from the deflection for certain distances from the axis of rotation at equilibrium. The problem was put aside for some time until Tiselius proposed to photograph a scale through the rotating cell which made the experimental application of Wiener's method much more convenient. The whole problem of the introduction of the scale method and its theoretical background was handed over to Ole Lamm when he came to work with Svedberg in 1927. Lamm worked out the principle into an practicable method in connection with the ultracentrifuge. One of the requirements was that the new method should be easily interchangeable with the

absorption method. The principle of the 'scale-method' was that a scale with equidistant lines was photographed through the solution. The light deflection caused by concentration differences had the effect that on the image of the scale the lines would appear to be shifted. Using Wiener's theory the concentration gradient in the cell could next be calculated from the amount of displacement on the image of the scale.¹³⁵

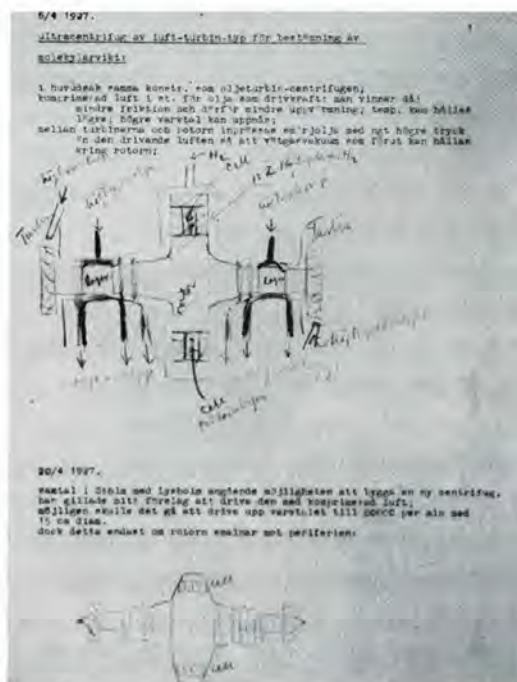


Figure 2.22

Sketch of an air-turbine ultracentrifuge. Translation of Svedberg's Comments: "6 April 1922. Ultra-centrifuge of air-turbine type for determination of molecular weight. In principle same construction as the oil-turbine centrifuge. Compressed air instead of oil as motive power. The gain is: less friction and thus less heating; the temperature may be kept lower; higher speed may be attained. Lubricating oil, having a slightly higher pressure than the compressed air, is pressed through (the bearings) between the turbines and the rotor, so that a hydrogen vacuum, just as before, may be kept around the rotor. 20 April 1927: dialogue in Stockholm with Lysholm concerning the possibility of building a new centrifuge. He approved of my proposal to drive it with compressed air; it should perhaps be possible to raise the speed to 80,000 r.p.m. with a (rotor) diameter of 15 cm; however, this only if the rotor gets narrower towards the periphery." (Pedersen, 1976, p.8).

For a number of reasons Svedberg was interested in increasing the centrifugal force: Sedimentation would occur faster, diffusion effects would be lessened and smaller particles could be investigated. Seeking ways to reach this goal Svedberg came up with the idea of driving the rotor with air turbines. Figure 2.22 shows a sketch he made of a possible air-driven rotor with some comments.

Svedberg wrote Nichols that he planned to develop a new air-turbine ultra-

centrifuge and that he hoped to start its construction in the spring of 1928.¹³⁶ Nichols, now working for the DuPont Company in Wilmington, Delaware, replied that he was considering to secure an oil-turbine ultracentrifuge for their research but that his colleagues had suggested to construct an air-turbine type (see Chapter 6). He had not been able to give them any very convincing reasons why he should not attempt it first instead of the oil-turbine type. For that reason he was glad that Svedberg would undertake that development in the near future and Nichols planned to start a similar construction about a year later, thus being able to make use of Svedberg's experience with this new type.¹³⁷ Svedberg replied that he and Lysholm were busy with calculations regarding the new centrifuge. Because they had some good experiences with some improvements on the oil turbine centrifuge they were first going to base the calculations on an oil drive, rather than an air drive. Svedberg therefore advised Nichols not to start the construction of an air drive before they had got on a little more with their new construction.¹³⁸ Shortly thereafter Nichols informed Svedberg about a paper by two Belgian researchers, E. Henriot and E. Huguenard who had reached 150,000 g with a 12 cm rotor.¹³⁹ (see Chapter 3) Nichols inquired what the advantages of the oil-turbine would be apart from easier lubrication.¹⁴⁰ Svedberg replied that they had almost finished their preliminary calculations on the new centrifuge and would soon go over to make the working drawings. They had carried out a number of measurements on the oil turbine centrifuge itself which showed that the oil turbines had an efficiency of more than 60%, which he considered very high for such a machine. A new oil had lowered the heat effect in the bearings and raised the speed. It allowed them to run 43,500 r.p.m. with 15° in the oil and 23.5° in the cell. The weakest point in the apparatus was considered to be the big oil compressor. It had an efficiency of about 33% which Svedberg hoped to improve for the new centrifuge. Their calculations showed that the best conditions would probably be reached with a rotor of 180 mm diameter and 50,000 r.p.m. That would give 200,000 times gravity as mean value in the cell. Getting back to Nichols' question he stated:

"One of the very great advantages of the oil turbines is their small diameter. With air turbines it would be difficult to get room enough for the optical arrangements. Our chief reason however is that now we actually know all the characteristics of the oil turbine system and can found our calculations on those, while if we go over to air we would have to experiment quite in the dark at first. Besides at present we don't see any real advantage in the air system, besides that it might be - although it is not certain - that the cost of running the centrifuge might be a little lower with air. The lower cost of running an air compressor would perhaps be compensated by the cost of running an extra oil pump for the bearings. So therefore we do not see any reason for going over to air at all."¹⁴¹

In September 1927 Lysholm proposed to Svedberg to try a new rotor construction. With some of the new steel alloys and an oval shaped rotor it was

thought possible to obtain 200,000 g if the diameter of the rotor was increased from 15 cm to 26 cm. Except for the rotor and turbine housing very little change had to be made in the rest of the equipment. There are no direct comments in Svedberg's notes until 15 March 1928, when he wrote Lysholm to tell him that he had new funds for developing the ultracentrifuge. After a number of tests and changes Svedberg came to the conclusion that they should stick to the oil turbines and not try the air turbine drive. However, a stronger steel should be used for the rotor which should be cylindrical with a diameter of 15 cm. The increase in the centrifugal field could be obtained by spinning the rotor at a higher speed rather than increasing its diameter which would also imply a new casing.

Before being able to start the calculation for a higher speed rotor, Lysholm needed more information from the old centrifuge on friction in the bearings and in the gas. Results from these measurements were sent to him in the middle of May 1928. At this time, however, Lysholm became chief engineer at Ljungström's Steamturbine Co., Stockholm, and he delegated the further work with the centrifuge to one of his younger engineers, Gustaf Boestad. When in Stockholm, Svedberg often spent some time at Boestad's office. In between they exchanged long letters. In Svedberg's correspondence, the letters to and from Boestad number in the hundreds. Boestad brought new ideas, and he proposed various modifications for the bearings, one of them being a distinct improvement. The old rotor could now easily be run at 45,000 r.p.m., and 48,000 r.p.m. was even reached once. He could now start the design and calculation of a rotor made with the new steel material. His first attempt showed that if the rotor was cylindrical with a diameter of 15 cm, it could not stand any higher speed than about 55,000 r.p.m. He therefore tried Lysholm's proposal of an oval shaped rotor with the same diameter. Calculations showed that such a rotor should be able to withstand a speed of up to 60,000 r.p.m. With the equipment available at Upsala it would probably be possible to reach a maximum of 55,000 r.p.m. Boestad and Lysholm recommended that Svedberg try such an oval rotor in the old apparatus. Svedberg did not have much faith in an oval shaped rotor but, finally, after much reluctance he agreed, and the material from the steelwork could be ordered.¹⁴²

Application to Proteins

From late 1926 onward Svedberg had two ultracentrifuges which were used in connection with two experimental methods. For the sedimentation equilibrium method centrifugal fields in the order of 5000 times that of gravity were needed but centrifugation lasted a relatively long time, generally two or three days and in some cases even more than a week. Unstable substances, like acid haemoglobin near

the region of hematin formation, might alter appreciably during this length of time. The sedimentation velocity method, on the other hand, used for molecules of the order of magnitude of the proteins required centrifugal forces of at least 70,000 times that of gravity. This introduced certain experimental difficulties, but enabled measurements to be made in as short a period as two hours of centrifuging. Although the sedimentation equilibrium method was considered sounder thermodynamically, the other method had certain advantages which justified the construction of an oil-turbine type of ultracentrifuge capable of running at a speed of 42,000 r.p.m. and giving an effect 104,000 times that of gravity. In addition to the much smaller chance for decomposition of an unstable substance in the short time of centrifuging, it was also possible to obtain more exact information about whether a mixture of molecules was present in a solution, whereas in the sedimentation equilibrium method only the resultant effect of centrifuging and diffusion was obtained; by using higher speed they determined the diffusion and the velocity of sedimentation separately. Under these conditions it was possible to detect anomalies in the diffusion produced by labile gel formation or hydration that might otherwise cancel out or be disguised.¹⁴³

On 5 March 1926 Svedberg had already demonstrated the sedimentation of haemoglobin in the ultracentrifuge to the members of the Royal Society of Sciences in Upsala.¹⁴⁴ However, it was not until September 1926 that the ultracentrifuge was finally ready to be used for routine runs, and that Svedberg could attack the main question about the uniformity of the protein molecules. Together with Nichols he started a new series of experiments on CO-haemoglobin with the sedimentation velocity method. The experimentally obtained curves were compared with the theoretical curves for the combined sedimentation and diffusion. In his laboratory record for an experiment made 17 September 1926 Svedberg wrote: 'Not the slightest indication of the presence of differently sized molecules could be noticed.'¹⁴⁵ For Svedberg this meant that the uniformity of the CO-haemoglobin had been confirmed by the new sedimentation velocity method, which also implied for him that a new criterion of protein purity had been introduced.

Even before this confirmation of the uniformity of the CO-haemoglobin was clear, Svedberg had decided to concentrate completely on the study of proteins. This is evident from correspondence he had with some prospective foreign students during the summer of 1926. In a letter to Eugene Chirnoaga he wrote:

"Before you finally decide upon coming to us, I think you need some information about the kind of work we are doing in my lab just now. During the last two years we have specialized on the colloid chemistry of the proteins, and due to the success which we have had, we decided to use all the resources of the lab in the service of this study. At the present time, therefore, all the facilities of the lab are organized for the study of the proteins, and in case you want to come to us, you would have to join in this big work. As you will see from the enclosed

reprint, our chief work, the study of the proteins by means of centrifuging, is rather interesting, and I think that a year spent in such work would not be wasted."¹⁴⁶

Several foreign students came to Upsala to study with Svedberg, and they were all set to study various proteins, mainly chromoproteins, as their sedimentation in the ultracentrifuge could easily be followed with the light absorption method.¹⁴⁷

After the first surprising results with haemoglobin Svedberg used his ultracentrifuge mainly to study a wide range of proteins. Together with Nichols he did experiments on egg albumin. Using the 'old' electrically driven ultracentrifuge in connection with the sedimentation equilibrium method they concluded from the first experiments:

"It is evident (...) that there is more than one size of molecule present. (...) a mixture of 94% of molecules 34,000 and 6% of molecules $5 \times 34,000$, or 170,000, satisfied the observed drift in molecular weight better than any other mixture, although 92% of molecules 34,000 and 8% of molecules $4 \times 34,000$, or 136,000, gave a fair agreement."¹⁴⁸

After further purification it seemed that there was only one size of particle present. They remarked, however:

"(...) it cannot *definitely* be decided that small amounts of molecules not greatly different in size from 34,000 are absent until determinations are made at sufficiently high speeds (about 40,000 r.p.m) (...)"¹⁴⁹

So, from a colloid chemist Svedberg became a protein chemist. This was not a big shift as proteins still were considered to be colloids. Svedberg thus concentrated on a specific class of substances within the colloid field. However, as time went by, colloids and proteins were more and more seen as separate substances and Svedberg, already being on the protein side, ended up in the protein camp. It would in fact lead to problems with respect to getting published in the *Journal of the American Chemical Society*.

Recognition by Colleagues - Nobel Prize

In the 1920s Svedberg already was a respected colloid chemist in Europe and his sojourn in Madison contributed to his recognition in the USA. Jerome Alexander invited him to write a Chapter on 'The Preparation of Colloidal Dispersion' or any other topic Svedberg would like to write about for a volume he was editing in colloid chemistry. Svedberg had concluded a monograph on the basis

of the lectures he had given in Wisconsin which was very well received and caused Alexander to call him one of the 'outstanding chemists in the world'.¹⁵⁰ Svedberg chose to write a chapter on 'Centrifugal and Diffusion Methods for the Study of Dispersity and Hydration in Sols'. Because he was very fascinated with the methods he was developing at that time he tried to get as much time as possible before sending off the final version in order to be able to include the latest developments.¹⁵¹ Shortly thereafter Svedberg was invited to contribute an article to a special issue of the *Zeitschrift für Physikalische Chemie* on the occasion of the 60th birthday of R.A. Zsigmondy, a pioneer in colloid chemistry and called the 'father of the ultramicroscope'.¹⁵² F.G. Donnan, a well-known chemist from London wrote that Svedberg's work on the ultracentrifuge would 'prove to be of the highest importance not only for colloid chemistry but also for a very wide field of research'.¹⁵³ Edwin Cohn from the Harvard Medical School was also impressed with Svedberg's 'simple and elegant' method. Cohn was a very respected protein chemist who had published a long review article on the physical chemistry of proteins in 1925.¹⁵⁴ Cohn asked Svedberg to determine for him the molecular weight of the Bence-Jones protein and the hemp seed globulin, edestin.¹⁵⁵ Svedberg also thought highly of Cohn. He replied that they were then, mid 1926, working on three different lines with respect to proteins: determination of diffusion constant, the mobility (cataphoresis) and molecular weight (by means of centrifuging).¹⁵⁶ Cohn visited Svedberg in the summer of 1926 during which visit they discussed his latest results on haemoglobin. On Cohn's suggestion Svedberg came to the conclusion that his results would be best explained assuming a molecular weight distribution of 33,400 (15%), 66,800 (70%) and 100,200 (15%).¹⁵⁷

A year before Svedberg and Fåhræus had sent their paper on the molecular weight of haemoglobin to the *Journal of the American Chemical Society*, G.S. Adair at Cambridge had found an average molecular weight of 66,700 for haemoglobin from ten different species by using a refined osmotic technique.¹⁵⁸ Adair wrote Svedberg that his technique was heavily criticized but he hoped that the concordance of their results, using two completely independent methods, would convince his critics.¹⁵⁹ Svedberg and Fåhræus did not become aware of this work until some time after they had submitted their paper to the *Journal of the American Chemical Society*. Because the publication of the paper was somewhat delayed Svedberg intended to add a note on Adair's results which were in 'striking concordance' with his. However, in the meantime they had also centrifuged egg albumin, finding the molecular weight differing by a factor two from Adair's results. This made Svedberg decide not to discuss Adair's work.¹⁶⁰ In the summer of 1926 Adair visited Upsala to meet and discuss with Svedberg and to see his ultracentrifuges. Adair believed that there were a good many points in which the ultracentrifuge would be of the greatest value in clearing up points which the

membrane work left doubtful, and that it was possible that advances could be made by carrying out experiments by both methods on the same protein preparations. Adair also had some reservations with respect to the ultracentrifuge method. While he was in Copenhagen he expressed to Arne Tiselius, one of Svedberg's students, his severe doubt whether the gas laws were valid for hydrophile colloids in the presence of electrolytes. Tiselius emphasized that in any case they could determine the thermodynamic properties of colloids from sedimentation equilibrium experiments. This had not appeared to Adair before. The next spring Adair wrote Svedberg that he had recalculated the work on egg albumin, now giving a molecular weight of 43,000 which, however, was still 'too large, compared with your work (...) and confirms your estimation that aggregation occurs'. Adair also thanked Svedberg for informing him that the new ultracentrifuge had showed evidence that haemoglobin was a mixture of aggregates.¹⁶¹ In a reply Svedberg wrote that the deviation from uniformity was only very slight and that the deviations he had spoken about were probably due to electric effects. The deviation now found might be due to experimental error. Therefore, he summarized:

"(...) we may say that the measurements with the new centrifuge have shown conclusively that haemoglobin solutions are built up *at least almost* entirely of equal molecules of a weight of about 68,000."¹⁶² (emphasis in original)

Early 1925 J.H. Mathews asked Svedberg how he would feel about becoming the director of research of a Colloid Institute to be created in Madison. Svedberg replied that it would be hard for him to leave Upsala because he had just received a 25,000 kronor grant. Also he would like to return to Upsala after his sojourn in the USA which would be possible if he would go away for about two years but could not be guaranteed if he remained for five years as Mathews had suggested. Svedberg also found the salary offered to low compared to his salary in Upsala.¹⁶³ Late 1926 Mathews definitely invited Svedberg to come to Wisconsin as a permanent member of the staff but Svedberg declined the offer. The research work in his laboratory was progressing and researchers from different countries wanted to come to Upsala to study with him. He also expected that parliament would vote the necessary money for a new physical chemistry laboratory and equipment the following year. Another factor which made it difficult for him to leave Sweden was that he had just been awarded the Nobel Prize.¹⁶⁴

The Nobel Prize awards of the 1920s show that colloid chemistry was considered to be a very important field of scientific investigation. In 1921 the Nobel Prize in Physics was awarded to Einstein for 'his services to Theoretical Physics (...)', one of which was his development of the theory of 'Brownian Movement'.¹⁶⁵ At the presentation of the prize to Einstein, the Chairman of the Nobel Committee for

Physics stated that colloid chemistry had grown into 'a large branch of science' and he explicitly mentioned the work of Svedberg, Perrin and Zsigmondy.¹⁶⁶ The 1926 Nobel Prize in Chemistry was awarded to Svedberg for his work on 'disperse systems'.¹⁶⁷ The 1926 Nobel Prize in Physics was awarded to Jean Perrin for work in the same field,¹⁶⁸ whereas the postponed 1925 Nobel Prize in Chemistry went to Zsigmondy, also for work on colloids.¹⁶⁹ The importance that the Swedish Academy of Sciences attributed to colloid chemistry was illustrated by Professor H.G. Söderbaum, secretary of the Academy, in his speech at the presentation of the awards:

"Inorganic chemistry has revealed more and more cases where only a colloid-chemical approach was able to clarify the observed phenomena.

For physical chemistry colloids form a rich and rewarding field of research.

In organic chemistry we meet the perhaps most important colloids, the proteins and the polymeric carbohydrates, which cannot be studied without the aid of colloid research.

As all living matter is built up largely from organic colloids, the importance of colloid research for physiology and the medical sciences is obvious.

Finally, colloids play an important part in the various branches of chemical industry, such as in dyeing and tanning, in the cellulose, nitrocellulose, celluloid and textile industry, in rubber manufacture, in the pottery and cement industry, in the photographic industry, etc."¹⁷⁰

Furthermore the investigations on colloid particles were seen as a possible way of demonstrating the real existence of molecules and atoms.¹⁷¹ The Nobel Prize was not awarded to Svedberg for his work with the ultracentrifuge. It was awarded to him for his many contributions to colloid chemistry of which his experimental confirmation of Einstein's theory of Brownian movement was mentioned explicitly.¹⁷² It was mentioned, though:

"During the last few years Svedberg has completed an extremely ingenious invention, the so-called ultracentrifuge, which enables highly interesting investigations to be made also on (...) molecular-disperse systems."¹⁷³

There had, however, been some controversy over his award. The Nobel Prize Committee for Chemistry (an advisory board to the Academy) had suggested to award the prize to someone else but the Academy did not follow the recommendation and awarded the prize to Svedberg. The procedure for selection of the Nobel prizewinners was for a committee in each discipline to nominate a candidate to the full Academy, where a final decision was made. There was support for Svedberg on the chemistry committee of which he was a member, and he was expected to withdraw in order that his candidacy be discussed. However, Svedberg declined to be considered and remained on the committee. Afterwards support for Svedberg for the 1926 prize developed on the floor of the Academy, in opposition

to the committee's recommendation. Next Svedberg reversed his decision and stepped out of the full meeting so that he might be considered. The Academy then decided that he should be awarded the prize.¹⁷⁴ Svedberg himself also had some ambiguous feelings about the prize. In his autobiographical notes he wrote:

"I myself had feelings of incredible happiness as well as some discomfort. I had been awarded the prize for my work concerning disperse systems, that is, more or less for my total body of work. It seemed to me that only my last investigations, the work on proteins used in the ultracentrifuge, could really be seriously considered. And these were just begun. Thus, actually, the Nobel prize committee in chemistry was right - I should have been allowed to wait at least a couple of years. I lay awake brooding all night and felt more and more unhappy. I promised myself to use the following ten years of my life to make myself worthy of the prize. And so it also worked out too. The comments from abroad, however, were very kind. Three prizes had been given to scientists in the physics and chemistry of colloids. That was a good hit by the Academy, it was explained. Concerning me it was said that the Academy of course had already had the opportunity to see my latest publications before they were generally known abroad. Their great importance was not doubted.

(...) Then it was time to think about the Nobel dinner on December 10th, where I had to give a speech and offer my thanks for the prize. At the suggestion of Professor Söderbaum - who was the secretary of the Academy - my Nobel Prize lecture was postponed until the spring. The reason was that the chemistry committee should not feel the humiliation so bitterly and also because it should be possible for me to collect some more material in my protein investigations. I felt a bit crestfallen, but on the whole this made things calmer and better."¹⁷⁵

On May 19, 1927 Svedberg gave his Nobel Lecture. He did not talk about the work he had been awarded the prize for. He only discussed his recent work with ultracentrifuge, especially with the oil-turbine type which he had only been using since a few months. He described the apparatus and method in detail and stated:

"With this ultracentrifuge it is possible to cover the entire sector of the colloids down to the smallest particle sizes and even penetrate slightly into the actual molecular solutions. In so doing we reach a field of the very greatest theoretical and practical importance, the substances of high molecular weight, such as haemoglobin, protein, starch, etc. The limit of the possible has not yet been reached. The author hopes that with a new ultracentrifuge it will be possible to double the field of force and thus link up the centrifugation method analysis with conventional molecular-weight analysis carried out on solutions by determining boiling or freezing point."¹⁷⁶

He described experiments on gold sols and experiments on haemoglobin. With respect to the latter he stated that calculations showed that at least 80-90% of the haemoglobin in question consisted of molecules of a weight of 68,000. More recent measurements by Nichols had given even higher percentages for this type of molecule and therefore the protein haemoglobin would be a substantially homogeneous chemical individual.¹⁷⁷ He also gave the molecular weight of three other proteins and concluded:

"Examination of highly disperse colloids and other solutions of similar properties by centrifugation is still at its very beginning. The results obtained clearly show that in this way it will be possible gradually to collect a valuable fund of knowledge concerning such medicinally and technically important groups as the proteins, polymeric hydrocarbons (for example rubber), polymeric carbohydrates (for example starch, cellulose), etc."¹⁷⁸

It was an unusual choice of topic for a Nobel award lecture; a lecture that was a preliminary report, almost akin to a proposal for a research grant rather than a review of achievement.

The Nobel Prize gave Svedberg an extra status which greatly assisted him in obtaining funds for further investigations. For some years Svedberg had been trying to find money for a larger laboratory because his experimental equipment, especially since the use of ultracentrifuges, needed ever more space. The first plans for building a new institute began to take form in 1924, immediately after Svedberg's return from America where he had developed a large number of ideas for further research. Within a few years new apparatus and new people crowded the old laboratories.¹⁷⁹ Some of the apparatus was housed in a former toilet. In October 1926 an article appeared on the front page *Dagens Nyheter*, a Stockholm newspaper which was headed: 'Professorn får arbeta i mörk kolkällare och hans lärjungar på W.C.' (The professor has to work in a dark coal-cellar and his students in a toilet.).¹⁸⁰ In the beginning, chances for getting the money seemed to be rather slim. After Svedberg was awarded the Nobel Prize things changed rapidly. In Svedberg's own recollection:

"The Nobel Prize meant a considerable economic alleviation for me, and more important, it strengthened my position. The question of a new building for physical chemistry was a burning one. The premises available for me and my coworkers were very small and to some extent of inferior quality. For a couple of years Yngve Björnståhl and I had been working on the planning of a new building for the department, and the last time I had discussed this with the university authorities was in the autumn of 1926. A number of obstacles were raised in my way: it was not my turn to be allowed to build, others should come before, the university could not demand such an expensive department now, and so on.

When I had got the prize the obstacles were rapidly removed. I went to Stockholm and talked to Börje Knös, who took his doctorate when I did and who was now secretary in the department of education. He promised to arrange for a possible petition from the university to be submitted to the 1927 Riksdag (the Swedish parliament; BE). He concluded: 'If the university hesitates, you may apply yourself directly to His Royal Majesty.' He added: 'Moreover, the press would make a big noise if the petition did not materialize.' As a matter of fact the press had interviewed me and photographed my worst premises in connection with the prize: 'The Nobel prize winner works in a toilet,' and so on. The Riksdag granted 1,225,500 crowns for the building of a department of physical chemistry (...)"¹⁸¹

Svedberg and Björnståhl, one of his colleagues, started planning a completely new building for physical chemistry which was also to include laboratories for the

ultracentrifuge work. Björnsthål made very comprehensive preparations in the years 1925-28 and made a number of journeys in order to study scientific institutes both in Europe and America. The building was constructed in the years 1928-31. It was built adjacent to the existing Chemical Institute and connected with the latter by corridors. The new Institute was well equipped with scientific instruments.¹⁸² An important problem, however, was that with the new building Svedberg also anticipated the need of a variety of new equipment that was not included in the grant.

September 1927 Svedberg informally inquired with Augustus Trowbridge from the European office of the Rockefeller Foundation's International Education Board in Paris. Svedberg asked whether the Board might contribute a sum towards the purchase of apparatus for his new laboratory. The cost of the laboratory was mentioned to be \$ 204,000. Svedberg included a list of 'new special research equipment' he would need the purchase of which would amount to \$ 80,000. He argued that the laboratory had in the past been visited by three fellows of the Board and that he expected that about 50% of the research workers in the new laboratory would be foreigners.¹⁸³ When he forwarded this inquiry to Wickliffe Rose at the Board's central office in New York Trowbridge advised that it would be a good thing to back this project. About Svedberg he wrote:

"Apparently SVEDBERG is a strong leader in the field of Colloid Chemistry. His work with the extra-ordinarily powerful centrifuge machines which he has designed has also been drawing foreigners to his laboratory, and he seems to have been able to get his own people to go in for considerable expansion of his facilities at Upsala".¹⁸⁴

Rose agreed with Trowbridge upon the desirability of backing Svedberg and gave Trowbridge a free hand in preparing a definite proposal. Rose stated that Svedberg was 'a Number One man'.¹⁸⁵ Trowbridge replied to Svedberg that he thought that his list was somewhat long and asked Svedberg to mark the list in an order of preference.¹⁸⁶ June 1928 Svedberg submitted a definite application to the Board, asking for \$ 75,000. Among the items listed were a contribution to a new oil-turbine ultracentrifuge (\$ 14,000), facilities for protein preparation (\$ 5,000), an electromagnet for the study of optical properties, diffusion, viscosity etc. in magnetic fields (\$ 10,000), X-ray apparatus (\$ 10,000), and a variety of optical and electrical equipment.¹⁸⁷ Trowbridge had some reservations as to whether all of the apparatus would really be needed. He had the impression that part of it would be needed directly upon the opening of the new laboratory while the rest might be needed in case his field of research work would enlarge beyond its present scope.¹⁸⁸ Svedberg replied, however, that all of the equipment would really be needed in view of the work that was already going on. Furthermore there would be

little hope to secure any of the apparatus mentioned in the list by making use of the annual support given by the University to meet the needs of the laboratory. The annual sum at Svedberg's disposal for buying apparatus and material for his research work was Skr. 8,000, or about \$ 2350.¹⁸⁹ When he forwarded the proposal to the President of the Board, Trowbridge strongly backed the proposal. He mentioned that Sweden had granted \$ 203,000 for a new laboratory building and \$ 125,000 for general apparatus. Furthermore he argued that the population of Sweden was about 6 million which meant that they had voted \$ 55,000 per million inhabitants for what was primarily a new outstanding research institute in one branch of chemistry. \$ 55,000 per million inhabitants would mean over \$ 6,000,000 for a country like the US. He continued writing about Svedberg:

"Svedberg's standing outside his own country is very high. He is 44 years of age and has had a remarkably brilliant career from the start of his scientific work; while on the average Swedes take ten years of graduate study for their Ph.D. degree, Svedberg obtained his in six years! He has the reputation of being a tremendous worker, spending as much as eight hours a day in his Laboratory. He was given full professorship at 28 years of age; has published some 90 scientific papers, and of these only a few of recent years in collaboration with students—the greatest part of his publications is independent, un-aided work. His situation in the University of Upsala as a Professor is very enviable, as he need only give 15 lectures a year and is permitted to crowd these into about two months of the Academic year, leaving him long periods for research work. Next to Siegbahn, who is also at Upsala, Svedberg is the youngest holder of the Nobel Prize.

There are no doubts whatever in my mind but that some measure of support to him in equipping his Laboratory will be an expenditure well made in the interests of Physical Chemistry in the international field."¹⁹⁰

Trowbridge recommended that the Board vote \$ 40,000 for this purpose, provided that Svedberg would receive from the University of Upsala, or other source, guarantees of a capital sum, not less than say \$ 20,000. Such would enable Svedberg to secure 4/5th of his present needs, the remaining 1/5th he might ultimately get from the current expenses.¹⁹¹ In November the Board of Trustees authorized to grant Svedberg \$ 50,000 'with the understanding that the University of Upsala would obtain from other sources additional sums required for the purchase of special equipment for the new Laboratory.¹⁹² This grant enabled Svedberg to procure most of the apparatus he needed. In addition, he designed special instruments himself, and stimulated his collaborators to do the same.¹⁹³

Protein Studies - Reception of Svedberg's Claims

When Svedberg had returned from Madison he had elaborate plans to develop new branches of physical chemistry which he judged important for future studies

of colloidal solutions. But he was now so intensely engaged in the work with the new ultracentrifuge and its application to proteins that he had to delegate other work to his students. The work on diffusion was taken over by Ole Lamm who in this connection developed the 'scale method' which for a long time remained the principal observation method both for diffusion and sedimentation. The work on birefringence (electric, magnetic and flow) by was pursued by Yngve Björnsthål.¹⁹⁴ Herman Rinde continued using the ultracentrifuge for the study of inorganic sols. In 1928 he completed his dissertation describing the use of the ultracentrifuge in the study of gold sols.¹⁹⁵ Arne Tiselius became Svedberg's research assistant in 1925 to study the electrophoresis of proteins, on which Svedberg had published some papers before. During his summer vacation in 1926, he started to study how the thermodynamic properties of colloidal solutions were influenced by the centrifugal field.¹⁹⁶ In a letter to Nichols on 16 July 1926, Svedberg wrote:

"It is quite funny that Tiselius is now starting a career as a theoretical physicist or chemist! He is trying to go through the main chemical laws and give their form in a centrifugal field. We think that the fact, that now actually the experimental facilities for a 'centrifugal chemistry' is existing, gives the right to make some theory also."¹⁹⁷

Svedberg attracted a number of foreign students who were interested in working with the ultracentrifuge. Alfred J. Stamm from Wisconsin wanted to study cellulose. The same was true for R.O. Herzog from Berlin who therefore suggested to make a division of labour.¹⁹⁸ Edwin Cohn also sent some students¹⁹⁹ and R.H. Aborn from MIT's research laboratory of applied chemistry asked Svedberg to send him some material of known particle size for further investigation using X-ray diffraction.²⁰⁰ Together with Eugene Chirnoaga from Rumania, Svedberg investigated the protein haemocyanin collected from the blood of German vineyard snails. According to its copper content the minimum particle weight should be 15-17,000. The ultramicroscope revealed no discrete particles in a solution of haemocyanin, but the cone of light could be seen distinctly even at a dilution of 0.0001%. When the first run with the haemocyanin had been started in the equilibrium centrifuge, Svedberg went home for a while, letting Chirnoaga supervise the run. This run was made with a solution of pH 8.0 and concentration 3.05% at a speed of 7000 r.p.m. (centrifugal force 2565 times that of gravity). He had hardly come home when a telephone call came from Chirnoaga, who said: 'Something funny has happened, come over and look.' Svedberg rushed back and was greatly amazed. The haemocyanin had already sedimented a short distance with a knife-sharp boundary. It was found that sedimentation equilibrium expected in analogy to the behaviour of the other proteins previously investigated, was not attained. Instead the molecules were centrifuged down. An estimation of the particle size

showed that it had to be in the millions, the sharp boundary indicating that all the particles had the same size. This finding made Svedberg write Nichols that 'this protein is very funny indeed'.²⁰¹ Three successive experiments were carried out with the above solution at speeds of 4000, 8000 and 11,000 r.p.m., all other conditions being equal. The values obtained for the diffusion constant indicated a variation approximately inversely proportional to the centrifugal force applied. At the same time it was noticed that during centrifuging some change took place in the solution, starting from the bottom of the cell, causing less light absorption and consequently undue darkening of the photographs in the affected region. This darkening extended rapidly upwards, altering the blurring of the boundary and therefore preventing accurate calculation of the diffusion constant. The effect was more marked with old than with fresh solutions. It was assumed to be due to reduction of the haemocyanin produced by the activity of bacteria present in the solutions since the medium was alkaline. A few experiments carried out at pH 3.8 indicated a breaking up of the molecule into smaller units of varying size. Because of the instability of the protein both in alkaline and extremely acid solutions, they decided to limit the investigation of the molecular weight to solutions near the isoelectric point, which offered better conditions of stability. With this large protein they did their final sedimentation equilibrium determinations at a speed of 1000 r.p.m., giving a centrifugal force only 50-60 times gravity. Equilibrium was then obtained in two to three days of centrifuging. In order to ascertain whether the particles were of uniform size, they carried out an experiment at a speed of 25,000 r.p.m., corresponding to a centrifugal force 37,000 times greater than that of gravity, with a solution at pH 4.7 and of concentration 0.051% at a temperature of 23°, taking photographs every three minutes, the whole experiment lasting only half an hour. During such a short interval of time no appreciable diffusion took place, and if the solution contained molecules of the same size, the photographs should display a sharp boundary between solvent and solution. This indeed appeared to be the case. They concluded that haemocyanin was at pH 4.7 a single molecule with a molecular weight of $5,000,000 \pm 5\%$.²⁰² In a later article Svedberg and Francis Heyroth showed that the protein was stable as to size in a range from pH 4.5 to 7.4.²⁰³

After having investigated a number of proteins Svedberg was struck by a certain regularity in the molecular weights found. To Nichols he wrote in 1928:

"(...) some recent results regarding the mutual relationship of the molecular weights are rather startling, but it is too early to say anything about it - even to you, my dear Burton - You would laugh at me."²⁰⁴

In 1928 the second edition of Svedberg's book *Colloid Chemistry* was released in which he also discussed the ultracentrifuge and its applications. He stated that he found it 'surprising' that the molecular weights of the five proteins he had thus far determined were all integer multiples of 34,500, the molecular weight of egg albumin. Furthermore it appeared that there existed proteins of widely different chemical properties and different elementary composition possessing the same, or almost the same, molecular weight. This was the case with haemoglobin and serum albumin on one hand and with serum globulin and phycocyan on the other. To Svedberg, these regularities seemed to indicate that the molecules of the proteins - or at least of a certain number of them - were built up according to some general plan with regard to the structural arrangement of their fundamental groupings. This assumption was supported by the observation that the specific sedimentation velocity and the diffusion constant for different proteins of the same molecular weight were practically the same.²⁰⁵

Mid 1929 Svedberg for the first time published a short note on his ultracentrifuge work in *Nature*. There he wrote:

"Our work has been rewarded by the discovery of a most unexpected and striking general relationship between the mass of the molecules of different proteins and the mass of the molecules of the same protein at different acidities, as well as of a relationship concerning the size and shape of the protein molecules.

It has been found that all stable native proteins so far studied can with regard to molecular mass be divided into two large groups: the haemocyanins with molecular weights of the order of millions and all other proteins with molecular weights from about 35,000 to about 210,000. (...) The proteins with molecular weights ranging from about 35,000 to 210,000 can, with regard to molecular weight, be divided into four sub-groups. The molecular mass, size, and shape are about the same for all proteins within such a sub-group. The molecular masses characteristic of the three higher sub-groups are - as a first approximation - derived from the molecular mass of the first sub-group by multiplying by the integers *two*, *three* and *six*. The molecules of the first and fourth sub-group are spherical (...), while the molecules of the second and third sub-group are non-spherical. (...)

Although not more than 11 different proteins belonging to the group which displays these regularities have as yet been studied, it would seem very improbable that the relationship between the molecular masses and sizes were incidental. Perhaps the most striking proof of the close relations between the different proteins is the fact that one and the same protein may, according to the pH to which it is brought, appear with the molecular mass, size, and shape of another protein.

When looking for an explanation of these unexpected regularities, it would be well to bear in mind the fact already brought out by many bio-chemical experiences, namely, that Nature in the production of organic substance within the living cell seems to work only along a very limited number of main lines. The great variety appears in the specialization of details. Thus it would seem that the numerous proteins are all built up according to some general plan which secures for them only a very limited number of different molecular masses and sizes when present in aqueous solution. By varying the constituents of the different proteins (different percentage of different amino-acids, etc.) the chemical and electro-chemical properties may be varied sufficiently to enable the cells to make use of them for their different purposes."²⁰⁶

Plans were now worked out for an extensive study of proteins from various sources: seed proteins, chromoproteins, respiratory proteins, etc. This made it desirable to have more ultracentrifuges available. The whole program of the laboratory at Upsala was changed. Svedberg showed a great interest in haemocyanins. Partly as a joke, but also with a serious purpose, he founded the 'Académie des Hémocyanines', with seventeen members.²⁰⁷ As the new laboratory was just being built, Svedberg got a large increase in research space and could arrange laboratory rooms especially adapted for the different types of ultracentrifuges. Svedberg once remarked to John Williams, who came to work with Svedberg for a while in the early 1930s, that if the Fåhræus and Chirnoaga results had not been so favorable, it was doubtful whether his program of ultracentrifugal analysis could have been continued. The problems of interpreting the data for polydisperse systems were soon recognized to be extremely difficult to solve, and it was only after the experiences gained over a number of years with the simpler protein systems that many of them became tractable at all.²⁰⁸

Already before Svedberg made his claims on the sizes of proteins there had been evidence that they were of an enormous size. However, in the first two decades of this century only a small minority of the chemists accepted these claims; this gradually changed in the 1920s. Especially the fact that Adair and Svedberg had, independently of each other, arrived at practically the same value for haemoglobin, made a great impression. But these results only meant something to a limited number of scientists. Proteins were considered to be colloids, but only few colloid chemists really studied them. In general, colloid chemists were a different group of people from the protein chemists. And generally the latter were not working on the sizes of proteins but largely on their amino acid composition and on their nutritional value - which amino acids were essential for nutrition, etc. Also work was being done on the kinetics of protein denaturation.²⁰⁹ October 1928 H.B. Vickery and T.B. Osborne published a 50 page long article in *Physiological Reviews* containing almost 200 references entitled 'A review of hypotheses of the structure of proteins'. From this article it is evident that many scientists were working on qualitative researches on proteins. However, they devoted less than half a page to the molecular weight, concluding that 'it is relatively certain that many of the soluble proteins possess truly gigantic molecules'. They based themselves on eight references, three of which referred to Svedberg's investigations.²¹⁰ In 1931 W.T. Astbury and H.J. Woods used Svedberg's 'multiple law' hypothesis as a basis for some speculations on the structure of proteins.²¹¹ However, quite a number of scientists would not believe that the proteins were so well defined in regard to size. Most scientists regarded them as lyophilic colloids. When Svedberg put forward his hypothesis about the molecular weights of the proteins as being distributed over a limited number of weight

classes, where the molecular weights of the higher classes could be expressed as simple multiples of the molecular weights for the lower classes, skepticism became even more prominent. Kai O. Pedersen illustrated this skepticism with some personal experiences from that time: before he left Copenhagen for Upsala, in January 1930, many chemists expressed grave doubt about the findings of Svedberg, and some were wondering if Svedberg and his coworkers were not measuring artefacts of some kind, perhaps due to the ultracentrifugation method. When, after his graduation in Copenhagen in 1929, Pedersen told Professor Bronsted that he wanted to go to Upsala to study with Svedberg, Bronsted was rather skeptical. He admitted that Svedberg was an excellent experimental physical chemist and a very charming man, but his ultracentrifuge could hardly be of any great importance. Bronsted thought that it would be much better for Pedersen to go either to Germany to study with Herbert Freundlich at Berlin-Dahlem, or to England to study with Rideal at Cambridge or with Hinshelwood at Oxford. Furthermore, at those places he could learn a useful foreign language. But Pedersen had become so fascinated by Svedberg's work and by his papers and books, that he went to Upsala in January 1930 to study there for a couple of years - he stayed there ever since. Before he went to Upsala, he visited the grand old man in protein chemistry, Professor S.P.L. Sørensen at the Carlsberg Laboratory in Copenhagen. Sørensen also expressed his doubt about Svedberg's multiple hypothesis: he did not expect it to be of a general nature, nor did he believe that proteins were substances so well defined in regard to mass and size as claimed by Svedberg.²¹²

H.R. Kruyt from Utrecht had objections against using the term 'molecular weight'. He held the opinion that one ought only to speak of 'particle weight' or 'micellar weight'. The ultra-centrifugal effect, both from the kinetic and from the equilibrium standpoint, depended on the mass of the particles and was independent of whether that particle was mono- or polymolecular. The development of the chemistry of the carbohydrates supported his doubt as to these enormous molecules; with cellulose, $(C_6H_{10}O_5)_n$ the n was formerly supposed to be very large, but in 1930 it was generally assumed that it was not larger than 4; the genuine cellulose was assumed to be built up by polymolecular fibers of these molecules. Kruyt argued that Svedberg's investigations were not inconsistent with the view that such would also be the case with the proteins.²¹³ A chemical molecule in the traditional sense was the smallest unit held together by covalent bonds, as well as the smallest subdivision of a sample of a substance that retained all the chemical properties of that substance. For the organic chemist, the concept of the molecule, since the time of Cannizzaro and Kekulé, included a structural formula eventually based on the synthesis of the compound in question; during the 1930s, however, this criterion was not applicable to the proteins. Also, if the natural proteins were composed of fundamental units of 17,600, as suggested by

Svedberg, were all the subunits of a given protein the same kind of chemical molecule? If not, comparison of the minimal molecular weight, as calculated from the value of the elemental or amino-acid analysis, with the value obtained in the ultracentrifuge was not justified, because the element (or amino acid) chosen might have been present in one kind of subunit and not in another. The experimental means for seeking answers to these questions were not available during the 1930s, and there remained a discussion whether the term 'molecular weight' should be applied to the values estimated from measurements in the ultracentrifuge or by the osmotic pressure method. Indeed, it was stated that 'it is certain that, in almost all these cases, what is measured is the size of a *micelle* and not that of a *molecule*'.²¹⁴ Svedberg himself, however, kept talking about molecular weights. Until 1930 they had investigated 28 proteins, 14 of which proved to be monodisperse. Because many proteins were very unstable, depending on a variety of circumstances, Svedberg thought it probable that the other proteins could probably also be brought in a monodisperse state.²¹⁵ The phenomenon that the proteins were so unstable made him argue that the ultracentrifuge was superior to the osmotic method as the latter could not reveal any inhomogeneity in the material studied.²¹⁶ For him, the scientific results obtained with his ultracentrifuges were very fascinating which made him put a large effort in the further development of the apparatuses.

FURTHER DEVELOPMENT OF ULTRACENTRIFUGES: 1928-1933

Svedberg's development work on the ultracentrifuge was partly made possible because he had a well-equipped and well-staffed workshop. The collaboration between the scientists and the mechanics was very close. The mechanic was just as often to be seen up in the laboratory acquainting himself thoroughly with the use of the apparatus, as the scientist appeared down in the workshop to study the available technical possibilities. The fact that the apparatus was made in the own workshop implied that, if an apparatus was damaged, it could often be repaired very rapidly, thanks to the fact that the work was carried out by the mechanic or mechanics who had once helped to construct it. Repairs that would otherwise take several weeks or months could thus often be done in a few hours. During all the years the development work on the ultracentrifuge was going on, Ivar Eriksson was head of the workshop the staff of which grew from one person in 1924 to 10 in 1944. During those years Eriksson especially developed a lot of craft skills in making various parts of the ultracentrifuge equipment, skills that were not easy to pass on to others: e.g. Svedberg once wrote Nichols that it was almost impossible to explain in a letter Eriksson's technique of cutting sectors.²¹⁷ Eriksson was not

only a mechanic but he had also worked in electrical and optical workshops before he came to Svedberg. This experience was also very valuable for the development of ultracentrifuges.²¹⁸ The close collaboration with Eriksson also contributed to Svedberg's knowledge of specific design and construction problems. His long-term interest in photography was very useful for his ultracentrifuge work and was also stimulated by the problems he encountered in its development. He even gave some classes on photography. He also once used his expertise in this field to photograph a manuscript in the university library from the 4th century using special techniques in order to obtain a readable copy as the characters in the original had almost completely faded.²¹⁹ Thus it was not only Svedberg's background in colloid chemistry that influenced the way in which he developed his ultracentrifuges further.

Equilibrium Ultracentrifuge

In order to get rid of some mechanical and thermal weaknesses of the first low speed centrifuge, a new type of ultracentrifuge with gearing drive was designed and built in the workshop of Svedberg's laboratory, using parts of a 'Baltic' cream separator. Mechanically it was superior to the first centrifuge and its design was much simpler. With a new and lighter rotor construction it was also possible to have the rotor chamber enclosed in a thermostated water-bath, thus giving better control of the cell temperature than before. The rotor used was 15 cm in diameter and 3 cm in thickness and could receive four cells. In practice, however, only two were used at the same time, the spaces for the other two being filled by aluminum blanks. As in the oil-turbine type, the casing of the centrifuge was also provided with two quartz windows, each fitted with an electromagnetic shutter.²²⁰

In 1929 new cells were developed for the equilibrium centrifuge. The cells were made as follows: an ebonite plate 25 mm, in diameter and with a sectorial aperture of 50° cut from the periphery down to 7.5 mm from the centre of the plate was coated with a solution of rubber in benzene and after drying for a few minutes covered with two quartz plates of the same diameter and 5 mm thick and solid into an ebonite collar. The latter was in its turn introduced into a steel collar threaded at the ends. By means of two steel guard rings and thin intermediate ebonite rings the quartz plates were firmly pressed together. Both the ebonite and the steel collar had openings coincident with the opening of the sectorial cell. The opening could be closed by an ebonite lid. Four different thicknesses were used for the ebonite middle plates, viz. 2, 4, 8 and 16 mm, giving the corresponding four thicknesses of solution and thus permitting a wide range of different concentrations to be studied. This new type of cell proved to be more reliable than

the cemented one previously described. The ebonite sector plates did not crack as the glass or quartz sector plates often did when exposed to the centrifugal force, the cell was easier to clean and the rubber was more resistant to salt solutions than the de Khotinsky cement. The ebonite collar around the quartz plates protected them from uneven strain.

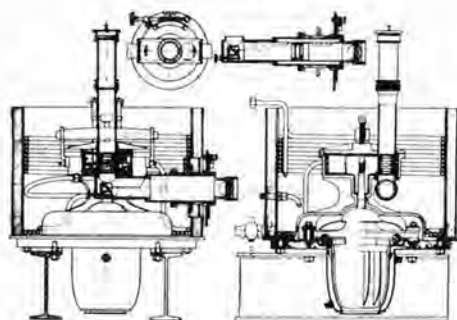


Figure 2.23

Low speed ultracentrifuge with direct drive. (Svedberg and Sjögren, 1929, p.3597).

By choosing the inner diameter of the cell smaller, a thicker steel collar could be used which was less easily deformed by the centrifugal force. Optically the cell was defined by two steel diaphragms with sectorial apertures of 30° , one on each side of the cell. A new rotor was developed which consisted of a chromium-nickel steel cylinder 15 cm in diameter and 4 cm thick which could receive two cells. One of them was used for the solution to be studied; the other was filled with a non-centrifugable solution for standardizing the intensity of the illuminating lamp. A further modification was applied by replacing the geared drive by a direct drive. The problem with the old drive was that due to the a-symmetric character of the gearing arrangement slight vibrations could not be prevented. In the new arrangement (shown in figure 2.23) these problems were overcome. The rotor was supported upon a vertical steel shaft directly connected to the rotor of a special electric three-phase motor. The speed could be varied from 12,000 r.p.m. down to about 2,000 r.p.m. by varying the frequency of the current feeding the motor. The centrifuge rotor as well as the rotor of the electric motor was surrounded by hydrogen of atmospheric pressure confined within a casing about the moving parts of the centrifuge. To further ensure constant temperature, the stator of the motor was water-cooled and the casing within which the centrifuge rotor moved was immersed in a water thermostat. Freedom from vibration was ensured by a special circular rubber support for the stator. Suitable arrangements for passing the light beam through the centrifuge and for taking exposures were made.

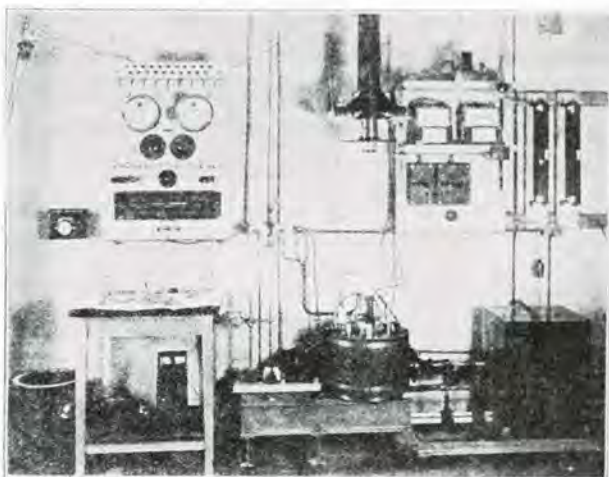


Figure 2.24

Low speed ultracentrifuge with direct drive (Svedberg and Sjögren, 1929, p.3598).

Figure 2.24 gives a view of the whole apparatus except the camera. The latter was placed in a room above the one where the centrifuge was mounted. The optical system used was about the same as previously employed. In figure 2.24 the water-cooled house for the mercury lamp can be seen to the right, then the light filter and the centrifuge follow from right to left. The horizontal illuminating beam was reflected vertically through the centrifuge by a quartz prism. Above the centrifuge was the photographic lens and part of the camera. On the wall were mounted the controlling instruments. The motor and the generator for the variable three-phase current were delivered by Siemens, Berlin; most of the other parts of the equipment were manufactured in the workshops of the laboratory.²²¹ This ultracentrifuge worked most satisfactorily. In 1930 Svedberg concluded that this type was sufficiently standardized.²²² Four of them were eventually installed in his new institute. Later a total of six were made, mainly for laboratories abroad.²²³ So, from the scientific point of view, the problems with the equilibrium ultracentrifuge were solved. Only 'cosmetic changes' were to follow further. The development stopped.

Oil-Turbine Ultracentrifuge

The oil-turbine type, however, left a lot to be desired. Seeking to increase the rotational speed the clearance between the bearings and the shaft was modified slightly which made it possible to reach 44,000 r.p.m. when the oil in the turbine was 25°. But the higher the temperature of the oil the higher also the temperature

of the cell which was an undesirable feature. Svedberg therefore preferred to lower the temperature of the oil even if they would lose some speed. Thus they kept the oil at 16.4° , giving 42,000 r.p.m. and 26° in the cell. In order to reduce the temperature in the cell further they started building a new oil-cooler to get the oil down to 10° and hoped to reach 40,000 r.p.m. at that temperature. In Svedberg's eyes it was better to lose a little speed and have such a low temperature.²²⁴ The introduction of a new oil of a lower viscosity improved the situation somewhat and made it possible to run at 43,000 r.p.m. with 15° in the oil and 23.5° in the cell.²²⁵ A further development of the bearings made it possible to reach 45,000 r.p.m. with 23° in the cell.²²⁶

In order to increase the accuracy of the experiments Svedberg found it desirable to have the cell further removed from the centre of the rotor. At the periphery the rotor was thicker than was considered necessary and only two of the four cell holes were used. The general form of the rotor was not designed with the purpose of reaching the highest rotational speeds. The lubrication was considered unsatisfactory because oil from the turbines leaked into the bearings. Because of dirt from the pipes etc., the oil leakage caused the bearings to wear out rather quickly at high speeds. Taking out the rotor and bearings for regrinding implied taking apart the apparatus almost completely which was very laborious. These and a number of other undesired features made Svedberg decide to construct a completely new oil-turbine ultracentrifuge.²²⁷

After funds for building a new institute of Physical Chemistry had been granted by the Swedish Parliament, Svedberg started planning a laboratory specially adapted to the ultracentrifuges. The experience gained with the first ultracentrifuges could be utilized for a complete reconstruction of all of the equipment. After some difficulties with the hardening of the steel at the steel work, the oval rotor suggested by Lysholm and worked out by Boestad was ready for testing in July 1929. After the first test run with this rotor, Svedberg wrote Boestad that they had obtained 55,000 r.p.m. without the rotor flying into bits. He expected that when the bearings and journals would be run in, they might reach 60,000 r.p.m., provided the rotor did not explode. Five days later he wrote again to Boestad. He was very disappointed. It had been quite hopeless, with very bad convection currents. Svedberg wondered if he had been lucky with his first oil turbine centrifuge, where the difficulties with convection currents had been less serious. However, no matter how the situation with the oval rotor developed, they wanted to continue the preparations for installing the new centrifuge. In any event they wanted to build a new and more convenient centrifuge, easier to handle than the old one, even if the centrifugal field was not as strong as Svedberg had hoped. In a long letter Boestad tried to explain the cause for the convection and proposed

certain measures. In the following six weeks they exchanged no less than 18 letters concerning a series of new experiments with the oval rotor. Svedberg was still skeptical with regard to this rotor. Finally on 14 September he said it would be safer to make the calculations for a cylindrical rotor for the new centrifuge. As a secondary matter one could of course do calculations for an oval rotor as well.²²⁸ During the next few days Svedberg had great troubles with strong vibrations in the centrifuge. He wondered whether the rotor could be made selfbalancing, or whether special damping bearings could be made. After some further tests with the oval rotor during the fall of 1929, it was put aside. Svedberg believed that due to the oval shape of the rotor the exchange of heat between the rotor and the casing was worse than in the case of the cylindrical type and that thus convection currents could occur more easily.²²⁹

In the beginning of May 1930 the first parts of equipment for the new ultracentrifuge laboratory were ready and could be installed in the basement of the new institute under construction. One month later the new rotor with 180 mm diameter, called Rotor I, was ready (the old rotor was 150 mm diameter). However, it was not until January 1931 that an oil-pump, constructed especially for the new ultracentrifuge, was ready to be tested. Two months later the first test run could be made with Rotor I in the new ultracentrifuge laboratory.²³⁰ However, a number of difficulties turned up: difficulty in getting the new cylindrical rotor up to the desired speed of 55,000 r.p.m., too long an acceleration time and too much heating of the rotor. A number of test runs were carried out with various shapes of turbines and turbine chambers, and the bearings were reconstructed to give better lubrication. It was not until June, four months after Rotor I was first tested in the new centrifuge, that it could be run up to 50,000 r.p.m. When finally a new driving oil with much lower viscosity had been introduced in September, the speed could be increased to 55,000 r.p.m..

Rotor I was next used for a systematic study of convection currents in the centrifuge cell. Svedberg studied how they started and how to avoid them; which precautions were necessary for obtaining convection-free sedimentation, and which ones could be omitted. Most of these runs were made with the coloured protein phycocyan. He often emphasized how important it was at the beginning that most of the investigations in the ultracentrifuge were first carried out with coloured metal sols and later with coloured proteins. In this way the convection currents could often be discovered as soon as they started and their development could be followed in detail and related to the experimental conditions, such as temperature distribution and cooling of the system. The effect of changed cooling conditions could often be investigated immediately in an already spoiled experiment.²³¹ A few ordinary ultracentrifugations were carried out during the spring and early summer,

whereas most of the time was spent on extensive test runs. In the late summer of 1931 the new centrifuge was considered ready for routine work.

Also a new method was developed for converting the microphotometric records of the sedimentation pictures into diagrams giving the relation between concentration and distance from the centre of rotation. This new method was applied to both the sedimentation equilibrium and the sedimentation velocity measurements. Previously a concentration scale was photographed onto the plate carrying the sedimentation pictures by means of filling the cell in turn with a series of different concentrations of the solution studied, speeding up the centrifuge and taking pictures with the same times of exposure as for the sedimentation pictures. However, this procedure was rather tedious. The intensity scale necessary for evaluating the sedimentation diagrams was now constructed in the following way. A plane parallel quartz cell of 10 mm thickness was placed between the lamp and the centrifuge and filled with the solvent used for the solution which was being centrifuged. In the case of a sedimentation velocity determination the following procedure was used. At the end of the run, when a layer of pure solvent had been formed at the top of the column of solution the cell outside the centrifuge was filled in turn with a series of different concentrations of a suitable solution, say, potassium chromate, and pictures were taken on the plate which carried the sedimentation pictures. A curve giving the relation between distance from the centre of rotation and blackening was then constructed, as well as a curve giving the relation between distance from the centre of rotation and blackening in the sedimentation picture. For pairs of points in the two curves corresponding to equal blackenings the ratio of the concentrations should be equal. The relative concentrations in the sedimentation picture corresponding to the different distances from the centre of rotation could therefore be found from the first curve. The only assumption which had been made was that the light absorption constant in both the arbitrary solution and the solution centrifuged was proportional to the concentration. This condition was fulfilled for the solutions studied until then. In the case of a sedimentation equilibrium measurement where pure solvent was not formed at the top of the column of solution, the cell rotating in the centrifuge had to be filled with pure solvent when the pictures of the arbitrary solution were taken.²³²

On 4 November 1931 Rotor I exploded at 50,000 r.p.m. after having been used daily for four months at varying speeds up to 56,000 r.p.m.²³³ The explosion was ascribed to fatigue. According to Boestad the mistake was that the testing of Rotor I had not been carried out properly. The rotor should have been run at overspeed at an early stage in order to remove the stress peaks in the material, as was the usual practice with steam turbines. In general the highest speed should be

attained in the third or fourth run. The maximum test speed was first put 5% higher than the highest permissible speed for routine runs. Later on, after several rotor explosions, it was increased to 10%. For the normal sized rotors the speed of the first test run was taken so low that no permanent stretching of the principal diameter would take place, usually at 50,000 or 60,000 r.p.m. After the rotor had been up to the maximum speed, the permanent stretching generally amounted to a little less than 0.1 mm.

Immediately plans were made for the construction of a new rotor; some modifications based on the experience gained from Rotor I were introduced in Rotor II. The thickness of the rotor was reduced from 60 to 54 mm and the cell holes were reduced from 34 to 30 mm. These measures should increase the strength of the rotor. Three months after the explosion of Rotor I, the new rotor was tested. Rotor II was tested at a maximum speed of 63,000 r.p.m. corresponding to a centrifugal force 285,000 times gravity at the centre of the cell and was since then run regularly at speeds up to 55,000 r.p.m., which gave 218,000 times gravity. It was found rather difficult to construct cells which would withstand these forces but this trouble was overcome. A further improvement was made by making the outer cylinder of the cell of duralumin instead of steel which reduced the weight of the cell from 194 to 120 grammes. This reduced the stresses exerted by the cells on the rotor. The limit of the centrifugal force attainable was set by the breaking limit of the material of the rotor.²³⁴

Shortly before Rotor II could be tested, a tiny crack was discovered at the periphery of the old cylindrical rotor, just outside one of the cell holes, and this old rotor from 1926 had to be taken out of use immediately. The demand for centrifuge time, however, was great and Svedberg therefore decided to try once more the old oval rotor they had tried in the fall of 1929. But, whereas in 1929 this rotor gave a lot of trouble, it could now easily be run in the old ultracentrifuge equipment after a few minor adjustments. It had an effective radius of 50 mm and could be run at 55,000 r.p.m. corresponding to a centrifugal force of 170,000 times gravity. More information could also be gained about an oval rotor. It was successfully used for five months until the entire old ultracentrifuge with all its equipment was dismantled during the summer of 1932.²³⁵

Late 1930 Svedberg discussed the question of the orientation of the proteins in the ultracentrifuge. Tiselius pointed out that the important point would be the gradient of the centrifugal force. Therefore, the orientation would probably be the highest at or near the centre of the rotor. On the other hand the strength of the centrifugal field was the lowest there. They had been thinking of constructing a special centrifuge in order to investigate the phenomenon but this never materialized. Another interesting problem, in Svedberg's view, would be the orientation in a magnetic field. He thought, however, that the necessary equipment

would be extremely expensive. The magnetic field had to be both intense and of great extension in order to permit the introduction of the centrifuge rotor. The magnet they were building at that time for other experiments cost about Skr. 50,000 while they did most of the work themselves and some of the material was given to them by the steel-works. A magnet one quarter of the size planned was offered by Siemens in Berlin for 120,000 Marks and would probably cost \$ 100,000 in the US. Apart from the cost of the electromagnet the centrifuge itself should be of a very special design. The rotor should be made of non-magnetic material, for instance beryllium, and even in that case induction currents in it would probably cause trouble. Furthermore they would have to use the expensive type of turbine centrifuge because any electric motor type would be paralyzed by the magnetic field.²³⁶ Because of these foreseen problems the plan never got any further than the paper stage.

In the early summer of 1931 Svedberg moved over to the new Institute of Physical Chemistry where he got much more laboratory space. The reconstructed centrifuge laboratory had the great advantage of having the ultracentrifuge separated from the observation and control room by a heavy wall. This gave much better facilities for testing new rotor-types which, in the case of rotor explosions, could create hazardous situations. He also got more grants-in-aid, enabling him to appoint assistants and technicians. In the autumn of 1931 he got Inga-Britta Eriksson as his private assistant; she had been studying chemistry for some years at the university. She was first engaged in a study of a number of different phycocyanins and phycoerythrins prepared from materials collected by Svedberg at various places in Sweden and at the Stazione Zoologica at Naples, Italy. At this time Kai O. Pedersen, who had come to Upsala two years earlier, became research assistant at the institute. At the new institute the protein studies were intensified and they got more technicians to help with the running of the centrifuges, with the photometer registration of the photographic plates from experiments with the light absorption method, and later on with the measurements of the scales from exposures taken with the Lamm scale method. Before that time they had to do all that work themselves. They also had to do all the routine calculations of the experimental results. A few of them were assisted by their wives with parts of these jobs.²³⁷

The large scale work on the proteins (ultracentrifugation, diffusion, electrophoresis) demanded extensive computational work of a recurring nature. To facilitate this a calculating department was initiated at the beginning of the 1930s under the direction of Evald Hellman and with a staff of sometimes up to nine persons. Such a department was a rather unusual feature for a chemical laboratory. The department took charge of, among other things, the measurement of

photographic plates, the plotting of curves, and above all the extensive calculating work connected with the numerical treatment of the experimental data. For instance, it took a number of hours to 'calculate' one photographic plate in ultracentrifuge experiments.²³⁸ This work was carried out by specifically trained personnel and was so divided into different tempos that the results came forth as in a 'well organised industry with moving belt production'.²³⁹ The calculating department was of quite special value to foreign research workers and other guests, who were able to stay for only a short time at the institute. They did not need to devote themselves to the - especially for a beginner - laborious calculating work, which was carried out more rapidly and efficiently by the trained personnel.²⁴⁰

Increasing Resolving Power

In order to increase the accuracy of his experiments Svedberg was very anxious to increase the resolving power of his ultracentrifuge. The resolving power was proportional to f^2xh where f was the number of revolutions per second at which the rotor spun, x the distance from centre of rotation and h the height of column of solution in the cell. Insufficient centrifugal force, which was proportional to f^2x , might therefore be compensated by a high column of solution, and vice versa. Furthermore, it would be important if the rotor design could be improved to prevent the development of even minor permanent deformations during the lifetime of the rotor. The first rotors all became gradually deformed by use, making the cell holes slightly oval. Svedberg had long discussions with Boestad about the possibility of new rotor shapes, and Boestad calculated the advantages of the different designs. After the success with the old oval rotor, Svedberg agreed that Boestad could start calculations for an oval rotor. Svedberg hoped that this rotor could be run regularly at speeds up to 65,000 r.p.m. which would give a centrifugal force of 300,000 g at the centre of the cell.²⁴¹ The new Rotor III was ready to be tested at the beginning of April 1932. The rotor weighed 9.2 kg whereas the cylindrical rotor II weighed 11.1 kg. Because there was a high demand for 'centrifuge time' on the new ultracentrifuge it took six weeks before Rotor III was tested. Finally from 22 to 25 May 1932 it was tested in the following succession: 50,500, 60,000, 65,000, and 70,000 r.p.m. Because the maximum deformation of 0.04 mm corresponded to the stretching calculated the rotor was considered ready for routine runs up to 65,000 r.p.m. (300,000 g). It replaced Rotor II in the new ultracentrifuge, named A.²⁴² The success with Rotor III resulted in the total abandonment of the cylindrical rotor shape for all the following high speed rotors.

The cells had also been an almost permanent source of trouble. As the speed of the rotor went up it was more difficult to get them leak proof, the rock-crystal windows often cracked, the cells got deformed, and some cells were more apt to give convection current than others.²⁴³ As mentioned earlier, Svedberg spent much time studying the problems with convection. He found that the solution in the cell should be well insulated from the metal part of the cell. It was also important that the sedimentation did not start before the centrifuge had reached full speed. There should therefore be strong convection and mixing of the cell content during the acceleration of the rotor. By postponing the introduction of the hydrogen until just before the rotor reached full speed, and by controlling the cooling of the turbine oil according to a certain scheme, this problem was solved.

The difficulties with leaking cells at the top speeds were not really solved until the problem with the deformation of the cells had been solved. In the first ultracentrifuge cells the centerpiece with the sector was made of ebonite; for the low speed ultracentrifuges this worked fairly well. As the centrifugal field was increased to 200,000 g and to 300,000 g this became a serious obstacle. The introduction of bakelite and other synthetic resins was an improvement.²⁴⁴ The cells were also further improved by manufacturing all metallic parts from light metals which further reduced the weight from 120 to 79 grammes. This reduced the stresses on the periphery of the rotor and also made the crystal windows break less easily.²⁴⁵

The method of photographing the cell in such a way that the recorded photographic plate would reflect the concentration gradients in the cell still caused problems. Lamm encountered exactly the same problems with his diffusion apparatus and had in 1928 developed the so-called scale method based on light refraction occurring in a concentration gradient. This refraction method was more accurate than the old absorption method and it was the only possible one in case where the substance under study did not show sufficient light absorption. The problem with the scale- (or refraction-) method was that it was rather complicated and that it was more time consuming than the absorption method.²⁴⁶ Furthermore, the investigator had to decide upon the scale distance to be used, before the run was started, which limited the use of the method, as they would like to have a short scale distance at the beginning of the run, when the refractive index gradient was very steep, and one wanted a long scale distance at the end of the run. This was especially true for solutions containing many components such as serum.²⁴⁷ A solution was developed by Lamm in 1933 in which a narrow slit (0.25 mm) was placed between the light source and the cell. With some other optical requirements an image of this slit could be obtained. This image, which under well chosen parameters of the optical system, would be sharp, was displaced and broadened differently by different concentration gradients at different heights in the cell.

Thus the image gave information on the concentration gradient in a narrow band of the cell of approximately the same width as the slit itself. By moving the slit over the entire height of the cell the whole concentration distribution in the cell could be analyzed.²⁴⁸

In the summer of 1932, the first oil turbine ultracentrifuge installation (from 1926) was dismantled and the laboratory was completely reconstructed, enlarged and made to fit the new type. Because of the heavy demand on centrifuge time, a second new ultracentrifuge was installed, named B. Next, Svedberg wanted to test different types of steel and different rotor designs in order to find the ones best suited for high-speed centrifuge rotors. Since at that time very little was known about the behaviour of metals at such high rotational speeds, the results from the test runs helped in the development of a sounder base for the calculations of rotors of different design.

Rotor	Diam. (mm)	Shape	Cell hole (mm)	R (mm)	Steel	Maxim. (rpm)	Date	Explod. (rpm)	Date	Cell weight (g)
	150	Cylind.	34	52		43 000 48 000	21 May 1928	[Tiny crack 8 Jan. 1932]		220 177
	150	Oval	34	50		56 400	15 Oct. 1929			169
I	180	Cylind. A	34	65		56 400		50 000	4 Nov. 1931	194
II	180	Cylind. B	30	65	LLL49 400 B	63 000	4 Feb. 1932			120
III	180	Oval. A	30	65	LLL49 400 B	70 000	25 May 1932	[50 000	[1 Jul. 1940]	79
IV	180	Oval. A	30	65	CN 2 400 B	65 000	3 Nov. 1932			79
V	180	Oval. A	30	65	CN 2 400 B	70 000	6 Jan. 1933			79
VI	180	Oval. B	30	65	LLL49 400 B		30 Mar. 1933	58 000	30 Mar. 1933	57
VII	180	Oval. B	30	65	CN 2 400 B	78 000	5 May 1933			57

Table 2.1

Rotors tested from 1926 to 1933 (Pedersen, 1976, p.12).

On 3 November 1932 Rotor IV was tested in the B-ultracentrifuge. It was of the same design as Rotor III, the steel was, however, somewhat less hard. It was tested successfully at a maximum speed of 65,000 r.p.m. Two months later an identical rotor, V, was tested, this time up to 70,000 r.p.m. It was used for routine runs in the B-centrifuge for almost 3 months until a new differently shaped oval rotor was ready to be tested. This Rotor VI was made of a hard steel similar to rotor III. It exploded in the first test run at 58,000 r.p.m. The reason for the failure proved to be a so-called "pipe" in the centre. Such 'pipes' were sometimes found in the upper end of an ingot, especially in its central part. All the following

materials for the rotors were therefore taken from the periphery of the lower end of the ingot. Just over a month later the next rotor, VII, was ready to test. It was of exactly the same design as the exploded Rotor VI, but Rotor VII was made of the same steel as Rotor IV and V. It was successfully tested at 78,000 r.p.m. and was since run several times at 75,000 r.p.m. (400,000 g).²⁴⁹ Most frequently it was run at 60,000 r.p.m. There was a problem with vibrations with this rotor; they set in somewhere above 30,000 r.p.m. and disappeared after 44,000 r.p.m., from where the centrifuge ran smoothly. On deceleration strong vibrations set in around 44,000 r.p.m. and disappeared suddenly at 40,000 r.p.m.²⁵⁰ Table 2.1 gives an overview of the rotors tested in the period 1926-1933.

His scientific interest made that Svedberg was continuously trying to modify the ultracentrifuge. This was in a certain sense counterproductive because he could not use the apparatus for scientific experiments at times that certain parts were being modified. As he wrote Nichols in 1933: '(...) we have been very busy in the laboratory with the centrifuging and always trying to improve the machinery'.²⁵¹ The dilemma between further development and scientific experiments was solved by installing a second ultracentrifuge in 1932 so that at least one would be available for scientific research all the time. Svedberg's scientific interest made him want to push the overall performance of the apparatus to the limit. It appeared that there was not just one aspect that was lagging behind, or one 'reverse salient' to use Tom Hughes vocabulary (see Chapter 1), but there were many aspects of the apparatus that caused trouble. By solving all these problems one at the time the apparatus became a kind of 'patchwork' of technologies kept together, which were modified by Svedberg's scientific interest in proteins. Existing technologies were also modified. Svedberg himself once remarked that the camera units 'differ in construction completely from what is usually called a camera'.²⁵² Late 1933 Nichols and Kraemer got interested in obtaining an ultracentrifuge for the DuPont company in Wilmington (see Chapter 6) and asked Svedberg a number of questions on how they would have to construct the various parts. In his answer Svedberg gave a beautiful picture of where his approach had led him:

"I am afraid I shall not be able to give you a full answer. As you know we have developed this machinery gradually, fitting the different units together and we do not really know all the characteristics which you want information about. (...)

The two aggregates which we are now using are, I believe, quite satisfactory with regard to general machinery. The operation is so simple and reliable that equilibrium runs can be made without difficulty. What we are still working on is the rotor and the cell construction. It is a great advantage, however, that no changes are required on the general machinery (compressor, motor-cooler, filter, centrifuge casing) for different rotors and different speeds. When a rotor of smaller diameter is used a sort of collar is fixed in the casing to fill out the space and other turbine chambers and bearings are put in. The high speed ultra centrifuge is now quite a different thing from what it was at the time when

Burton was here, especially with regard to easy handling. But this is the result of proper adjustment of the different parts of the machinery most of which has been done by trial. It will be rather difficult for us to finish all the data necessary for you in order to built such important parts of it as the compressor. I do not doubt at all that you could do it as well as we can but we simply have not got the data. The compressor has been changed several times to get it to fit our requirements. We would have to carry out a series of measurements on the machinery in order to collect this information and that would mean stopping our investigations for some time. I have planned to publish a description of the new type of oil-turbine ultracentrifuge but this has been postponed in the hope that still more improvements could be made. For this publication I would need exactly the kind of data you want to have and we will therefore have to collect them sooner or later but it will take a considerable time and it is difficult to get it now because of other work that we are doing.

(...) We have tried several kinds of pumps without success. The Imo oil pump we have considered but not yet tried since a similar one did not give good results. I do not think there is a pump on the market filling our requirements. The compressor which we now use was designed especially for this purpose and has given excellent results. I don't think it is the only solution possible but I am anxious to get your equipment so that it will work, and I think it is better to stick to the well known machinery which has proved satisfactory here during several years intense work than to start experimenting with unknown things. One of the important points about the compressor for the centrifuge is that it must not let in any air and our construction is quite safe in this respect. Burton can tell you about the endless trouble we had with the domestic pump which was used for the first high-speed ultra centrifuge. After you have got to know this equipment through handling it I trust you will be able to introduce improvements but for the time being I am inclined to think that it would be better to copy our installations as closely as possible.²⁵³

With patchwork apparatus kept together by experience, the problem clearly is that the whole set-up could only work satisfactorily within very narrow boundaries. In a later letter to Kraemer, Svedberg warned him to follow his advice very closely because otherwise they might be forced to rebuild the whole thing later on which would cost many times the amount of money they tried to save by applying certain modifications.²⁵⁴

Further Protein Studies

In the beginning of 1932 Astrid Hedenius finished her study in biology, zoology being the main subject. She intended to be a teacher but in those days it was hard to get such a job as a teacher. When one day she met Tiselius he suggested to her to go to the institute of Physical Chemistry where they needed a secretary. She was given the job but it appeared that in the new building there was no special room for a secretary so her office was housed in the instruments store room. Her job was to handle all the correspondence either by phone or typing letters, make arrangements for foreigners like renting apartments, helping them with their shopping because they did not understand Swedish, etc. After a while, however,

Svedberg found out that she was a biologist and suggested that she participate in his investigations. Svedberg had the idea to go through all of the animal kingdom, taking blood and sedimenting the respiratory proteins. Thus Astrid Hedenius became an assistant instead of a secretary.²⁵⁵

An advantage of the respiratory proteins was that they were usually coloured and that they were the only distinctly coloured substances in the blood of the animals, which meant that they could often be run in the centrifuge without being isolated from the blood. This was just diluted with 1% NaCl solution to a suitable concentration before being run in the centrifuge. The sedimentation could be followed visually with the simple light absorption method. Svedberg considered it a great advantage to study the proteins under conditions as nearly native as possible and without first having been precipitated with salts.²⁵⁶ He wanted to get proteins from as many different groups of animals as possible. Much of the material for the protein studies was obtained on trips to the woods and lakes in the surroundings of Upsala or further away. All kinds of snails, worms, snakes, crayfishes, and tiny creatures were collected and brought to the laboratory. In the summer Svedberg gathered material near his cottage at the west coast of Sweden as well as at the nearby Marine Zoological Station at Kristineberg. Some material, considered important in the systematic study, could not be found in Sweden and was collected on his journeys abroad. Thus, in the autumn of 1931, he obtained blood from *Octopus vulgaris* when he visited Naples, Italy. In 1933 he got various samples of haemocyanins from the Oceanographic Institution at Woods Hole, MA, while being in the USA. Many of the proteins studied were from closely related species and had very similar sedimentation coefficients. Important questions for Svedberg were: Were they identical? Were the values for the sedimentation constant identical? Were the chemical compositions of the proteins from related species identical? The first question was studied by means of the so-called 'mixture test'. The second question was determined by electrophoresis experiments. In the mixture test two proteins were mixed in about equal proportions and centrifuged. If only one boundary appeared in the sedimentation diagram, the two sedimentation constants were taken to be identical.²⁵⁷ During the years 1932-34 about one hundred different respiratory proteins were collected and examined at Upsala. Their sedimentation coefficients were found to belong to a small number of groups, whereas their electrophoretic behaviour varied from species to species even between closely related ones, which meant that they were chemically different. Referring to the small number of sedimentation constants found, Svedberg said:

"It is obvious from these regularities that biological kinship is usually accompanied by identity in the sedimentation constant. On the other hand, the number of different sedimentation constants observed is so small that the same constant must with necessity occur in more than one animal class and in

respiratory proteins containing different active groups. It seems that only a few molecular masses are stable, and it would depend upon the composition of the molecules with regard to various amino acids whether one or the other possibility is realized. The constancy of the molecular weight within a certain animal group would then be a measure of the similarity of certain chemical processes leading to the formation of the respiratory protein."²⁵⁸

Later in the same paper Svedberg stated:

"One gets the impression that the protein molecules are built up by successive aggregation of definite units. It seems that the higher the molecular weight, the fewer are the possibilities of stable aggregation. The steps between the molecular weights, therefore, become larger and larger as the weight increases."²⁵⁹

Svedberg also pointed out that for example the Isoelectric Points (IP) of the blood pigments of the invertebrates were all very low compared with the IP of haemoglobins, the respiratory proteins of the vertebrates. He stated that "The situation at the isoelectric point is therefore to a certain degree a measure of the kinship." He summarized the results as follows:

"The sedimentation constant and the molecular weight may be used as a group characteristic, the isoelectric points as a species characteristic."²⁶⁰

This work on the influence of electrical charge on the sedimentation velocity was carried out primarily by Tiselius. Especially for the smaller particles such charges had an effect of increasing the friction which caused the sedimentation to slow down. These charges could be (partly) neutralized by using appropriate salt-concentrations.²⁶¹ An extensive study of the pH-stability range of haemocyanins from different classes of animals showed that on changes in the pH they could dissociate or associate to molecules of the mass found for haemocyanins from other classes of animals. In 1936 Svedberg and Eriksson-Quensel wrote:

"At certain critical pH-values a profound change in the number and percentage of the components takes place. The shift in pH necessary to bring about the reaction is not more than a few tenths of a unit, consequently the forces holding the dissociable parts of the molecule together must be very feeble. This fact makes it all the more surprising that an equal backwards shift in pH does really cause an association of the parts to exactly the same molecule. For this reason it is justified, we think, to use the term molecule for the haemocyanin particles despite their enormous size. Their mass cannot be changed continually as in the case of an ordinary colloid particle and they have a finite stability range with regard to the surroundings. The haemocyanin particle, therefore, most probably possesses a definite structure."²⁶²

At the beginning of the thirties, quite a number of scientists brought up in the tradition that 'proteins were very complicated substances' had difficulties in

believing that the soluble proteins were so well defined with regard to size as found by Svedberg in his ultracentrifuge work. Furthermore, when Svedberg elaborated his idea about 'a periodic system for proteins', namely that the molecular weights of the higher groups could be expressed as simple multiples of those for the lower groups, the skepticism became still more pronounced. Some chemists privately expressed their severe doubts about the findings of Svedberg, and some were wondering whether it could be some kind of artefacts that Svedberg and his co-workers were measuring. However, investigations in other laboratories at about the same time confirmed that the proteins were large, well defined molecules. J.H. Northrop had crystallized pepsin and had made a very thorough study of this crystalline enzyme. He showed that its composition, proteolytic activity and optical activity remained constant through seven successive crystallizations. Studies on the solubility of the crystalline material in a number of salt solutions and of its diffusion rate gave no evidence for the theory that it should be a mixture or a solid solution. Finally Northrop came to the conclusion that pepsin was a protein, and that its molecular weight was 35-36,000.

Svedberg became most enthusiastic when he learned about Northrop's results and in 1933 John Philpot came to Upsala to study pepsin in the ultracentrifuge. He prepared the enzyme according to Northrop's method and got beautiful crystals; the pepsin appeared homogeneous in the ultracentrifuge. He was very proud of his crystals and when he left, he took a test tube with these pepsin crystals in their mother liquor back with him to England. Some months later J.D. Bernal and Dorothy Crowfoot (1933) published a 'Letter' on 'X-ray photography of crystalline pepsin', where they described their experiments with Philpot's crystals. They wrote:

"Not only do these measurements confirm such large molecular weights, but they also give considerable information as to the nature of the protein molecules and will certainly give much more when the analysis is pushed further. (...) From the intensity of the more distant spots it can be inferred that the arrangement of atoms inside the protein molecule is also of a perfectly defined kind, although without the periodicities characterizing the fibrous proteins."²⁶³

This first successful X-ray study of a water soluble globular protein gave an independent confirmation of the proteins being well-defined high molecular weight substances. When Staudinger had proposed the existence of macromolecules in the 1920s many organic chemists disbelieved his claims. They held the opinion that forming a crystal was the only proof of uniformity of molecular weight. Now the first X-ray diffraction studies of proteins gave nice patterns indicating a well-ordered structure. This stimulated the idea that proteins indeed were well-defined molecules, an idea which soon became generally accepted. All the new findings

about the proteins as well-defined molecules gave a strong impetus to new studies on proteins abroad and at Upsala. It also resulted in an increasing number of scientists coming to Upsala to work with the ultracentrifuge.²⁶⁴

In May 1930 Svedberg received a letter from Herbert Freundlich in Berlin asking if it would be possible to send one of his students, Paul von Mutzenbecher, to Upsala to study some serum proteins. They had developed a new method for preparing these proteins which they believed was a very 'mild' fractionation method and therefore thought that the proteins obtained were native and had a uniform molecular weight. They would like to have these proteins studied in the ultracentrifuge. Svedberg himself was very interested in this problem as he and Sjögren had already studied albumin and globulin prepared by salt fractionation of horse serum.²⁶⁵ Von Mutzenbecher came to Upsala in the autumn of 1930 and made a number of preparations finding that the pseudoglobulin as well as the euglobulin obtained were polydisperse,²⁶⁶ just as Svedberg and Sjögren had found earlier. During Von Mutzenbecher's stay at Upsala Svedberg discussed the possibility that Von Mutzenbecher could return to Upsala and study native serum, when the new high-speed ultracentrifuge would be ready for routine runs, hopefully at 200,000 g. Von Mutzenbecher was granted a Rockefeller Fellowship and returned to Upsala in October 1931. A month later Rotor I in the new ultracentrifuge exploded and Von Mutzenbecher had to start his experiments with serum in the old centrifuge. The centrifugal field appeared to be too weak to observe a sedimenting boundary. When the new rotor was ready for centrifuge A in March 1932, giving a field more than twice as intense as in the old centrifuge, the sedimenting boundary could be resolved. Now the problem of the independent existence of the albumin and the globulin in serum turned up to be much more complicated than anticipated. As long as the centrifuged solution was dilute, the concentration of the albumin component calculated from the sedimentation diagram corresponded fairly well with the value from chemical analysis. For more concentrated solutions or in undiluted sera the concentration calculated was considered to be too high. In the case of human serum the situation was still more complicated than for the horse serum. Besides the apparent stronger increase in the concentration of the slower sedimenting albumin after increase in the total serum concentration a new 'component', sedimenting slower than the albumin, was observed in the sedimentation diagram from the more concentrated serum solutions. Von Mutzenbecher assumed this component to be a degradation product from serum proteins.²⁶⁷ Before Von Mutzenbecher left Upsala in March 1933, he and Svedberg sent a note to *Naturwissenschaften* where they stated that albumin and globulin in serum existed as free molecules and not combined to some kind of a serum molecule.

While Von Mutzenbecher was still working at Upsala, Svedberg got a letter

from A.S. McFarlane asking for permission to come and work in Svedberg's laboratory for a period of six months to one year, assuming he got the fellowship he had applied for. McFarlane was in charge of the biochemical laboratories of the Glasgow Royal Cancer Hospital, and his main interest was in chemical pathology. He had been studying particle sizes of proteins and viruses by means of graded filtration through collodium membranes; now he wished to acquire first-hand experience of the ultracentrifuge technique for measuring the size of protein molecules in the hope of applying it at a later date to the problems presented by pathogenic viruses. Svedberg answered that he should be glad to receive him at his laboratory and added that the problems mentioned in the letter were of great interest and were in line with the work going on at the laboratory. Svedberg was anxious that Von Mutzenbecher's studies should be continued and his conclusions further tested. After his arrival in Upsala in September 1933, McFarlane made preparations to start directly on a study of normal sera. From Von Mutzenbecher's work it was quite clear that the sedimentation studies on serum had to be carried out by means of a refraction method and not by the light absorption method. On the other hand the scale method with a fixed scale, as used by Von Mutzenbecher, was too inflexible; an improvement in the method of observation was therefore considered a most urgent task. Hitherto it had been necessary to select a certain scale distance before the run was started and keep that scale distance fixed during the entire run. The difficulties were overcome when Lamm proposed the use of a scale projecting system whereby it became possible to change the scale distance during the run and at any moment select the most suitable one. It even became possible to project the scale image very close to the middle of the rotating cell so that even undiluted serum could be studied. McFarlane made a comprehensive study of the problems connected with ultracentrifugal studies on normal sera and on a few pathological sera. After his stay at Upsala he moved to London where he was going to continue his studies as a Beit Memorial Fellow at the Lister Institute of Preventive Medicine, where plans had been made to set up a department for biophysics. He planned to start with electrophoretic studies on serum proteins as a supplement to his ultracentrifugal studies on these proteins.²⁶⁸

Another line of experiment was started in 1932. In the beginning of the 1930s there was a lively discussion about the concept of macromolecules mainly based on the work and propositions made by Hermann Staudinger. The debate also included the applicability of various methods for determination of molecular size because a knowledge of this parameter would be a conclusive proof of the existence of threadlike macromolecules in which the repeating units were linked together by covalent bonds. Staudinger expressed some doubt about the use of the osmotic method because of the low osmotic pressures. He was also critical of diffusion measurements. About the use of sedimentation in centrifugal fields he stated:

"Die Methode von Svedberg, die Teilchengröße von Kolloiden mittels der Ultrazentrifuge zu bestimmen, dürfte zur Bestimmung des Molekulargewichts hochmolekularer Stoffe, deren Teilchen Fadenmoleküle sind, ebenfalls nur mit Vorsicht angewandt werden."²⁶⁹

The reason for this view was mainly based on the opinion that threadlike molecules due to their large surface area would exhibit such a high frictional resistance that the movement of these molecules would be extremely slow even in very strong centrifugal fields. Furthermore the velocity would depend upon the orientation of the molecules with respect to the field. Hoping to clarify the situation, Rudolf Signer and David Gross in October 1932 began at Svedberg's laboratory an investigation into the sedimentation behaviour of various polystyrene samples prepared and viscosimetrically characterized by the Staudinger school. The results of this work were collected in three papers; the first one treating the sedimentation velocity properties of polystyrene²⁷⁰, the second reporting molecular mass determinations from equilibrium sedimentation²⁷¹ and the third exploring the ultracentrifugal separability of polystyrene fractions.²⁷² This work introduced new problems with respect to the cells because the substances investigated necessitated the use of organic solvents which were much more volatile than water. This created new problems making the cells tight for these substances and also because they attacked some of the materials used in the construction of the cell. Evaporation of the liquid also created problems because it gave rise to convection currents.²⁷³

From 1925 onward Svedberg had used the sedimentation equilibrium method in which the molecular weight of a dissolved substance was obtained by a combination of sedimentation and diffusion measurements and for many years diffusion coefficients were calculated from the broadening of the boundary in sedimentation velocity experiments. In 1932 Tiselius and Gross began separate diffusion experiments in which the blurring of the boundary was studied by a light absorption method. This renewed interest in the determination of the diffusion constants of the proteins was triggered by a considerable improvement in the accuracy in the sedimentation equilibrium measurements. Extensive replications with the new apparatus had shown that some of the earlier molecular weight values were too low. In 1934 Svedberg published an article in the *Kolloid Zeitschrift* containing a table on the molecular weights of proteins in which in some cases new values were introduced. The discrepancy which previously existed between molecular weight values calculated from sedimentation equilibrium determinations and from the combination of sedimentation velocity and diffusion measurements had now vanished.²⁷⁴ Svedberg considered it therefore important to carry out diffusion determinations on proteins and combine those with their sedimentation velocity

values. This method was considered to be the most reliable existing.²⁷⁵

Putting more and more emphasis on the study of proteins made it more difficult for Svedberg to get his results published in chemical journals. In a letter to Laura Krejci, who had worked with him and had encountered the same problem, he wrote:

"It seems to be rather difficult to get things published in America just now, at least in the leading periodicals. I for my part have altogether given up the thought of publishing any more protein papers in the *Journal of the Amer. Chem. Soc.* I cannot help feeling it a little humiliating to have to ask for it like asking for a favour. Dr. Redfield has promised to publish our zoo-chemical papers in the *Biological Bulletin*. As for the other protein papers I shall probably have them published in England for the time coming. Tiselius, Pedersen and Lamm publish their work in the *Zeitschrift für physikalische Chemie* (in Germany); we get things printed in about three weeks there. In case you find Lamb too difficult try '*The Journal of Biological Chemistry*'; if you write to Dr. Edwin Cohn, Harvard Medical School, Cambridge. Mass. about it, I think he will help you out.; please, mention that I have advised you to write him."²⁷⁶

Rockefeller Foundation Grants

As has been mentioned already, Svedberg had obtained a large grant from the International Education Board of the Rockefeller Foundation for the instrumentation of his new laboratory. In the early 1930s he wondered whether they might be willing to finance his further investigations. The Rockefeller Foundation was one of the institutions funded by John D. Rockefeller Jr. and Sr. which were to promote education and research. On 14 June 1901 the Rockefeller Institute for Medical Research was incorporated and its overall goal was to catch up American backwardness in Medical Science.²⁷⁷ The institute started by creating a number of scholarships and fellowships to be used in existing laboratories throughout the country. This program diminished in significance after 1903 when the institute's own laboratories were opened.²⁷⁸ When the Rockefellers were thinking over the establishment of an institute for medical research they were at the same time interested in stimulating education in general. From this grew the 'General Education Board', founded in 1903, which was devoted to the promotion of education throughout the United States. In 1910 the 'Rockefeller Foundation' was incorporated which was to promote a wide range of activities in science, the arts, agriculture, citizenship, and civic virtue throughout the world. Out of the General Education Board came in 1923 the 'International Education Board' and in 1928 these boards were merged with the Rockefeller Foundation.²⁷⁹

May 1931 Svedberg came to Paris to deliver lectures at the Sorbonne and on the occasion called at the Rockefeller Foundation's European Office where he spoke to Lauder W. Jones, Associate Director of the Foundation's Natural Science

Program. He brought with him pictures of the new Institute of Physical Chemistry, together with photographs of some of the interior equipment of the rooms of the Institute. He reported that the Institute and most of the equipment were completed and they were carrying out experiments in practically all phases of his work. He said that for the current year, the University had granted him Skr. 35,000 definitely for support of research and that he had been receiving from the Andersson Foundation Skr. 10,000 annually, a grant for a period of three years which would terminate at the close of the current year, but might possibly be renewed. Svedberg pointed out that at the time a large number of assistants were carrying on research work in his institute. Furthermore, from time to time visiting scientists from other countries desired to come to his laboratory, because of the opportunity to use the ultracentrifuge. As a result of this the demands on the staff were very great: the assistants and the mechanics of the Department had to take care of the complicated machinery of his laboratory if it was to be available for research. Therefore, Svedberg argued, it would be necessary for the successful carrying on of investigations to increase the number of technical assistants and mechanics. He inquired whether the Rockefeller Foundation would be willing to make a contribution towards the increase in the staff. He pointed out that with the addition of one technical assistant and one mechanic, the annual expense would be \$ 2,000, but that it would be more desirable if two technical assistants and two mechanics were appointed, which would increase the annual expenses by \$ 4,000. At this point of the meeting, Jones called Doctor Daniel P. O'Brien in to hear from Svedberg concerning the investigations which had been in progress in his laboratory bearing indirectly upon medicine. Svedberg reported that he had investigated the problem of the molecular weight of insulin with the ultracentrifuge. This had been carried out at the request of Professor Abel of Johns Hopkins, who had supplied him with samples of crystalline insulin. Svedberg's methods indicated a value of approximately 35,000 which placed insulin definitely in a class of compounds to which egg albumin belonged. Svedberg said that the inference to be drawn from this result, which was unexpected, was that the problem of synthesizing insulin was not so simple as had been expected, that the problem resembled somewhat in difficulty that which would be met in trying to synthesize a complex albumin molecule. The result of his experiments, however, indicated that insulin was composed of definite molecules. Svedberg said that they were now working on similar experiments with pepsin and expected to undertake investigations with other substances of interest biologically.

Jones recommended that Svedberg would formulate more definitely the request, in which he would outline a number of his investigations, particularly with respect to the medical aspects. Furthermore they agreed that he would endeavour to obtain if possible some assurances of partial assistance from other sources in Sweden

before he presented his request for assistance to the Rockefeller Foundation.²⁸⁰ Shortly thereafter Svedberg applied for a grant of \$ 12,000, to be utilized over a three year period. When O'Brien forwarded the request to the Trustees of the Rockefeller Foundation he strongly recommended it. He felt that this undertaking would be a sound investment and would enable a distinguished leader to accomplish discoveries of importance to medicine.²⁸¹ December 1931 the Trustees awarded the grant. The appropriation was based upon the following considerations:

1. The Swedish government and the Foundation itself had already given large support to Svedberg.

2. Svedberg was considered to be one of the outstanding figures in the field of physical chemistry in Europe.

3. It was expected that a grant of 10,000 Swedish Kroner a year would be furnished by the Andersson Foundation for a three-year period to take care of current expenditures involved in his investigation.

4. There was urgent need, however, of additional assistants and mechanics in connection with operation of certain special equipment in the Institute. The technique of the ultracentrifuge was very complicated and the apparatus difficult to manage. Each operation took from two to seventy hours and during operation the apparatus had to be constantly watched. The enormous forces involved (for the new oil-turbine-centrifuge 225,000 the force of gravity) required very careful handling of the machinery.

5. The laboratory was used by investigators from various medical faculties, who came with their protein preparations in order to utilize the ultracentrifuge in the solution of their medical problems. The number of these workers had created a burden which could not be borne unless additional personnel was provided to attend to the preparation of material and the running of the machinery of the ultracentrifuge. It was seldom possible for the medical workers (and it was usually unnecessary) to spend the long period of time which would be needed to acquire the technique of handling the complicated machinery.

6. In order to operate the present installation consisting of three smaller and two larger ultracentrifuges it was essential for Svedberg to add to his staff two assistants and two mechanics at an annual salary of \$ 1,000 each. It was expected that at the end of a three-year period local support for this expense would have been secured.²⁸²

In 1931 Warren Weaver had come to the Rockefeller Foundation as the director of the Natural Sciences Division. Weaver wanted to create a 'new biology' which should be inspired by the application of techniques of molecular physics and chemistry and by the standards of experimental rigour of the physical sciences. Weaver's program took various names - 'vital processes', 'psychobiology',

'experimental biology', and 'molecular biology' - but the idea behind it was constant.²⁸³ Svedberg's work with the ultracentrifuge fitted this new program very well. In May 1933 Weaver visited Svedberg at Upsala. At that time, a group of about twelve were actively engaged in research under Svedberg. Weaver wrote in his diary that the institute, in the completeness and character of its equipment, was a 'scientist's dream'. Svedberg reported some of the results they had recently obtained in the study of the physico-chemical properties of the respiratory proteins of animal species. In a systematic study of blood pigments, he had measured over eighty species. Essentially he made two measurements, that of sedimentation constant (ultracentrifuge) and that of iso-electric point (cataphoresis). Those two physical quantities appeared to be remarkably constant for a given species. The same snail, for example, collected in Sweden, Germany, or France, would approximately give the same distribution of sedimentation constants, just as if these proteins were limited to a relatively few combinations of molecular weight. The iso-electric points, however, varied continuously, and were considered very useful in identifying varieties of species. Svedberg, for example, had determined in this way a difference between two variants of what was considered to be one variety of snail. Upon Svedberg's determinations biologists recognized them as two entirely different species. These constants seemed to furnish a quantitative scale for the evolutionary process. Certain very low fish forms, for example, gave values nearer to that for worms than to that for the higher fishes.

Svedberg showed Weaver his four smaller ultracentrifuges, capable of setting up fields of about 5,000 times gravity, as well as his two large ultracentrifuges of the new type, with rotors making 78,000 r.p.m and setting up a field of 400,000 times gravity. These rotors, due to a new design just completed, might be run about 200 times before fatigue had destroyed the quality of the chrome-nickel steel of which they were constructed. According to Weaver this work represented an unusual combination of mechanical genius of patience and experience, and of imagination. It was one of the most interesting laboratories he had ever visited and it certainly rated high in a vital process program that Weaver anticipated.²⁸⁴

Two months later Svedberg was visited by Alan Gregg from the Foundation. Gregg mentioned the possibility that the Rockefeller Foundation would be interested in further aid to Svedberg's application of physical methods in the study of problems in the biological field. Svedberg replied that this would be very important for him in order to be able to continue his present studies after the present grant would terminate in December 1934. Both agreed in this respect that a slightly longer period of help would be more effective as it would facilitate Svedberg a better planning of his work.²⁸⁵

January 1934 Svedberg sent Lauder Jones of the Rockefeller Foundation a 20-page report on the investigations he had carried out under the Foundation's grant,

also including statements on the necessity of further grants in 1935. The new large electromagnet which was being built and towards which the Foundation's International Education Board had contributed \$ 10,000, would be completed by the end of the year. Under these circumstances, Svedberg argued, an extension of their activities to comprise investigations in very strong magnetic fields would be very much desired. Thanks to the generosity of the Rockefeller Foundation, the Nobel Foundation and the Andersson Foundation as well as the Swedish Government their institute had uncommonly good equipment, but, he continued, in order to utilize their machines and instruments and preserve them in good working condition, numerous additional personnel would be required, especially in view of the rather complicated nature of some of the apparatus. The report described his apparatus and included various photographs of it. He also included a list of about 25 publications of research on high molecular compounds carried out in 1932 and 1933. In order to be able to continue his work on high-molecular compounds at the present level he argued he would need one research assistant, two technicians and four mechanics. In order to take on new lines of attack one additional research assistant and one extra technician would be needed. This would amount to Skr. 28,000 or about \$ 7,500.²⁸⁶ Jones forwarded Svedberg's report to Weaver at the Foundation's central office in New York. Weaver's reaction to the report was:

"I have been much interested in examining the report which he has sent. This seems to me to be an extraordinarily interesting and promising program which is clearly at the heart of our present interest. The facilities in Prof. Svedberg's laboratory are, I suppose anyone would agree, quite unique for work of this sort, and the available personnel seems to me to measure up entirely adequately to the opportunities. I feel that we should not only support Prof. Svedberg's request, but that this is one of the rare situations where we are justified in indicating our interest in an expansion of program. I do not mean by this that I think we ought to urge Prof. Svedberg to do more work of just the same sort, but it does seem of great potential significance that he broaden his attack. I am therefore particularly pleased with the suggestions in his present report. It would seem to me of extraordinary interest if Prof. Svedberg would eventually broaden still further so as to include various applications of spectroscopic methods. In this way the unusual resources of Siegbahn's laboratory could perhaps be brought to bear on problems of fundamental biological interest."²⁸⁷

April 1934 Svedberg was visited by W.E. Tisdale from the Foundation. Svedberg was very skeptical concerning possible cooperation with Siegbahn. Regarding their work on proteins he informed Tisdale on recent work done by McFarlane as a continuation of work done by Von Mutzenbecher in 1931-32. McFarlane, under a Scottish fellowship, took blood serum and by centrifuging had shown a uniform size of blood corpuscles in normal blood. If, however, the blood giver had had horse serum injections, it appeared that there were 2, 3 or 4 different sizes of blood corpuscles. McFarlane had tried the same technique on cancer patients and patients

suffering with other diseases and had found that blood serum from these showed also more than one size of blood corpuscles. Further work would be on the study of normal blood from the umbilical cord of newly born and more controls of blood from infective cases from cancer and from kidney diseases. McFarlane was just beginning his work and had very few tests completed, but Svedberg felt that the possibilities opened up in this field by McFarlane were the most important that had happened in his laboratory for a long time. In his view it brought up the possibility of the necessity for this type of analysis in medicine. After his work in Upsala McFarlane would go to the UK to work in the Lister Institute of Preventive Medicine. Svedberg thought that it would be very fruitful to set up an ultracentrifuge apparatus in the UK and that the Lister Institute would be the most appropriate place to locate it, especially because McFarlane would go there. The possibilities of the ultracentrifuge in the field of immunology and blood serums might be of great importance, because the determinations of proteins (albumin and serum globulin) were more accurate and much more rapid than the usual chemical methods permitted.²⁸⁸

Svedberg also raised the point of the possibility of further grants. For 1934 he got Skr. 10,000 from the Nobel Foundation and Skr. 8,000 from the Andersson Foundation. From the Astra Co. he got Skr. 10,000 for a period of 3 years. The University budget was Skr. 35,000 but that included teaching and other maintenance expenses. He presented a request for approximately \$ 7,500 to the Rockefeller Foundation, but felt that that was a bare minimum which he needed. Svedberg and Tisdale discussed the possibility of his developing different lines in which his technique could be applicable. Svedberg showed his enthusiasm over this possibility, but felt then his budget was too limited to think seriously on this question. He suggested that if the Foundation could give him \$ 10,000, it would permit him to do a great deal more than he was then doing. For example he mentioned that he had only two cataphoresis set-ups, and he had no means of either raising or having raised for him the pure strains and hybrids which he would like to go into from the genetic as well as chemical point of view.²⁸⁹ During this visit Tisdale also discussed with him a centrifuge which he had seen in the laboratory of Jesse W. Beams in Charlottesville, Virginia in which he was interested because it was so extremely cheap (see Chapter 3). Svedberg, however, explained away all possibility of its replacing his machine. Svedberg's argument was based on the assumptions that the inhomogeneity of the centrifugal force should not be greater than 20% and that the minimum length of the column of solutions should be 5 mm. In view of Svedberg's experience Tisdale felt that he could 'not do other than believe' Svedberg's judgement and wrote Weaver that it seemed that the spinning top would have a very limited usefulness. He explained that he was sure that Svedberg was not blindly limiting himself to the machine

which he had developed, because he had investigated the limits and possibilities of the top type of centrifuge Beams was working on.²⁹⁰

Shortly after his visit to Svedberg Tisdale wrote Warren Weaver that, when he had requested an amount of \$ 7,500 which he had asked them to contribute to him for 1935, he had limited himself in his request to a bare minimum. Tisdale suggested that they should think of his project in terms of not less than \$ 10,000 for the year 1935. He mentioned that it was relevant in this connection that Svedberg had just uncovered a new phenomenon which concerned the size of blood corpuscles in the blood stream and seemed to offer large possibilities. Tisdale continued stating that Svedberg had also in the back of his mind a problem in genetics in which he would study the nucleic acid in the eggs of pure strains and in their hybrids. There were several problems with possibilities in immunology and serum studies that have much to commend them. Tisdale spoke off Svedberg's 'rather fertile imagination' and that he had a fairly good group of young people with him to contribute still further, so that he thought a little more than this absolute minimum demand would be money most advantageously invested. Svedberg had also pointed out the handicap of a year to year commitment which made Tisdale argue that if there were any chance of a commitment over a three or five year period, he would be glad to take it up. He realized the restrictions which the Trustees had placed on grants, and if they would still be in effect, he would not try to press the matter. Nevertheless he suggested to Weaver to let Svedberg know that they, as officers, were prepared to present recommendation of somewhat similar sums over a three or a five year period. This latter arrangement would relieve Svedberg somewhat and permit him to make more advantageous arrangements in his laboratory concerning staff, etc.²⁹¹ In view of these considerations Tisdale recommended to grant Svedberg \$ 10,000 for 1935 and also recommended that the Foundation should consider giving him assistance for a longer period of time.²⁹² September 1934 the Trustees appropriated a grant of \$ 11,000 or as much thereof as might be necessary to purchase Skr. 37,000.²⁹³

Shortly thereafter Tisdale wrote Svedberg that especially the fact that his grant from local sources amounted to more than half of the grant he applied for with the Foundation had been particularly forceful in securing the grant that had just been made to him. This might also bear upon the possibilities for securing grants for longer periods of time. In the preceding years it had been the Foundation's policy not to award grants for periods longer than one year but, Tisdale expected, this policy might soon change so that a request from Svedberg for such a grant might also be considered. When such a matter would be discussed, Tisdale wrote, he felt quite certain that the promise of local funds for future years would be a very considerable asset in the presentation of a proposal to the Foundation.²⁹⁴ November 1934 Tisdale visited Svedberg to discuss the matter. Svedberg told him

that there existed a Swedish Foundation established by the Wallenberg family, with a capital of some twenty million Swedish Crowns which was primarily interested in applied science. Shortly before Svedberg had had a talk with the older Wallenberg, who spent his time in connection with the administration of the Foundation. Wallenberg had told him that for the present year it would not be possible to consider any new activities, but that in of 1935 he hoped to renew the talks, expecting that the Foundation would give some Skr. 20,000 for a period of 3-5 years to Svedberg, on the condition that the Rockefeller Foundation would make a grant available comparable to the one it had just made. Svedberg told Tisdale in addition that the Swedish Government had made an appropriation of Skr. 50,000, which was to be used to complete the installation of his new magnet, most of which was then on the premises.²⁹⁵

January 1935 Svedberg wrote Tisdale that he had taken up again his discussions with the Wallenberg Foundation and that the negotiations had progressed very fruitfully. The Foundation had made an appropriation of Skr. 18,500 annually (half the sum given by the Rockefeller Foundation in 1935) for the years 1936-1940 upon the condition that the present aid (Skr. 37,000) would be given by the Rockefeller Foundation during these years.²⁹⁶ As Tisdale had expected the Foundation indeed changed their policy towards the appropriation of long term grants. Svedberg's subsequent request was easily agreed upon because of the importance of Svedberg's work for the development of the Foundation's Natural Sciences program. Furthermore, because of the appropriation by the Wallenberg Foundation, an appropriation by the Rockefeller Foundation would be 'of unusual importance to Svedberg in that it would stabilize his work over the long term essential for such work'.²⁹⁷ The Foundation's program was described as follows under the heading 'Application of physical and chemical techniques to biological problems':

"The program in experimental biology has a special interest in researches in which the analytical and quantitative procedures of chemistry, physics, and mathematics are directed towards the solution of basic biological problems. In studying the opportunities for Foundation co-operation, the officers have been impressed by the number of important centers where physical and biological leaders are thinking and working together on such problems. (...)

The items of this group have in common the important factor of collaboration between biologists and physical scientists of high ability. The program at Columbia is under the general direction of Professor H.C. Urey, and concerns the biological importance of the so-called 'heavy' hydrogen for the discovery of which Professor Urey recently received the Nobel prize. The substances which contain hydrogen are the most numerous and the most important, from the point of view of the chemistry of vital processes. The researches of Professor Svedberg at Upsala constitute one of the most noteworthy instances of the application of physical techniques to biological problems. The opportunity at Copenhagen is a particularly attractive one since it arises out of the group interest of Professor Krogh, a distinguished biologist, Professor von Hevesy, one of Europe's leading physical chemists, and Professor Niels Bohr, theoretical physicist.²⁹⁸

Svedberg's work thus was considered to be quite central in the Rockefeller Foundation's Natural Sciences Program. For him, the grants from the Foundation were an important resource in the further development of ultracentrifuges.

Development of Ultracentrifuges after 1933

In 1934 Svedberg published a number of articles in which emphasis was put on the apparatus and method, e.g. in *Die Naturwissenschaften*²⁹⁹ and in the *Kolloid Zeitschrift*.³⁰⁰ In June 1933, he presented a paper to a joint session of the sections of chemistry and of the medical sciences, at the Century of Progress Meeting of the American Association for the Advancement of Science, held in Chicago. It was published in *Science* in April 1934. There he discussed the principal problems in designing ultracentrifuges. At given speed the centrifugal force was proportional to the distance from the centre of rotation. The resulting inhomogeneity of the gravitational field within the rotating column of solution was accounted for theoretically but nevertheless, the accuracy of the determination suffered considerably if the inhomogeneity of the field was great. On the basis of his experience Svedberg had concluded that the centrifugal force should not change more than about 20% from top to bottom of the column of solution. Furthermore, in the case of sedimentation velocity measurements, it was found desirable to use a column of solution not lower than 6 mm and preferably 12 mm high, in order to obtain sufficient separation of the different molecular species present in a mixture. The permissible inhomogeneity of the centrifugal field then gave as the minimum distance of the mid-point of the column of solution from the centre of rotation 33 mm and 66 mm, respectively. In the case of equilibrium measurements the height of the column of solution needed not be more than about 5 mm, and the distance from the centre of rotation could therefore be chosen as low as 28 mm.³⁰¹ On the other hand, striving for the highest possible rotational speeds implied that for a given material and shape the rotor should be as small as possible. Svedberg felt that with a 12 mm column of solution he had reached a maximum with rotor VII, obtaining 400,000 g. But for the study of substances of comparatively low molecular weight, for example, 1,000 or 2,000, or for the sedimentation analysis of mixtures of low molecular weight, such as the decomposition products of the proteins, this field was not strong enough. Therefore a smaller rotor was designed with a diameter of 102 mm, containing a column of solution 6 mm in height at a distance of 36 mm from the centre of rotation. This rotor VIII was successfully tested at 135,000 r.p.m. (750,000 g) but exploded later at 125,000 r.p.m.³⁰² Nevertheless, the experiment showed the possibility of regular sedimentation measurements at this speed. Svedberg therefore wanted to try a new rotor of about the same dimensions,

but of better material and improved construction. He did not expect much of this route of development but he wanted 'to go to the limit and see what can be done with such low columns of solution'.³⁰³ After determination of the hardness of various parts of the exploded rotor, Boestad made new calculations of Rotor VIII. As a result he recommended that the following two small rotors planned be made of a much harder steel than used for the exploded Rotor VIII. Rotor IX was of an entirely different design, having a diameter of 104 mm. The distance from the centre of the cell from the axis of rotation, R , was 36 mm and it was driven by twin turbines. On 7 June 1934 it was tested at 133,000 r.p.m. According to the plan it should have been taken up to 160,000 r.p.m. After a number of tests and changes of the turbines and bearings, etc., it became possible to attain 160,000 r.p.m. on 15 June. However, on the fourth test run with haemoglobin the rotor burst around the cell holes at 144,000 r.p.m. Nevertheless, the fact that the cell with its windows of crystalline quartz withstood the strains and that convection-free sedimentation was obtained showed that accurate measurements might be performed in centrifugal fields of the order of one million times the force of gravity. Svedberg and his colleagues felt sure that it would be possible to improve the mechanical design and to utilise to advantage the convection-free sedimentation which had been demonstrated to take place even in these very intense centrifugal fields under the experimental condition realised in the ultracentrifuge.³⁰⁴

The last small rotor, Rotor X, was of the same steel material as Rotor IX, but the design was quite different. Its diameter was also 104 mm but R was 32.5 mm. It was successfully tested in a series of runs at the end of September 1934, where finally 155,000 r.p.m. was attained. A number of runs were carried out to see if these centrifuges could be used for sedimentation velocity runs. Some runs were made at the maximum permissible speed of 140,000 r.p.m. However, as was already indicated by the calculated value for the resolving power of that ultracentrifuge, the experiments were worse than those obtained with the 'standard' sized rotors having $R = 65$ mm. This rotor could now be used for routine work but Svedberg thought that the bigger rotor would, on the whole, be more efficient, although the centrifugal field would be a little lower. With these he hoped to reach 500,000 times gravity. The height of column of solution and the distance from centre of rotation were considered of great importance when they wanted to perform accurate determinations. Therefore they planned to start manufacturing a rotor of standard size but permitting of taking cells for 16 mm height of column of solution (centrifugal field probably 400,000 times gravity) as soon as the present one would be finished. Maybe the last type would represent the optimum.³⁰⁵

Another problem with the smaller rotors was that the tiny cells were difficult to seal tight and gradually became deformed. In case of equilibrium determinations, the more intense centrifugal field (up to 700,000 g) obtainable with small rotors

could be an advantage, and the low column of solution together with the short distance from the axis of rotation to the centre of the cell should not cause difficulty. In 1934 Pedersen started a series of sedimentation equilibrium experiments with various inorganic salts in the oil-turbine ultracentrifuge. In the following year some equilibrium measurements were carried out at 120,000 r.p.m. (525,000 g) on such low molecular weight substances as NaCl, LiCl and glycocoll, in one of the small rotors. These sedimentation equilibrium experiments with salts were later continued by Carl Drucker, who had come to Upsala as a Jewish refugee from Leipzig.³⁰⁶ The experiments gave satisfactory results but they were complicated by a gradual deformation of the cell. For this reason it was necessary to use an interpolated reference scale obtained from runs before and after the actual equilibrium run. Nevertheless, while the small rotors were considered of no value for the development of ultracentrifugation technique, the results from the exploded rotors did give valuable information to Boestad for his further work on the design of new rotors.³⁰⁷ When Svedberg was visited by W.E. Tisdale from the Rockefeller Foundation in November 1934 he also explained that smaller rotors were not of much use for sedimentation velocity experiments. This in reaction to Tisdale raising the question of the possibilities and limitations of the spinning top type of centrifuge (see Chapter 3). Svedberg told him that he had found that with a 32 mm radius rotor, he was unable to do his sedimentation work within the speeds possible, and that he had to go back to his larger diameters, about 65 mm radius. For equilibrium measurements he felt that he could do work with his 32 mm rotor, but for his refined work he thought he needed a column of solution of 12 mm in length and 65 mm from the centre of rotation. Svedberg also referred to the equipment they were just building for Dupont in Wilmington, indicating that they too had canvassed the field very thoroughly before they spent the sum necessary to install one of his types of machines (see Chapter 6). He thought that for work such as E.N. Harvey, Princeton, had done in the separation of certain parts of eggs, where more qualitative than quantitative results were desired (see Chapter 6), the spinning top could be used, but that for refined quantitative measurements it was not sufficiently accurate or powerful.³⁰⁸

From time to time the runs in the centrifuge were disturbed by weak vibrations. At the beginning it was usually taken as an indication that the bearings were worn out and had to be renewed and that the journals of the rotor had to be repolished. Usually this helped for some time. As the speed of the centrifuge was increased and the oval type rotors came into use, the problem became more serious and treacherous. The centrifuges could run without trouble for some time and then suddenly one day they might get frightful vibrations and the centrifuge had to be stopped. Svedberg was much concerned about the situation. Finally in the fall of

1934 they got the idea that the balancing machine did not measure the dynamic balance of the rotors properly. It was next reconstructed so that it could register not only the static, but also the dynamic balance. Existing apparatuses on the market did not suit their needs well enough and also appeared to be rather expensive.³⁰⁹ They therefore started reconstructing their own apparatus and after the reconstruction concluded that the dynamic balance was much more important for a smooth running of the centrifuge than the static. With the new machine a dynamic unbalance of as little as 10 mg near the cell holes could easily be discovered. They found it necessary to maintain such accurate dynamic balance that already a shift of one of the guard rings of a cell to a 1/4 of a turn was inadmissible. This required the rebalancing of a cell after recementing. The reconstructed balancing machine cost around \$ 600 which was about half the cost of a commercial balancing machine while the accuracy they gave was not 1/5 of the precision they attained with their arrangement.³¹⁰

The rotors usually got deformed during the test runs, and some grams of material had to be removed in order to get the rotor back into perfect balance. The cell holes got deformed as well, and their diameters were therefore kept 0.1 mm smaller than necessary for the cells in the routine runs. After the test runs they were ground to the proper size. But also during the subsequent use the rotors all became deformed, making the cell holes slightly oval. Boestad therefore tried to improve the design of the rotors around the cell holes in such a way that even minor permanent deformations could be prevented during the life time of the rotors. In a first attempt, a series of normally sized rotors was designed in similar way as the small Rotor X, all exactly alike. Two different types of very hard steel were used. The maximum test speed was set to 84,000 r.p.m. They all failed and exploded through the centre, Rotor XI in the second run at 50,000 r.p.m., rotor XII at 84,000 r.p.m. in the fourth test run. Rotor XIII in the first test run at 50,000 r.p.m. A careful metallographic examination of the pieces from the broken rotors failed to bring out any imperfections in the material. They concluded that higher speeds could only be reached using a different design. An overview of these rotors is given in table 2.2.

Mid 1935 Boestad started designing a new series of rotors, this time with maximum diameters of 184 and 188 mm and with three different cell hole diameters. As seen from table 2.3, four rotors (XIV to XVII) were successfully tested and have since been used for hundreds of runs. The same is true for rotor XIX which is identical with XVI and XVII except for small twin turbines and thinner journals (10 mm instead of the usual 18 mm). Experience with the smaller rotors had shown that it was important to keep the mass at the periphery of the rotor as small as possible. For this reason new cells were constructed which also proved their value in the new larger rotors. The total cell-diameter could be

reduced without decreasing the length of the column of solution. The parts of the rotor outside the cell were given the shape shown in figure 2.25 and the vanes used for shielding of false light were made thinner and smaller.³¹¹

Rotor	Diam. (mm.)	Shape	Cell hole (mm)	R (mm)	Steel	Maxim. (rpm)	Date	Explod. (rpm)	Date	Cell weight (g)
VIII	102	Oval. C	16	36	CN 2 400 B	135 000	12 Dec. 1933	120 000	20 Dec. 1933	12
IX	104	Oval. D	16	36	LLL 49 470 B	160 000	15 Jun. 1934	145 000	19 Jun. 1934	12
X	104	Oval. E	14	32.5	LLL 49 470 B	155 000	28 Sept. 1934			12
XI	178	Oval. F	19.6	65	LLL 49 470 B	65 000	29 Nov. 1934	50 000	29 Nov. 1934	
XII	178	Oval. F	19.6	65	LLL 49 470 B	80 000	2 Apr. 1935	84 000	3 Apr. 1935	
XIII	178	Oval. F	19.6	65	KRO 866 430 B		23 Jul. 1935	60 000	23 Jul. 1935	

Table 2.2

Rotors tested from 1933 to 1935. (Pedersen, 1976, p.13).

Rotor	Diam. (mm)	Shape	Cell hole (mm)	R (mm)	Steel	Maxim. (rpm)	Date	Explod. (rpm)	Date	Cell weight (g)
XIV	184	Oval G ₁	20.4	65	CN 2 400 B	84 000	22 Oct. 1935			23
XV	184	Oval G ₂	24.5	65	CN 2 400 B	80 000	27 Jan. 1936			34
XVI	188	Oval G ₃	27	65	CN 2 400 B	73 000	14 Mar. 1936			42
XVII	188	Oval G ₃	27	65	CN 2 400 B	73 000	9 Jun. 1936			42
XVIII	188	Oval H	27	65	CN 2 400 B		2 Nov. 1936	53 200	2 Nov. 1936	
XIX	188	Oval J ₁	27	65	CN 2 400 B	73 000	1 Feb. 1937			42
XX	188	Oval J ₂ no vane	27	65	CN 2 400 B	70 000	8 Dec. 1937	61 000	8 Dec. 1937	42
XXI	188	Oval K	27	65	CN 2 400 B	75 000	5 Jan. 1939			42
XXII	188	Oval K	27	65	CN 2 400 B	75 000	30 Sep. 1940			44 (55)
XXIII	188	Oval K	27	65	CN 2 400 B	75 200	14 Dec. 1944			44
XXIV	188	Oval K	27	65	CN 2 400 B	75 000	15 Dec. 1945			44

Table 2.3

Rotors tested from 1935 to 1945. (Pedersen, 1976, p.15).

Another option with the new cells was to stick to their original diameter while increasing the height of the column of solution. This would increase the resolving power of the cell, a highly desirable feature from Svedberg's point of view. They therefore started the manufacture of cells with a height of column from 14-18.5

milimitres which fitted in the old cell holes.³¹² For special purposes Svedberg was interested in having some extra long cells available. Boestad designed a rotor that would allow a cell thickness of 24 mm as compared with the usual 12 mm. The length of the cell hole was increased from 40 mm to 50 mm. This rotor XVIII exploded at 53,200 r.p.m. during the first test run, which was attributed to a flaw in the material.



Figure 2.25

Rotor XIX for the oil-turbine ultracentrifuge (Boestad, Pedersen and Svedberg, 1938, p.347).

Boestad thought that a further increase of about 10 percent in resolving power could be gained if the vanes on the rotor could be omitted. The blank for the rotor could then get a better pretreatment. But the omission of the vanes meant a considerable complication with regard to the observation technique. Rotor XX was made, and for the first time Svedberg was not present at the test runs because he was in bed with influenza. The first two test runs gave the expected small stretching; in the third test run, however, the rotor exploded. When Pedersen called Svedberg on the telephone, he had a definite impression that Svedberg felt it as a relief. He felt that he had developed his ultracentrifuge to the practical limit of efficiency that was attainable with the materials available at that time. Even if it would have been possible to construct a rotor that could stand a routine speed of 80,000 to 85,000 r.p.m., they should have had to face several new problems: cracked quartz windows, leaking and deformed cells, more complicated technique for the synchronizing of the illumination and exposures, etc.³¹³ Still, according to Boestad, the rotor design could be improved. Even though the long-time deformation of the cell holes had already been much reduced in the rotors XVI, XVII and XIX, it might be possible to redesign the surrounding of the cell holes in such a way that they would remain cylindrical for the life time of the rotors. In the final set of rotors, from rotor XXI onwards, all material was removed which was not necessary for carrying a cell weighing, say 44 g, at the

maximum speed. If the cell weight had been increased to perhaps 50 g, the rotor might burst around the cell holes as rotor IX did. All the rotors from rotor XXI onwards were tested without any mishap. Some of these were used for thousands of runs. The bearings and the thin journals worked perfectly and very little overhaul was necessary. Even for running 8 to 10 hours every day there could be 2 to 3 years before the journals had to be reground and polished and the bearing had to be recast. In the early days, bearings and journals often had to be corrected with an interval of a few weeks. Likewise no changes in the dimensions of the cell holes could now be observed even after decades of use.³¹⁴

Despite all the work done on balancing of the rotors experience showed that even a perfectly balanced rotor could develop vibrations. These were attributed to slight irregularities in the driving force and friction. In the earlier types they tried to damp these vibrations by surrounding the bearings with a rubber or ebonite collar. This, however, hardly damped out the vibrations whereas the convection of heat from the bearing to the casing got worse. Therefore, rotor was carried in specially designed cylindrical journal bearings. A damping arrangement in the bearings took care of the tendencies to vibration and ensured smooth running. This was attained by dividing the bearing surface into six parts, three of which were fixed. The others formed the end surfaces of loose pistons which were held against the journals by oil pressure. The play of the pistons was restricted by means of micrometer screws so that less clearance (diametrically about 0.02 mm) was left between the shaft and the pistons than between the shaft and the fixed parts of the bearings (diametrically about 0.12 mm). This reduced the friction considerably. Figure 2.26 shows the construction of these damping bearings.

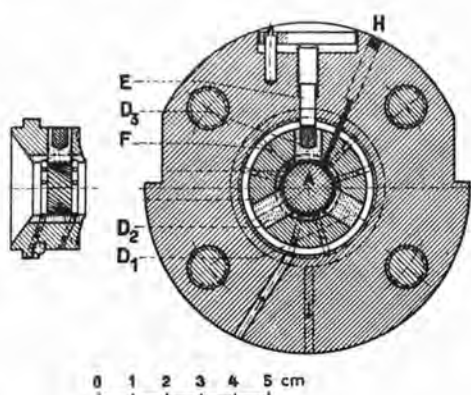


Figure 2.26

Damping bearings for rotors XIV-XVIII. A, Rotor shaft; D₁, D₂, and D₃, Damping pistons; E, Micrometer screw; F, Oil channels; H, Thermoelement. (Svedberg and Pedersen, 1940, p.137).

The diameter of the rotor journals was chosen with regard to the unbalance forces, about 400 kg, occurring when the content of a 12 mm cell filled with an aqueous solution would leak out. Calculations showed that 10 mm would give a sufficient margin of safety as regards the strength of the shaft. This new type of bearing appeared to be a great success. After a year of almost daily use it still appeared unnecessary to rebabbit them. The only thing they had to do was to adjust from time to time the upper bearing piston by means of the micrometer screw. The clearance was tested by means of a slightly conical steel 'don'.³¹⁵

Early 1938 they introduced a magnetic brake which reduced the time of stopping considerably and they were also experimenting with a thermostating device for the centrifuge casing. This should help to keep the temperature low and constant. Svedberg and Pedersen carried out a series of measurements on the efficiency of the various parts of the ultracentrifuge, like the electric motor, the oil pump, and the turbines. These determinations convinced them that with recent improvements, like thin shafts etc., the overall efficiency was quite good.³¹⁶ The results were published in *Review of Scientific Instruments*. Compared to earlier designs which used a journal diameter of 18 mm the friction losses in the bearings at 60,000 r.p.m. were reduced from 2280 watt to 269 watt. The only other direct source of energy consumption during operation at full speed was the friction loss in the surrounding hydrogen which amounted about 32 watt. A reduction in bearing friction therefore was very desirable from the perspective of the overall performance of the ultracentrifuge.³¹⁷

With respect to the turbines a number of different designs were tried. Experience with rotor I had shown that the precise form of the turbine blades was not critical whereas the way of introducing the oil was. It should reach the turbine through a spiral shaped channel. Theory indicated that the maximum speed of the periphery of the turbine plates could not exceed the speed of the incoming driving oil. For a given pressure of the oil this implied that the highest rotational speed could be reached with the smallest turbines. On the other hand the turbines should not be too small because then the total area of impact for the oil would become too small for the large mass to be driven. In the earliest designs the turbines were typically between 15 and 20 mm in diameter and in these cases the strength of the rotor was the limiting factor for the highest rotational speeds. For the smaller rotors, however, this size of turbine could not reach the speed the rotor could stand and thus a smaller, 10 mm turbine was designed. In this case the total area of impact was increased by constructing a so-called 'twin-turbine' at each end of the rotor axis (figure 2.27). This arrangement performed very satisfactorily and was later also applied to the larger rotors.³¹⁸

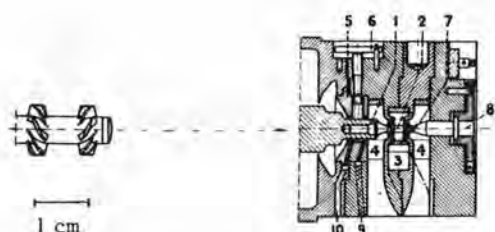


Figure 2.27

Twin turbines for rotor XIX (also shown in figure 2.25). Side view (left) and Cross section through turbine chamber (right). 1, Rotor shaft; 2, Turbine; 3, Turbine-oil inlet; 4, Turbine oil outlet; 5, Main bearing; 6, Micrometer screw for adjustment damping piston; 7, Pressure bearing; 8, Micrometer screw for adjustment pressure bearing; 9, Bearing-oil inlet; 10, Bearing-oil outlet. (Svedberg and Pedersen, 1940, p.139).

The years 1932 to 1937 were probably the most hectic ones in Svedberg's life. The testing of new rotors, which he personally directed in every detail, put a heavy stress on him. In 1932 three rotors were successfully tested. In 1933 four rotors were tested, two exploded. In 1934 three rotors were tested, two exploded. In 1935 three rotors were tested, two exploded. In 1936 four rotors tested, one exploded. In 1937 two tested, one exploded. In connection with the test runs Svedberg used to say that every new rotor tested meant a shortening of his life by one year.³¹⁹ A final rotor design was introduced in 1939 resulting in a maximum centrifugal field of about 300,000 g. More than 10 rotors of this type have since been put into use at various places in the world. In the mid 1970s two oil-turbine ultracentrifuges of the final design from 1939 were still in use at Upsala.³²⁰ In 1972 Claesson and Pedersen wrote that motor-driven ultracentrifuges of later design might be used over a more extended temperature range and were in certain respects easier to operate but they stressed that the Svedberg ultracentrifuge was never surpassed in accuracy or reliability.³²¹

In 1937/38 Svedberg wrote some articles in *Nature*,³²² *Industrial and Engineering Chemistry*³²³ and *Review of Scientific Instruments*,³²⁴ in which the emphasis was on the apparatus and the method. In *Nature* he described his two different methods and machines indicating that with the sedimentation velocity method an independent determination of the diffusion constant would be needed. Svedberg had also seen the equipment designed by Pickels and Bauer at the Rockefeller Foundation laboratories in New York in which an air-turbine drove a duralumin rotor. (see Chapter 5) He expected that these ultracentrifuges would be of great service in many cases, although the resolving power had not yet been pushed to the height obtainable with the steel rotor of the oil-turbine ultracentrifuge.³²⁵ Comparing the two he stated:

"Oil-turbines have been chosen by us for the following reasons. There is no danger of contaminating the atmosphere around the rotor by gas from the turbine. The same compressor may be used for delivering the lubricating oil and the oil operating the damping bearings. The output of our oil-turbines compares favorably with that of air-turbines of similar power dimensions."³²⁶

The electric power necessary for driving the air-driven centrifuge at 60,000 r.p.m. was slightly more than was used in the case of Svedberg's oil turbine type whereas the primary electrical energy necessary for accelerating the air-driven rotor was also considerably higher.³²⁷ Svedberg also indicated that steel had proved best as rotor material as compared to duralumin used by Pickels/Bauer. A comparatively soft chromium nickel steel of ultimate strength about 140 kg/mm² corresponding to a Brinell hardness of 400 should be chosen. Hard steel of higher tensile strength often cracked under the influence of centrifugal stresses. The use of some light metal alloy, e.g. Duralumin or electron metal, with a ratio between strength and density slightly higher than steel, according to Svedberg, should not be recommended because with the steel rotor the stresses around the cell holes were already to about 50 percent due to the outward pull of the cell, the weight of which had been reduced to the lowest possible amount. The highest resolving power could, therefore, be reached with steel rotors.³²⁸

Although Svedberg felt that he could not reach higher rotational speeds without decreasing the overall performance of his apparatus there were a number of points that created problems that led to further development of parts of the apparatus and method. One of them was the method for speed measuring. The angular velocity entered to the second power in the formulae for sedimentation constant and molecular weight. The accurate determination of this quantity was therefore of great importance in ultra-centrifugal technique. In the case of direct drive by an A.C. motor, a measurement of the frequency of the electric current sufficed, because with ball-bearings and the rotor running in hydrogen there was no noticeable slip. For the high-speed oil-turbine centrifuge, a stroboscopic tachometer was at first used. In the late 1930s a more convenient magneto-electric method for speed measurement was worked out. Part of the shaft of the centrifuge rotor was magnetized and surrounded by a two-pole soft iron armature provided with coils. This device constituted a magneto-electric generator which produced an A.C. current of the same frequency as the rotational speed of the rotor. After amplifying, the current was fed to a vibration frequency. The part built in the centrifuge and the amplifier were comparatively inexpensive but the frequency meters used cost R.Mark 1400,- (over \$ 500,-). In the long run it would pay, though.³²⁹ Nevertheless Svedberg also developed a cheaper method based on projecting the signal generated by the rotor on an oscillograph. This arrangement, however, required a very skilled operator.³³⁰

Also the optical method for registering the sedimentation left a lot to be desired. In 1937 Arne Tiselius, one of Svedberg's colleagues, applied the so-called Toepler *Schlieren* method for registering concentration gradients to electrophoresis measurements with quite satisfactory results. They therefore also tried to apply the method in observations of sedimentation velocities in the ultracentrifuge. In the method a lens was placed as closely as possible behind the centrifuge cell which projected an image of a horizontal slit through the cell on the camera objective. In front of this was a vertically movable screen, having a horizontal edge with which any part of a deviated image of the slit might be cut off. When the screen was properly arranged, any gradients occurring in the cell would give rise to corresponding black bands visible to the eye in the image of the cell and recorded on the plate in the camera. A tungsten ribbon lamp with a condenser lens was used for illumination of the slit. The method offered the advantage of rapid and convenient observation of components in mixtures and their sedimentation velocities. It also gave a rough idea of the relative amounts of the differently sedimenting substances. They indicated that it might also be modified to give a more accurate determination of concentration, but for this purpose it did not seem to offer any advantage over the scale method. However, the method never became a success.³³¹

Another problem was that, although they considered their optical methods for registering the sedimentation as being very accurate, these methods for many important problems needed to be supplemented by some procedure allowing chemical tests to be performed in the same run. This was especially the case in connection to questions as whether enzymes and antibodies were proteins. Tiselius and Pedersen had already made several attempts to take out samples of the ultracentrifuged solutions after concluding an experiment, but the arrangements were not considered sufficiently perfect to allow quantitative application. If they knew the amount of substance above or below a certain level in the cell before and after centrifugation, the difference would give the sedimentation velocity. To avoid mixing the layers of the centrifuged solution when stopping the rotor, and especially when pipetting out the samples, they had divided the contents of the cell into two parts of about equal volume separated by a thin wall of bakelite with a large number of fine holes, supporting a piece of hardened filter paper. This arrangement effectively prevented mixing for a time sufficient to remove the cell and to pipette out the contents of the upper compartment and rinse it quantitatively. On the other hand, as optical observations indicated, an arrangement including such a highly permeable membrane did not obstruct the free sedimentation. They indicated that the arrangement might be modified in several ways according to the purpose of study; one could use several compartments and differently placed walls. The cell described allowed optical observations to be made

in the same experiment, which was a great advantage. The method should be of much value not only for the study of substances of specific activity, as mentioned above, but also for a number of other important problems. The sedimentation of substances of low molecular weight was difficult to observe optically, as the rapid diffusion prevented the boundary from leaving the meniscus completely, a circumstance without influence in the analytical procedure described. Interesting possibilities were offered in the field of mixtures of substances of different chemical nature, like carbohydrates and proteins. Separations for preparative purposes, guided by optical observations, should be possible with small quantities of material.³³²

Further Protein Studies - Inquiries by Other Researchers

In Svedberg's view, in 1935 the utilization of the ultracentrifuge for the study of high molecular compounds was only at its beginning. He expected that, as research went on, new problems would present themselves for treatment with this new tool. In 1935 he wrote in *Current Science*:

"So far the main interest of applications has been in the field of biology and medicine because of the various kinds of new information which the ultracentrifuge has made available with regard to the behaviour of the proteins - those substances of paramount importance to all living beings. But there are also the vast fields of the carbohydrates, the hydrocarbons and the synthetic organic high-molecular compounds. A number of important chemical industries are handling materials belonging to one or the other of these classes of substances. The research laboratories connected with such industries are beginning to realise that the ultracentrifuge may be able to render services of great value in elucidating the properties of the molecules and particles which are the building-stones of cellulose, artificial silk, varnishes, rubber, dyes and many other products."³³³

In 1937 Svedberg gave a lecture at the dedication of the Chemistry building of the University of Delaware in which he focussed on the apparatus and the method. There he stressed that macromolecules were prevailing in both organic and inorganic substances and that the ultracentrifuge would be a very powerful tool in their investigation.³³⁴ Elmer O. Kraemer added in a discussion to Svedberg's presentation that in many cases it would not be necessary to use the costly oil-turbine apparatus and that in many cases the electrically driven equilibrium ultracentrifuge would suffice. This machine would be relatively simple in operation and construction and Kraemer communicated some of its possibilities by illustrating examples from researches at the DuPont Experimental Station. These examples were meant to indicate the wide applicability of the low-speed ultracentrifuge to problems of industrial importance, as well as of purely scientific interest. In fact,

in view of simplicity of the equipment and its operation, Kraemer felt that any university claiming to do thorough work in colloids should by all means possess a low-speed ultracentrifuge when it could not finance an oil-turbine machine. 'In former years the first piece of equipment installed in a new colloid laboratory was an ultramicroscope, but today, it should be an ultracentrifuge.'³³⁵

Svedberg's work was well known among his European and American colleagues. Many researchers sent him requests for investigating a certain substance for them or for being allowed to work in his laboratory for a while. During the late 1920s and 1930s hundreds of this type of requests were addressed to Svedberg. Burt Johnson from the department of agriculture from the University of California asked Svedberg in 1931 if he could work in Svedberg's laboratory for a year in order to study tobacco mosaic virus. He had been using chemical, filtration and electrical techniques with the hope of obtaining a preparation more or less free from salts and other plant products, leaving the virus as a suspension in a comparatively small volume of liquid. He would be anxious to determine its particle weight. Because the virus appeared to be a protein or a protein-like substance this might be done in the ultracentrifuge.³³⁶ Svedberg replied that he would be welcome but, in order to avoid misunderstanding as to the method, stressed that the ultracentrifuge was not a preparative method and that it could not be used in fractional centrifuging. Biologists often used centrifuges for these latter type of applications.³³⁷ At the beginning of the 1930s the inorganic colloids had almost completely disappeared from the research agenda of the institute. In 1931 he wrote Laura Krejci that there interests were 'almost completely devoted to the study of proteins by means of special methods developed in this institute'.³³⁸ For this reason he did not allow her to work on adsorption, as she had requested, but invited her to work on some problem connected with the investigations which were then going on. R.O. Herzog from Istanbul asked Svedberg late 1934 if one of his students could be accepted to investigate acetylcellulose in Svedberg's laboratory.³³⁹ Svedberg replied that he would be welcome, that it would take him two or three weeks to learn the method and that such a determination would take approximately three months.³⁴⁰ The requests were so numerous that in many cases Svedberg had to decline requests for the investigation of certain substances. In 1934 he wrote B. Jirgensons from a Chemical Institute in Riga (Letland) that they did not have time to investigate the decomposition products from proteins but that he would be welcome to do these experiments himself in Upsala. At that time they were working on an ultracentrifuge for 1,000,000 g and Svedberg wrote that he planned to take up such an investigation when this machine would be ready.³⁴¹ To Edwin Cohn he also answered that they could not investigate the suggested substance but that he would be welcome to come and do it himself.³⁴²

July 1935 W.M. Stanley from the Rockefeller Institute for Medical Research, department of animal and plant pathology in Princeton, wrote Svedberg that he had obtained crystalline tobacco mosaic virus protein. Because of its disease-producing properties Stanley expected that this protein would probably become the most studied protein in the course of the next few years. The crystallization of this virus had caused widespread discussion in the US and in Europe. Stanley wrote that McBain (see Chapter 4) had asked him a sample in order to determine its sedimentation velocity to which he had agreed. Because of Svedberg's experience in the field Stanley asked him if he would also be willing to make an ultracentrifugal study of this protein.³⁴³ Svedberg replied that he would be pleased to do so and that a fairly complete study could be made with only a small quantity (say 0.3 gramme) but that it would be more convenient to work if a somewhat larger quantity were available (say 1-2 grammes). They would determine the sedimentation constant as a function of pH and measure molecular weight both from sedimentation equilibrium and from the combination of sedimentation constant and diffusion constant. Furthermore he advised Stanley that according to their experience very few proteins were quite stable towards drying. He would therefore prefer to receive the sample as a solution or as crystals covered with liquid.³⁴⁴ Stanley sent Svedberg the sample in November 1935 in a solution including instructions on how to recrystallize it. Stanley wrote that he was extremely interested to learn whether or not the ultracentrifugal investigation would reveal the presence of more than one component. During the next few months he would be engaged in determining, using chemical methods, whether or not the crystalline protein could be separated from the virus activity. This he considered a fundamental and all-important question, since most virus workers granted that they had a crystalline protein, but they felt, despite much evidence already obtained to the contrary, that the virus was something alive adsorbed on the protein. Stanley, however, could not see how this would be possible in view of what they had already done with the crystalline protein. But since they were working with a new type of material, he felt that it would be desirable to obtain as much data as possible regarding its nature.³⁴⁵ It would be of prime importance to him to know whether or not the crystalline tobacco-mosaic virus protein consisted of only one molecular species.³⁴⁶ Two months later Svedberg reported back his first experimental results which had taken some time because they wanted to be 'absolutely sure' before stating them. He had found that the virus protein was not homogeneous with regard to molecular weight. It was not composed of a small number of well-defined compounds either, but had molecules varying almost continuously over a certain range. Recrystallization had shown no marked change. The mean molecular weight appeared to be about 19 million under the assumption of spherical shape. They next planned to investigate the degree of polydispersity as

well as the pH-stability region.³⁴⁷ Stanley replied that during the preceding year an ultracentrifuge had been set up at the Rockefeller Institute in New York (see Chapter 5) and that they had also made some runs on the same crystalline proteins. The sedimentation constant found in these preliminary or test runs had appeared to be practically the same as the value Svedberg had found. Stanley would be very much interested in the results of Svedberg's further experiments.³⁴⁸ After Svedberg had published his results³⁴⁹ Stanley wrote him that he was afraid that in his efforts to prepare as especially 'pure' sample of protein, he had defeated his own purpose. The repeated fractionation to which he had subjected the sample, in an effort to obtain an especially homogeneous preparation, evidently had caused it to become very inhomogeneous with respect to molecular weight. In the meantime they had learned that preparations which had had but little treatment gave the best results on the ultracentrifuge. Wyckoff (see Chapter 5) had also obtained a blurred boundary when he used a 'highly purified' sample, but using Stanley's regular so-called 'crude' material Wyckoff obtained boundaries that were fully sharp as those given in Svedberg's paper for the haemocyanin from *Helix Pomatia*. McBain had also made a run using their crude material and he had reported that he obtained a good boundary and that the material was definitely monodisperse. Therefore, Stanley would like Svedberg to examine some of the material, which had not been subjected to extensive treatment, for its molecular homogeneity.³⁵⁰ However, the new sample also appeared to be inhomogeneous in Svedberg's ultracentrifuge. Svedberg suggested that it might be so unstable that it underwent change during transport. Under these circumstances he did not think it worthwhile to make a more detailed investigation.³⁵¹ The same year Wyckoff moved to Princeton and set up an ultracentrifuge laboratory there (see Chapter 5) which made it much more convenient for Stanley to examine his samples in the apparatus. Especially using the quantity type of ultracentrifuge for the isolation of the virus in connection with the analytical type proved to be very fruitful. When Stanley informed Svedberg about these developments³⁵² Svedberg replied that he had some objections against the naming used for the apparatus. He suggested that it would be advisable to reserve the term ultracentrifuge for an instrument by means of which sedimentation in a centrifugal field was measured quantitatively. An ordinary laboratory centrifuge of high speed might be called supercentrifuge. In Svedberg's opinion Stanley's 'quantity ultracentrifuge' should be called 'super centrifuge' and their 'analytical ultracentrifuge' could be termed simply 'ultracentrifuge'.³⁵³

Johannes Bauer from the International Health Division Laboratories from the Rockefeller Foundation asked Svedberg to let Frank L. Horsfall learn the electrophoresis technique in Svedberg's laboratory, using both the visual as well as photographic methods of determination. In addition, they should like to have him

learn the technique of diffusion measurement as used in Svedberg's Institute. When Horsfall returned he would be collaborating with Edward Pickels (see Chapter 5) in the ultracentrifugal studies of viruses and antibodies, and therefore Bauer found it highly desirable if he were also given an opportunity to learn the technique employed in Svedberg's laboratory for the determination of partial specific volume protein molecules. When Horsfall would have returned IHD Laboratories would need the necessary apparatus to carry on the electrophoresis studies, and they would greatly appreciate it if Svedberg could to have these either built in his Institute or assist us them securing them elsewhere.³⁵⁴

In 1939 K.J. Sommerfeld from the UK wrote Svedberg that he was working on the determination of criteria for air raid shelter materials. He had calculated that the peripheral velocities in Svedberg's ultracentrifuge were in the order of 2,000 ft/sec whereas the maximum velocity of bombs in actual warfare was about 850 ft/sec. He therefore wondered if a rotating wheel could be used in setting up test procedures in this respect.³⁵⁵ Svedberg gave a very short reply saying that he doubted that the scheme would be practicable and that a detailed criticism would take too much time to formulate.³⁵⁶ In the late 1930s Svedberg got so many requests from foreign researchers to work in his laboratory that he had to decline many of them.³⁵⁷

In the fall of 1938 Karl Drucker, a Jewish refugee from Leipzig, was working on various physico-chemical experiments. Kabat from Heidelberg had worked on anti-globulins and Basil Record tried to measure sedimentation velocities of glycogen acetates. In this study he wanted to use bromoform as solvent but he had too much trouble with cells that he left without getting any entirely satisfactory results. Adair studied the Electro-chemical properties of haemoglobin with the electrophoresis apparatus and combined these experiments with ultracentrifugal analysis of haemoglobin. Elmer O. Kraemer did most of his experimental work on Daktose, pending the construction of a cell that would hold organic solvents. In that period there was only one velocity machine in operation owing to the fact that the second one had to be dismantled and shifted a few feet to permit a third one to be mounted along side. The two machines were so arranged that they could be run by a single operator. Because of the heavy demand on ultracentrifuge time a third oil-turbine ultracentrifuge was put into operation early 1939. The demands increased because of the interests shown by foreigners and because of the nature of the research. In the beginning the idea was to run a protein, determine its molecular weight and then turn to the next. It appeared, however, that the weight determined depended largely on the experimental conditions - proteins tended to decompose and recombine under a variety of circumstances. Thus the ultracentrifuge became tool in the investigation of the effects of various preparative methods and the study of a single protein could then easily take a few

months. In the late 1930s machines were run for 16 hours a day, turning out 4 or 5 experiments a piece.³⁵⁸ In the course of time more than fifty scientists from all parts of the world have spent varying lengths of stay in Svedberg's laboratory. They came to work with the ultracentrifuge or to study proteins. Sometimes they brought new research problems, sometimes they participated in the work that was going on.³⁵⁹

In the 1930s a number of people asked Svedberg to write a monograph on the ultracentrifuge. In 1933 W. Ostwald, editor of the *Kolloid Zeitschrift*, would like to publish such a book in German, assuming that Svedberg had already concluded a contract with an English or American publisher. In his series of handbooks in colloid chemistry a book by Pauli and Valko on the *Colloidchemistry of Protein Bodies* would soon be released and a study on ultracentrifugal studies of proteins would fit well in that series. He also invited Svedberg to give a talk on proteins in Germany because there were still influential organic chemists there who believed that reproducible monodisperse systems of molecular weight over 10,000 did not exist.³⁶⁰ Regarding the book Svedberg responded that they had been playing with the idea but that they were still developing the apparatus and did not have much time for writing.³⁶¹ In 1937 P.A. Thiesen from Berlin would like to publish such a monograph in his series *Kolloidforschung* because the ultracentrifuge method had become ever more important³⁶² and in 1939 Hans Thirring from Vienna had interested a local publisher for such a book.³⁶³ However, shortly before Thiesen's offer Svedberg had decided to compile a monograph for Ostwald's series which would also be published at the same time in an English edition. Svedberg invited various researchers who had worked with him to write the various chapters. Because he was always anxious to have the latest results included³⁶⁴ it took about three years before the book was finally published. Because of the prevailing situation in nazi-Germany of that time the German publisher was very anxious that nobody in Germany would know that the 'original' was written in English and certainly not that the German edition was translated from English by Drucker. The books were eventually published in 1940³⁶⁵ and were very well received.³⁶⁶ Although many protein chemists in those days held the view that proteins were very distinct from inorganic colloids many colloid chemists also investigated proteins with the 'traditional methods' of physical chemistry. For instance, many papers presented at the Colloid Symposia dealt with proteins and triggered discussions on whether one was allowed to speak of molecular weights or not.³⁶⁷ For this reasons publishers were interested in publishing Svedberg's book in a series on colloid science.

Proteins as a Driving Force behind the Ultracentrifuge Development

In November 1938 the Royal Society of London organized a symposium on 'the Protein Molecule' for which Svedberg was invited to give the opening address. He started by saying:

"The proposal of the subject for this discussion is in itself a remarkable thing and the symbol of the spirit of this meeting. A few years ago, the proposal would have looked preposterous. Proteins were known as a mysterious sort of colloids, the molecules of which eluded our search. What is it then that has happened in these years? Why is the most distinguished scientific society of this country inviting a discussion on the protein molecule?"³⁶⁸

He discussed the theory of his method and results obtained in protein investigations and included a table of 'Molecular Constants of Proteins'. He also discussed his finding that only a limited number of molecular weights of proteins existed:

"A (...) result of ultracentrifugal and diffusion is the finding of a rule of simple multiples for the molecular weights of the proteins. Not only nearly related substances such as the red blood pigments obey the rule but the masses of most proteins, even those of widely different origin, show similar regularities (...). If we choose 17,600 as the unit the majority of the proteins may be divided into eleven classes with molecular weight which are multiples of this unit by factors containing powers of 2 and 3. The rule is only approximate, indicating that the underlying principle which probably means a similarity in the architecture of all proteins, is obscured by some secondary factor. If the proteins are built up of amino-acid residues according to a common plan the differences in percentage of the amino acids of different molecular weight might be regarded as this obscuring factor."³⁶⁹

Svedberg also discussed the various other methods for studying proteins like osmotic pressure, X-ray technique, electrophoresis, etc. These methods had given important information but many more questions remained. Also the mechanism of protein synthesis was practically unknown. Svedberg concluded, stating:

"We have still a long way to go before reaching our goal-the complete elucidation of the architecture of the protein molecule. But looking back on the stretch already traversed we may feel justified in stating that the application of physico-chemical methods to the protein problem has already given us much valuable information. The vague term 'colloid' for a protein has been replaced by precise information concerning the mass and electrochemical behaviour and in certain cases even of the shape and structure of the protein particles in solutions and crystals. These entities appear so well defined that we really feel justified in denoting them as protein molecules."³⁷⁰

In the late 1930s and early 1940s, when studies of proteins other than the respiratory ones became more extended, severe criticism was raised against the

multiple law. Also in Svedberg's own laboratory many of his colleagues did not believe it to be valid.³⁷¹ Many proteins were found, at Upsala and elsewhere, with molecular weights considerably lower than 17,600. Other proteins that were studied did not fit into the system of multiples. Eventually Svedberg himself also admitted that the multiple law did not have the generality that he had expected. According to Claesson and Pedersen, however, irrespective of its acceptance, this hypothesis was very important to the development of the protein chemistry, especially in the 1930s and early 1940s. It initiated greater interest in proteins among chemists and provided an impetus for new work. The introduction of sedimentation velocity ultracentrifugation, and later of the Tiselius electrophoresis technique, made it possible to visualize much more directly to what extent the isolation of an individual protein had been successful.³⁷²

The results obtained with the proteins greatly stimulated Svedberg to work on the development of the ultracentrifuge. He worked in the laboratory almost day and night, read as much of the literature as he could manage and knew very well what was going on in the various fields that related to his work. In this respect Pedersen wrote:

"I wonder what would have happened, if Svedberg, instead of the proteins, had started to investigate cellulose or some other macromolecular substances with his first ultracentrifuge. I doubt very much whether he would then have had enough enthusiasm to develop his ultracentrifuges as far as he did. In 1934, when we had all the troubles with vibrations and explosions, he was about to drop any further development. Had it not been for the proteins and his overwhelming interest in the multiple system for the molecular weight of the proteins, he might have stopped further work on the ultracentrifuge."³⁷³

Although Svedberg's hypothesis on the multiple system for protein sizes was considered to be an artefact it meant much for the development of protein chemistry, especially in the 1930s and at the beginning of the 1940s. It initiated greater interest in this group of substances. Several chemists and physicists came to the conclusion that proteins no longer had to be considered ill-defined lyophilic colloids, but rather well-defined exceedingly interesting and important substances, which were well worth studying.³⁷⁴

Research at Upsala in the 1930s

The protein studies gave the work at the Institute a biochemical and even medical trend. Enzymes were studied by R. Kekwick, J.B. Sumner, H. Theorell and others, antibodies by M. Heidelberger, Pedersen and Tiselius. The latter two also collaborated with F.B. Seibert on tuberculin and with a number of Swedish and

foreign investigators on various biochemical and serological problems. A great stimulus was given to the biochemical research when in 1938 a new chair of biochemistry could be established thanks to a gift of 500,000 Swedish crowns to the University by a Gothenburg foundation. Tiselius was to become the first occupant of that chair and received his appointment in May 1938. Svedberg, on whose initiative the professorship had been established, offered accommodation and equipment for the biochemical research which was to follow.³⁷⁵

At the end of the thirties, Svedberg had taken up some new problems. Together with Sven Brohult he had started investigations on the effect of ultraviolet light and ultrasonics on solutions of proteins, particularly haemocyanins, as these substances were easy to study with the ultracentrifuge.³⁷⁶ At this time Svedberg began to extend his investigations to other macromolecules of biological interest, such as for instance the polysaccharides. He had been wondering if he could find similar well defined regularities for the molecular weight of carbohydrates in native solutions as he had found for the proteins. Together with Gralén he showed the existence of soluble carbohydrates of high molecular weight in the sap of the bulbs from different species in the family Liliaceae.³⁷⁷ After an exhaustive investigation of about 75 different species in the Liliiflorae they distinguished the presence of two classes of carbohydrates, distinguished by their sedimentation behaviour. They found that there was in general a similarity among the same genus with regard to the content of high molecular material which could elucidate problems in systematic botany.³⁷⁸ An ultracentrifugal investigation of the brewing process was started in collaboration with a Swedish brewing industry.³⁷⁹ In 1936 Svedberg and Olof Quensel studied different steps in the brewing process by means of sedimentation in the ultracentrifuge, diffusion and electrophoresis experiments. Later on Quensel made a detailed study of various barley globulins leading to his dissertation in 1942, *Untersuchungen über die Gerstenglobuline*.³⁸⁰ Similarly a collaboration with Swedish cellulose industries was initiated by Svedberg who was interested in studying the cellulose molecule. In 1947 Svedberg published a review of this work.³⁸¹ During this period investigations of cellulose as well as cellulose derivatives were started, and some doctoral theses dealing with cellulose problems were published. Svedberg stimulated Nils Gralén to study cellulose and other carbo-hydrates from plants. He hoped that these would prove to be just as monodisperse as the proteins he had investigated in the preceding decade.³⁸²

The ultracentrifuge was not the only experimental tool used in Svedberg's laboratory. During the 1930s and 1940s work was going on in a number of different research using various experimental techniques. Björnsthål published studies of the Kerr-effect, of dielectric properties of matter, of magnetic double refraction and of streaming birefringence. In the latter a beam of light was send

through a solution and its deflection and absorption was studied in order to give information on that solution. In the magnetic measurements the Upsala electromagnet³⁸³ was used. It had been designed at ASEA and for many years it was the strongest in Europe (60,000 gauss). The birefringence measurements were continued by O. Snellman, who wrote his thesis on this subject.³⁸³ In the mid 30s Sven Arrhenius started dielectric measurements on protein solutions leading to his thesis *Eine dielektrische Untersuchung von Kohlenoxyd-Hämoglobin* (1940). Carl Drucker, formerly professor of physical chemistry in Leipzig, continued in Upsala his studies on the form of liquid menisci, on surface tension and capillarity corrections in viscometry and many other related topics. In 1940, Gralén and Svedberg, in search of new methods to separate macromolecules, investigated protein solutions subjected to a temperature gradient. Svedberg, Jullander and B. Enoksson designed an osmotic balance capable of very accurate determinations of osmotic pressure. A recording surface balance of the Wilhelmy-Dervichian type was designed by K. Andersson (Groth), S. Stållberg-Stenhagen and E. Stenhagen and was built at the workshop of the Institute. Stig Claesson (formally working at the Institute of Biochemistry) made many important contributions to equipment innovation and improvement, designed a widely used diffusion cell on the shearing principle and worked out an isopiestic method for molecular weight determination. His main work, however, was the pioneering experimental and theoretical investigations on absorption analysis and frontal analysis.

In 1938 Svedberg also secured an air-driven preparative ultracentrifuge of the Pickels type³⁸⁴ (see Chapter 5). Sven Gard used it for the concentration of a variety of viruses which were subsequently investigated by other means. Gard's work marked the beginning of a new important line of research in the laboratory.³⁸⁵ For instance, L.W. Janssen from the Dutch State Veterinarian Research Institute used it for the preparation of the mouth- and foot disease virus. The virus was next further analyzed in Svedberg's equilibrium ultracentrifuge.³⁸⁶

In the early 1920s Svedberg had worked on the electrophoresis of proteins. When he got heavily engaged in the further development of ultracentrifuges he turned the electrophoresis problems entirely over to Tiselius who further developed the electrophoresis technique. In the 1930s it became an important experimental tool in many biochemical laboratories and in 1948 Tiselius was awarded the Nobel Prize, partly for the development of this apparatus.³⁸⁷

Evidently, the activities of the Institute were very diversified and had a strong inclination towards development of new and refined methods of investigation, features which were continued when, after Svedberg's retirement in 1949, Stig Claesson became Professor of Physical Chemistry. Svedberg himself is credited by his students for creating an atmosphere that stimulated this type of approach. He was always open for new ideas and stimulated developing new experimental

methods.³⁸⁸

His scientific achievements were highly recognized in the scientific community. Svedberg was given honorary doctors degrees from several universities: 1914 at Groningen; 1923 at Madison, Wisconsin; 1932 in medicine at Upsala; 1936 at Harvard; 1937 at Oxford and Delaware; and 1950 in Paris. He was elected Member or Honorary Member of more than 30 learned societies all over the world. He was elected Member of the Royal Swedish Academy of Sciences at the early age of 28 years; 1944 Foreign Member of the Royal Society, London; 1945 Foreign Member of the National Academy of Sciences, Washington, D.C., and 1966 Honorary Fellow U.S.S.R. Academy of Sciences, Moscow.³⁸⁹

Further Support by the Rockefeller Foundation

After 1935, when the financial relations between Svedberg and the Rockefeller Foundation had been made stable for a period of five years by means of a long term grant, the exchange of correspondence and visits became a lot less frequent. The Foundation's officers paid occasional visits to Svedberg's laboratory in order to keep up with the progress he was making and to ask his opinion on the work of others who were working with or intended to work with ultracentrifuges.³⁹⁰ The Foundation started to play an active role in the procurement of several ultracentrifuges by foreign researchers (see Chapter 6). They also made grants available to researchers who wanted to work in Upsala for a while and asked Svedberg to make some recommendations as to whom he thought should be given such grants.³⁹¹ In the case of Signer (see Chapter 6), where they had been prepared to grant the purchase of the apparatus but where Signer was unable to raise funds for its maintenance, the Foundation appropriated a grant which made possible a cooperation of three years between Signer's Institute in Bern and Svedberg's laboratory.³⁹² Svedberg also approached the Foundation in 1938 because Tiselius had been appointed to a personal chair of biochemistry which was made possible by an endowment by a private Swedish Foundation. For Svedberg this meant that Tiselius would be connected indefinitely to the institute but in order to make full advantage of the new situation, more funds would be required. As a response to the donation of money for a chair in biochemistry the Wallenberg Foundation had agreed to increase their donation to Svedberg from Skr. 18,500 to 30,000 annually. This, Svedberg argued, implied that the proportion 2:1 between the grants from the Rockefeller and the Wallenberg Foundations was now considerably lowered. In view of the fact that even with the higher contribution from the Wallenberg Foundation it would be impossible to finance Tiselius' new research program, Svedberg asked whether the Rockefeller Foundation might be willing to

raise their grant so as to maintain the proportion 2:1. This would mean an increase from Skr. 37,000 to Skr. 60,000 or from about \$ 10,000 to \$ 16,000.³⁹³ This request, however, was not awarded. According to Weaver the Swedish help for Tiselius was very good and they could not contemplate the indefinite expansion of Svedberg's laboratory.³⁹⁴

Because Svedberg's work was at the heart of the Foundation's program Tisdale asked Svedberg late 1938 to prepare a report for the Trustees of the Foundation which should play a role in an internal discussion of their program.³⁹⁵ In his report Svedberg summarized the work he had done under the Foundation's assistance and also how it had stimulated assistance from other sources. Concerning the Wallenberg Foundation he mentioned that in addition to their Skr. 18,500 grant for five years they had appropriated an extra Skr. 11,500 for the period 1938-1940. He also mentioned cooperation with other institutions like the Academic Medical Clinic at Upsala, The Rockefeller Institute for Medical Research (New York), The Henry Phipps Institute (Philadelphia), The Lister Institute of Preventive Medicine (London), the Department of Biochemistry (Oxford) and the Department of Chemistry (Bern). Furthermore the National Swedish Committees for the study of tuberculosis and of infantile paralysis had sought contact with a view of establishing joint research work. Investigations on tuberculosis had just started in cooperation with the Bacteriological Institute at Upsala and Studies on infantile paralysis would be postponed until the bacteriologist appointed for work in their institute had returned from a year of training and studies in the US.³⁹⁶

Early 1939 Svedberg wrote Tisdale that he would be interested in obtaining further assistance from the Rockefeller Foundation after his present grant would have expired in 1940. He had already started negotiations with the Wallenberg Foundation and would like to have some statement from the Rockefeller Foundation as to its possible future interest in his laboratory. Tisdale replied that only the Trustees could make definite statements in this respect but that it might be sufficient inform the Wallenberg Foundation that he himself and Weaver were certainly interested in the continuation of Svedberg's researches.³⁹⁷ Shortly thereafter Svedberg informed Tisdale that the Wallenberg Foundation had appropriated a yearly sum of Skr. 30,000 for the period 1941-1950 upon the condition that the Rockefeller Foundation would give a yearly contribution for the same period of at least the same amount as that given at that moment, viz Skr. 37,000.³⁹⁸

After World War II had broken out Svedberg informed Weaver and Tisdale that the situation in Sweden looked quite normal and that in his institute work was going on as usual but that he could understand that the Foundation Officers would not sail for Europe. He also reported some of the latest developments, both with respect to the ongoing researchers as well as the development of the apparatus.

The third high-speed ultracentrifuge had been in operation for some time which had a somewhat higher resolving power than the earlier ones. The cost of running was now actually lower than for an air-driven ultracentrifuge. Furthermore their monograph on the ultracentrifuge would soon appear.³⁹⁹ Concerning possible further support Tisdale replied that it was their usual custom to arrange for a visit during which they could talk over all the details concerned far more effectively than they could write about them. Under the present circumstances, however, Tisdale advised Svedberg to send them a brief resume of his researches under the grant of funds from the Foundation and, because Svedberg envisaged a period of ten years, an outline of his plans for that period. Svedberg used the report he had sent a year before and carried it on to the present date. He also enclosed summarized budgets for the period of the Foundation's assistance (from 1932 onward) showing sources for funds and expenditures. He expressed his hope that the Rockefeller Foundation would be willing to appropriate an annual grant of \$ 15,000 for the period 1941-1950 and wondered if he would have to apply for a grant in a formal way. Concerning his future plans he intended to continue his investigations of the general molecular properties of high molecular compounds, especially proteins and polysaccharides, using the techniques of ultracentrifugal sedimentation, diffusion and electrophoresis. The molecular shape would be studied by orientation determinations in electric, magnetic and hydrodynamic fields. Also studies on the enzymatic splitting of proteins were envisaged and special attention would be devoted to the physiological functions of the serum proteins, the change in the composition of serum in pathological conditions, and the relations between antibodies and serum proteins. He expected that the cooperation with the Swedish Anti-tuberculosis League, which appropriated yearly grants from Skr. 12,500 to Skr. 20,000, would continue after 1941 and that cooperation with the Swedish Anti-Poliomyelitis League, including a yearly grant of Skr. 45,000, was planned for the period 1940-1944. The decision of a yearly grant from the Swedish State (Skr. 35,000) so far had just been a matter of form but Svedberg envisaged that under the strained conditions of the war this grant would probably be reduced.⁴⁰⁰

Under the conditions of the war the officers did not consider it appropriate to award a long term grant and advised the Trustees to award Svedberg Skr 45,000 (\$ 11,250) for 1941. Concerning Svedberg they stressed the uniqueness of his work and also his willingness to cooperate with other researchers:

"He was able to determine their (proteins; BE) molecular weights and their dimensions by the centrifuge, but with these measurements established, his curiosity was aroused to learn of their other characteristics, with the result that at the present time his laboratory is one of the principal ones of the world concerned with the study of proteins - their weight and structure; their chemical behaviour, especially at and near their isoelectric points; their behaviour under the action of light, heat, magnetic fields, and electric forces. Indeed, their reaction in

an electric field stimulated one of his assistants, Dr. Tiselius, to develop the electrophoresis technique to such a stage that it is now playing an important role in science, quite apart from its relation to the centrifuge technique. Dr. Tiselius has recently been made a professor, and he doubtless will eventually succeed Professor Svedberg as Director of the Physical Institute. Not only have studies on the proteins been emphasized in the laboratory of Professor Svedberg, but also studies on polysaccharides in unchanged states, as found in potatoes and other plant material; studies on haemo compounds with globulin and with cyanins; and more recently plans are maturing for studies on virus problems.

Professor Svedberg has placed the facilities of his Institute at the service of science - he has constructed duplicates of his equipment for installation in other centres, such as London, Oxford, and Madison; he has cooperated with many investigators in whose laboratories his techniques have served to complement the studies of other disciplines; he has opened his laboratories to visiting scientists, a score or more of whom have been sent to him under our fellowship programs; and he has in all ways exhibited those rare qualities which mark their possessors for leadership.⁴⁰¹

The one year grant was awarded, also considering that in normal times, the officers would be prepared to recommend long term support for this project, but, under the uncertain conditions then prevailing, it was felt that both the interests of this laboratory and those of the Foundation could best be protected under a short-term grant of one year, with the intention either to recommend a renewal, or, if stable conditions would arise, a period grant.⁴⁰² The grant was renewed each year until 1945.⁴⁰³ A terminal appropriation of \$ 50,000, made in 1946 to carry support until Svedberg's scheduled retirement in 1951, brought the total of Rockefeller gifts to \$ 242,500.⁴⁰⁴

Svedberg's Activities after 1940

After the outbreak of World War II Svedberg became heavily engaged in work for the government and for other State Agencies. One activity, which took much of his time, was the development of a Swedish production of synthetic rubber. Owing to the blockade during the war, no oil-resistant rubber could be obtained from abroad while the Swedish armed forces considered it essential to have this material available. Thereupon Svedberg opened his institute for experiments on the production of neoprene. A large part of the work at the institute was devoted to this task and the methods were worked out on different scales, from the laboratory experiment to the complete small scale rubber mill, which was built in one of the corridors. Parallel to this work a study of the properties of rubber was started. Shortly thereafter most of the engineering work was transferred to the Swedish Rubber Research Institute at Upsala, still under Svedberg's supervision. Based on the experience and results of the early researches a factory was built for the production of neoprene on a large scale during the war.⁴⁰⁵

Svedberg had also to advise and direct experimental work in his own laboratory as well as in outside institutes and industries closely related to the war situation. This gave him less opportunity than before for experimental work with his own hands and forced him to devote more time to planning and directing all the various activities. He was at this time one of the most influential scientists in Sweden, and he was in the position of playing a very important role in the creation in 1942 of the Research Council for Technology. This was the first Research Council in Sweden and was soon followed by several others. He was a member of the Council from 1942 to 1957.

Closely connected to this activity were his relations with the Atomic Research Council (founded 1946) of which he was a member from 1946 to 1959. From 1947 to 1956 he was also a member of the Board of AB Atomenergi which was partly owned by the government. Svedberg's had had a long term interest in radioactivity and in other processes occurring inside the atom. After the existence of the neutron particle was proposed in 1932 and readily accepted soon thereafter Svedberg's interest in radioactivity was extended to this neutral particle. He had already studied the effect of alpha-particles on proteins, and wondered what the action of an uncharged particle would be. According to Pedersen it was a typical example of his enthusiasm and openness towards new ideas and methods that he was able to build a small neutron generator. This apparatus was used for irradiation purposes and also for production of some radio isotopes for tracer work. Though only actively used for a short period, it stimulated Svedberg's interest in various aspects of nuclear physics. He became interested in building a cyclotron to be used in the production of radioactive isotopes and in the field of radiation chemistry. Svedberg had been collaborating in the use of radioactive tracers produced by the neutron generator with one of his old friends in the Medical Faculty, John Naeslund. The latter, who had personal contact with a public spirited industrialist in Gothenburg, Gustaf Werner, suggested that they should approach Gustaf Werner about the possibility of getting financial help to build a large cyclotron. This would enormously increase their research potential in the field of radiation chemistry and radioactive isotopes. Svedberg was most enthusiastic about this idea, and the response from Gustaf Werner was equally positive, partly because of his general interest in the possible medical applications of such research. The Gustaf Werner Institute with its big synchrocyclotron (185 MeV) in its 1,000 m underground hall was inaugurated in December 1949. This was soon after Svedberg's 65th birthday. After Svedberg's retirement Stig Claesson became his successor. In the 1950s the research at the institute gradually turned away from the proteins and fields like photochemistry became ever more important. Pedersen, who had come to Upsala in 1930 and who had been Svedberg's first assistant in the further development of the ultracentrifuge, kept studying proteins until his retirement. For

these experiments he always used the oilturbine ultracentrifuge which was still in operation in the mid 1970s.⁴⁰⁶

Svedberg retired from his chair in physical chemistry at the mandatory age of 65. However, by a ruling unique in Swedish administration, he was allowed to remain head of the Gustaf Werner Institute as long as he desired. He next set himself the task of creating a new research institute around the cyclotron. The work here should be focused on biological and medical applications, but should also include radiation effects on macromolecules as well as radiochemistry and radiation physics. He resigned as head of the Werner Institute in 1967 and then left Upsala for good. Some years earlier he had moved together with his fourth wife and their three young children to an old mining inspector's farm, Sundet, Kopparberg, situated not far from the place where he spent most of his boyhood.⁴⁰⁷ He died on 25 February 1971.⁴⁰⁸

Notes

Notes, like 'Svedberg (1907)' refer to published sources given in the bibliography at the end of this book. Other notes refer to unpublished material, e.g. private correspondence, that can be found in various archives. This material is referred to by a code, indicating where it can be found, and an indication of the source. For instance, 'Svedberg to Nichols, 27 July 1928' refers to a letter from Svedberg to Nichols of the given date. The codes used have the following meaning:

(RAC:1.1/800D/9/75) - Collection at the Rockefeller Archive Centre, North Tarrytown, New York. This example indicates series 800D, Box 9, Folder 75.

(RAC/IEB:1.2/42/590) - International Education Board collection, also at the Rockefeller Archive Centre, series 1.2, Box 42, Folder 590.

(UVa/7265-b/2/@) - Manuscripts Department of the Library of the University of Virginia, Charlottesville, Virginia. Accession No. of Collection 7265-b, Box 2. The symbol @ concerns an indication of a folder, e.g. 'occupational papers' or a letter from the alphabet.

(UUp-Lib) - Svedberg's private correspondence and papers, University of Uppsala Library, Uppsala, Sweden. This material had just been handed over to the library when I came to study it and had not yet been sorted out and catalogued.

(HML) - Dr. J. Burton Nichols' private collection of correspondence and papers, Hagley Museum and Library, Wilmington, Delaware. This material had just been handed over to the library when I came to study it and had not yet been sorted out and catalogued.

(EGP) - Private collection of correspondence and papers, Dr. E.G. Pickels, Cupertino, California.

The notes sometimes refer to persons that are not discussed in the main text. These people are characterised further, sometimes in code, by the organization or company they were associated with which stands between brackets behind their name. The codes used are the following meaning: AAAS - American Association for the Advancement of Science; AISI - American Iron and Steel Institute; BLC - Bausch and Lomb Company; IEB - International Education Board; JACS - Journal of the American Chemical Society; LI - Lister Institute of Preventive Medicine; LKB - LKB-Produkter AB; NMRI - (American) Naval Medical Research Institute; NRC - (American) National Research Council; RF - Rockefeller Foundation; RI - Rockefeller Institute; SU - Stanford University; UUp - Uppsala University; UVA - University of Virginia; UWi - University of Wisconsin.

1. Claesson and Pedersen (1972), p.595 and Pedersen (1983), p.235.
2. Nowadays, the name Upsala is written with two p's, hence Uppsala. As is evident from Svedberg's correspondence a change in spelling must have occurred somewhere in the early 1940s. As most of the material presented here is concerns the 1920s and 1930s the name Upsala is written with one p throughout this study.

3. Pedersen (1983), pp.235-236; Claesson and Pedersen (1972), pp.595-596; Sunderlöf and Pedersen (1976), p.167.
4. Sunderlöf and Pedersen (1976), pp.153-154.
5. Graham (1861), p.183.
6. Hess (1970), p.666.
7. Eugen Chirnoaga in the Rumanian Journal 'Nature', October 1927 (UUp-Lib).
8. Svedberg (1935), p.297.
9. Tiselius and Claesson (1967), p.2.
10. Svedberg (1905).
11. Pedersen (1983), pp.235-236.
12. Rånby (1987), p.3.
13. Claesson and Pedersen (1972), p.596.
14. Siedentopf and Zsigmondy (1903).
15. Einstein (1905 and 1906).
16. Edsall (1962), p.17.
17. Svedberg (1906a and 1906b).
18. Tiselius and Claesson (1967), pp.2-3.
19. Svedberg (1907).
20. Claesson and Pedersen (1972), pp.617-619. On pp.617-627 Claesson and Pedersen give a full bibliography of Svedberg's work.
21. Svedberg (1909).
22. Claesson and Pedersen (1972), p.597; Pedersen (1983), pp.235-238; and Stenius (1987), pp.17-18.
23. Odén (1913).
24. Pedersen (1983), pp.235-238; Claesson and Pedersen (1972), p.598.
25. Svedberg (1912).
26. Quoted in Lepsius (1964), p.717.
27. Claesson and Pedersen (1972), p.599.
28. Claesson and Pedersen (1976), p.160.
29. Svedberg (1935), p.297.
30. Svedberg and Estrup (1911), pp.259-260.
31. Svedberg and Rinde (1923), pp.943-944.
32. Odén (1915).
33. Svedberg and Rinde (1923), p.944.
34. Svedberg and Rinde (1923), p.944.
35. Svedberg and Rinde (1923), p.949.
36. Svedberg and Rinde (1923), p.950.
37. Svedberg and Rinde (1923), pp.949-953.
38. Svedberg (1938), p.114.
39. Claesson and Pedersen (1972), p.600.
40. Mathews (1966) p.410.
41. Svedberg, 'Distribution Curves: Distribution of Concentration', unpublished memo, 1923 (UUp-Lib).
42. Dr. J. Burton Nichols, private communication.
43. Nichols (1987), p.45.
44. Nichols (1927), p.32; and Dr. J. Burton Nichols, private communication.
45. 'Program of the first Symposium on Colloid Chemistry', Graduate School University of Wisconsin, 1923 (UUp-Lib)
46. Svedberg (1923), pp.75-76.
47. Svedberg (1923), pp.84-85.
48. Svedberg and Nichols (1923), pp.2911-2912.
49. Svedberg and Nichols (1923), pp.2916-2917.
50. Svedberg (1935), p.297.
51. Pedersen (1976), p.14.
52. Pedersen (1976), p.4; Claesson and Pedersen (1972), p.600.
53. Tiselius and Claesson (1967), p.3.
54. Claesson and Pedersen (1972), p.600.
55. Giro Instruments to Axel Ljungströms Agentur A.-B., 4 October 1923; Axel Ljungströms Agentur to Svedberg, 19 November 1923; and Giro Instruments to Svedberg, 26 November 1923 (UUp-Lib).
56. Svedberg to Nichols, 27 December 1923 (UUp-Lib).

57. Nichols to Svedberg, 24 December 1923 (UUp-Lib).
58. Svedberg to Nichols, 6 February 1924 (UUp-Lib).
59. Svedberg to Nichols, 24 July 1924 (UUp-Lib).
60. Quoted in Pedersen (1983), pp.239-240.
61. Quoted in Pedersen (1976), pp.5-6.
62. Svedberg and Rinde (1924).
63. Svedberg and Rinde (1924), pp.2677-2678.
64. Svedberg (1926), p.67.
65. Svedberg to Adam Hilger Ltd., July 1925 (UUp-Lib).
66. Adam Hilger Ltd. to Svedberg, 22 July 1925 (UUp-Lib).
67. Svedberg to Adam Hilger Ltd., 25 July 1925 (UUp-Lib).
68. Rinde (1928), p.92.
69. Svedberg and Rinde (1924), p.2686.
70. Rinde (1928), p.93.
71. Svedberg and Rinde (1924), pp.2686-2687.
72. Svedberg (1925), p.54.
73. Svedberg and Rinde (1924), p.2690.
74. Rinde (1928), pp.96-97. See also: Svedberg and Rinde (1924), pp.2677-2681.
75. Svedberg and Rinde (1924), pp.2682-2683.
76. Svedberg and Rinde (1924), p.2684.
77. Svedberg (1924), p.152.
78. Svedberg (1924), p.153.
79. Svedberg (1925), pp.55-56.
80. Svedberg (1925), pp.59-60.
81. Pedersen (1976), p.7.
82. Svedberg and Jette (1923).
83. Svedberg (1923), pp.86-87.
84. Svedberg, 'Remarks on the Physical Chemistry of Proteins', unpublished memo, 23 April 1923, (UUp-Lib).
85. Svedberg to Mathews, 12 June 1924 (UUp-Lib).
86. Quoted in: Pedersen (1976), p.5.
87. Quoted in: Edsall (1962), p.12-13.
88. Schulz (1903), p.101.
89. Edsall (1962), p.14.
90. Flory (1953), pp.3-28.
91. Edsall (1962), pp.15-16.
92. Hess (1970), p.666.
93. Hess (1970), p.666. See also: Edsall (1962); Pedersen (1983), pp.233-235; and Fruton (1972), pp.136-137.
94. Pedersen (1983), pp.233-234.
95. Edsall (1962), p.17.
96. Hess (1970), p.666 and Edsall (1962), p.17.
97. Edsall (1962), p.18.
98. Claesson and Pedersen (1972), pp. 3-4.
99. Svedberg to Nichols, 24 July 1924 (UUp-Lib).
100. Svedberg to Nichols, 28 April 1925 (UUp-Lib).
101. Svedberg (1930a), p.10.
102. Pedersen (1983), p.241.
103. Pedersen (1976) p.7; and Pedersen (1983) pp.240-241.
104. Svedberg (1930a), p.10 (Translated from German by the author). Original German text: 'Als der Verf. nach einigen mit J.B. Nichols (...) und H. Rinde (...) ausgeführten Messungsreihen an anorganischen Kolloiden, spez. an Goldhydrosolen, an die Aufgabe ging die Dispersität der Proteine zu studieren, war er in der festen Überzeugung, dass die letzteren ebenso wie die Goldhydrosole sich als polydispers herausstellen würden. Die Aufgabe, die er sich stellte, war also die Bestimmung der Teilchenverteilungskurven der Eiweisskörper unter verschiedenen Versuchsbedingungen.'
105. Svedberg and Fåhræus (1926), p.430.
106. Svedberg and Fåhræus (1926), pp.432-433.
107. Svedberg and Fåhræus (1926), pp.435-436.

108. Svedberg and Fåhræus (1926), p.436.
109. Svedberg (1930a), p.10.
110. Svedberg (1938), p.114. See also: Pedersen (1983), p.242; Claesson and Pedersen (1972), p.603.
111. Boestad, Pedersen and Svedberg (1938), p.346.
112. Svedberg to Nichols, 15 February 1925 (UUp-Lib).
113. Claesson and Pedersen (1972), p.7, Pedersen (1976), p.603, Pedersen (1983), pp.242-243.
114. This situation essentially continued until after the Second World War when the manufacture of commercial scientific instruments on a larger scale began.
115. Sunderlöf and Pedersen (1976), pp.165-166; and Pedersen (1983), p.243.
116. Pedersen (1983), p.243.
117. Svedberg and Nichols (1927).
118. Svedberg and Lysholm (1927).
119. Svedberg (1927a).
120. Svedberg and Lysholm (1927), p.4 and Svedberg and Nichols (1927), pp.2922-2923.
121. Svedberg and Lysholm (1927), p.4.
122. Svedberg and Nichols (1927), pp.2922-2927; Svedberg (1927a), pp.57-65; and Svedberg and Lysholm (1927), pp.2-17.
123. Svedberg and Lysholm (1927), p.5, footnote.
124. Nichols (1928), p.289.
125. Svedberg and Nichols (1927), pp.2927-2928; Svedberg (1927a), pp.65-67; Svedberg and Lysholm (1927), pp.17-19.
126. Svedberg to Nichols, 20 June 1928 (HML).
127. Svedberg to Nichols, 8 September 1928 (HML).
128. Svedberg and Nichols (1927), pp.2921-2922; Svedberg (1927a), pp.52-57; Svedberg and Lysholm (1927), pp.19-22.
129. Svedberg and Lysholm (1927), pp.23-24.
130. Nichols (1927), p.91.
131. Nichols (1928).
132. Bäcklin (1927).
133. Nichols (1927), pp.127-129.
134. Quoted in: Pedersen (1983), pp.243-244.
135. Lamm (1928), p.313.
136. Svedberg to Nichols, 20 January 1928 (HML).
137. Nichols to Svedberg, 21 March 1928 (HML).
138. Svedberg to Nichols, 6 April 1928 (HML).
139. Nichols to Svedberg, 14 April 1928 (HML).
140. Nichols to Svedberg, 11 May 1928 (HML).
141. Svedberg to Nichols, 5 June 1928 (HML).
142. Pedersen (1976), p.9.
143. Svedberg and Nichols (1927), p.2920.
144. Claesson and Pedersen (1972), pp.603-604.
145. Quoted in: Pedersen (1983), pp.245-246.
146. Quoted in: Pedersen (1983), p.246.
147. Pedersen (1983), pp.245-246.
148. Svedberg and Nichols (1926), pp.3089-3090.
149. Svedberg and Nichols (1926), p.3092.
150. Alexander to Svedberg, 2 July 1923; and Alexander to Svedberg, 10 April 1924 (UUp-Lib).
151. Svedberg to Alexander, 9 September 1924 (UUp-Lib).
152. Barham to Svedberg, 30 September 1924 (UUp-Lib).
153. Donnan to Svedberg, 24 June 1926 (UUp-Lib).
154. Cohn (1925).
155. Cohn to Svedberg, 26 April 1926 (UUp-Lib).
156. Svedberg to Cohn, 30 May 1926 (UUp-Lib).
157. Svedberg to Cohn, 11 August 1926 (UUp-Lib).
158. Adair (1925).
159. Adair to Svedberg, March 1926 (UUp-Lib).
160. Svedberg to Adair, 22 March 1926 (UUp-Lib).
161. Adair to Svedberg, April 1927 (UUp-Lib).
162. Svedberg to Adair, 14 April 1927 (UUp-Lib).

163. Svedberg to Mathews, 1 February 1925 (UUp-Lib).
164. Svedberg to Mathews, 20 November 1926 (UUp-Lib).
165. Arrhenius (1921), p.479.
166. Arrhenius (1921), p.479.
167. Söderbaum (1927).
168. Perrin (1926).
169. Söderbaum (1926).
170. Svedberg (1927b), pp.65-66.
171. Svedberg (1927b), p.63.
172. Svedberg (1927b).
173. Svedberg (1927b), p.65.
174. Kerker (1986), pp.279-280.
175. Excerpt from Svedberg's autobiographical notes. Quoted in Kerker (1986), p.281.
176. Söderbaum (1927), p.68.
177. Söderbaum (1927), pp.79-80.
178. Söderbaum (1927), p.83.
179. Brohult and Gralén (1944), p.624.
180. Nichols (1987), p.48.
181. Excerpt from Svedberg's autobiographical notes. Quoted in: Kerker (1986), pp. 681-682.
182. A detailed description of the new laboratory is given in: Bjornstål (1934).
183. Svedberg to Trowbridge (IEB), 7 September 1927; quoted in: (RAC:IEB-1.2/42/590) Trowbridge to Svedberg, 21 September 1927; and in (RAC:IEB-1.2/42/590) Trowbridge to Rose (IEB), 22 September 1927.
184. (RAC:IEB-1.2/42/590) Trowbridge to Rose, 22 September 1927.
185. (RAC:IEB-1.2/42/590) Rose to Trowbridge, 3 October 1927.
186. (RAC:IEB-1.2/42/590) Trowbridge to Svedberg, 21 September 1927.
187. (RAC:IEB-1.2/42/590) Svedberg to Trowbridge, 17 June 1928.
188. (RAC:IEB-1.2/42/590) Trowbridge to Svedberg, 23 June 1928.
189. (RAC:IEB-1.2/42/590) Svedberg to Trowbridge, 27 June 1928.
190. (RAC:IEB-1.2/42/590), Trowbridge to Arnett, 7 July 1928.
191. (RAC:IEB-1.2/42/590), Trowbridge to Arnett, 7 July 1928.
192. (RAC:IEB-1.2/42/590) Brierly to Svedberg, 13 December 1928.
193. Brohult and Gralén (1944), p.626.
194. Claesson and Pedersen (1972), pp.602-603.
195. Rinde (1928).
196. Tiselius (1926).
197. Svedberg to Nichols, 16 July 1926 (UUp-Lib).
198. Herzog to Svedberg, 31 January 1928 (UUp-Lib).
199. Svedberg to Cohn, 3 June 1927; and Cohn to Svedberg, 16 June 1927 (UUp-Lib).
200. Aborn to Svedberg, 17 October 1927 (UUp-Lib).
201. Svedberg to Cohn, 3 June 1927 (UUp-Lib).
202. Svedberg (1928b).
203. Svedberg and Heyroth (1929).
204. Svedberg to Nichols, 6 April 1928 (HML).
205. Svedberg (1928a), p.165.
206. Svedberg (1929).
207. Kinell (1987), p.11.
208. Williams (1974), p.3.
209. Prof. John T. Edsall, private communication. See also Flory (1953), pp.3-28.
210. Vickery and Osborne (1928), p.411.
211. Astbury and Woods (1931).
212. Pedersen (1983), pp.249-250; Prof. Kai O. Pedersen, private communication.
213. Svedberg (1930b), p.744.
214. Fruton (1972), p.138.
215. Svedberg (1930a), p.19.
216. Svedberg (1930a), p.17.
217. Svedberg to Nichols, 6 April 1928 (HML).
218. Brohult and Gralén (1944), pp.628-629.
219. Lepsius (1964).

220. Svedberg and Heyroth (1929), pp.552-553.
221. Svedberg and Sjögren (1929), pp.3597-3598.
222. Svedberg (1930a), p.12.
223. Pedersen (1976), p.11.
224. Svedberg to Nichols, 20 January 1928 (HML).
225. Svedberg to Nichols, 5 June 1928 (HML).
226. Svedberg to Nichols, 8 September 1928 (HML).
227. Svedberg and Pedersen (1940), p.99.
228. Quoted in: Pedersen (1976), pp.9-10.
229. Pedersen (1976), p.10.
230. Svedberg (1931b). See also: Pedersen (1983), p.257.
231. Pedersen (1976), p.11.
232. Svedberg and Eriksson (1932), pp.4000-4001.
233. Svedberg and Eriksson (1932), p.3998.
234. Svedberg and Pedersen (1940), pp.104-106.
235. Svedberg and Eriksson (1932), pp.3998-3999.
236. Svedberg to Nichols, 15 August 1930 (HML).
237. Pedersen (1983), p.259.
238. Nichols to Svedberg, 3 June 1929 (HML).
239. Brohult and Gralén (1944), p.631.
240. Brohult and Gralén (1944), pp.631-632; Sunderlöf and Pedersen (1976), p.161.
241. Svedberg and Eriksson (1932), p.3999.
242. Svedberg and Pedersen (1940), pp.106-107.
243. See e.g. Svedberg to Nichols, 20 January 1928; Svedberg to Nichols, 6 April 1928; and Svedberg to Nichols, 8 September 1928 (HML).
244. Pedersen (1976), p.16.
245. Svedberg and Pedersen (1940), p.107.
246. Nichols to Svedberg, 23 March 1933 (UUp-Lib).
247. Pedersen (1976), p.16.
248. Lamm (1933).
249. Svedberg (1934c), p.10.
250. Pedersen (1976), pp.11-12.
251. Svedberg to Nichols, 25 January 1933 (HML).
252. Svedberg to Kraemer, 10 October 1934 (UUp-Lib).
253. Svedberg to Kraemer, 20 February 1934 (UUp-Lib).
254. Svedberg to Kraemer, 10 October 1934 (UUp-Lib).
255. Astrid Hedenius, private communication.
256. Svedberg (1931a).
257. Svedberg (1933), pp.314-315.
258. Svedberg (1933), pp.319-320.
259. Svedberg (1933), pp.321-322.
260. Svedberg (1933), p.324.
261. Tiselius (1932).
262. Quoted in Claesson and Pedersen (1972), p.609.
263. Bernal and Crowfoot (1933).
264. Claesson and Pedersen (1972), pp.609-610 and John T. Edsall, private communication.
265. Svedberg and Sjögren (1928).
266. Von Mutzenbecher (1931).
267. Von Mutzenbecher (1933a and 1933b).
268. Pedersen (1983), pp.263-264.
269. Staudinger (1960), p.101.
270. Signer and Gross (1934a).
271. Signer and Gross (1934b).
272. Signer and Gross (1934c).
273. Kinell (1987), pp.37-38.
274. Svedberg (1934d).
275. Svedberg to Krejci, 31 July 1934 (UUp-Lib).
276. Svedberg to Krejci, 17 July 1934 (UUp-Lib).
277. Corner (1964), p.38.

278. Corner (1964), pp.43-45.
279. Corner (1964), pp.71-71.
280. (RAC:1.1/800D/9/75) Jones' diary, 18 May 1931.
281. (RAC:1.1/800/7/75) O'Brien to Gregg, 27 October 1931.
282. (RAC:1.1/800/7/75) RF-31150: 'Grant appropriation to the University of Upsala (Svedberg)', 16 December 1931.
283. Kohler (1979), pp.257-258. See also: Abir-Am (1982) for the Rockefeller Foundation's policy in Molecular Biology.
284. (RAC:1.1/800/7/75) Weaver's diary, 6 May 1933.
285. (RAC:1.1/800/7/75) Gregg's diary, 5 July 1933.
286. (RAC:1.1/800/7/76) Svedberg to Jones (RF), 22 January 1934.
287. (RAC:1.1/800/7/76) Weaver to Jones, 15 February 1934.
288. (RAC:1.1/401/18/244) O'Brien's diary, 14 April 1934 and (RAC:1.1/800/7/76), Tisdale's diary, 14 April 1934.
289. (RAC:1.1/800/7/76) Tisdale's diary, 14 April 1934.
290. (RAC:1.1/800/7/76) Tisdale to Weaver, 19 June 1934.
291. Tisdale to Weaver, 30 April 1934; quoted in an annex to (RAC:1.1/800/7/76) Tisdale's diary, 14 April 1934.
292. (RAC:1.1/800/7/76) Tisdale to Weaver, 23 June 1934.
293. (RAC:1.1/800/7/75) RF-34111: 'Grant appropriation to the University of Upsala (Svedberg)', 28 September 1934.
294. Tisdale (RF) to Svedberg, 23 October 1934 (UUp-Lib).
295. (RAC:1.1/800/7/76), Tisdale's diary, 2 November 1934.
296. (RAC:1.1/800/7/76) Svedberg to Tisdale (RF), 14 January 1935.
297. (RAC:1.1/800/7/76) RF-35044: 'Grant appropriation to the University of Upsala (Svedberg)', 17 April 1935.
298. (RAC:1.1/800/7/76) RF-35044: 'Grant appropriation to the University of Upsala (Svedberg)', 17 April 1935.
299. Svedberg (1934b).
300. Svedberg (1934d).
301. Svedberg (1934a), p.329; Svedberg (1934b), p.225.
302. Svedberg, Boestad and Eriksson-Quensel (1934).
303. Svedberg to Nichols, 10 March 1934 (HML).
304. Svedberg, Boestad and Eriksson-Quensel (1934).
305. Svedberg to Nichols, 19 October 1934 (HML).
306. Pedersen (1935) and Kohler (1976), pp.160-161.
307. Svedberg and Pedersen (1940), pp.118-125.
308. (RAC:1.1/800/7/76) Tisdale's diary, 2 November 1934.
309. Svedberg to Carl Schenck, GmbH., 1 December 1934; Carl Schenck, GmbH., to Svedberg, 10 December 1934; and Svedberg to Carl Schenck, GmbH., 12 December 1934 (UUp-Lib).
310. Svedberg to Kraemer, 5 March 1935 (UUp-Lib).
311. Svedberg and Pedersen (1940), p.125.
312. Svedberg to Kraemer, 27 January 1936 (UUp-Lib).
313. Pedersen (1976), p.15.
314. Pedersen (1976), p.16.
315. Svedberg to Nichols, 13 May 1936 (UUp-Lib).
316. Svedberg to Nichols, 19 May 1938 (HML).
317. Boestad, Pedersen and Svedberg (1938), p.352.
318. Svedberg and Pedersen (1940), pp.138-139.
319. Claesson and Pedersen (1972), pp.607-608.
320. Sunderlöf and Pedersen (1976), p.159.
321. Claesson and Pedersen (1972), pp.607-608.
322. Svedberg (1937).
323. Svedberg (1938).
324. Boestad, Pedersen and Svedberg (1938).
325. Svedberg (1938), pp.115-116.
326. Svedberg (1937), pp.1053-1054.
327. Boestad, Pedersen and Svedberg (1938), p.352.
328. Boestad, Pedersen and Svedberg (1938), pp.347-348.

329. Svedberg to Kraemer, 28 February 1936 (UUp-Lib); and Svedberg (1937), p.1054.
330. Svedberg to Kraemer, 28 February 1936 (UUp-Lib).
331. Tiselius, Pedersen and Eriksson-Quensel (1937); and Pedersen (1976), p.17.
332. Tiselius, Pedersen and Svedberg (1937), p.848.
333. Svedberg (1935), p.303.
334. Svedberg (1938).
335. Kraemer (1938).
336. Johnson to Svedberg, 17 August 1931 (UUp-Lib).
337. Svedberg to Johnson, 1 September 1931 (UUp-Lib).
338. Svedberg to Krejci, 4 June 1931 (UUp-Lib).
339. Herzog to Svedberg, 22 December 1934 (UUp-Lib).
340. Svedberg to Herzog, 3 January 1935 (UUp-Lib).
341. Svedberg to Jirgensons, 23 March 1934 (UUp-Lib).
342. Svedberg to Cohn, 12 April 1935 (UUp-Lib).
343. Stanley to Svedberg, 10 July 1935 (UUp-Lib).
344. Svedberg to Stanley, 28 July 1935 (UUp-Lib).
345. Stanley to Svedberg, 14 November 1935 (UUp-Lib).
346. Stanley to Svedberg, 9 January 1936 (UUp-Lib).
347. Svedberg to Stanley, 7 March 1936 (UUp-Lib).
348. Stanley to Svedberg, 24 March 1936 (UUp-Lib).
349. Eriksson-Quensel and Svedberg (1936).
350. Stanley to Svedberg, 9 July 1936 (UUp-Lib).
351. Svedberg to Stanley, 10 October 1936 (UUp-Lib).
352. Stanley to Svedberg, 26 March 1937 (UUp-Lib).
353. Svedberg to Stanley, 12 April 1937 (UUp-Lib).
354. (RAC:1.1/100/10/81) Bauer to Svedberg, 22 November 1937.
355. Sommerfeld to Svedberg, 29 March 1939 (UUp-Lib).
356. Svedberg to Sommerfeld, 31 March 1939 (UUp-Lib).
357. See e.g. Svedberg to Brouchère, 8 February 1938; and Svedberg to Miller (RF), 17 August 1939 (UUp-Lib).
358. Kraemer to Nichols, 10 September 1938 and Kraemer to Nichols, 7 February 1939 (HML).
359. Sunderlöf and Pedersen (1976), p.161.
360. Ostwald to Svedberg, 24 January 1933 (UUp-Lib).
361. Svedberg to Ostwald, 30 January 1933 (UUp-Lib).
362. Thiessen to Svedberg, 23 August 1937 (UUp-Lib).
363. Thirring to Svedberg, 25 April 1939 (UUp-Lib).
364. See e.g. (RAC:1.1/800/7/76) Svedberg to Bauer, 25 September 1936; and (RAC:1.1/100/10/81) Bauer to Svedberg, 27 April 1938.
365. Svedberg and Pedersen (1940a and 1940b).
366. See e.g. Bauer to Svedberg, 1 May 1940 (UUp-Lib); Claesson and Pedersen (1972), p.610.
367. Kraemer to Svedberg, 2 July 1937 (UUp-Lib).
368. Svedberg (1939), p.40.
369. Svedberg (1939), p.45.
370. Svedberg (1939), p.54.
371. Prof. Sven Brohult and Prof. Nils Gralén, private communication.
372. Claesson and Pedersen (1976), p.162.
373. Pedersen (1976), p.17.
374. Pedersen (1976), p.17.
375. Brohult and Gralén (1944), p.633.
376. Svedberg and Brohult (1938 and 1939).
377. Svedberg and Gralén (1938).
378. Svedberg and Gralén (1940).
379. Quensel and Svedberg (1938).
380. Quoted in: Sunderlöf and Pedersen (1976), p.161.
381. Svedberg (1947).
382. Prof. Nils Gralén, private communication.
383. "Some Measurements of Magnetic Double Refraction", 1944.
384. Kraemer to Nichols, 7 February 1939 (HML).
385. Bauer to Svedberg, 1 May 1940 (UUp-Lib); and Gard (1944).

386. Janssen (1941), p.103.
387. Pedersen (1976), pp.169-170.
388. Kinell (1987), p.42; Kai O. Pedersen; Sven Brohult; Nils Gralén - private communication.
389. Claesson and Pedersen (1972), pp.615-616.
390. See e.g. (RAC:1.1/800/7/76) Weaver's diary, 27 June 1936 and (RAC:1.1/200/164/2013) Mason's diary, 16 January 1937.
391. Miller (RF) to Svedberg, 4 February 1937 (UUp-Lib).
392. Tisdale to Signer, 31 May 1938 (UUp-Lib).
393. Svedberg to Tisdale (RF), 23 March 1938 (UUp-Lib).
394. (RAC:1.1/800/7/77) Weaver to Tisdale, 4 April 1938.
395. Tisdale (RF) to Svedberg, 12 October 1938 (UUp-Lib).
396. Svedberg, 'Summary of Researches carried out under the Assistance from the Rockefeller Foundation', Report to the National Science Division of the Rockefeller Foundation, 1939, (UUp-Lib).
397. Tisdale (RF) to Svedberg, 1 February 1939 (UUp-Lib).
398. (RAC:1.1/800/7/77) Svedberg to Tisdale, 11 February 1939.
399. (RAC:1.1/800/7/77) Svedberg to Weaver, 9 October 1939.
400. (RAC:1.1/800/7/77) Svedberg to Tisdale, 23 November 1939.
401. (RAC:1.1/800/8/78) 'Officers Recommendation to the Executive Committee of a Grant appropriation to the University of Upsala (Svedberg)', 30 January 1940.
402. (RAC:1.1/800/7/75) RF-40026: 'Grant appropriation to the University of Upsala (Svedberg)', 15 March 1940.
403. Svedberg to Miller (RF), 28 September 1945 (UUp-Lib).
404. (RAC:1.1/252/1/13) 'Excerpt from Trustees Bulletin', December 1950.
405. Brohult and Gralén (1944), pp.635-636.
406. Prof. Kai O. Pedersen, private communication.
407. Pedersen (1983), pp.268-271.
408. Pedersen (1983), p.277.

Chapter 3

JESSE WAKEFIELD BEAMS

Education - UVa School of Physics

Jesse Wakefield Beams was born on a farm in Summer County Kansas on Christmas Day 1898. His father, Jesse Wakefield Beams, senior, while yet a boy, went west from Kentucky, across the Mississippi River. Later, he settled on a farm in Summer County, Kansas. Jesse's mother, Kathryn Wylie, migrated with her parents in a covered wagon from what is now West Virginia to Kansas. Among Jesse's duties on the farm was the turning of a centrifuge cream separator which constituted one of his first acquaintances with rotating systems. He spent his first seven years at school in a one-room schoolhouse, several miles from his isolated farm home. He walked to school, or skated when there was ice. He obtained his undergraduate training at Fairmount College, in Wichita, where he worked at various jobs to pay his expenses. He achieved high honors and was president of his senior class. In consideration of his fascination with physical phenomena, it is not surprising that he chose physics as his major subject. After graduation from Fairmount College in 1921, Beams attended the University of Wisconsin for one year and obtained the M.A. degree in 1922 with a major in physics. In the fall of 1922 he interrupted his graduate education to accept an instructorship in physics offered him by Fred Allison, chairman of the Physics Department of Alabama Polytechnic Institute, now Auburn University.¹ Allison was impressed by his ability and enthusiasm and told Llewellyn Griffith Hoxton, head of the school of physics at the University of Virginia at Charlottesville, Va., about him. Thereupon Hoxton offered Beams a teaching fellowship for 1923-24. Carroll M. Sparrow, who had directed the thesis research of Allison concerning experimental investigations in the field of light, also became Beams' thesis professor.²

Until 1907 Francis H. Smith was chairman of the School of Natural Philosophy at the University of Virginia. Smith had been trained in Newtonian Mechanics, and Helmholtz Sound. He worked with many simple machines, tops, tuning forks,

pendulums and Helmholtz-resonators, sensitive flames and some things in light. He did not include in the beginning course any electricity. In 1907 he was succeeded by Hoxton who also included electricity in his courses as well as the new developments in physics like X-rays and radioactivity.³ The school of Natural Philosophy was housed in the Rouss Physical Laboratory, named after Charles Broadway Rouss, head of a New York department store who had contributed a large grant for its construction. The building was designed primarily for educational purposes with hardly an eye to research.⁴ In 1906-7 a laboratory course especially for the premedical students was instituted. The following year the laboratory work was expanded and instruction was added in sound, electricity and light. It included at first both academic and engineering students. Soon after 1911 the engineers were put in a separate lecture section with different text books but essentially the same laboratory. The courses, however, appeared too hard for the academic students. In other universities, moreover, less time was required for courses in physics. Usually, at Virginia, students would not take physics until their third or fourth year chiefly. They were scared of it. College Topics one September in its guide for new students printed 'Like the peace of God it passeth all understanding. Good for mental masochists'. So students, being afraid, would not come in contact with physics until too late to go on with it.⁵ Before 1906, two PhD's were awarded in physics while from 1906-1921 none were awarded.⁶

In 1916 the School of Natural Philosophy was renamed the School of Physics. Hoxton set himself two main goals, first: bring the courses in physics up to date and second, developing a spirit of research.⁷ With respect to research it appeared to be hard to get things going. One of the reasons was that there was hardly any money available for research. From 1907 up to 1928 this money came partly from student laboratory fees (\$ 15 per year) and partly from appropriation. It fluctuated from \$750 to \$2000 which was far less than laboratories at 'good universities' spent. From this money all laboratory work, apparatus, instruments, equipment, supplies, gas and various services had to be paid.⁸

In the early 1920s practically all classes were on a three-hour basis with many beginning science classes on a six-hour schedule - 3 hours of lecture and 6 hours of laboratory work a week. Once a week students and faculty came together in the so-called 'Journal Club'. There, usually one of the faculty would give a report on material in the recent journals, hence the name Journal Club. Toward the end of the year graduate students might report on their own work if it were far enough along. Only on rare occasions were there out of town speakers, though at times one passing through Charlottesville would stop off and be a guest speaker. Those were rare and very special events, for in those days there was no budget for anything of the kind. In fact, according to Brown, there was practically no budget at all.⁹

The laboratory work and problem drill were handled almost entirely by students. In 1922 and 1923 the group of instructors included some upper class engineers and physics majors for lack of sufficient graduate students, and at times mathematics or chemistry majors were used. The teaching experience was considered to be very valuable in itself and furthermore they were about the only fellowships available in physics. A full time teaching fellow was expected to put in 12 hours in laboratory or classroom and grade all the problems and weekly quiz papers for his students and a proportionate share of the laboratory reports. The fellowships paid \$400 to \$500 in cash plus fees and tuition and a careful student could live on this for the nine-month school year.¹⁰

An important prerequisite to the proper functioning of a research laboratory was a machinshop. According to Hoxton, a shop was a *sine qua non*. Without a shop a physics laboratory would be helpless. This applied to instruction also, but chiefly to research. At the Rouss Physical Laboratory a shop had been installed in 1906 by W.J. Humphreys, one of the staff members in those days. His idea was that it would be potent for research. Smith's idea that it was ancillary to the lecture room. It is an illustration of conflicting views of that day in the University. In the early days, the work in the shop was mainly done by students working at 25 cents an hour and others when obtainable. Three outside men were tried at different times but none of them stayed for very long. In 1920, 14 years after the establishment of the shop, an instrument maker, Arthur J. Weed was secured on a permanent basis, supported at first from laboratory fees.¹¹ Weed had been at the Weather Bureau Station on Mount Weather before coming to Virginia. He was the oldest member of the staff. In 1922 he had white hair and mustache and was commonly spoken of as 'Father Weed'. One of his favorite sayings was, 'you tell by finding out', and he used to enjoy experimenting to find out if he did not already know. This trait sometimes had its exasperating sides - as when he would modify a test model without saying a word about it to the experimenter working with it. The results of the subsequent trial might be mystifying to the principal experimenter who knew nothing of the changes Weed had introduced while making the item in the shop. Another of his expressions was: 'it looks like he did it himself'. This was applied to any sloppy job or to one that clearly showed the ineptness or inexperience of the worker. Weed's family continued to live in Washington, D.C. until some years after 1922. Weed himself had quarters in R.P.L. where he also slept until his wife moved to Charlottesville in the late 1920s or early 1930s. Weed became interested in seismology and about 1925 completed the construction, in his own time, of a very sensitive seismograph.¹² Weed himself published an article on this seismograph and had also published a number of books and papers on various other instruments and methods for physical investigations.¹³

When Beams came to the University of Virginia in 1923 to work for his PhD he was most welcome but the staff could not offer him much of a research tradition. The thesis project that Sparrow assigned to him was that he measure the time interval between the arrival of the quantum and the ejection of the electron in the photoelectric effect. For this investigation two basic devices were required, 1st a short and very sharp flash of light whose instant of birth would be known and whose life-time could be measured. And 2nd a device for measuring what were then considered very short time intervals of the order of 10^{-7} to 10^{-9} of a second. The first was secured by means of a high speed rotating mirror, the second by use of a Kerr Cell for which the cut-off or time of closing was determined by the length of wire between the activating voltage that opened it and a spark discharge that relieved the potential and closed it. The latter was controlled by, and measured in terms of the varied length of wire from spark gap to Kerr Cell. The second of these main problems led to the actual work on which Beams' Ph.D. was awarded. He found that if he used the Kerr Cell between his eye and the discharging spark gap with a variable length of trolley line between them, this line might be so long that the drop in potential, which would close the Kerr-Cell, would not reach the cell until the light from the discharging spark had gotten through - so that the light from it was clearly visible. Then by decreasing the length of this 'delay-line' the drop in voltage could be made to close the cell before all the light got through; and if shorter still before any of the light got through the cell to the eye. This indicated that the light was not produced instantly between the electrical discharge which knocked the electrons into higher energy levels, and the production of light that resulted from the return of the electrons from higher energy states to lower states. A close examination of this light with a direct-vision spectroscope between eye and Kerr-Cell indicated that the spark lines of air were the first to appear regardless of the metal of the electrodes. After them the spectral lines of the metal of the electrodes were produced in a definite sequence depending on the metal used for the spark electrodes. This basic spark-Kerr-Cell arrangement led to many subsequent uses in other studies by Beams and his graduate students. These experiments and the results were presented at meetings of the American Physical Society, the South-eastern Section and the Virginia Academy of Sciences and were printed in the corresponding publications. High rotational mirrors were also applied by Beams and Snoddy to a study of electrical discharges including metallic sparks and lightning and as a device to trigger a spark gap by a flash of ultra-violet light and so produce a discharge at a precisely known instant.¹⁴

Hoxton was most impressed by Beams' work. In 1925 he wrote in the annual report of the School of Physics:

"The work of Beams deserves especial honorable mention. He has been carrying out a beautiful piece of experimental investigation whose implications are fundamental and has shown all along the qualities that belong to the competent research man, imagination, thoughtfulness, persistence and enthusiasm. A preliminary published notice of this work will appear soon and a full detailed account later. He has measured the duration of important events in atomic processes although they take place in a few hundred millionths of a second the time that light takes to go a few tens of feet!"¹⁵

After Graduation - Spinning Tops

Beams was awarded a National Research Fellowship for his thesis research. Following their established policy, the Research Fellowship Board required him to go elsewhere at once. Hoxton, however was very keen to keep him in Virginia and asked the Board to make an exception, arguing that: (1) Beams had already attended two other institutions so that migration would be less important in his case; (2) Permitting Beams to work at Virginia for one more year would be an entering wedge for the encouragement of *research in the South*, which from the Board's point of view was desirable; (3) A great deal of work including the cutting of a hole in a wall of the building had already been done for and by him to get his apparatus going; (4) although more apparatus would be necessary Hoxton felt that the Administration would consider furnishing it favorably within reason. These arguments had the desired effect, and Beams was allowed to stay at the University of Virginia for another year.¹⁶

During his National Research Fellowship Beams continued his investigations in optical phenomena. After this year he was reappointed as a National Research Fellow, which was an exception to the usual policy of the Council and he went to Yale from 1926-27. Following his research fellowship he was appointed instructor at Yale for a year.¹⁷ There he cooperated with Ernest O. Lawrence, a young experimental physicist who, like himself, had been reared on an isolated midwestern farm. They carried out several studies, primarily on experiments concerned with measurements of short time intervals, comparable to the type of research Beams had done for his dissertation. After further refinement of the techniques that he developed at Virginia, Beams, with Lawrence, returned to the problem assigned to him for his Ph.D. thesis: measurement of the time interval between the light quantum and the ejection of the electron in the photoelectric effect. By this time, physicists, including Beams and Lawrence, had become more aware of their limitations with respect to gaining experimental information about the interactions of individual quanta with single electrons. They consequently adopted the goal of measurement of the time between impending flashes of light and the onset of photoelectric emission. Although this interval of time proved too short for them to

measure, they were able to set definitive upper limits for the intervals. They concluded, for example, that photoelectric emission began in less than 3×10^{-9} seconds after the beginning of illumination of a potassium hydride surface.

In January 1927 Beams and Allison published an article in *Physical Review* on 'The differences in the time lags of the Faraday Effect behind the magnetic Field in various Liquids'.¹⁸ Beams and Lawrence published abstracts on 'A study of the lag of the Kerr effect for several liquids as a function of the wave length of the light'¹⁹ and on 'The instantaneity of the photo-electric effect'.²⁰ They also published an article on 'The Nature of Light' where they stated:

"(...) there is no definite information on the length of time elapsing during the process of absorption of a quantum of energy photo-electrically by an electron, and so-called length of a light quantum - if such a concept has meaning - is equally unknown experimentally."²¹

Early 1928 they published another abstract in *Physical Review* entitled 'On the time required for the Photo-electric ejection of an electron by visible light'²² and in September 1928 a 9-page article was published in the same journal on 'The element of time in the Photoelectric effect'.²³ Also in 1928 Beams published an article on 'the Time Lag of the Spark Gap'.²⁴ In some of these experiments they used rapidly rotating mirrors and during this work they started experimenting with a new scheme for reaching high rotational speeds based on work done some years before in Belgium. In 1925, two Belgian researchers, E. Henriot and E. Huguenard, built an apparatus that was easily capable of very high speeds. The turbine (figure 3.1, left) consisted of a stator with a cone-shaped recess. The stator was connected to an air compressor which filled the cone-shaped recess with air jets through several channels. When the rotor, also cone-shaped and with flutings, was lowered into the stator the air jets caused it to rotate. In earlier machines, rotating objects had a solid connection with their driving mechanism. Now, the air jets caused the rotor to hover above the stator on a very thin air cushion, allowing it to seek its own axis of rotation. In this way, the airturbine seemed to have overcome problems resulting from critical speeds and imperfect balancing. With this type of drive Henriot and Huguenard reached rotational speeds of over 660,000 revolutions per minute (r.p.m.), a factor of almost 10 more than was possible with other rotating devices at the time. With respect to applications, they indicated that the small rotors might be made hollow in order to separate liquids (figure 3.1, right), or that it might be mounted with a mirror in order to record extremely high speeds at extremely short intervals through observation of a reflected beam of light.²⁵ This method of measuring was very common in physics; it has served, for instance, as a method for determining the speed of light.

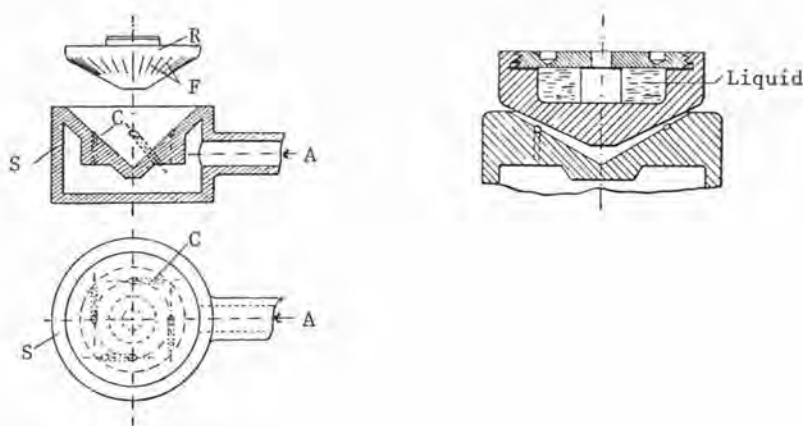


Figure 3.1

Henriot and Huguenard's Spinning tops. S, Stator; R, Rotor; A, Air; C, (air) Channel; F, Flutings. (Henriot and Huguenard, 1927, p. 436 and 437).

The design of Henriot en Huguenard was picked up by Beams and Lawrence in 1928. The design seemed to promise much higher rotational speeds for their mirrors which would enable them to measure shorter time intervals in their experiments. However, experimenting with this design they found that vibrations in the nozzle from which the compressed air jet issued, caused the rotor to become unstable. They solved this problem by means of a rubber mounting in the nozzle. This facilitated them to reach steady speeds of rotation for a rotor 16 mm in diameter of between 5000 and 6000 revolutions per second (r.p.s.).²⁶

Hoxton was very anxious to have Beams return to Virginia because he wanted to establish a research tradition in physics at the University of Virginia (UVa). He was active in founding the Virginia Academy of Science and in the formation of the Southeastern Section of the American Physical Society.²⁷ To the president of the university he argued that with Beams working there results had been produced not only in the putting out of worthy research but also in the putting others to work and keeping them at it. Without him there would be a reduction in output that would seem out of proportion to the absence of one person.²⁸ At Yale, Beams was offered an assistant professorship at a salary of \$ 3000. In order to make it more attractive for him to return to Virginia, Hoxton suggested to the president to offer him \$ 3500.²⁹ Hoxton also requested an additional \$ 500 for research which would be necessary to attract Beams.

This would have meant an increase in the physics budget of almost 30% which was not very likely to be approved. However, soon the financial situation for physics changed rather drastically. Sometime about 1927 a committee from the

General Education Board of the Rockefeller Foundation, without solicitation or notice, appeared at the University to investigate its possibilities as one of the places where research could be promoted in the southern USA. The fields chosen were Physics, Chemistry and Biology. They had finished a program with Medicine and had just turned to these three fields as basic. They were satisfied with the set-up at the UVa as promising. The initial plan contemplated a beginning contribution of \$25,000 for all 3 sciences for the first year (1928-9) and \$30,000 for the second. Then the University was to start contributing more and more, the Board less and less until, at the end of an eight-year period, the Board would bow itself out and the University would carry on with an annual appropriation of \$45,000. The share of each science was determined internally, that for physics being 28%, for biology 32% and for chemistry 40%.³⁰ In physics the money was partly used to add Beams and, a few years later, Leland B. Snoddy to the staff, thus increasing the number of faculty from three to five. About the same time the DuPont company announced that it was going to offer scholarships and Fellowships for promising researchers. The GEB grant made a rapid increase of research activities possible which in its turn proved to be a lever for obtaining DuPont fellowships.³¹ The General Education Board fund combined with the DuPont Fellowships formed the financial foundation for the rapid growth in research in physics. This made the UVa school of Physics better known and attracted increasing numbers of graduate students, especially from the southern USA.³²

When the research activity in physics expanded, the demand on shop work expanded accordingly. It became too much work for Weed alone and therefore part of the new funds were used to add a second instrument maker. The first man attracted did not fit the job to well and he left after one year. By this time the 1929 crash of the stock market was affecting the Northern Universities and some of their staff members were being let out. The Physics Department learned of a German instrument maker being dropped by the University of Michigan, and he was secured. Fritz Linke proved to be a good choice as he remained working in the shop for more than thirty years.³³ Members of the faculty who needed glassware still did their own glass blowing. It was one of the techniques needed by all who experimented in physics or chemistry and was taught in the 'research preliminaries' course along with other skills. Gradually the idea grew that it would be more efficient to employ a skilled glass blower than to use the time of an expert experimentalist, especially if there was enough work to keep the glass blower busy. So as the demand increased for more and at times more complicated glass work, and through contracts money became available to pay one, a glass blower was added to the staff.³⁴

In 1930, Hoxton, in his annual report to the president of the UVa, asked for a considerable increase in the physics budget. Part of the money would be needed for

a remodeling of the laboratory building because the original design did not contemplate research to the extent that was going on in 1930.³⁵ Furthermore Hoxton suggested to promote Beams to full professor and give him a \$ 750 raise in salary. Beams had an offer from the General Electric Company of a position in their research laboratory carrying a salary which was \$ 2000 more than he received at the UVa. However, because of the freedom of research, he would rather stay at the university under the conditions Hoxton suggested. Hoxton argued that it was especially Beams who had given the university its present good reputation.³⁶ Hoxton's proposals were agreed and Beams was promoted to full professor in 1930 after which he remained at the university for the rest of his career.

In the late 1920s Beams continued his research in optical phenomena, sometimes using the spinning top in his experiments. He used it for instance to measure the very small time differences in the appearance of spectrum lines in spark discharges³⁷ and for the study of the propagation of luminosity in discharge tubes.³⁸ Furthermore, he invested much effort in improving the stabilization and ease of operation of the apparatus, and in 1930 published an article in *Review of Scientific Instruments* entirely devoted to this. In the introduction he stated:

"The need for an apparatus, by which it is possible to obtain high rotational speeds, often arises both in the course of original investigations and in ordinary laboratory or lecture demonstrations. In most of these cases the value of the experiment or the success of the demonstration is definitely limited by the maximum rotational speed that can be attained. In the case where the rotor is mounted in metal bearings it is usually not possible to obtain speeds of rotation much in excess of 1000 r.p.s. and then only by the most skilful workmanship. However, this difficulty has been overcome to a considerable extent, at least for some purposes, by the recent work of Henriot and Huguenard. The method which they developed consisted essentially in both driving and supporting the rotor by means of a whirling film of air. In a series of experiments requiring the use of a mirror which rotated from 2000 to 3000 r.p.s. the writer has successfully employed the above method and found it simple to use and the parts easy to construct. During the progress of the experiments the original design of Henriot and Huguenard was modified somewhat and a greater stability and flexibility obtained."³⁹

The apparatus is shown in figure 3.2. The rotor, carrying a stellite mirror, was usually made of phosphor bronze. The air pressure was admitted through the valve V_1 until the desired pressure as read on G_1 was obtained. Either V_2 or V_3 was then opened until G_2 registered the correct pressure which had previously been determined by trial. The rotor was then placed in the stator and steadied for a few seconds by a light touch on its rim by a cloth. When the cloth was removed the rotor quickly came to full speed and sought a position of equilibrium a fraction of a millimetre from the surface of the stator where it continued to rotate at

approximately the same speed until the pressure on the air jets was changed. The dotted line KK shows the position of a cloth to catch the rotor if it should fly out of the stator. One of the principal troubles with the above apparatus arose from air vibrations in the tube II' but it was found that these could be almost completely eliminated by loose steel wool (shown at W) filling the pipe II'. Metal plugs having holes drilled with a No. 73 drill or smaller were also effective. Vibrations in the metal tube itself seemed not to be so important, although these could be easily eliminated by splicing the metal tube with rubber pressure tubing.

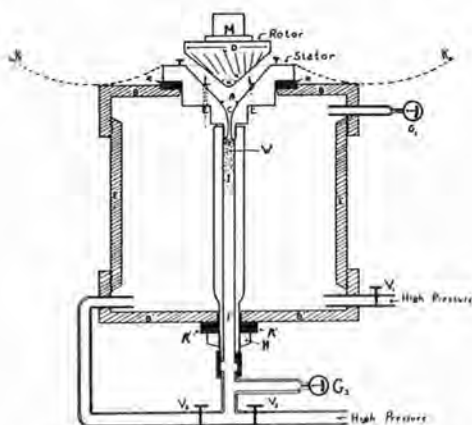


Figure 3.2

Stabilised spinning tops. Explanation: see text. (Beams, 1930c, p.668).

In most of the work the air was furnished by a compressor. In order to damp out the pulsations of the compressor the air was passed through an auxiliary tank before entering the apparatus. The pressure could be changed over a rather wide range without the rotor 'grabbing' and becoming unstable. This was especially the case when it was possible to close the valve V_2 completely and let the air into CC' through V_3 . The air pressure could be varied over a wide range but it was found that each different set of dimensions of the holes, their angles P and Q, size and angles of the stator, diameter and weight of the rotor, etc., worked best over a definite range of pressures which was determined by trial. If a large capacity compressor delivering air at a lower pressure was used, some rough experiments indicated that it was advisable to use larger diameter holes LL' and at the same time make $(\alpha-\beta)$ greater. If rotational speeds not exceeding 3000 r.p.s. were desired and a non-pulsating source of air supply was available the long tube II' could be dispensed with and a rod substituted in its place.

The speed of rotation was tried to measure by several different methods. The first method tried was to place a magnetized needle inside the rotor with its

centre on the axis of rotation and its length making a right angle with it. This whirling magnet induced an alternating current in a nearby coil which after amplification produced a note in a pair of earphones. The frequency of the note was determined by finding the number of beats made with a known-frequency audio oscillator. The second method consisted in reflecting the light of an incandescent lamp from the rotating mirror into a photoelectric cell. The pulsating photo-cell current was then amplified and the frequency determined by beating it with the audio oscillator mentioned above. It was soon found by these methods that the loudest natural note given out by the rotor (about the only one that could be distinguished after the rotor had reached full speed) was equal to the frequency of the rotor. It was therefore possible to dispense with the magnet, or lamp and photo-cell, and beat the frequency of the note given out by the top directly against the note of the audio oscillator. Beams concluded his article by stating:

"The constancy of the speed of rotation is indeed striking when the pressure remains constant. Even with the mirror mounted upon the rotor the speed of rotation can be made as constant as the audio oscillator. The nutation and precession of the rotor can also be made remarkably small. For example, in either of the cases mentioned above, when the light from a horizontal slit passes through a lens, is reflected from the rotating mirror, and comes to focus on a screen a meter distant from the mirror, the resultant streak of light did not shift up or down by as much as one millimetre in one minute."⁴⁰

Ultracentrifuges

From 1930 onwards Beams' attention gradually shifted from using spinning tops as an instrument in scientific research to the actual development of the apparatus. In 1931, he published an article in *Science* entitled: 'A simple ultra-centrifuge'. In the introduction he stated:

"It is hardly necessary to emphasize the value of the centrifuge to science in general. Its numerous uses in so many fields of experimental investigation have made it almost a necessary laboratory tool. As a consequence of this wide usage considerable energy has been directed toward the development of centrifuges with our modern high speed machines as a result. However, there is still very much to be desired in the way of improvement. Many problems of utmost importance remain unsolved because of the insufficient separating power of our best centrifuges. Among the factors which limit the separating power of the centrifuge are, of course, rotational speed, suitable bearings, strength of materials, troublesome vibrations, and simple means of making the centrifuging continuous. During the last few years we have been engaged in a series of researches that required apparatus for obtaining high rotational speeds. Some time ago we undertook to apply this comparatively simple technique to the centrifuging problem and have obtained such remarkable results that it seems worth while to call the attention of others to its possibilities."⁴¹

One of Beams' goals was to reach rotational speeds as high as possible. Early 1931 they had reached half a million revolutions per minute which generated a gravitational field over a million times gravity. It appeared that the rotational speed was limited only by the molecular speed of air and the strength of the rotating parts. Another problem arose when Beams decided to use the spinning top as a centrifuge: how to get the material to be centrifuged in and out without touching or rubbing while the rotor was at full speed? Beams developed several schemes in order to solve this problem. For the centrifuging of small amounts of material the arrangement shown in figure 3.3, left, appeared to be satisfactory. The rotor was filled with liquid and allowed to come to full speed. After the components of the liquid had had time to separate, a somewhat heavier substance, with which the liquid under investigation would not mix, was very slowly dropped into the tube AB (which was slightly larger at B than at A). This forced the lighter fractions out of the tubes EF where it was collected by the cylindrical collector K. Figure 3.3, centre, shows a scheme where the centrifuging could be continuous. The rotor was first filled through the tube AB then brought to full speed and allowed to rotate for some time. More of the liquid to be centrifuged was then slowly introduced through AB and thus emerged at C. Its heavier constituents moved to D and the lighter to E where it was forced up the small hole EF and collected by the collector K_1 . The heavier material was forced out through the tube DPG and collected by K_2 . MP had a symmetrically placed identical tube while NE (drawn in figure 3.3, centre, at right angles to its real position) also had a symmetrically placed tube to keep the centrifuge in balance. The distance of the tubes PG from the axis of rotation and the height of its opening depended upon the approximate ratio of the densities of the substance to be separated, so it was necessary to design the rotor specially for each ratio of densities.

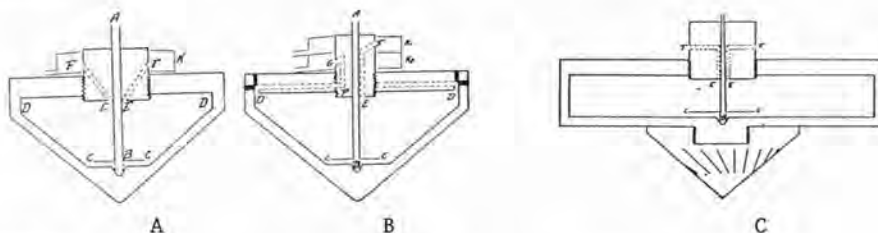


Figure 3.3

Spinning tops as centrifuges (Beams and Weed, 1931, p.45 and p.46).

The practical separating power of a centrifuge depended not only upon the maximum magnitude of the rotational speed but also upon the radius of the rotor. Beams found it desirable to make the peripheral velocity as large as possible.

Figure 3.3, right, shows an arrangement developed for this purpose which appeared to be very stable. The size of the rotor could be varied over wide ranges. They had used them, for example, from 1 cm to 10 cm in diameter, but the size did not seem to be restricted. Peripheral speeds of over 300 m/sec. were frequently attained. A convenient size one inch in diameter made of steel would rotate, when loaded with water, 3,500 r.p.s. with the compressor giving about 1,200 cubic inches of air at a pressure of 100 lbs per square inch above one atmosphere, per minute. By adjusting the air pressure the speed of revolution could be varied over wide ranges. The speed remained remarkably constant when the pressure was held constant. Beams found it also striking that there were no vibrations in the rotor when it was filled with a liquid which reduced stirring or remixing to a minimum. He indicated that, therefore, the theory of separation by centrifuging should hold with good approximation.⁴²

Early 1932 Beams published an abstract in *Physical Review* entitled 'A simple ultracentrifuge'. He described that he had devised a 'simple arrangement' by which the light absorption and approximate index of refraction of the materials being centrifuged could be measured as a function of the distance from the axis of rotation of the rotor at full speed. Mounted in a channel cut along a diameter of the top of the rotor was a Pyrex or quartz rod polished flat on its ends. The rod was ground along a narrow strip parallel to its axis which appears illuminated when light entered from either end. Above and next to this strip was mounted a Pyrex tube containing the substances under investigation, through which the strip was observed. With this arrangement he had obtained centrifugal forces of the order of 10^5 g. He indicated that this should not be the upper limit for he had already obtained forces in the order of a million gravity with small all-metal rotors.⁴³

Pickels - Sedimentation Ultracentrifuge

Post graduate students in physics could choose from a variety of topics for research. Some of them chose to work with Beams on problems of ultracentrifugation. W.D. Garman made a theoretical analysis of the conditions for optimum performance of the spinning tops. He deduced the optimum shape for the airports, the most effective angle of the jets, optimum design of the grooves and optimum conditions for maximum speed, i.e. whether or not the maximum speed could be expected to be obtained under the most economical conditions. He hoped also that the correct design of the blades would eliminate the necessity of stabilizing by means of central jet.⁴⁴ Another student of Beams, Edward Greydon Pickels, chose as a topic for his masters thesis 'An adaptation of the Beams

ultracentrifuge to the determination of micellar and molecular weights'.⁴⁵ Pickels was born in 1911 in Richmond, Virginia, where he also visited high-school. There he had signed up for a chemistry course, having to take some science course, but found out the last minute that the class was already filled. Thereupon his teacher suggested that they were starting a new course in 'what they called Physics'. It was something quite new in Richmond in the early 1920s. Chemistry and Biology were quite common but physics was not. When he followed the course he found out that the subject matter neatly fitted his early interest in mechanical things like making small steam engines and things like that. After he had finished high school he went to college in Richmond where he pursued physics. After the first year he became student-instructor which meant that he assisted in the laboratory work and helped the other students perform the experiments. In 1932 he got his bachelors degree. His physics professor at Richmond knew Beams and suggested Pickels to go to Charlottesville and was also instrumental in getting him accepted at the university.⁴⁶

After Pickels had finished his masters in 1933 Beams suggested two possibilities to him for Ph.D. work. One of these was to develop the spinning top further to the point that it could be used for sedimentation experiments, including the sedimentation of proteins. The second was to use the spinning top for the measurement of the speed of light which was a kind of repetition of the experiment Michelson and Morley had done some years before. The main difference was that the Beams spinning tops rotated much faster. This implied that, whereas Michelson and Morley had performed the experiment with the rotating mirror on one mountain top and a fixed mirror on another, the experiment could now be done in the hallway of the laboratory. Pickels, however, chose for the adaptation of the spinning tops to sedimentation experiments. He felt that in the measurement of the speed of light there was nothing basically new to contribute and that there would not be much challenge for him.⁴⁷ In the introduction to his dissertation he wrote:

"The pioneer spirit which is the motivating force of every true experimental investigator has often found its most complete expression in some adventure into the realm of extremes. The stories relating to the attaining of high temperatures, of low temperatures, of high gas pressures, of low gas pressures, of high speeds, of large forces, of high microscopic and telescopic resolving powers, of high speed electrical particles, and of highly charged bodies are all stories of ever advancing frontiers; and in the wake of every advance there has usually followed a wealth of experimental investigation and subsequent data which have affected in a most vital fashion our ideas about the true state of physical things.

Recent years have witnessed a rapidly increasing interest in the production of high rotational speeds and large centrifugal forces. Perhaps the most outstanding example of practical application is the work of T. Svedberg and his collaborators who have used high speed centrifuges of the electrically driven and oil turbine types to determine the molecular weights of a great many organic materials,

particularly proteins. The fixing of the molecular weight of haemoglobin as approximately 69,000 is indeed one of the classical experiments of modern times. The particular disadvantages of their higher speed ultracentrifuges are the excessively high costs of construction and operation, and the fact that the design is not so easily varied to meet the needs of different investigators.

In 1925, Henriot and Huguenard reported a simple method for both driving and supporting small cone shaped rotors by jets of compressed air. Beams and Weed, among other investigators, made various improvements in the apparatus and used it experimentally as a means of imparting high rotational speeds to revolving mirrors. The writer joined these investigators in making further improvements and in adapting the air driven ultra-centrifuge for the observation of colloidal sedimentations in solutions, and for the collection of the liquid phase of a colloidal solution after sedimentation. However, it was found that particles of molecular size could not be separated from solution with the simple centrifuge, although sufficient centrifugal force was available to give ample separation according to theoretical considerations. The main portion of the writer's research has been an effort to locate and to correct the causes of this departure from theory and to make as many related adaptations as possible. As frequently happens in the course of experimental investigation, several seemingly unrelated techniques and types of apparatus have been developed.⁴⁸

Pickels work was carried out under several fellowships: DuPont Senior Fellow,⁴⁹ Charles M. Coffin Fellow,⁵⁰ and Baylay-Tiffany Fellow.⁵¹ The general start problem was to see whether it would be possible to make optical observations with the spinning top. They should be adapted in such a way that it would be possible to see, with the naked eye or with a camera, what was going on in the ultracentrifuge. Thus, the first problem was to provide a window somehow. In all of the first models, as opposed to the cells Svedberg had, Pickels was working with a complete annulus of fluid. Referring to Svedberg's work,⁵² Pickels developed several rotors which would allow the observation of the sedimentation process during centrifuging. Figure 3.4, left, shows a cross-section of a rotor designed to permit observation of the rate of sedimentation, while the rotor was in motion. Parallel light of a wave-length that was absorbed by either the heavier or lighter (but not both) portions of the substance to be centrifuged was reflected or scattered from the bottom of the chamber A and entered the camera. A photograph was taken first with the rotor turning a few revolutions per second and then at regular intervals with the rotor at high speed. The photographs gave a record from which the rate of sedimentation could be found and hence the particle weight. Some difficulty was experienced, at first, in getting the glass disk D strong enough to stand the necessary stresses. This was solved by a special heat treatment of the glass. A circular disk cut from ordinary plate glass 3 mm thick was slowly rotated with face vertical in a furnace which was gradually heated until the glass just began to soften. The disk was then quickly removed from the furnace and dropped into compressor oil. After this treatment its strength was increased several times and withstood forces of 250,000 gravity. The rotor itself, however, could withstand 400,000 g. The joint between the metal rotor and glass disk was made tight by a

ring of special wax made of 25 parts by weight beeswax, 10 lead oxide, 7 rosin, 6 shellac, 3 venice turpentine, 2 paraffin; heated until brown colour appeared. The wax ring was formed by first heating and then cooling the rotor while it was spun in a lathe. The lower scattering surface of A was made by carefully baking white Duco paint on the steel. This white surface was then covered with a thin film of paraffin. The chamber A was partially filled through the tube T.⁵³

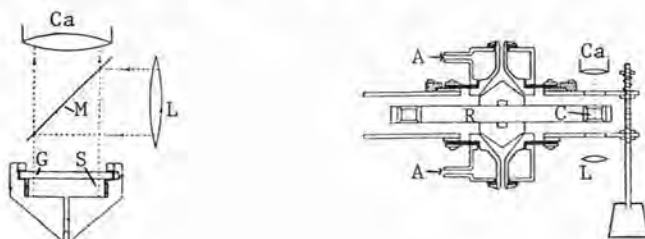


Figure 3.4

Rotors for sedimentation experiments. A, Air; C, (sedimentation) Cell; Ca, Camera; G, Glass disk; L, Light source; M, Semi-permeable mirror; R, Rotor; S, Sedimentation chamber. (Beams, Weed and Pickels, 1933, p.339).

Another type of rotor suitable for sedimentation observation is shown in figure 3.4, right. As in the Svedberg ultracentrifuge, this rotor had separate cells in which sedimentation might be observed. It was driven by two turbines in order to increase the maximum speed. The stators were mounted on three supports S. There were additional adjustments 'KK' so that the upper stator could be moved perpendicular to and the lower parallel to the plane of the paper. When properly adjusted, the rotor was extremely stable. The process of sedimentation was observed with transmitted light through a cell C with two glass windows. The cell was fastened into the disk-shaped rotor near its periphery and balanced by a dummy cell C' of exactly the same dimensions and placed diametrically opposite C. With transmitted light the rate of sedimentation would be obtainable either by light absorption or index of refraction measurements. Figure 3.4, right, shows a top of the cell C. A slit A of 3.5 mm average width was machined in the cylindrical cell. The glass disks were then cemented to the surfaces B. The cell A was filled through the tube T and the cell 'squeezed' into a hole bored in the disk-shaped rotor. This type of cell was not very satisfactory but would stand up to approximately 100,000 gravity if sufficient care was taken in the construction. With the 3½ inch rotor shown 100,000 g was generated using a garage 'Dayton' V-30 compressor, the capacity of the air compressor being the limiting factor.⁵⁴

Pickels did part of the actual manufacture of the apparatus himself. They had a small student shop with a simple lathe, drill-press and other simple tools where students could do their own work and where Pickels manufactured some of the

parts of the apparatus. The precision parts were made by Weed or Linke in the larger workshop. Pickels also himself gave the glass its heat treatment. He started developing the transparent ultracentrifuges making explicit references to Svedberg's work. However, Beams and Pickels were not primarily interested in duplicating Svedberg's work but rather in investigating the possibilities of various alternatives for his apparatus. As Pickels wrote in his dissertation:

"The writer's research has been almost entirely qualitative, the purpose being to develop types of apparatus which would be practical for later quantitative work."⁵⁵

From Svedberg they copied the idea of using a cylindrical cell using a sector shaped sedimentation chamber. For qualitative investigations of molecular sedimentations they used haemoglobin because of its very pronounced red colour, because of its large weight and comparatively rapid sedimentation, and because of the ease with which an impure solution could be prepared.⁵⁶ After some months of research they concluded that these 'simple observation rotors' proved inadequate for molecular sedimentations because convection currents were too active. Attempts to reduce temperature gradients by controlling the temperature of the compressed air proved fruitless. Another scheme tried was to use a rotor constructed as shown in figure 3.5, left (see also figure 3.7, left, second from the top).



Figure 3.5

Rotors for sedimentation experiments (drawn after Pickels, 1935, p.31½).

The top portion of the rotor spun in a housing, the bottom of which was a thin brass plate fitted with a hole through which passed the central narrow neck of the rotor with a slight clearance. In an attempt to maintain the upper rotor section at a uniform temperature, air was continually forced through the housing, which contained a window to permit observations. The air passed out through the bottom clearance about the rotor neck. The top portion of the rotor, which was 1½" in diameter, was fitted with a circular cavity for the solution chamber, a heat treated concentric glass disc 3 mm thick being used for the top window. This window was held in place by a screw ring and sealed to the steel rotor with de Khotinsky cement. The metal bottom of the cavity was painted white to act as a light scattering surface and then covered with a thin layer of paraffin. No separation of

very small particles could be observed, although the centrifugal force was above 100,000 gravity and although the solution chamber was made as thin as 1 mm and divided into several sections so that any stirring actions from changes in speed would be minimized. In another experiment, a small all-glass sector shaped cell was used in place of the circular solution chamber, but no success was had either.⁵⁷

Despite the limitations of these rotors, Beams and Pickels were concerned to underline the advantages of their ultracentrifuges. In 1933 they wrote in *Science* under the title 'The Ultracentrifuge':

"The need of the ultracentrifuge as a research tool in so many different fields of science perhaps makes a brief description of some of our experiments in this journal worth while. (...) certain important variations and improvements in design will be described, as they make for greater ease of construction and less expense."⁵⁸

They indicated that many adaptations for specific purposes were possible, that the rotor could also be spun inverted or sidewise, and concluded by stating:

"(...) we believe that the air-driven type of ultracentrifuge described above offers certain important advantages as follows: First, it is simple and easy to construct; second the design may be widely varied to suit the need of the experimenter, and still remain extremely stable; third, the cost is very little if air pressure is already available; forth, the centrifugal forces developed are as high as any materials (as yet tried) of the rotor will safely stand."⁵⁹

Because for highest speeds possible speeds the strength of the rotor was one of the limiting factors, particular attention was be given to the selection of a suitable metal from which to machine the rotor. For simple rotors, the ratio between the breaking strength (yield point) and the specific gravity should be as high as possible because the mass of the rotor that would cause a breakdown. Thus, duralumin was often preferred to ordinary steels, although it was not as strong. Pickels pointed out that Svedberg had used special grades of treated steel exclusively in his experiments but the main objection to special steels was the high cost of machining. On the other hand, a steel rotor would often be more suitable than a duralumin one, even when its strength-density ratio was a bit lower than that of duralumin. Such was be the case when extra arrangements such as a solution cell were to be added, for they had to be prevented by the strongest possible anchorage from dislocating themselves. Another very important factor was that some alloys showed much greater fatigue effects than others did.⁶⁰ Because of the great danger of explosion by the rotor by the centrifugal forces, the whole apparatus was always surrounded by a barricade to insure the safety of the observer.

The Problem of Convection

During the winter of 1933-34 Beams and Pickels were visited by Johannes Bauer who was a scientist at the International Health Division of the Rockefeller Foundation. Bauer was studying the yellow fever virus and wondered whether the spinning top could be used for its sedimentation. After some discussion he invited Pickels to spend the summer of 1934 at the Foundation's laboratory in New York and perform some experiments there. There Pickels extensively tested the double cone rotor with the Svedberg type cells. He used carbon particles as a testing material as these could be easily seen with the naked eye. He got very nice boundaries which, however, should not be the case as the particles should be a whole 'mess of sizes'. Also boundaries would sometimes suddenly disappear. He concluded that he got large convection currents. With viruses, as Bauer intended to study, this would be very problematic because they would be working with extremely low concentrations. This also posed the problem that probably nothing could be seen with optical means and that biological tests would have to be performed after centrifugation.⁶¹

Because of Bauer's interest in viruses convection now had become the major problem with the ultracentrifuge. Pickels became convinced that his scheme was not appropriate. He had to get some basic new design in order to solve the convection problem. Ideally, it should be thermally isolated, but how to do that? After some schemes, such as previously warming the air, etc., were found to be impractical, Pickels developed the scheme shown in figure 3.5, right. The depth of the centrifuge chamber was reduced to about 0.6 mm and bounded at bottom and top by specially prepared strong glass disks sealed around the periphery with soft DeKhotinsky. Just below the centrifuge chamber a deeper chamber was provided which could be filled with a liquid to act as a temperature equalizer. Liquids with high temperature coefficients such as turpentine were preferred for this purpose because of the temperature equalization by their own convection action, but usually some of the solution being centrifuged would serve the purpose.⁶² However, this model would not produce haemoglobin separations when the depth of the top solution chamber was increased to 3 mm. They did not consider this centrifuge as a satisfactory solution to the problem at hand, because the chamber could be made only so thick, because quantitative measurements could not be thoroughly depended on in view of the uncertainties of convection actions, because the force gradient was too steep, because the solution chamber could not be easily cleaned, and because it would be much more practical and precise to photograph sedimentations with transmitted light than with scattered light. Nevertheless, for Beams and Pickels it demonstrated for the first time the possibilities of the air-driven turbine in this type of work. With an arrangement very much like this they observed the

first sedimentation of haemoglobin ever to be obtained with any centrifuge other than that of Svedberg and his collaborators.⁶³ Trouble arising from convection currents was eliminated in principle so that the centrifuge could run for many hours without appreciable remixing, e.g., haemoglobin molecules were separated from the clear fluid with the above arrangement utilizing centrifugal forces of about 10^5 gravity. They indicated that in order to increase the capacity of the centrifuge, several centrifuge chambers might be placed one above the other or a large chamber might be divided into a series of thin partially insulated layers.⁶⁴

Besides tackling the convection problem Beams and Pickels also continued developing small centrifuges in order to give the highest centrifugal forces. With a rotor 9 mm in diameter driven by four jets of hydrogen (pressure 160 lbs. per square inch) instead of air a rotational speed in excess of 20,000 r.p.s. was obtained. This rotational speed produced a centrifugal force of about seven million times that of gravity, on the periphery of the rotor. They indicated that these small centrifuges should be especially suitable for the microscopic observation of small particles in intense centrifugal fields by methods similar to those of Harvey.⁶⁵ (see Chapter 6). This rotor was exhibited at the Fourteenth Exposition of Chemical Industries in New York City, in the booth of the Sharples Specialty Company. A description of this rotor appeared in *Scientific American* under the heading 'A world's record for rotational speed!'⁶⁶

The Vacuum Ultracentrifuge

Although Beams and Pickels had succeeded in sedimenting haemoglobin in one of their ultracentrifuges and also in obtaining convection-free sedimentation, this was not reached in one and the same ultracentrifuge. Thus, they were not yet able to copy the type of experiments Svedberg was doing and the scheme still would not be of much use for Bauer. They faced the problem that, as Svedberg had indicated, the rotor had to be at least 10 cm in diameter but that this, in their scheme, considerably limited its speed because of air friction which also created considerable convection currents. Pickels thought of spinning the rotor in a low pressure hydrogen atmosphere which was a good practical solution as Svedberg had demonstrated. But it was not the 'ultimate'. It still caused heating because of friction and Pickels set out for the ultimate: no heating; perfect temperature isolation. Especially because he wanted to work with viruses where they could be working with concentrations of 0.001 % convection should be 'completely eliminated'. Then he came to the idea of separating the rotor and the drive and spinning the rotor in vacuum. Such a rotor would not heat up anymore because of air friction and, if the drive could be kept much smaller than the rotor, the speed

limitations would be less severe. Pickels first thought about a rotor spinning in a vacuum around a horizontal axis because that was the conventional way of doing it. Svedberg had also done that and the optics could be more easily arranged. It would not be necessary to bend the light path or go up very high. Also, he set out to make something that resembled the Svedberg apparatus as closely as possible, except that it would be spinning in a vacuum. This, however, implied that he would need a rather thick shaft and bearings which would cause heating again. Then came the idea of spinning the rotor vertically and, for a moment, worry less about the optics. This idea implied that the rotor and drive would have to be connected by a shaft which would have to pass through a vacuum tight gland or bearing. This bearing, however, should not heat up too much because the heat might be dissipated to the rotor which would cause the scheme to lose its advantages. But, because of the vertical orientation, the shaft could be made very thin which would minimize the bearing surface and, thus, the production of heating.⁶⁷ Figure 3.6 shows one of the first vacuum-ultracentrifuges.

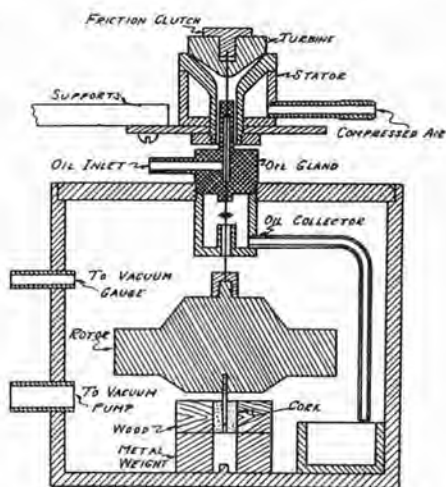


Figure 3.6

Vacuum ultracentrifuge. (Beams and Pickels, 1935, p.303).

In *Science*⁶⁸ Pickels and Beams described the rotating member as consisting of three main parts: a small, conical, air driven, air supported turbine; a much larger and heavier rotor of any desired shape, which spun in the vacuum chamber; and a steel piano wire extending vertically downward along the axis of rotation from the apex of the turbine above the vacuum chamber to the larger rotor which it supported and drove. The wire entered the chamber through a small hole that left

a very slight clearance. Viscous oil slowly fed into this clearance both lubricated the bearing and served to make it vacuum tight. The vacuum obtainable was limited only by the slight vapour pressure of the oil. The rotor became vibrationless soon after the turbine was started and the air pressure had been raised sufficiently to support it. Great precision in machining and balancing the rotor appeared not to be essential, as was attested by the smoothness with which a 3-inch steel rotor spun after having a ¼-inch hole drilled near the periphery. An air turbine weighing less than 50 grams would rotate an 800 gram rotor at a speed just slightly less than that of the turbine alone. The unguided sections of the wire were not long enough to permit objectionable standing waves being set up. The vacuum obtainable was limited only by the slight vapour pressure of the oil. Oil consumption in the gland amounted to less than 1 cc per hour. In stopping the rotor, wear on the turbine and stator could be minimized by lowering the stator and allowing the rotor to drag on the wooden block below it. Windows were conveniently arranged for observing or photographing any desired operations. The rotational speed was limited only by the strength of materials. The rotor described above exploded when the speed reached a little above 2,200 revolutions per second. With respect to possible modifications and applications they wrote:

"The method described offers numerous advantages and opportunities for research. The apparatus is simple and inexpensive to build and to operate. Where compressed air is not available, it should be well adapted for operation with other gases or perhaps steam, since the main rotor and the driving mechanism can be easily thermally isolated and controlled. Also slower types of motors could be substituted for driving the rotor if necessary. The flexibility of the wire makes possible and extremely smooth and even rotary motion not usually obtainable otherwise. This, coupled with the fact that the rotation takes place in vacuo, makes the apparatus highly suitable for the centrifuging of solutions and suspensions, especially where the particles separate so slowly that convection currents in the liquid are apt to give trouble. The poor results of many high-speed centrifuge experiments can often be traced to very slight temperature gradients within the rotor which have been introduced through friction or some other external source. The new arrangement allows a considerable increase in both the capacity and the speed of an air-driven centrifuge.

In view of the foregoing facts, we believe the apparatus affords not only a most efficient centrifuge, but a means of investigating many different phenomena."⁶⁹

October 1935 Pickels and Beams publish a 10 page long article in *Review of Scientific Instruments* entitled 'The Production of High Rotational Speeds'. In the introduction they stated:

"In many problems in physics as well as in the other sciences it is essential to utilize high mechanical speeds of rotation. Frequently it is necessary that the rotating member even be mounted in vacuum or at reduced gas pressure and maintained at a constant known temperature. The purpose of this paper is to describe simple inexpensive methods of fulfilling these needs."⁷⁰

They first described their one piece spinning tops to which they had added certain 'helpful variations' in the design. They stressed the flexibility of the scheme by indicating that automatic adjustment of the supporting air cushion allowed the rotor to seek its own axis of rotation within certain limits. Rotors had been purposely unbalanced by boring small holes near their peripheries and were found still to spin smoothly on the air cushion. This freedom which the rotor possessed of seeking its own axis of rotation would add greatly to the utility of the method since it made feasible the mounting of apparatus on rotors that would be almost impossible to balance accurately around a previously determined axis of rotation. They indicated that the Bernoulli forces could be made so strong that the rotor would run smoothly with the apparatus inverted or tilted. The stator might be made of almost any easily machined metal such as brass, bronze, duralumin or soft steel. The rotor, however, should be made of the strongest possible material since in general the maximum rotational speed was set only by the breaking strength of the rotor, provided sufficient pressure and quantity of air were available.⁷¹



Figure 3.7

Spinning tops: stator and miscellaneous collection of rotors. At bottom right are some pieces of exploded rotors. (Beams and Pickels, 1935, p.300).

Figure 3.7 shows a typical stator and also gives an impression of the variety of rotors Pickels and Beams had developed. They indicated that air friction was the major limitation for the performance of these spinning tops:

"It has been our experience that the great difficulty in the use of the air-driven rotor as a centrifuge is to keep the centrifuge 'bowl' at uniform temperature throughout. Since convection currents are essentially a buoyancy phenomenon, it is easy to see that inequalities in density arising from non-uniformity of temperature will produce increased 'stirring' or remixing when the centrifugal force on the fluid is increased. As can be seen from the curves in (figure 3.8) considerable energy is dissipated in air friction at the surface of the centrifuge. This gives rise to a heating effect. On the other hand, the rapid

expansion of the air in the air jets impinging on the cone-shaped under side of the rotor tends to cool the rotor so that temperature gradients are set up. Complicated means have been devised for equalizing the temperature in the centrifuge bowl to a very high degree of approximation. However, in many experiments for obtaining the rate of molecular sedimentation, the air-driven rotor, surrounded by air at atmospheric pressure, is less satisfactory than the very beautiful but more expensive method of Svedberg.⁷²

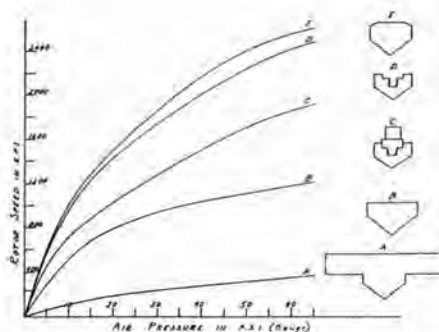


Figure 3.8

Curves of the relation of air pressure to rotor speed for the case where air surrounding rotor is at atmospheric pressure. At right are sketches of rotors to scale with which the curves were secured. Diameter of D was 1 1/8 inch. (Beams and Pickels, 1935, p.302).

They continued describing their recently developed vacuum ultracentrifuge as shown in figure 3.6. Below the rotor was a circular block composed of wood, metal and cork. This was free to move about the floor of the chamber over a limited range. A small steel rod (about 1/16 inch in diameter) fastened in the bottom of the rotor fitted with a slight clearance into the lubricated cork. This fit had to be just loose enough for the friction to be negligible. The purpose of this arrangement was to prevent pronounced precessions from being set up in the rotor. It could also serve as a brake in stopping. The steel wire which supported and drove the large rotor passed through a closely fitting hole along the axis of the turbine and was fastened at the top to a friction clutch which rode upon the turbine. This prevented sudden accelerations and decelerations from unnecessarily twisting the wire, especially in the stopping and starting. The size of the steel wire could be varied over a considerable range. They had used from 0.2 mm to 0.5 mm in this apparatus.⁷³

The vacuum chamber was cylindrical and usually made of 1/4 inch brass. The top wall of the brass chamber was carefully machined so that the top itself could be made vacuum tight with wax or other sealing compounds. In this apparatus the rotating members were both driven and supported by air jets. As a result the rotors spun very smoothly as long as the air pressure was great enough to support them but in stopping care had to be taken to prevent twisting the wire or

damaging the rotor. When stopping, the air pressure was usually reduced to a value just sufficient to support the rotors and then the stator was lowered so that the rotor was brought to rest by rubbing on the lower cork guide. However, this could unduly heat the rotor.⁷⁴ Furthermore, the wires used were so flexible that a very slight, slow precession set up in the rotor and made it impossible to photograph sedimentations with the definition required. In that type of work exposures of at least several seconds were needed. Although the apparatus had its undesirable characteristics, Pickels and Beams considered it as a definite advance toward the ideal, economical centrifuge.⁷⁵

In order to overcome the troubles mentioned above, an apparatus was designed in which the rotating members were supported by an air cushion. The pressure of the air in this cushion could be regulated independently of that in the driving air jets. Hence in stopping it was only necessary to turn off the driving jets completely and let the rotor 'coast' smoothly on the supporting air cushion to a standstill. If more rapid deceleration would be desired reverse jets could be provided. At first they introduced a separate supply of air into the bottom of the stator which acted as an independent air bearing so that the rotors could be slowly stopped by abruptly turning off the air jets and letting the rotors lose their speed.⁷⁶ Various arrangements were tried for the air bearing, and it was reasoned out and experimentally demonstrated that an essential point in design was to supply the air to the bearings in such a way that it encountered the smallest openings possible just before it formed the cushion, i.e. the air stream should experience its maximum resistance to flow just before it escaped to the bearing surfaces. Pressure from the same air line could be used for forcing the oil and supporting the turbine.⁷⁷ Figure 3.9 shows a cross section of one of their next designs in which the drive and support were completely independent. Figure 3.10 shows a photograph of the same apparatus. The rotating parts consisted of a large rotor R inside the vacuum chamber, the wire T, the oil disk Z, and the air driven turbine C. In this type, 1/25 inch and 1/16 inch wires had been employed but other sizes could be used as the size of the wire did not seem to be very critical. C was a cylindrical turbine wheel about 13/16 inch in diameter and 3/8 inch thick (not including stems). Around the periphery were 15 flutings cut with a 3/8 inch miller. The turbine was driven by 8 air jets whose lines of action were in a plane perpendicular to and about 5/16 inch from the axis of rotation. They stroke the turbine wheel at the centre of the flutings. The turbine C would ride upon an air film formed between its lower surface and the upper surface of the Bakelite collar K. In addition to the flat air bearings spherical air bearings had been used successfully. They indicated that they intended to perform an investigation of the numerous kinds of air bearings with the hope that further simplifications could be made.⁷⁸

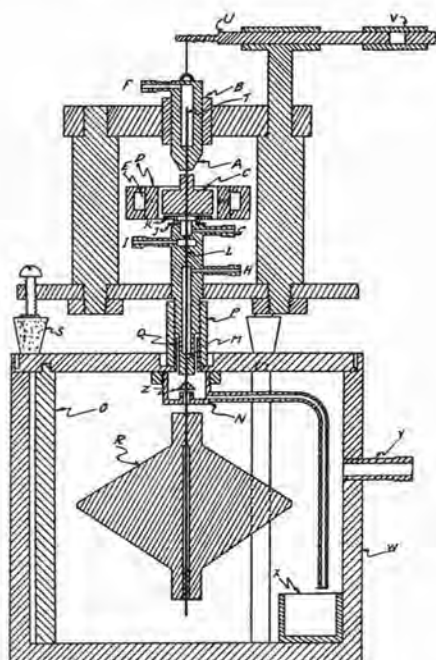


Figure 3.9

Vacuum ultracentrifuge with drive and support separated. Explanation: see text. (Beams and Pickels, 1935, p.305).

The bottom guide (figure 3.6) was found unnecessary with the type of apparatus which employed larger wires and a flexibly mounted bearing. Incidentally, it was found that a slight precession sometimes found in the apparatus of figure 3.6 was absent. At very low speeds the rotor wobbled a little without the guide but did not bend the wire. If a completely smooth start or stop was desired the guide should be made removable and used only when stopping and starting. Lower bearings constructed similar to A, L and M had been tried with success. They should be flexibly mounted and provided with forced lubrication. This lower bearing would especially useful if long rods (figure 3.10) were spun or where the rotor should not be allowed to wobble at low speeds. Figure 3.10 also shows the vacuum chamber surrounded with cooling coils for regulating temperature. A problem with the bearings was that even with proper lubrication they heated up appreciably, especially until they had been broken in. In some experiments, particularly when centrifuging of molecular particles, they should be water-cooled.⁷⁹ Further improvements were possible by developing a more efficient water jacket that would completely surround the chamber and a system of water cooling for the bearings. For quantitative work, careful consideration should be given to the illuminating source to see that minimum heat would be conducted or radiated to the rotor.⁸⁰

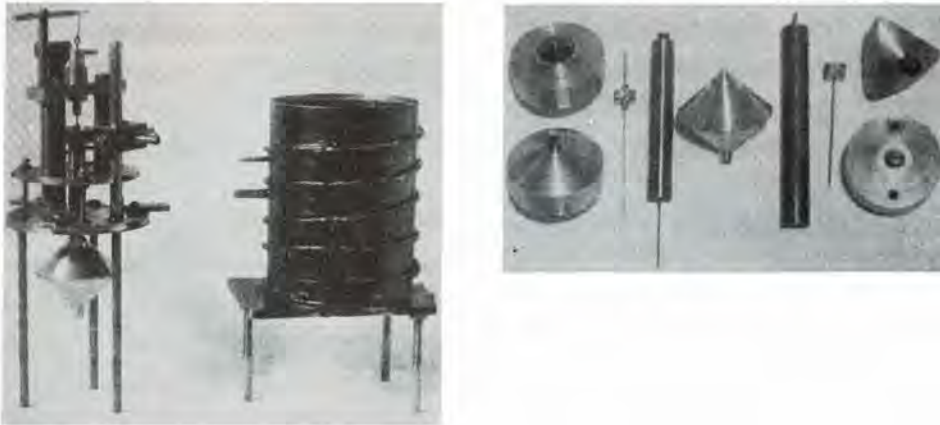


Figure 3.10

Photograph of apparatus of figure 3.9. To the left can be seen the main rotor, oil bearings and turbine assembled. A large tube with window on top for observing the rotor can be seen in place. Adjacent stands the vacuum chamber. The photo to the right shows a number of vacuum rotors and driving turbines. (Beams and Pickels, 1935, p.305).

In order to start the apparatus the oil pressure was first turned on, followed by the air pressure at G. The driving jets were next applied for a few seconds in order to set the rotor in motion. If the rotor spun smoothly for some time after the driving jets were turned off the chamber could be sealed and evacuated. The rotor would then spin smoothly up to the speed required to explode it.⁸¹ As was mentioned previously the maximum rotational speed was set only by the strength of the rotor. Since for solid metal rotors their bursting speeds depended upon their bursting strength divided by their density, they tried some rotors made of lighter alloys. These light rotors were found to reach higher speeds than any other material they had tried.

Figure 3.11 shows the pieces of some rotors as well as the vacuum chambers after explosions. The rotors were $3\frac{1}{2}$ inch in diameter and were shaped similarly to the rotor R in figure 3.9. On the left the rotor was made of duralumin and the vacuum chamber of brass. It was spinning 2600 r.p.s. when the explosion occurred. The centrifugal force on its periphery was about 1,200,000 times that of gravity. On the right the rotor was of Dow metal and the chamber of $\frac{1}{4}$ inch steel. The rotor burst at a rotational speed of 2800 r.p.s., which gave 1,400,000 times the force of gravity on the periphery. The steel vacuum chamber split into halves by the exploding rotor while the brass was twisted out of shape. They therefore stressed that brass chambers were preferable as they retarded the flying rotor pieces better than steel. They also stressed the importance of surrounding the rotor by barricades to protect the operator from rotor explosions. Therefore the

apparatus was always completely surrounded with a wall composed of 4 inch of sand on either side of which was 1½ inch of wood. For larger and heavier rotors the barricades would have to be made correspondingly thicker.⁸²



Figure 3.11

Solid metal rotors and vacuum chamber after explosion by centrifugal force. (Beams and Pickels, 1935, p.304).

The apparatus offered a wide range of possibilities which Beams and Pickels described as follows:

"No attempt will be made here to make a detailed list of the numerous uses of apparatus described in this article for obtaining high rotational speed in vacuum. The fact that rotors of a wide range of sizes, shapes and weights can be spun smoothly in a really good vacuum obviously adds greatly to their utility. Also the only parts to wear out are the bearings which may be made replaceable. Actually the same bearings if properly made will last for days of continuous use. (Figure 3.10) illustrates the variety of rotors that can be spun successfully. At the lower right is a rotor designed to observe the rate of molecular sedimentation in a way similar to that of Svedberg. At the left top and bottom are rotors which have already separated molecules like haemoglobin from their solution, the two fractions being collected. In the centre are shown steel rods now being used for experiments on the Barnett effect, etc. In the upper right-hand corner is a triangular rotor used for a velocity selector of gas molecules in some rough preliminary experiments. Stellite mirrors can also be easily spun up to their breaking speed. It may be worth while to note that the rotors may be spun in various gases at different pressures as well as in air. Also that if the chamber is properly constructed, the rotor may be spun in gases at many atmospheres as well as in vacuum."⁸³

Some experiments were carried out with the axis of rotation horizontal instead of vertical. For his dissertation, Pickels had already developed an horizontal bearing for a rotor spinning in air. He had experimented for a while with various kinds of horizontal air bearings and succeeded, in one instance, in obtaining a speed of 1100 r.p.s. with a 1½" rotor. However, the rotors were never gotten dependably stable at high speeds, and because of the discovery of a more promising scheme, work was discontinued on horizontal air bearings before they were sufficiently developed to be practical. Nevertheless, Pickels felt that they offered a

field for investigation. He believed that most of the troubles encountered were traceable to the fact that the bearings were rigidly mounted when they should be flexibly mounted. The bearing itself was like an ordinary oil bearing except that the shaft fitted fairly loosely in the stationary bearing. Into the centre of this bearing were directed two or more fine jets of compressed air, approximately tangentially to the shaft. They were all directed with the sense of rotation. Shafts varying in diameter from $1/4$ " to $3/4$ " had been used with success, especially at lower speeds. The main rotor rode on the shaft between two such bearings, and the actual driving was done with larger jets directed approximately tangentially to the rotor and impinging on deep flutings cut at its periphery. In some cases, two small driving wheels were used to spin a $3\frac{1}{2}$ " rotor. The friction losses in these bearings appeared to be remarkably low when they were working correctly."⁸⁴

Using horizontal bearings driving a larger rotor in vacuum implied that more friction was developed in the oil bearings which then had to carry the full weight of the rotors. Pickels spun a $3\frac{1}{2}$ inch duralumin rotor 2000 r.p.s. about a horizontal axis while the unguided sections of the wire on either side of the rotor were each about $\frac{1}{2}$ " long. The general arrangement of the apparatus was very much like that of the flat-bearing type, except that each bearing was simply a $3/4$ " length of brass rod stuck into a section of rubber hose. In some cases, a bearing was put on either side of the turbine wheel. At the time of these experiments, only 1 mm spring steel wires were available, and they appeared to be too flexible for the heavy $3\frac{1}{2}$ " rotors. They would seldom run for more than an hour at high speed without breaking. Smaller rotors, and small turbines alone seemed to work very nicely when they were well balanced, when the free lengths of wire were correctly adjusted and when the bearings were damped to the right degree. The oil bearings were made of bronze or brass as described above and stuck into sections of rubber tubing which in turn were supported by the ends of the vacuum chamber. The general arrangement of the vacuum chamber and driving apparatus was the same as in the type where the axis of rotation was vertical. However, when possible, they advised to make the rotors spin around a vertical axis not only because of less bearing friction but because of the bending of the wire by the weight of the rotor. This bending apparently caused the wire to fatigue and break after a few hours running unless the rotor was comparatively light or the wire large. Nevertheless, the rotor spun smoothly and they recommended the method when the axis of rotation would have to be horizontal. Pickels felt that there would be many possibilities for research if this horizontal bearing idea would be further developed.⁸⁵

In May 1935, Pickels completed his dissertation entitled *The Air-Driven Ultra-Centrifuge*. It is striking how Pickels 'always' formulated *general* problems and presented *general* solutions. Concrete designs were usually presented as *an example*

of general solutions. According to Pickels a particular advantage of air bearing, flexible and damped oil bearing, and flexible shaft arrangements was that vibrations could be reduced to a negligible amount even when the rotating parts were quite appreciably unbalanced. It was his opinion that many unsuccessful experiments had been bleared on vibrations when convection currents were the real cause of the trouble. Sedimenting systems had, in several instances, been observed to be uninfluenced to any marked degree by a long and pronounced shaking of the rotor, when the frequency of the vibration or shaking was much lower than the frequency of rotation. This was to be expected, since the centrifugal force would hold the solution firmly in place. However, it might be that very high frequency vibrations, which would occur with an unbalanced rotor spinning in a rigidly mounted bearing, would cause considerable trouble. Therefore, Pickels found it highly desirable to provide for the stationary portions of the bearings some sort of a flexible mounting which would suitably damp out any vibrations that tended to set up. Whenever an apparatus failed to operate smoothly, the first thing to do would be to try various mounting and damping arrangements and perhaps various shaft lengths to ascertain the optimum conditions.⁸⁶

With a 3½ inch rotor and made of duralumin he was able to sediment haemoglobin and take photographs of the sedimentation process like Svedberg did. To him this demonstrated the possibilities of the flatbearing vacuum centrifuge. The speed of the centrifuge, though varying with changes in air pressure, was a little above 1200 r.p.s. most of the time. The average force in the cell was in the neighborhood of 200,000 gravity. The photographs were taken at ten minutes intervals with an exposure time of 30 seconds.⁸⁷ But Pickels was also interested in other types of applications. The vacuum centrifuges developed until then were not well suited for centrifuging large quantities of material because of their large starting and stopping times. In order to solve this problem Pickels started the development of so-called continuous-feed centrifuges. However, according to Pickels, for such types of centrifuges, which necessitated the introduction of a solution into the chamber while the rotation continued, it would be impossible to maintain a high vacuum because the solutions would vaporize and increase the pressure. However, the vapour pressures of 'ordinary solutions' were comparatively small, particularly at lower temperatures. Considerable trouble was had introducing fluid into the centrifuge without having a part of it thrown out into the vacuum chamber. Several arrangements were tried to overcome the trouble. The first separations with haemoglobin also gave trouble. The rotors were fitted with small windows so that the operations could be studied visually. It was observed that the particles were separating beautifully, and that the trouble was being caused by a too rapid introduction of the solution.⁸⁸ Pickels also experimented with a type of velocity selector suggested by Beams. The general idea was to partially separate

gas molecules lying within certain ranges of molecular speeds, i.e. to partially separate one gas from another. A 3½" duralumin rotor was shaped like an equilateral triangle with blunt corners, each of which was equidistant from the axis of rotation (figure 3.10; rotor in upper right-hand corner). Holes were so arranged near the three corners that they were continually 'running away' from the gas molecules as the rotor spun at high speeds, so that the slower molecules could not 'catch up' and get in these holes. These holes in turn were connected within the rotor to an opening in a steel needle used in place of the lower wire shaft on the rotor. The needle opened on the lower side of the bottom oil bearing into a separate chamber which was fitted with an external outlet. The pressure within the chambers was kept low enough for the mean free path of the molecules to be at least one cm. During his thesis research Pickels had not yet investigated the scheme in sufficient detail to say much about the possibilities of the scheme, but the mechanical arrangement did work nicely and furthermore he was found that a much lower pressure would continually exist in the chamber connected to the needle than in the other. He indicated that the arrangement might be used as a pump for very high vacuum work.⁸⁹ In the conclusions to his dissertation Pickels stated:

"Perhaps the most appropriate concluding remark is the confession that the research has been rather diffuse and that there is considerable room for further improvement in the types of apparatus that have been discussed. On the other hand, the writer finds some satisfaction in the hope that other investigators may be able to use these new and tested principles in building apparatus suited to their own particular needs. For the study of biological materials, particularly filterable viruses and bacteria, the contributions may be a definite step in opening an entirely new field of research. The simple methods of obtaining high rotational speeds in vacuo should prove useful in many physical problems, especially where vibrations and temperature gradients are undesirable characteristics."⁹⁰

Rockefeller Foundation - Steam and Electrical Drives

From the early 1930s onward the Rockefeller Foundation became interested in stimulating research that applied the methods used in the physical sciences to the study of biological materials. Early 1934 Warren Weaver, Director of the Foundation's Natural Science Division, wrote Beams because he had 'a vague impression' that Beams was in charge of an inquiry into the Allison magneto optical method. This method was developed by Fred Allison in the late 1920s for the chemical analysis of substances in solution. The principle of the method was that the transmission of monochromatic light, sent through the solution, changed under the influence of a magnetic field acting upon the solution. Allison had found that minima of light intensity, characteristic of the substance in solution, were

always found for well defined settings of the circuit generating the magnetic field. Thus, the apparatus might be used to analyze unknown solutions by merely observing the settings at which minima of light intensity appeared.⁹¹ The Rockefeller Foundation had become interested in the applications of optical methods to the analysis of biologically significant material. They were thinking, in the first instance, of the application of spectroscopic methods to blood serum, spinal fluid, urine and other body fluids, with particular emphasis upon the possibilities relative to hormones, vitamins and enzymes. At that time they were attempting to get a general background of information about technics and opportunities, as well as about people who were interested in the Allison stunt.⁹² Beams replied that L.B. Snoddy, one of his colleagues together with a graduate student called Bradley, a graduate student, had started a study of the Allison phenomena about half a year before. At that time they were visiting Allison to study his apparatus and Beams promised to send a full report of their work when they had returned. Beams also took the opportunity to inform Weaver about his centrifuges:

"Incidentally, you may be interested in a little air driven centrifuge that we have been playing with in the hope it could be made into a useful tool. We now believe that we have solved its chief difficulty, namely that of non-uniformity of temperature which gave rise to remixing by convection currents. Recently, Mr. Pickels, one of my graduate students, separated the haemoglobin of the blood from the clear solution and collected the two fractions using only about 10^5 gravity. This same centrifuge was capable of doing at least 3.5×10^5 gravity, and therefore might be able to separate the various substances from different body fluids and thus get them quite pure or at least concentrate them considerably. I am enclosing a recent reprint and copy of a short note that we just sent in for publication. If you are interested in applying these centrifuges in any of your biological investigations we shall be delighted to tell you all that we can about them, or assist you in any way possible."⁹³

Weaver responded extending his appreciation for information concerning the latest developments in the ultracentrifuge. He also informed Beams that Dr. Sawyer of the International Health Division of the Foundation was planning to make use of this device in connection with certain researches which his group was carrying on at the Rockefeller Institute on yellow fever and malaria.⁹⁴ Some weeks later, after a recommendation from the National Research Council (NRC) who had previously given him a grant⁹⁵, a grant was awarded for Snoddy's further investigations into the Allison method.⁹⁶

Mid 1935 Weaver informed Beams that, during a visit in Europe, he had come upon developments of interest in connection with ultracentrifuge work. He would like to discuss these developments with Beams.⁹⁷ Beams responded that Weaver would be most welcome, also stating that they had made some recent improvements in the design of their vacuum ultracentrifuge which he would like Weaver to see.

He enclosed some reprints of 'preliminary notes on the general methods'.⁹⁸ Weaver visited Beams in October and was very impressed by what he saw. It appeared to him that Beams' technique, when and if perfected, would serve in many instances as a 'ridiculously cheap and simple substitute for the Svedberg technique'.⁹⁹

About a year later Beams wrote Weaver a long letter concerning the possible further development of his ultracentrifuge:

"I am writing to ask your opinion as to the advisability of undertaking a new development of the 'vacuum' ultracentrifuge. It has been pointed out to me that in many places, especially biological laboratories, air pressure is not readily available to drive the centrifuge and that, although the costs of construction of the driving parts of the ultracentrifuge is very small, an air compressor - even such as is used in small garages - costs two or three hundred dollars to install. The principle which we developed of driving and supporting a rotor with air and hanging from it, a small steel rod, which passes through a vacuum tight oil bearing, a large centrifuge in vacuo, can easily be adapted to other types of drives besides the air turbine. For example, steam could easily be used (or) the problem could be solved for the lower speed ultracentrifuge by an electrical drive.

In the past I have hesitated to develop the above types of drive for the ultracentrifuge because the air drive is quite satisfactory for our own experiments in physics. Also I was not certain of the real need for the development in biology of medicine. Furthermore, to carry out these developments properly would add too much of a burden to our funds available here for research in physics so that it would be necessary for me to raise outside funds for the purpose. However, I am now much interested in carrying out the new development if there is a genuine need for it in biology and medicine because when once developed there is always a good chance that it will find applications in physics as well. Dr. Hoxton has also kindly agreed to join me in the proposed development of the steam turbine.

We would like very much to know whether, in your contacts with scientist in other fields, you have found a need for the steam or electrical drive, also if you could unofficially tell me whether you could consider the application for grants to carry on work of this nature. I realize, of course, that you may perhaps not want in any way to indicate an answer to the latter question, but I shall much appreciate your frank opinion as to feasibility and need for the new developments."¹⁰⁰

Weaver replied that Svedberg would be coming to the US the following month and that he would like to discuss the matter with him first. Beams was also invited to a dinner for Svedberg which, however, he was unable to attend because of other obligations.¹⁰¹ The following month Beams sent Weaver a memorandum outlining his plans for further development of the ultracentrifuge. He stated:

"Numerous test have demonstrated that our new air-driven 'vacuum' centrifuge is able, at least, to separate most of the heavier molecules from their solution. Its simplicity and flexibility have made possible its use in two principal ways. In the first way the rate of sedimentation of the material was observed and the molecular weight or size of the molecules determined in a manner similar to that of Svedberg. In the second way the lighter and heavier fractions were collected after the separation had taken place. The value of the centrifuge as used in the first way mentioned above has been amply demonstrated by the very important advances made by Svedberg and his collaborators. Our new centrifuge should by its ready availability enable a great many workers to employ this beautiful technique

developed by Svedberg to their own problems. However, in the writer's opinion, the second method of using the centrifuge holds even greater promise than the first. A mechanical method of separating mixtures of molecules has long been needed not only in chemistry but in medicine and biology as well. (...)

In view of the above possibilities for the general use of the 'vacuum' centrifuge, we are hoping to undertake its development to a point where it should be usable and available to practically any laboratory worker who has need for it. In other words, to make it 'fool-proof' and at the same time keep its cost and operating expense low. Although the centrifuge in its present form is comparatively simple, a certain amount of skill is still required to operate it. Also, although the cost of the apparatus is comparatively low, it requires a source of air pressure which is not readily available to workers outside the field of physics. We therefore propose to develop a steam-driven centrifuge utilizing the same principles as have been so successfully employed in the air-driven centrifuge. Also we plan to investigate the possibilities of driving the centrifuges with a high speed electrical motor.

Already one of our students, Dr. T. Davis, has driven a vacuum centrifuge over 1,000 R.P.S. with an electrical motor drive so that for the larger rotors we feel sure that this type of drive can be used successfully. However, the most promising type of drive seems to be steam. The operator would only have to attach a connection to the water faucet and plug in the heater on the ordinary 110 volt supply. With the exception of setting the governors to the desired speed, the remainder of the operation of the centrifuge could be made automatic. Dr. L.G. Hoxton, who has kindly consented to collaborate with the writer in the development of the steam drive, has had considerable experience with problems of this type and he can see no reason why the cost of such an apparatus could not be made within the means of most laboratory workers."¹⁰²

He continued stating that, in order to carry out the above program and at the same time keep their present developments under way, it would be necessary to raise funds in addition to those now available for their physical research. The increase in the number of graduate students doing research in physics caused them to hesitate to spend funds now allotted to research in physics on the above projects. He indicated that for the projects mentioned they would need a full time instrument maker and enough money for supplies and auxiliary equipment. Beams expected that with this available, the work could be carried to completion in the course of two years. Therefore, he would like to raise \$ 4,000 per year for a period of two years, of which \$ 2,500 would be for an instrument maker and \$ 1,500 for supplies and auxiliary apparatus.¹⁰³ The following month, while in New York, Beams and Hoxton discussed the plans with Weaver. The proposed program would be primarily directed toward the development of a new driving mechanism but Beams and Hoxton would also wish to give some attention to a systematic investigation of materials available for large high-speed rotors. They were not convinced that this problem had been sufficiently carefully studied, and they wished to look into the possibilities of all of the latest types of a high tensile strength alloys, latest annealing procedures, the possibility of gaining great tensile strength by shrinking of circumferential bands, etc. Weaver indicated that he wished to discuss this problem further with other persons, such as Bauer and

Pickels, and that he would write to Beams if any further questions would occur.¹⁰⁴ Upon consultation Pickels informed Weaver that he thought that Beams' proposal was a very sound one but that they should not attempt an investigation of the best rotor material because that problem would be well in his own and in Svedberg's hands. In his formal reply to Beams Weaver expressed some doubts about the heat effects of the steam drive but also considered the importance of a wider availability inasmuch as the new drive would make use of services universally available. Further important considerations would be simplicity, initial cost and operating cost. Weaver advised Beams to restrict their work primarily to the question of the development of a steam or electrical drive; and not attempt to undertake a systematic investigation of the various materials, designs, annealing procedures, etc., which might lead to a greater limiting speed for the rotor. He indicated that, since Svedberg's visit at the Rockefeller Institute, Bauer and Pickels had constructed an elliptically shaped rotor which permitted them to reach speeds roughly 30% greater than the previous one (see Chapter 5). Weaver did not doubt that improvements could and should be made, but it seemed likely that this would be a rather expensive game, and it was his general impression that Beams' facilities and energies should be wholly absorbed by the development and perfection of new drives, including the matter of very accurate control of speeds.¹⁰⁵ A few weeks later Beams submitted a formal request for a grant. He indicated that he expected that the problem of preventing the heat from the hot turbine from flowing into the centrifuge could be solved. On top of that, he held the opinion that the thermostatic apparatus and heat insulation would allow the temperature of the air-driven ultracentrifuge to be better controlled.¹⁰⁶ The grant was awarded to Beams considering the usefulness of the apparatus in biology and medicine, and the fact that separation could be accomplished at a constant arbitrary temperature, which often was essential in biological chemistry where one sought to avoid killing or inactivating the materials being separated. Comparing the air-driven ultracentrifuge with Svedberg's apparatus the Rockefeller Foundation held the opinion that an essential difference between the two was that the latter, utilizing an oil turbine drive, was much more elaborate and expensive. Although the Svedberg centrifuge was essential for certain delicate quantitative experimentation, the simpler air-driven type had a wider range of application. A steam or electrical drive, which would be 'self-containing' would make this technique available to a large number of biologists and medical men who would not be prepared to undertake the maintenance of the more complicated machine.¹⁰⁷

Weaver was not only interested in the biological applications of the ultracentrifuge but also in its application for isotope separation. Mid 1937 he asked Beams some information on the rotors they planned to use and on the theoretical background to the method. Weaver himself would like to go into the theory in

order to solve some problems connected to the method.¹⁰⁸ He was a mathematician by training and in the early 1920s had worked on the theory for sedimentation in centrifugal fields. Beams replied that he would be very interested in having these theoretical problems solved because, if they had a general solution to the differential equation, they would not have to wait for equilibrium to be established. He outlined that they also attempted to use a new type of centrifuge for molecular weight determinations which would not need expensive optical equipment. Furthermore he included a copy of a recent publication in *Nature* of Holmes and himself¹⁰⁹ describing an axial magnetic suspension. He indicated that this problem had no connection with their problem of getting a practical electrical drive for the ultracentrifuge but he thought Weaver had a personal interest in getting very constant rotational speeds.¹¹⁰

September 1937 Weaver informed Beams that Edwin J. Cohn of the Department of Physical Chemistry of Harvard Medical School was very much interested in obtaining an ultracentrifuge. Because the Rockefeller Foundation considered giving Cohn a grant for this purpose he inquired how the developments at Beams' laboratory were going. Beams replied that they were making definite progress and that he expected that an electrically driven machine would be ready for use by Mid 1938. Cohn had visited Beams half a year before and was shown the air driven continuous flow ultracentrifuge for solutions.¹¹¹ By that time they had only just begun developing the other types of drive. A detailed progress report followed in December. In the accompanying letter Beams also referred to Weaver's interest in the mathematical investigation of the settling of small particles and molecules in the centrifuge. He stressed that if a mathematical solution to the differential equation could be found better methods of separation might be devised, and also that Svedberg's methods might be improved upon and made simpler. Svedberg had given a lecture at Beams' laboratory two months before at which occasion Beams had also raised this matter. Svedberg had pointed out that two of his students, Lamm and Faxen, had tried to solve the problem, but that their results were not in a form which could be readily used. However, Beams wrote, 'our optimism and genuine need for a usable solution made us feel that more work should be attempted.'¹¹² Beams had asked a 'very brilliant all-round student', W.J. Archibald, to look into the problem of the settling in the centrifuge in his spare time. As a result Archibald had now produced a solution which was in a form that could be used. Professor McShane of the UVa Mathematics Department had assured Beams that the mathematics was all right, and they were pretty certain of the physics. However, although in Beams' opinion, Archibald's solution would be a real help, it applied only to special cases of dilute 'ideal' solutions. Personally Beams believed that a very thorough theoretical investigation of the settling in gases, vapors and liquids, would be needed and also that the separation of liquids other than when

they are dilute and 'ideal' solutions should be investigated theoretically. Beams argued that work of this kind might be of considerable value to biology, medicine and chemistry as well as physics, and therefore wondered if it would be possible for him to send in an application for a Rockefeller Foundation Fellowship.¹¹³ Weaver responded that it was not likely that Archibald would be given a fellowship because these were only given to men who had demonstrated, usually a few years after the taking of their degree, a 'really outstanding capacity in original research'.¹¹⁴ In 1938 Archibald published his findings for the 'ideal' solutions in two papers, the first for the case of a sector-shaped cell extending to the centre of the centrifuge,¹¹⁵ the second for the types of cell used in practice with two bounding cylindrical ends.¹¹⁶

In the progress report Beams discussed the development of both the electrical and steam drives. The steam drive had turned out to be much easier to develop than the electrical type. It was 'only necessary' to insulate thermally the driving and supporting parts of the air driven centrifuge from the vacuum chamber and rotor, and steam could be used instead of air. A simple thermal insulation was sufficient to keep the centrifuge at practically uniform temperature. Although many improvements could be made it was already in a usable form. However, it was Beams' opinion that, where air would be available, the air drive would be superior to the steam drive because of the thermal insulation problem. Moreover, although excellent results were obtained, it required between 7 and 10 kilowatts of electrical energy to generate steam with sufficient rapidity. The electrical machine of the same size took less than one kilowatt. Furthermore, steam had no essential advantage over the air-driven machine and it was more complicated in every way to operate. However, it could be used with some advantage where steam would be available.¹¹⁷ Therefore, they intended to direct the major effort in the future toward the development of the electrical drive rather than the steam drive although the latter would be completed and put into a practical form.¹¹⁸ In 1938 the steam drive was published in *Physical Review*. Again, the maximum rotational speed was limited only by the bursting strength of the rotor. The centrifuge and the vacuum chamber were maintained at a constant temperature by circulating water around the chamber.¹¹⁹ Beams and Linke indicated that these alternative drives could also be used for their inverted ultracentrifuge.¹²⁰

In 1937 the electrical drive was described by Beams and Snoddy in *Science*. They indicated that the amount of air required to drive the air turbine was not large (2 to 3 cubic feet per minute, 15 to 20 lbs/in² gauge pressure in their latest design), while the amount of air required to support the rotating parts was in comparison almost negligible and needed only be supplied at from 5 to 15 lbs/in² gauge pressure. Nevertheless, they indicated as a problem that in many laboratories air compressors of sufficient capacity were not available, so that, in

order to run the air-driven centrifuge, an auxiliary compressor had to be installed. If it were possible to spin the turbine by some other means, the amount of air required to support the rotating parts could then be supplied by a small 'blower' or compressor, which was available commercially at the cost of only a few dollars. As a solution to this problem Beams and Snoddy developed an electrical drive as shown in figure 3.12. The driving rotor T was a so-called 'familiar squirrel cage type' of armature so that an alternating current in the field coils F caused it to spin. The principle of the induction motor was thus used to spin T, while a small amount of air at a pressure of a few lbs/in² was used to support it. The centrifuge would start from rest and gradually accelerate until a rotational frequency was attained practically equal to that of the alternating current in the field coils F. The fact that in practice the rotor T reached this speed resulted from the almost negligible friction except for that of the air on the small rotor itself. It appeared to be possible to construct electrical circuits and field coil magnets to give fields of considerable magnitude at the desired frequency so that the maximum rotational speed was set by the breaking strength of T or the centrifuge A. In most biological, chemical or medical experiments A would have to be 8 to 10 inches in diameter. Such rotors would usually explode if driven much above 1000 r.p.s. In practice it was not difficult to construct T to stand this speed.

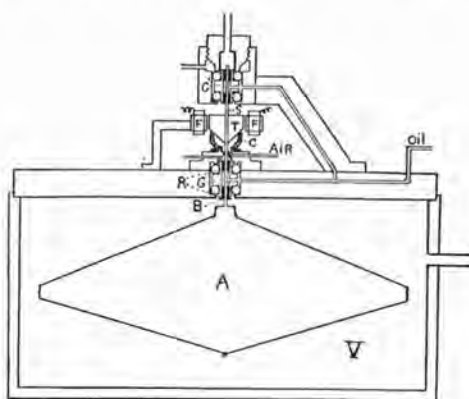


Figure 3.12

Electrically driven ultracentrifuge. Explanation: see text. (Beams and Snoddy, 1937a, p.185).

The A.C. power supply for the motor was constructed in Beams laboratory from transformers, capacities, etc., which could usually be found in any laboratory or obtained at small cost. The circuit was capable of furnishing considerable power at frequencies which could be changed gradually or abruptly by a variation in circuit constants. This was of advantage in the initial acceleration of the centrifuge as the frequency might be set initially at some low value and increased as the

centrifuge speeded up. Experience showed that the induction motor type of drive gave a speed practically as constant as the frequency of the circuit and therefore better than usually required in most work they anticipated. They pointed out that several other types of electrical circuits and drives might be used besides the one they had used. Although the air turbine drive still should be used to obtain the very highest rotational speeds, the electrical drive served equally well for many purposes and had the advantage, after once being set up, that it was automatic and required no attention from the operator to keep the speed constant.¹²¹ Beams thought that the air-drive was a thing of the past. A satisfactory compressor and power source for the air-drive model cost about \$ 500 and he thought it quite likely that the much more satisfactory and simpler electrical drive would eventually cost less.¹²²

Other Types of Research

Besides developing ultracentrifuges, various other types of research were carried out in the Rous Physical laboratory. In the 1932-33 annual report 3 major fields of investigation were listed: (1) electric and dielectric properties of matter, (2) electrical discharges and (3) thermal properties of matter. Beams' ultracentrifuge work was not listed as a separate item.¹²³ This changed in the subsequent years when it was mentioned explicitly. The 1933-34 annual report stated:

"Considerable attention has been drawn to the further development of the 'ultracentrifuge'. The Franklin Institute of Philadelphia, for instance, has received from us a model for their museum of Science."¹²⁴

Although from the early 1930s onward Beams did a lot of work on ultracentrifuges it was certainly not the only field he was working in. The 1934-35 annual report listed his research activities as follows: (a) The production of high rotational speeds and their application to the study of various physical phenomena, (b) The acceleration of ions and electrons to very high velocities without the use of high potentials and their application to the study of nuclear and other high energy phenomena, (c) Electrical break-down.¹²⁵ Item (a) was carried out mainly in cooperation with Pickels, and item (b) in cooperation with Snoddy. Snoddy's work was also highly valued and after a personal grant from the Rockefeller Foundation in 1935¹²⁶ he was added to the staff of the Rous Physical Laboratory as an associate professor in 1936.¹²⁷ Until that time Beams had mainly directed the research in the laboratory but after Snoddy's appointment they directed the work together.

When the depression that had begun in the north had reached the south, salaries were being cut. On of the instructors at the laboratory, G.G. Quarles was fired and it was decided that Brown could make a greater contribution to the Department by teaching than by continuing this research.¹²⁸ This hardly influenced the total research output because, once the UVa became better known as a place where good physics research was done, the number of Ph.D. students grew steadily. The number of Ph.D's awarded grew from 1 or 2 in the years 1925-1930 to 7 in 1935.¹²⁹ Gradually all the space in the RPL was converted from educational purposes to research. Together, Beams and Snoddy were very successful in securing grants for further investigations.¹³⁰ Beams was not only interested in carrying out research himself but also in the development of physics and science in a more general sense. In the mid 1930s he became a member of a number of boards and committees. In 1936 he was elected to the council of the Physical Society and also made a member of the Council Representing Physics of the American Association for the Advancement of Science.¹³¹ In 1937 he was appointed a member of the Fellowship Committee of the council of the American Physical Society. He was elected President of the Southeastern Section of the American Physical Society and, furthermore, was appointed consultant to the Biochemical Research Laboratory of the Franklin Institute of Philadelphia.¹³²

Beams considered himself as an experimental physicist though he had also an interest in theoretical matters e.g. in the field of electronics. For instance, late 1933 he wrote in a letter to a colleague:

"Since I am trained just as an experimental physicist I find it rather hard to follow readily some papers in the general field of transients and electrical circuits although I am trying to learn as fast as I can."¹³³

Although Beams developed ultracentrifuges for every possible application he could think of, his main love remained to be physics. E.g., when applying for a grant in 1936 he wrote the Rockefeller Foundation:

"In *our own field* of physics high rotational speeds such as are employed for the ultracentrifuge are being used in the study of the numerous physical phenomena that occur in very short intervals of time as well as those affected by very large centrifugal forces."¹³⁴ (italics mine; BE)

In their own laboratory they wanted to use the rotating mirrors for different kinds of study, like: Magnetization by Rotation (Barnett Effect); Magnetic effect produced by moving charges (Rowland experiment); Velocity of light; Propagation of luminosity in discharge tubes; etc.¹³⁵ Seeking very constant rotational speeds was also primarily motivated by their own background in physics:

"While (...) very constant speed may not be of much value in ordinary centrifuging problems, at the present time it is not inconceivable that uses might develop because the angular velocity squared enters into many results. Our interest in the problem originates from a desire to measure the velocity of light."¹³⁶

Beams himself investigated how the human eye integrated short flashes of light. In these experiments he used a rotating mirror driven by a spinning top.¹³⁷ Together with Snoddy and E.J. Workman he investigated the behaviour of lightning flashes.¹³⁸ T.E. Gilmer continued Beams' work on the integrating power of the eye for short flashes of light. He used various apparatuses made in the workshop, including rotating mirrors, to produce flashes of light in order to investigate to what extent the eye would experience flicker. He was concluded that the response of the eye depended only upon the total amount of light in the beam and was independent of the length of the light flash.¹³⁹ J.A. Chiles investigated vacuum spark discharges between electrodes of several different elements by means of a camera and high speed rotating mirror. He found that, with very rare exceptions, the luminosity always appeared at the anode before it appeared at the cathode. Measurements were made of the time interval between the appearance of luminosity at the anode and its later appearance at the cathode, and of the velocity of the luminous vapour from the anode. He formulated hypotheses of the mechanism of the discharge and to account for the observed vapour velocities.¹⁴⁰

Further Development of Ultracentrifuges

The development of the ultracentrifuge had made it necessary for Beams to measure rotational speeds over wide ranges. In some of their experiments the speed was varied from about a hundred to over twenty thousand revolutions per second although usually the working speeds were between 500 r.p.s. and 3,000 r.p.s. Not only should the speed be known for the interpretation of the experimental results but also in order to stay away from the bursting speed of the rotor. Such explosions could be very dangerous for the experimenter. For instance, one of the tiny spinning tops blew up in the hand of Jim Davis, one of Beams' students, and severed several fingers. An explosion in Pickels' laboratory once sent a piece of rotor through the wall.¹⁴¹ Hence the vacuum chamber was always either heavily barricaded or made very strong to protect the operator in case of an explosion. The latter procedure was preferable although the former was less expensive. Bauer and Pickels recommended that the vacuum chamber be a heat treated nickel-steel alloy cylinder with wall thickness of at least an inch for the type of Duralumin rotors used in their work, while Pollock and Collie employed a short segment of a discarded cannon barrel for their chamber.¹⁴² However, it was considered a lot

better to prevent an explosion by knowing the rotor speed and not spinning the it to fast. Several different methods of measuring speeds of rotation in this range could be used, but in practice they were comparatively complicated and required special or expensive equipment. Also, as in the case of some forms of the stroboscopic method, care had to be taken by the observer to distinguish between the fundamental and its harmonics. In order to overcome these drawbacks Beams devised a scheme in which a small magnet was fastened to the high speed rotor or driving turbine. This magnet induced an alternating current in the coil, which was connected across a so-called 'electrical bridge' that could be balanced at only one frequency. He indicated that the method possessed the following advantages:

- 1) The apparatus was inexpensive, simple to operate and easily obtainable or constructed.
- 2) The rotational speed was read directly, and no special skill was required of the observer, since only one frequency would balance the bridge.
- 3) Its calibration did not change. That is, the settings were independent of the strength of the magnet and the position of the coil.
- 4) The readings could be made about as accurately and quickly as desired, which made it possible to follow rapid fluctuations in the speed of the rotor.
- 5) The balance of the bridge might also be used indirectly to control the rotational speed when this would be desirable.¹⁴³

For 'special applications', in which the observing apparatus would have to be placed directly over the centre of the centrifuge or where one rotor would have to be spun inside another, Beams developed an ultracentrifuge in which the air turbine was placed below the vacuum chamber rather than above it (figure 3.13). The size of the turbine T and the shaft S were determined by the size and weight of the centrifuge C, i.e., both the diameter of S and T should be increased when C was increased. Before starting the centrifuge the axis of rotation was made vertical by the leveling screws and care had to be taken to see that the shaft was straight. Beams indicated that the rotating centrifuge C mounted on S had some of the properties of both the inverted pendulum and the ordinary spinning top. Consequently when the centrifuge was first started it passed through two speeds in which it might wobble considerably. The first speed was critical and depended upon the length and stiffness of S and the dimensions and weight of C. It was approximately equal to the period observed when the centrifuge, while not spinning, was displaced and allowed to vibrate. The second speed was less critical (band of frequencies) and had a much smaller amplitude than the first. Above these speeds (about 100 r.p.s. in apparatus of figure 3.13) the centrifuge spun smoothly ('slept'). If trouble from wobbling was encountered in starting, the centrifuge might be steadied by touching it at P with a pointed wire until it passed the critical

speeds, or if desirable a small flexible shaft might be attached through an oil gland in the top of V. However, they always found it easy to get the centrifuge through these disturbances by suddenly turning on the driving air to 40 or 45 lb/in². The centrifuge was accelerated so rapidly that it passed the troublesome speeds before the amplitudes of the disturbances could build up to appreciable magnitude.¹⁴⁴ The inverted ultracentrifuge appeared to be a little more stable than the 'normal' type because, like a top spinning on a point, it tended to right itself if violently disturbed while spinning. The arrangement was to be preferred where the rotor should be viewed optically, because of convenience and simplicity. The observing apparatus could then be placed directly above the centrifuge.¹⁴⁵

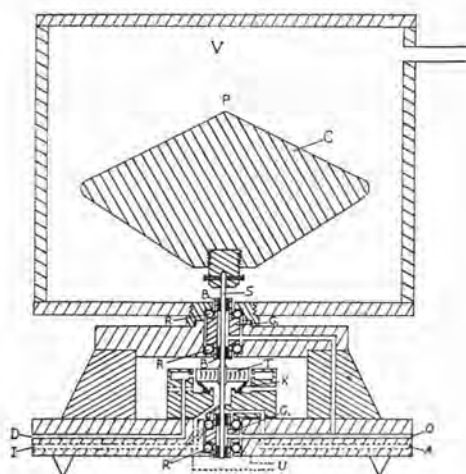


Figure 3.13

Arrangement with drive below the rotor. Explanation: see text. (Beams and Linke, 1937b, p.160).

In 1937 Beams started in new line in the development which he called the 'tubular vacuum type centrifuge. Cooperating with Linke and Skarstrom he wrote in *Science*:

"The air-driven vacuum type ultracentrifuge has been found to be an efficient apparatus for purifying many different organic and inorganic materials. It has proven useful especially in the separation and purification of biological substances such as the so-called 'macromolecular proteins.' In this work it is standard practice to centrifuge the liquid in a rotor the diameter of which is greater or approximately equal to its length. The rotor is supported in a vacuum chamber by a single flexible shaft which passes out of the chamber through a vacuum-tight gland and connects with an air-supported air-driven turbine above the chamber. The rotor is constructed to hold several test-tube containers for liquid and is equipped with a vacuum-tight cover. Consequently, in making a single separation it is necessary for the operator not only to start and stop the centrifuge but to evacuate the chamber containing the rotor as well. Since the largest rotors employed so far hold only from 120 to 150 cc, this procedure may become time-

consuming if large quantities of material are to be centrifuged. Clearly, if the apparatus could be modified so that the materials could be passed continuously (or intermittently) through the centrifuge and the lighter and heavier fractions separately collected (in the manner of the familiar cream separator), without stopping the centrifuge or without lowering the efficiency of separation appreciably, the quantity centrifuged would be much increased.

In connection with a problem on the separation of gases (isotopes), we have been spinning long cylindrical tubes in such a manner that the gas enters at the bottom. Recently the same type of apparatus has been applied to the separation of liquids and has proven effective enough to warrant possibly a short description."¹⁴⁶

The tubular ultracentrifuge is shown in figure 3.14, left. In this apparatus, the quantity of liquid which could be separated in a given interval of time was directly proportional to the length of the rotating cylinder C. Since the maximum speed to of the rotor was limited only by its bursting strength, it was advantageous to employ long small-diameter tubes for the centrifuge. Two-inch cylinders two feet in length were spun successfully. With this apparatus they obtained an easily observable separation of haemoglobin from the solution when it was introduced at the rate of from 20 to 30 cc per hour with C spinning 1000 r.p.s. A drawback of this arrangement was that the tubular rotor was not as strong as certain other shapes. However, by employing high strength alloy steels and special construction, Beams expected that tubular rotors might be built, the bursting speed of which could be made to approach the best rotors of the same effective diameter that had been in practical use. Also the efficiency of C might be increased by mounting properly designed plates or discs inside it. They also indicated that it would be possible to replace the rotor by other shapes (the angle centrifuge, for example) obtaining, with a slight change in internal construction, the advantage of continuous quantity separation. Further, the use of three or more hollow, concentric flexible shafts and vacuum-tight glands would make it possible to adapt the 'ordinary type' of air-driven ultracentrifuge to continuous operation.¹⁴⁷

In 1938 Beams developed a new type of bearing for this ultracentrifuge (figure 3.14, right). The gland was now mounted in larger metal plate N which floated on a thin film of oil on the upper lid of the vacuum chamber. The oil served to conduct the heat generated in the bearings to the larger metal plates in which the glands were mounted. A number of additional outlets made it possible to circulate the oil in order to maintain the shafts at uniform temperature. Water cooling of U had also been used for this purpose but circulation of the oil was considered preferable. In practice it was found unnecessary to circulate the oil except when large shafts were used at very high rotational speeds and liquids were being centrifuged slowly. In most cases the outlets were plugged. This bearing also served to prevent breaking of the shafts. As the rotors speeded up R passed through certain rather sharp frequencies where the floating plate N was observed to move around or 'wobble' freely upon its oil cushion. Above or below these

frequencies, N remained stationary and sought a position which made the axis of rotation vertical. It appeared to be very difficult to get R through these critical frequencies when N was fastened solidly to the upper plate. Invariably the shafts were sheared off. However this never happened with N floating on oil. Also the acceleration of R remained practically uniform in passing through these frequencies. The machine was always operated at rotational speeds well removed from these critical frequencies. With an air pressure of 60 lb./inch² the rotor attained almost 1200 r.p.s. in 30 minutes. Because of the large moment of inertia of the long cylinder the rotational speed could be made very constant if the driving pressure was carefully regulated.

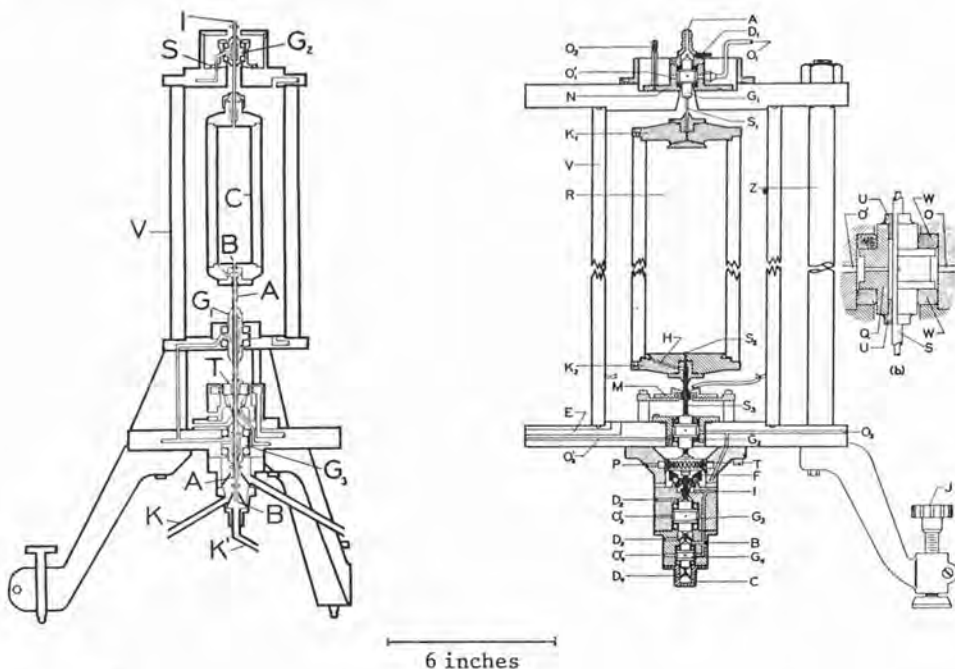


Figure 3.14

Tubular ultracentrifuges (Left: Beams, Linke and Skarstrom, 1937, p.293. Right: Beams, 1938b, p.414).

When the centrifuge was used to separate materials in the liquid state a solid rod was mounted inside the rotor in order to direct the liquid flow through the strongest part of the centrifugal field. Where back diffusion was slow, as in the case of liquids, this arrangement greatly increased the rate of separation. Since the bursting speed of an empty spinning tube was roughly proportional to x^2f^2 , where x was the radius and f the number of revolutions per second, while the centrifugal force was proportional to xf^2 , smaller diameter tubes were usually used for centrifuging liquids. In most of the experiments with liquids 'rustless' steel

cylinders from 2" to 3" in diameter with $\frac{1}{2}$ " wall thickness were used. They had not found an upper limit to the length of the rotor. Hence, the upper limit to the rate of centrifuging, which was directly proportional to the length of the rotor, had not been reached. Also, the turbine could always be made to spin much faster than the bursting speed of the tube so that the separation could be much increased if stronger materials could be found for the rotor. The above machine was originally designed for the separation of isotopes, but, they indicated, is should be applicable to many other centrifuging problems. It should be especially useful for the purification of large quantities of biological materials which would not be injured by contact with oil.¹⁴⁸ He continued the development of this ultracentrifuge in cooperation with Albert Chanutin and A.V. Masket, who had studied with Beams, from the UVa Medical School. It appeared to be necessary to make the rotor and core of stainless steel or else to plate them with gold to prevent corrosion. Guards were also placed between the inlet and exit chambers to prevent the material being centrifuged from coming in contact with the oil leaking from the vacuum-tight oil glands. With this arrangement the material flowed into the centrifuge at the top at a continuous rate, and a heavy fraction and a light fraction were separately collected at the bottom in a manner similar to that of the cream separator. They tested the machine with substances like egg albumin and haemoglobin. The tests showed that the separations attained were in approximate accord with the predictions of the theory which indicated that no stirring or mixing was taking place. Because the separation was proportional to the length of the tube and since tubes several feet long could be spun up to their bursting point, this tubular ultracentrifuge for liquids should hold considerable promise as a method of separating materials rapidly.¹⁴⁹

Beams applied the tubular ultracentrifuge to the separation of a mixture of carbon tetrachloride and methyl alcohol. Comparing their arrangement with other separative methods they wrote in the *Journal of Chemical Physics*:

"The separation of a mixture into its pure constituents by the usual methods such as fractional distillation, fractional crystallization, etc., sometimes is a very slow and tedious process. This especially true in the case of many constant boiling point mixtures. Therefore, it might be of interest to mention some experiments in which our vacuum type tubular centrifuge was used to separate a mixture of substances of different molecular weights while in the vapour state."¹⁵⁰

The rotor used in this experiment was an alloy steel tube 2.6 cm internal diameter and 12.5 cm long. The vapour entered the spinning tube at the top through a stainless steel hypodermic needle tube and the lighter and heavier fractions were collected at the bottom through two coaxial stainless steel hypodermic needle tubes communicating with the axis of rotation and the periphery

of the spinning tube, respectively. The inlet to the spinning tube was sealed (by vacuum tight oil glands) to a flask containing a mixture (constant boiling point) of carbon tetrachloride and methyl alcohol, and the outlets which collected the lighter and heavier fractions were sealed, also by vacuum tight oil glands, each to a separate trap immersed in dry ice. The system was evacuated and the vapour passed through the centrifuge at the rate of approximately a cubic centimetre of liquid per minute. In each experiment precaution was taken to make sure that practically all of the mixture placed in the flask passed through the centrifuge and was collected in the dry-ice traps; also, that approximately equal light and heavy fractions were collected. Care was taken to insure that each fraction contained only the carbon tetrachloride-methyl alcohol mixture and hence was free of possible impurities such as vacuum pump oil, etc. With the tube or centrifuge spinning 1800 r.p.s. the density of the heavier fraction in the liquid state was roughly 4.7 percent heavier than that of the lighter fraction in the liquid state at the same temperature. According to the theory for the centrifugal separation of gases the density should have changed 5.7 percent. Theory also indicated that with their fastest hollow rotors almost complete separation in one single centrifuging would be possible. They indicated, that by drawing off a smaller amount of the substance to be concentrated, greater purification could be obtained. It would also be possible to design a multistage centrifuge which should greatly increase the concentration as well as the speed with which the centrifuging took place. Therefore centrifuging might become a useful supplement to fractional distillation for the separation of some substances that had different molecular weights.¹⁵¹

Separation of Gases and Vapors - Isotope Separation

In 1935/36 Beams, together with F.B. Haynes, started developing ultracentrifuges for the separation of gases and vapors. In one of their first rotors, which had a horizontal circular cross section, the gas entered the rotor through a channel along the radius. The gas velocity selector described above, which had a triangular cross section was also applied to the problem of isotope separation. They first set out to check how well the Aston-Lindemann theory explained their experimental results. Some preliminary results on the separation of nitrogen from carbon dioxide roughly agreed with the values predicted by the theory which made them conclude that the apparatus could be successfully used for the separation of isotopes.¹⁵² Next, they tested the relative efficiency of the two types of rotors by carrying out experiments upon the separation of a mixture of N_2 and CO_2 at room temperature. The results obtained with both rotors were in fair agreement with the theory of Aston and Lindemann. The rate with which the gas could be centrifuged depended

upon the design and speed of the rotor, the temperature, viscosity, density of the gas. In Beams and Haynes' experiments, 1 cc. was collected every five minutes, but they indicated that this could probably be increased by a new rotor design. Since the experimental results were in fair agreement with the theory they used the theory as a rough guide to find the optimum conditions for separation. Table 3.1 gives some theoretically deduced values for the separative power of their ultracentrifuge. The values in the Table were computed for the case of an ideal gas from the formula $K_0/K = \exp\{(v^2/2RT)(M_2-M_1)\}$. The peripheral velocity used in the computation (800 m/sec) was the bursting speed of their best rotor. K_0 = ratio of quantities of light to heavy isotopes at the centre; K = ratio of the same quantities at the periphery; T = absolute temperature; M_1 = molecular weight of lighter, and M_2 = molecular weight of the heavier isotopes. They indicated that, if the rotors could be made stronger, v and hence the separation, could be much increased as the driving turbine reached less than half speed when the rotors exploded. The theory also indicated that the separation would be more effective at lower temperatures. Although at $T = 20^\circ$ most substances had too low a vapour pressure for gas centrifuging many could be centrifuged at 80° . For this reason they developed a rotor that would spin at liquid air temperatures or even lower. The dependence of the separation factor on M_2-M_1 rather than on their absolute values gave the centrifuge method a decided advantage over those methods which depended upon the absolute values in the case of heavier elements. The 'velocity separation', using the triangular shaped rotor, increased the tabulated separation factors. For example, for neon at 300° it alone was 1.35. However, this became a disadvantage in some cases as it decreased the supply of gas.

M_2-M_1	K_0/K			
	$T = 300^\circ$	$T = 200^\circ$	$T = 80^\circ$	$T = 20^\circ$
1	1.13	1.21	1.62	6.8
2	1.29	1.47	2.61	47
3	1.47	1.78	4.23	300
4	1.67	2.16	6.9	2000

Table 3.1

Theoretically deduced values for the separative power of ultracentrifuges for several differences in molecular weights and separation at various temperatures. (Beams and Haynes, 1936b, p.491).

This ultracentrifuge was also used for the separation of substances containing different isotopes. Isotopes are defined as atoms of the same chemical element, but

with different masses. Thus, for instance, a distinction is being made between the isotopes chlorine-35 and chlorine-37. In 1919 Ashton and Lindemann had developed a theory for the separation in centrifugal fields. However, experiments by Joly and Poole, and Mulliken in the early 1920s showed that the separations reached were too small to be of any practical value.¹⁵³ Referring to this work, Beams and Haynes wrote in *Physical Review* in September 1936:

"Although the separation of isotopes by centrifuging has generally been abandoned as impractical, the development of our new air-driven centrifuge has encouraged us to examine again the feasibility of the method."¹⁵⁴

In a report to the Rockefeller Foundation Beams wrote:

"While one can not predict the future course of investigation, the writer believes that recent developments of the ultracentrifuge have opened a fertile field for exploration in physics. One need illustrate this by only one example - the separation of the isotopes. We are now convinced that in time the centrifuge will enable us to concentrate the isotopes of chlorine in quantities large enough for biological and physical experiments. Since this method of separation depends upon the differences of molecular weights rather than their absolute values, it is obvious that if one pair of isotopes can be separated, all of them of the same mass difference can be, thus giving the chemist a large number of new chemical compounds, the physicist many new nuclei, and the biologist his tracers, etc."¹⁵⁵

Applying the ultracentrifuge to isotope separation Beams and Masket tried out a modification of a method first suggested in 1922 by Mulliken on the separation of CCl_4 .¹⁵⁶ Because of the presence of different isotopes of chlorine this substance contained particles of a different mass. The liquid was placed inside a hollow vacuum tight rotor which was spun in an evacuated chamber. The CCl_4 evaporated near the periphery of the rotor and the vapour passed out at the centre through the 'driving' tube. The lighter fractions distilled off first, leaving the heavier ones in the rotor. They obtained a decided change in the density of CCl_4 in the two fractions, but a mass-spectrographic analysis would have to be made before the theory could be definitely tested. Although the rotors burst at lower speeds with this method, the separation was quite fast, and comparatively large quantities could be centrifuged.¹⁵⁷ In the following years this work was continued on a limited scale. In 1937 Beams and Masket collected one cubic centimetre of liquid CCl_4 in dry ice traps every 6.5 minutes. Successively, light, medium and heavy fractions were collected and separately re-centrifuged. Density measurements of these successive fractions showed that the results were roughly in agreement with the theory.¹⁵⁸

In 1939 Beams and Skarstrom made a more thorough investigation of the

procedure. Theory predicted that, if the process of drawing of vapour according to Mulliken's method, would take place slowly enough for an equilibrium to be established between sedimentation and diffusion, and if the vapour approximately obeyed the ideal gas laws, then the separation factor should be equal to:

$$S = \exp \{(M_2 - M_1)(2\pi f)^2 r^2 / (2RT)\} \quad (1)$$

This formula should also apply to a mixture of two isotopes, where S was defined as the ratio of the concentrations of light to heavy isotopes at the axis divided by the same ratio at the periphery of the rotor. M_2 and M_1 were the atomic weights of the heavy and light isotopes, respectively; f was the number of revolutions per second; r was the radial distance from the liquid surface to the axis; T the absolute temperature; and R a gas constant. Since according to the theory the separation to be expected should be the same for any compound element, it was decided to carry out the development work with carbon tetrachloride (CCl_4) because of its availability, non-inflammability, suitable vapour pressure at room temperature, and easy condensability at dry-ice temperature. Furthermore, the isotopic analysis was simplified because it was suitable for density measurements, and chlorine could be conveniently used in a mass spectrograph available. In some of the preliminary experiments a rotor having a hollow flat cylindrical chamber 8.9 cm diameter and 0.64 cm high was spun in a vacuum at 1550 r.p.s. The CCl_4 vapour was drawn out of the centre at the rate of 2 cc of liquid per hour. Under these conditions the observed separation was about 40 percent of that to be expected from the equilibrium theory. If the rate of drawing out vapour was decreased, the separation was increased, so it was concluded that the rate of withdrawal of vapour was too rapid for approximate equilibrium to be established without stirring. In order to correct this, the 'long bowl' rotor was developed (figure 3.15). The tubular rotor C was made of chrome molybdenum steel alloy 11" long, 4" outer diameter and $\frac{1}{2}$ " wall-thickness. This tube was usually spun at speeds from 1000 to 1100 r.p.s. On one occasion the speed was increased to 1200 r.p.s. which made the rotor stretch radially, causing the gaskets between the tube and the end caps to leak. Upon examination the internal diameter of the rotor was found to have increased 0.02". Afterwards, the tube was boiled in water for 30 minutes and was used since at about 1060 r.p.s. Care was taken to machine carefully both the inner and outer walls of the tube and to see that it was dynamically balanced. The small steel tube M was uniformly perforated with a large number of fine holes so that the vapour was drawn out at a uniform rate along the axis of the spinning tube. N were circular Duralumin ST14 disks perforated with holes, which served to brace the tube M.¹⁵⁹

To operate the machine 105 cc of CCl_4 were either injected into the rotor

through A by a long small hypodermic needle or were distilled in while the rotor was running. The former method was usually used when the rotor was started from rest, and the latter when the material had to be put in with the rotor at full speed, i.e., when several different 'batches' were centrifuged the same day. Since the pressure of the CCl_4 vapour at the centre was only about one-seventh that at the periphery, the rotor acted as a pump and pulled the CCl_4 in very rapidly, especially when the air was removed from the system. In their first experiment the rotor was initially charged with 105 cc of CCl_4 and accelerated to 1000 r.p.s. The spinning tube was then evacuated through the hollow shaft. The CCl_4 evaporated at the periphery and was collected at the rate of $\frac{1}{2}$ cc of liquid per minute in separate fractions in dry ice traps in series with the pump. Repetition of this process reduced 3150 cc of liquid to a set of fractions of various isotopic compositions, the heaviest of which (16 cc of liquid) had a density 0.1 percent above that of ordinary CCl_4 . Analysis of this fraction in a mass spectrometer showed the ratio of $\text{Cl}_{35}:\text{Cl}_{37}$ had been decreased five percent below that in ordinary CCl_4 .¹⁶⁰

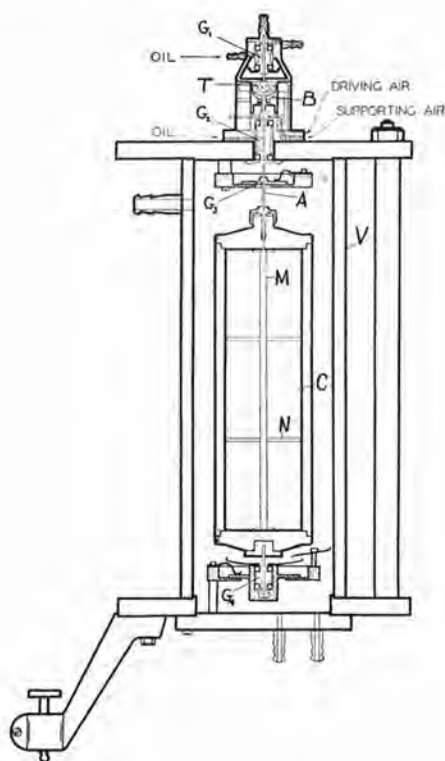


Figure 3.15

Evaporative centrifuge. Explanation: see text. (Beams and Skarstrom, 1939, p.267).

The condensation of the CCl_4 at first heated the rotor but not enough to give serious trouble because of the rotor's size. The variations in the rotational speed were very slow because of the large moment of inertia of the rotor, so that the air valves could be adjusted manually. After reaching the desired speed the air was quickly pumped out of the rotor. The CCl_4 vapour was allowed to flow out through A at the desired speed and was condensed in dry-ice traps in a number of successive fractions. The first fractions collected showed a concentration of the light isotope, while the last fractions and the residue showed a concentration of the heavy isotope. The changes in the isotopic ratio were determined by differential density measurements and by a mass spectrometer. In the density measurements considerable quantities of material were necessary and it was essential to purify it carefully.¹⁶¹

The experimental results obtained were in good accord with theoretical expectations. Because of the small changes obtained with small cuts, the measurements were carried out on samples which were residues with cuts from 6 to 330. The circles in figure 3.16 give the ratio of the separation obtained experimentally, divided by the separation computed from Mulliken's theory, plotted against the rate of removal of the material from the hollow tube of figure 3.15.

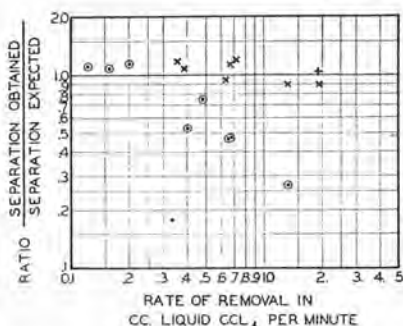


Figure 3.16

Comparison of observed separation with the separation expected theoretically. The circles give the results obtained with the hollow tube shown in figure 3.15. The crosses give the results obtained with 'spider-shaped baffles' (Beams and Skarstrom, 1939, p.269).

When the rate of removal exceeded about 1/5 cc per minute, the efficiency of separation began to fall off. In the absence of a complete theory of the separation, it was impossible to compute the time required for equilibrium to be established, although rough estimations indicated that it might be more rapid than indicated by the experiments. The possibility that the isotopic composition at the surface of the liquid was changed to an enrichment of the heavy isotope, which would cause the efficiency of separation to decrease at high withdrawal speeds, was also ruled out.

When the evaporation took place from the liquid surface, it was cooled. This increased the density of the surface layer and caused violent stirring in the liquid so that it was automatically kept uniformly mixed during the centrifuging. The possibility of stirring in the vapour due to thermal gradients also was eliminated by theoretical calculations and experimentally by introducing hydrogen at a few mm pressure into the rotor to minimize temperature gradients. The introduction of the hydrogen produced no appreciable change. It was decided finally that the decrease in efficiency was caused by stirring or remixing in the vapour. Since the angular momentum of the vapour was conserved as it moved from the liquid surface near the periphery toward the centre, it rotated at a higher angular velocity than the centrifuge. This 'whirlwind' apparently became large enough to stir or remix the vapour at withdrawal speeds above one-fifth of a cc per minute. In order to reduce this type of stirring, a star-shaped spider made of Duralumin ST14 was introduced into the rotor. This formed long sector-shaped cells for the diffusion to take place and should reduce circulation. With this arrangement it was found that no decrease in efficiency was observed with a rate of withdrawal of 2 cc of liquid CCl_4 per minute (represented by the crosses in figure 3.16), which was the highest rate they could obtain through the gauge 14 shaft at room temperature.

An important problem was that a tube was not a very strong mechanical construction for a centrifuge. They had obtained a peripheral velocity of only about 250 meters per second which was appreciably lower than they had obtained with other shapes. However, the very high speed with which the vapour could be withdrawn from the long tubular rotor gave it a great advantage. Beams concluded, that in order to get large changes in the isotopic ratio, very large 'cuts' would have to be made. This meant that one had to start with large volumes of material and recentrifuge many times. The intermediate fractions should also be collected and recentrifuged. Such a procedure, however, would be rather slow and tedious unless several machines were available that might be run simultaneously. On the other hand, if large quantities of material were desired, with, say, 15-20% or less change in the isotopic ratio, the method was comparatively fast. Apparently, from experiment, equilibrium was established very quickly when stirring was eliminated by baffles, so that even in the case of compounds of the heaviest elements, it should be possible to pass the material through the machine rapidly. Since the separation factor depended only upon the differences in the masses, the results obtained with chlorine should be practically duplicated in any element whose isotopes would have a mass difference of two. If they should have a greater mass difference or spread, as in the case of many of the heavier elements, the separation factor would be increased by this difference in the exponent of e . The evaporative centrifuge method could only be used for substances which could be liquefied at the periphery of the rotor which, at the same time, had a considerable

vapour pressure. This limitation appeared to be not as serious as was thought at first, because many of the compounds of the elements (including the metal organic compounds) could be used. Furthermore, the vacuum-type centrifuges had been operated successfully in Beams' laboratory with the rotor temperatures varying from 100°C to the liquid-air temperatures. Beams pointed out that the absolute temperature entered into the equation for the separation factor in the denominator of the exponent of e . Consequently the separation increased with decreasing temperatures.¹⁶² In the above experiments, when stirring was prevented by baffles, it was not possible to draw out the vapour fast enough to obtain a measurable decrease in separation due to absence of equilibrium. However, it was considered possible to more than double the diameter of the tubular shaft so Beams expected that the rate at which equilibrium was established would set the final limit to speed with which the material could be centrifuged.

Theoretical considerations indicated that the amount of material that could be passed through a single machine and still have equilibrium practically established should be proportional to the length of the tube. They had found no upper limit to the length of the tube that could be spun, and they did not doubt that the tubes several feet long could be spun successfully. They expected that equilibrium would be established faster in smaller diameter tubes. The separation factor could be increased considerably over the values obtained in the above experiments with somewhat stronger material available. Even a small increase in rotor strength, and hence greater permissible peripheral velocity, should make possible considerable increase in the separation factor, since the peripheral velocity was squared in the exponent of e , as shown in formula (1). In a next experiment he used ethyl chloride at dry ice temperature (approximately 200 °K). The vapour was drawn off and collected in 2 cc samples in traps cooled by liquid air. The isotopic ratio measured by a mass spectrometer in the first and in the last samples differed by 12 percent, which was in fair accord with the theory.¹⁶³

For large concentrations of the isotopes in smaller quantities of material, Beams expected that the evaporative centrifuge method would be inferior to other possible centrifuge methods. The continuous-flow vacuum-type tubular centrifuge, which he was working on at that time, possessed several points of superiority over the evaporative method. He had already used this type of ultracentrifuge for the separation of a mixture of CO₂ and N₂. The mixture entered the spinning tube at the top and was collected at the bottom in two equal fractions by volume, one taken from the axis, the other from the periphery of the tube. The chrome-molybdenum steel tube was 14" in length, 4" in external diameter, ½" in wall thickness. At speeds of 1000 r.p.s. with steady rates of flow up to 500 cm³ per minute, the observed separation agreed with the equilibrium theory within a few percent. At rates of flow of 1000 and 2000 cm³ per minute the observed

separations were 85 and 68 percent of the theoretical values, respectively. Beams believed that a part of this reduction, at least, was due to stirring at the exits of the tube. At a series of rotational speeds from 500 r.p.s. to almost 1100 r.p.s., with steady rates of flow of about 100 cm³ per minute, the theory was verified within the limits of experimental error which was taken to be three percent.¹⁶⁴

Another possibility for increasing the separation was suggested to Beams by Harold C. Urey. Urey thought that, without some method of greatly increasing the effectiveness of the method, it certainly could not compete with other methods of separation. However, if an apparatus somewhat analogous to his fractionating columns could be mounted in a long tubular centrifuge in such a way that the separation would result from the effective diffusions of the material through the centrifugal field many times, then the separation could be greatly increased.¹⁶⁵ The principle idea was to let the material diffuse from periphery to centre, and then let it be thrown back out without diffusion. This process would have to take place over and over again until a large separation factor would be obtained. If such an arrangement would prove to be feasible experimentally, it should be a relatively fast method of separation - first, because of the large values for the separation factor; and second, because of the high speed with which equilibrium between diffusion and sedimentation was apparently established. Beams planned to make a test of this method.¹⁶⁶

Quantity Heads

In 1937 Beams started working on an ultracentrifuge that could be used for biophysical research. One of these was made for Alfred Chanutin, a biochemist at the university of Virginia.¹⁶⁷ August 1938 Beams, together with Linke and Sommer,¹⁶⁸ published an article on this apparatus in *Review of Scientific Instruments* in which they also referred to the work of Bauer, Pickels and Wyckoff (see Chapter 5). In the introduction they wrote:

"In this paper a description will be given of a vacuum type air-driven centrifuge, which is suited for the separation of materials in solution or suspension. The apparatus was designed for biological and medical research, in which it has been used for the purification of biological materials, but it seems likely that it might prove a useful tool in other fields as well.

The vacuum type air-driven centrifuge possesses five principal virtues which are responsible for its usefulness and efficiency: First, the maximum centrifugal forces which it develops are limited only by the strength of the rotors and in practice are very large. Second, it is free of vibrations while in operation. Third, the material is maintained at a very constant and uniform temperature (which may be in practically any range desired) during the centrifuging. Fourth, the centrifuge or rotor is self-balancing; hence accurate dynamical balancing is not required. Fifth, it need not be difficult or expensive to construct or operate."¹⁶⁹

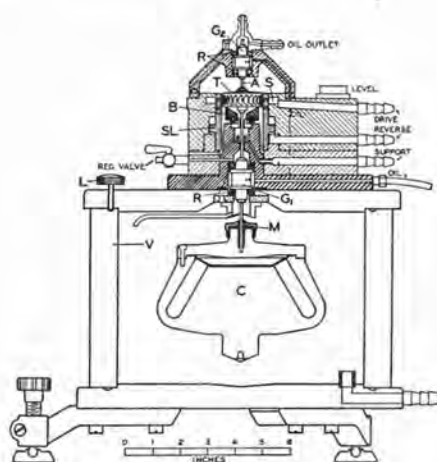


Figure 3.17

Quantity ultracentrifuge. (Beams, Linke and Sommer, 1938, p.249).

The apparatus is shown in figure 3.17. The rotor consisted of a forged Duralumin ST14 block that was machined and bored to hold celluloid test tubes in which the material to be centrifuged was placed. If it would be necessary to increase the length of the rotor to a value greater than its diameter, it was advisable to put in a flexible shaft and bearing below C in a manner they had described before. If C would have to carry considerable material to be centrifuged, it would stand greater rotational speeds if made of heat-treated alloy steels than if made of Duralumin or the light magnesium alloys. However, the fact that Duralumin was not only easier to machine but also needed no heat treatment after machining usually made it preferable. They used separate air supplies for the support and the drive of the centrifuge which added greatly to its flexibility. They supported from one to seventy-five pound rotors by simply increasing the air pressure on the tube marked 'support'.¹⁷⁰

The rotor C and the surrounding vacuum chamber could be brought to any desired temperature by mounting the chamber in a thermostat or by circulating oil or water through copper coils (not shown in figure 3.17) which were in good thermal contact with the upper and lower plates, as well as the cylinder of the vacuum chamber. The air consumption was somewhat higher than in their smaller centrifuges but this made it also possible to reach a higher rate of acceleration, which would be desirable, especially in most biological work. An ordinary constant pressure valve was sufficient to maintain the speed uniform enough for most purposes, although when the rotor was spinning near its bursting point, it would be advisable to measure the rotational speed as well as to control it. One possibility was to view the upper surface of T stroboscopically. With a little practice it was

easy to pick out the note or frequency of sound always given off equal to the rotational frequency of the turbine and beat it with a known frequency. A tuning fork, siren disk, harmonica, etc., would be excellent for the purpose. As the rotor speeded up, it had to pass through the various resonance frequencies of vibration. However, the flexible mountings of G_1 and G_2 were adjusted to prevent the amplitude of these from building up to a point where the acceleration of the centrifuge would be cut down appreciably. The centrifuge was always operated at speeds well removed from these vibration frequencies. For this reason care was taken not to over-damp the glands G_1 and G_2 so that the vibration periods could easily be detected. They stressed the advantage of the flexible shaft and self-balancing rotor arrangement by pointing out that, if one of the test tubes in C contained one more drop of liquid than the others, the unbalancing force exerted for a 4" rotor was roughly a force of ten times the weight of the rotor.

The maximum deceleration of the rotor without remixing depended upon the size of the test tubes in C and the material centrifuged. In general, the slowing down could be greater at high rotational speeds than at lower ones. Referring to Svedberg they mentioned that a partition composed of a thin Bakelite plate, perforated with a large number of small holes and covered with hardened filter paper, could be constructed in a cell which would allow the biological materials to pass through freely during the centrifuging but which would prevent remixing upon slowing down. An 8" rotor had a capacity of 100 cc, while a 6" rotor would hold about 88 cc. The maximum rotational speed was determined by bringing the rotor up to a speed somewhat below its estimated bursting speed, running it for a short time, then stopping it and carefully measuring its diameter. Next, the rotor was again speeded up to approximately 20 r.p.s. faster than before, and the procedure repeated until a slight increase in diameter was detected. The rotor was then operated at from 50 to 100 r.p.s. below this value.¹⁷¹

In 1940/41, A. Victor Masket, one of Beams' students, developed this 'quantity' type ultracentrifuge further. For Masket, the design of an angle rotor represented a compromise between capacity, centrifugal force, and efficiency. The basic factors which affected the design were the density and tensile strength of the rotor metal and the inclination of the holes to the axis of rotation. For an optimalization of these factors he referred to the work of Wyckoff and Lagsdin (see Chapter 5). He himself had made a comparison of separation efficiencies among rotors with holes drilled at 20°, 25° and 30° to the axis which showed that the smaller the angle the greater the efficiency of concentration. A quantity rotor developed by Bauer and Pickels accommodated fourteen test tubes in holes, drilled symmetrically about, and at an angle of 30° to, the axis of rotation. With this rotor a maximum of 250,000g at 60,000 r.p.m could be developed. However, in excess of 50,000 g, the unsupported portions of the test tubes required inserts to prevent their collapse.

Moreover, in improving efficiency by diminishing the angle of inclination, a considerable capacity became unavailable. This because at high speeds the meniscus of the solution in the tubes would become vertical which, at small angles, might cause the solution to spill out from the top of the tubes. Referring to this work, Masket developed a rotor which overcame these limitations. The holes accommodating the Lusteroid test tubes were drilled at 10° to the axis and were rounded at the bottom to fit the tubes. The holes were drilled somewhat longer than the length of tubes used in order to accommodate tapered sealing plugs and tightening screws. With tubes filled to just below the taper, the seal so obtained was found to be unfailingly vacuum tight under a maximum hydrostatic pressure of about 3000 lb./in.² at 57,000 r.p.m. for over six months of almost daily use. Explosion tests on angle rotors had not been made but Masket indicated that such tests would be needed. He estimated that a rotor of $5\frac{1}{4}$ " diameter, 66 cc in 12 tubes, would become unbalanced or explode in the neighborhood of 72,000 r.p.m. when loaded. At this speed, the maximum centrifugal force would be 325,000 g.¹⁷²

Electrically Driven, Magnetically Suspended Ultracentrifuge

In 1937 F.T. Holmes, one of Beams student started working on axial magnetic suspensions. He indicated that many devices involved an element turning about a vertical axis. The element was sometimes mounted on mechanical bearings and sometimes hung from a flexible strip or fiber. The first method involved friction though restoring torque might be absent while the second involved restoring torque with a very small amount of friction. For certain applications, however, it would be desirable if a rotatable element could be suspended in a simultaneously frictionless and torque-free manner. Although this would be impossible in the strict sense, Holmes indicated that for a vertical magnetic needle of arbitrary weight supported by the coaxial field of a solenoid, there was apparently no theoretical lower limit for the frictional torque per unit angular velocity and the torsion constant. At Beams' suggestion and with his help Holmes spun a magnetically suspended element weighing about 6 g in an exhausted chamber having a residual gas pressure estimated at 10^{-5} mm Hg. To the lower end of a 55 mm long shaft an aluminum alloy pin 10 mm long was attached, bearing a vane 15 mm in diameter and 5 mm thick of the same material. Driving torque was supplied by the field of a small bar magnet mounted horizontally on an air driven turbine spinning below the glass-bottomed vacuum chamber at about 1500 r.p.s. After some experimentation a set of adjustments was found which allowed the suspended rotor to attain macroscopic stability. This was maintained up to about 1200 r.p.s., with no indication of incipient instability. Remaining frictional torques were chiefly due

to: (1) residual gases; (2) currents induced in the vane by the components perpendicular to the shaft of the earth's magnetic field and of all stray fields; (3) hysteresis in the steel shaft due to the above components; (4) hysteresis due to lack of coaxiality of the supporting field and the needle. In this survey (4) was probably appreciable and no attempt was made to eliminate (2) and (3). Damping observations with the driving magnet removed, at speeds in the neighborhood of 600 r.p.s., showed that the suspended rotor was decelerating at about 2×10^{-3} rev./sec.². Considering the weight and speed of the rotor, Holmes believed that the frictional torque of this arrangement was at least one order of magnitude lower than that which had been achieved using other types of bearings.

He concluded that the combination of properties exhibited during his survey by the axial magnetic suspension should make it an occasionally useful research tool. Because of its low frictional torque the arrangement would be most interesting for applications in which continuously rotating elements are involved. For example, very constant rotational speeds should be attainable under equilibrium conditions with a large electromagnetic 'slip' between driver and rotor. In torque indicating instruments the fiber or ribbon type of suspension had several advantages. However, the fragility of that type of suspension would be a disadvantage which became more serious as the load increased, because the ratio of its torsion constant to its tensile strength was proportional to the square of its thickness.¹⁷³

Developing an axial magnetic suspension was not motivated by the work on ultracentrifuges.¹⁷⁴ At a certain point, however, Beams saw the possibility of applying it in connection with the electrically driven UC. After some initial tests of the scheme he believed that the arrangement might replace the air driven centrifuges in most researches and applied with the Rockefeller Foundation for a grant for its further development. He wanted to develop it to the point where it would operate satisfactorily in the hands of an experimenter who had no special skill or training in mechanics or electrical circuits. Furthermore, he hoped to increase the efficiency of the rotor and the power supply to the point where both the cost of the complete initial installation and the operating costs would be less than in the case of the air driven machines.¹⁷⁵ The Rockefeller Foundation awarded him the \$ 2,500 grant he requested.¹⁷⁶ But Beams indicated that the magnetic suspension also had a value apart from its application to centrifugation. The very constant rotational speed should make the scheme adaptable to a great many problems in physics, including the measurement of the velocity of light or of high speed particles. Also, since the rotor was freely supported without mechanical connections and could be driven by induction, it could be completely sealed in glass, thus making a very high vacuum possible. This same property made it also possible to spin rotors at extremely low or high temperature.¹⁷⁷

Having applied the scheme to their ultracentrifuges, Beams, together with

Shepard A. Black, described the 'electrically driven, magnetically supported' ultracentrifuge in *Review of Scientific Instruments* in 1939. In the introduction to the article the enumerated the many features of their designs:

"In the self-balancing vacuum-type ultracentrifuge the rotating parts are supported and driven by compressed air. This type of centrifuge possesses many properties which have made it a useful tool in several types of research. (...) On the other hand, the air-driven vacuum-type ultracentrifuge has been criticized by some workers as not being sufficiently 'fool-proof.' In most problems where the above type of centrifuge is used, it must run at a constant speed not far below the region where rotor explosion should occur. This not only requires that the air pressure be maintained constant but that a careful check be kept on the rotational speed by the operator. Furthermore, many laboratories do not have compressed air available in sufficient amounts to operate the air turbines. In previous reports descriptions have been given of an electrically-driven air-supported ultracentrifuge which had an inherently automatic maximum speed control. However, it was still necessary to have available compressed air for the air-bearing support."¹⁷⁸

They eliminated the need for an air compressor by supporting the rotating members by an electromagnet consisting of an iron core M and windings L (figure 3.18). The current through L was so adjusted that the magnetic attraction between M and the small iron rod S, rigidly attached to and coaxial with A, was just greater than necessary to lift S, A, D, and C. The end of the shaft S fitted into a bronze bushing and lightly pressed against a bronze plug or stop, both anchored in M. The rotor D was a so-called 'squirrel-cage' type of armature, and F the field of an induction motor, so that an alternating current in the field coils of F caused D to spin. The electrical circuit used for driving the motor was made of standard commercial parts. Several different single-phase induction motors were used, two of which were specially constructed. It was found, after making a few simple alterations, that certain commercial electric fan motors were also well suited for the purpose. The 6-inch rotor shown in figure 3.18 was accelerated to 800 r.p.s. in about 15 minutes with a power input to the motor of approximately 260 watts (total input to power supply was 1600 watts). With the same power input to the motor, the rotor was accelerated to 1050 r.p.s. in 30 minutes. When allowed to coast freely, it required over two hours for the rotor to come to rest from 1050 r.p.s., although it could be stopped from 1050 r.p.s. in 10 minutes by driving it down by the power supply. The rotational speed was not increased beyond 1150 r.p.s. because of the danger of rotor explosion, but they did not doubt that, with stronger rotors, this could have been exceeded with the power available. It was found that as the power applied to the motor was increased, the time required for acceleration was decreased. The rotational speed remained remarkably constant. For example, it was maintained at 1050 r.p.s. for a running period of five hours without any variation that could be detected with the measuring apparatus, which would have recorded a variation of ± 1 r.p.s. In this run no attention was required

of the operator. They attributed this constant speed to the fact that the 'slip' remained remarkably constant at high rotational speeds. Furthermore, the slip was only about 30 cycles per sec. During this run the temperature of the rotor did not vary from that of the cooling water.¹⁷⁹

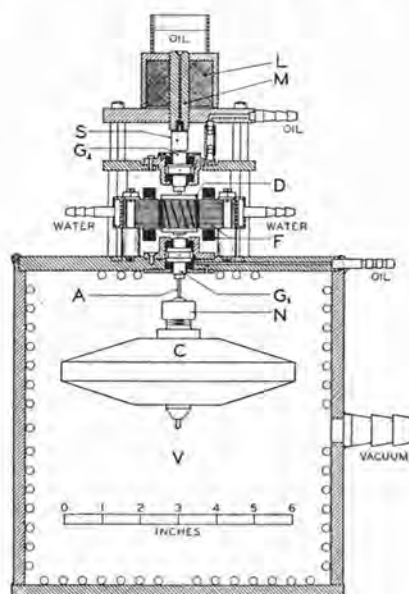


Figure 3.18

Electrically driven, magnetically supported ultracentrifuge. (Beams and Black, 1939, p.60).

The cost of the electrically driven machine alone was about the same as an air driven machine alone, and the cost of the power supply was roughly the same as that of an air compressor. The cost of operation was less than that of the air driven machine. The resolving power of the machine for sedimentation experiments was proportional to f^2rh where f was number of revolutions per second, r the radius of the rotor and h the observable height of the column of liquid in the centrifuge cell. As Svedberg had also argued, Beams concluded that an increase in resolving power would require stronger rotors. However, for very large molecular weight compounds there was an additional problem because these tended to settle out already during the period of acceleration, before the observations could be made. Beams succeeded in solving this problem by passing the solution from the periphery of the centrifuge toward the axis of rotation through the cell at the same speed with which the material under observation settled out. In other words, the molecules were made to settle for longer distances and, hence, if they had a different rate of settling, would separate more completely. If the rate of flow of the solution was exactly equal to the rate of sedimentation, the sedimentation

boundary would remain stationary in the cell for a very long period of time. This not only allowed the sedimentation constants to be measured with precision but also made it possible to determine the sedimentation constants for two or more molecular species in a mixture with very small differences in molecular weight.¹⁸⁰ Two machines were tried out and both were found to have a much increased resolving power, especially for large molecular weight compounds. One surprising result to Beams, using this scheme, was the great homogeneity of haemoglobin.¹⁸¹ A second method of testing the homogeneity of large molecular weight substances was also developed at Virginia. In this method the sedimentation in the cell was balanced by electrophoresis, a technique developed by Arne Tiselius, one of Svedberg's students. Electrodes were placed in the centrifuge cell in such a way that a current could be passed through the cell along the radius. When during centrifugation the sedimenting boundary would have moved to the middle of the cell, an electrical current through the solution would remain the boundary stationary. If the material would be nonhomogeneous, the boundary would no longer remain sharp.¹⁸²

December 1938 Beams informed Warren Weaver that he was working on two methods of improving Svedberg's techniques. The optical equipment for the refractive index method cost about \$ 2,000. This being far beyond their possibilities, Beams tried to think of some simpler way to measure the refractive index at various depths in the cell. He has devised a system whereby the cell, while being centrifuged, was effectively placed in one arm of an ordinary Michelson interferometer. This method, which had so far been tried out only with a rough experimental set-up, promised to measure refractive indices with precision from 10 to 100 times greater than that obtained by Svedberg. The cost of the optical parts of this method, moreover, was a matter of \$ 25 to \$ 50.¹⁸³ In sedimentation experiments the general procedure for recording the effect of centrifuging on the particles in the cell was to pass light through the cell. Differently sized particles influenced this light beam in a different way and thus an analysis of the light passing through the cell could give information on the process of sedimentation. However, as Beams wrote in a report to the Rockefeller Foundation, this procedure was very tedious and involved a number of uncertainties limiting the accuracy of the method. In theory it would be much more accurate if, after centrifugation the separated fractions could be taken out of the cell for further chemical analysis. Such a method was hardly used because of the difficulty of dividing the material in the cell while the centrifuge was spinning. Svedberg had used a membrane in his cell which allowed sedimentation to take place but prevented remixing while slowing down. The precision of this method suffered from the fact that sedimentation took place while his machine was speeding up and slowing down; also the amount of material in his cell was too small for precise

determination of concentrations. Beams was also faced with the problem of determining the effective molecular weights of electrolytes with the view of identifying the atomic masses of the radioactive isotopes. Since the radioactive isotopes existed in such dilution that the ordinary optical methods of Svedberg could not be utilized for determining the concentration as a function of the radius of the cell, it seemed necessary to develop an essentially new technique. Beams solved these problems by developing a centrifuge in which the material to be centrifuged or analyzed was injected into the sector-shaped centrifuge cells (several cells were contained in the same centrifuge) while it was at full speed. The centrifuging was then continued at a constant angular velocity for the desired time. A liquid heavier than the solution was next introduced through the hollow shaft. This liquid flowed into the sector-shaped cells near their periphery and about half of the solution was forced into a chamber above the cells. After the rotor was stopped, the sedimentation constant was determined from analysis of the original solution and of the material collected in the upper chamber of the centrifuge. Preliminary experiments with solutions of egg albumin and haemoglobin indicated that a somewhat better precision could be obtained (in the case of homogeneous compounds) than by observing the rate of sedimentation directly by the usual optical means. Beams stressed the fact that the method avoided completely the use of expensive optical equipment, although at the time he would not recommend doing away with the optical methods. He intended to further improve the method in order to increase its precision.¹⁸⁴

In 1940 Beams and Skarstrom further modified the electrically driven magnetically supported vacuum type ultracentrifuge. In *Physical Review* they wrote:

"In previous reports descriptions have been given of such machines which, although in many respects superior to the air-driven apparatus, required considerable care and attention during the period of acceleration and were only semi-automatic in operation. Furthermore, the torque was very small when the slip was large. In this paper, a description of an electrically driven, magnetically supported vacuum type ultracentrifuge which is completely automatic and possesses sufficient torque with large slips for rapid acceleration is given. It operates from the 110-volt power lines. The centrifuge starts from rest and accelerates to a predetermined rotational speed, then remains at this speed within at least 0.05 percent for as long as desired. The electrical drive may then be used to bring the rotor to rest quickly if this is desirable. The operator's attention is required only for setting the controls at the beginning and end of the run."¹⁸⁵

This ultracentrifuge is shown in figure 3.19. The speed of the rotor appeared as an alternating voltage in a pick-up coil. The frequency of this voltage was used to automatically adjust the power input to the driving motor and in this way an automatic speed control was obtained. With 1-kw input at 1188 cycles per second the motor alone accelerated to 1000 r.p.s. in 15 seconds. When a 7½ pound rotor

was attached and spun in a vacuum, the starting time ranged from 18 to 25 minutes, depending upon the condition of the bearings. With a maximum input of 1 kw, the motor speed was inherently limited to about 70 r.p.s. less than the synchronous speed (1188 r.p.s. in this case). While the motor could be operated using the full output of the power amplifier, it was more economical to select a running condition at which the power input for constant speed was less, i.e., in the region where the slip speed would be between 100 and 180 r.p.s. This was accomplished by the inclusion of the slip speed control in the electric circuit which automatically adjusted the power delivered to the motor so as to maintain a constant and pre-assignable slip speed. Because the ultracentrifuge rotor was usually operated just below its bursting speed, it was well for reasons of safety to have the inherent speed limit of the motor kept close to the operating speed. In this way, failure of the slip speed control for any reason could only result in a small increase in the absolute speed of the machine (30 to 110 r.p.s.). This was in contrast to other types of drive and control methods with which failure of the controlling mechanism might result in an explosion if not prevented by the operator. A further advantage of having the speed control operate on the slip speed rather than on the actual speed lay in the precision of the control obtainable with inexpensive and relatively non-precision equipment.



Figure 3.19

Electrically driven, magnetically supported ultracentrifuge. The power amplifier rack is shown in the background. (Skarstrom and Beams, 1940, p.399).

This ultracentrifuge was accelerated to 1026.3 r.p.s. in 22 minutes. This speed was maintained by the action of the slip speed control within $\frac{1}{2}$ r.p.s. throughout a

10-hour run. At the conclusion of the run, one of the motor fields was reversed and the machine was brought to rest in 10 minutes. Repetition of this procedure in a subsequent 10-hour run, without any readjustment of the slip speed control showed that the speed of the machine could be reproduced in successive runs. This would be of importance in any planned program of centrifugation, wherein it would be desired to subject successive batches of material to the same centrifugal field. The residual variations of speed were attributed to thermal drift in the electric circuits, variation of the voltage of the a.c. service mains, and variation of bearing friction in the machine.¹⁸⁶ With sufficient power there appeared to be no limit to the rotational speed attainable by this driving method other than that determined by the bursting speed of the rotating system.

Beams and Skarstrom had developed this motor primarily for use as a drive for ultracentrifuges but they indicated that it should also find immediate application as a drive for high speed spindles for drilling, grinding, routing, etc.; for constant high speed rotating mirrors and optical shutters; for the rotating element of small gyroscopic instruments; or for a wide speed range constant torque pulley.¹⁸⁷ Thus, they indicated that this type of drive by itself was interesting for further development. C. Scudder Smith, another of Beams' students, developed an arrangement in which rotors from 7 to 1200 grammes were spun in a glass chamber which was highly evacuated. In these arrangements the rotors made no mechanical contact at all with the stationary parts of the apparatus. They were only suspended magnetically and driven by electrostatic or electromagnetic motors. The highest speed obtained was 3200 r.p.s. using a 14-gramme rotor. The arrangement implied that the rotor experienced only very little friction. For instance, the deceleration of a 47-gramme rotor was equal to 2.2×10^{-4} rev./sec.². About sixty-eight days would be required for the rotor to come to rest from a speed of 650 r.p.s. Whether the friction present was mostly due to residual gas pressure or to the effect of magnetic fields was not known. Smith considered it likely that a deceleration of from one-tenth to one-hundredth of the observed value of 2.2×10^{-4} rev./sec.² should be attainable either by using an all-glass vacuum system and degassing it, or by shielding the rotor from the effects of the magnetic fields. With proper design he found it reasonable to suppose that the ultimate speed obtainable should be limited only by the strength of the material used for the rotor. It should be possible to maintain the rotor speed very constant by running it in synchronism with a piezoelectric oscillator or by adjusting the driving torque to just balance out friction. He concluded that it would appear that systems magnetically suspended in a high vacuum and driven by electrostatic or magnetic forces should prove useful for experiments in which very high and constant rotational speeds would be needed.¹⁸⁸

The idea that with such an arrangement even higher rotational speeds might be

possible made Beams suggest to L.E. McHattie, one of his students, to investigate the limits of the method. McHattie spun small steel rotors in a highly evacuated chamber by means of a rotating magnetic field having a frequency of the order of 100 kilocycles. Rod rotors tended to precess in the absence of horizontal damping which was remedied by placing a copper block just above the upper end of the rod. He also rotated steel balls which had the advantage of not being subject to precession. However, on starting to spin they soon built up a circular orbital motion of increasing amplitude. A damping needle situated outside the vacuum system and immersed in oil was found to eliminate this motion satisfactorily. A $3/32$ " diam.ball was spun to 110,000 r.p.s. which corresponded to a centripetal acceleration at the periphery of 58 million gravity. The rate of free deceleration at 106,000 r.p.s. was about 1 percent per hour. The rotational speed was measured by observing the rotor in stroboscopic light whose frequency could be matched with the speed of the rotor.¹⁸⁹

Applications of Ultracentrifuges

In a paper, written in 1938, Beams indicated that the ultracentrifuge might be a powerful tool in unraveling the mysteries of life. However, they themselves were interested primarily in the physical processes of centrifuging itself.¹⁹⁰ At the UVA ultracentrifuges were used for a number of purposes, like: (a) separation of isotopes; (b) separation of constant boiling point mixtures and of gases; (c) separation of liquids (biological materials in collaboration with other laboratories); (d) rotating mirrors at very high speed; (e) study of electrical discharges between rapidly rotating electrodes; (f) separation of materials at dry ice and liquid air temperatures; (g) study of the strength of thin films; (h) study of air friction at high surface speeds; (i) determination of masses of radioactive isotopes.¹⁹¹ Beams had considerable success in convincing others of the value of the ultracentrifuge for their work. By 1939, Fritz Linke, one of Beams' instrument makers, had constructed nineteen 'vacuum type air-driven' ultracentrifuges for different biologists in the USA and other countries.¹⁹² In cooperation with Prof. Chanutin and Dr. Masket, of the Biochemical Department at Virginia, Beams had applied the tubular centrifuge to the separation of biological materials.¹⁹³

Late 1940, George W. Gray of the Rockefeller Foundation wrote Beams that he would like to include a section on ultracentrifuges in the so-called 'Confidential Monthly Report'. This report was to inform the Trustees of the Foundation of the progress of research projects to which they had given support. Because the trustees usually were laymen the researches were to be described in 'simple terms'. Gray was interested in having a full description of possible applications of the

ultracentrifuge and had some detailed questions on the limitations of the various designs.¹⁹⁴ In his answer Beams indicated that the electrically driven, magnetically supported ultracentrifuges were superior to the air-driven ones in the following ways: (1) higher speed (especially for small rotors) as well as more constant speed; (2) automatic control as well as much more 'fool proof'; and (3) less expensive to operate because it utilized the power more efficiently (if one included a compressor in the cost of the air-driven machines, the electrically-driven machines were also a little less expensive to install). Furthermore, the noise of the electrical machine was much less than that of the air drive, which was important in hospitals, etc. He included a detailed quantification of the various possibilities. Concerning applications Beams listed the following fields of research:

1. Concentration and purification of substances such as viruses, hormones, enzymes, etc., of interest in biological and medical research.
2. Determination of molecular weights and molecular sizes and shapes; also particle size and weight. In this field of research the electrically-driven machine made possible higher precision because of much better speed control. (Shortly before a new analytic centrifuge method had been devised in their laboratory for increasing the precision).
3. Determination of activity coefficients and transport numbers in electrolytes.
4. Determination of the atomic weight of radioactive substances (which they had just started working on).
5. Study of the living cell, i.e., the relative density of the different components of the cell.
6. Spinning very high speed rotating mirrors. With mirror faces ground on a small ball, it was possible to observe two events which happened within less than a billionth of a second of each other, which was about one-tenth the time required for an atom to radiate. These mirrors facilitated the determination of the velocity of light with short light paths. Also, with these rotating mirrors many phenomena which happened in short intervals of time had been studied, such as the electric spark, the discharges through gases at low pressure, and the electrical discharge through liquid insulators and conductors.
7. General physical properties of matter in very high centrifugal fields. These were of considerable theoretical interest and were under general investigation in their laboratory.

Beams concluded stating that there were other uses for the ultracentrifuge but that the ones listed would serve to illustrate their value in science.¹⁹⁵ Beams' information was included in the Trustees Confidential Bulletin under the heading *6,600,000 Revolutions per Minute*, the opening sentence reading:

"Faster! Faster!" cried the Red Queen to Alice as they raced on the fantastic chessboard in Lewis Carroll's *Through the Looking Glass*, and 'Faster! Faster!' might appropriately be taken as a slogan for the physicists who design ultracentrifuges".¹⁹⁶

Next the ultracentrifuge was presented as an apparatus with incredible properties which was applied at the forefront of the medical and physical sciences. Svedberg's work was also briefly mentioned in connection with the fact that both Beams and Svedberg had been supported by the Rockefeller Foundation.

For Beams, almost anything that rotated fast was an ultracentrifuge. In a 1938 review article describing his various design, including the simple spinning top, he wrote:

"All of the centrifuges described in this paper are entitled to the name ultracentrifuge."¹⁹⁷

Although it may seem that Beams was interested in centrifugation for its own sake he remained primarily a physicist, in the first place interested in their applications. As he stated himself:

"To the physicist high-speed rotation is not an end in itself; it is a means for solving scientific or technological problems. But making things spin at ever higher speeds has been fascinating in its own right (...)"¹⁹⁸

But the possible uses of centrifugation were so many that almost any modification would open the way to a new application. This implied that there was not one 'best' ultracentrifuge after which development could stop. Each design had to be valued in view of its own applications. For instance, although for many applications the vacuum-type ultracentrifuges were far superior to the tops spinning in open air, the latter were still very valuable because they were so extremely simple to construct. Beams often gave them as a problem in machine-shop practice to first-term graduate students.¹⁹⁹ Being interested in any application, over the years Beams spun rotors ranging from less than a thousandth of an inch in diameter to more than a foot. Their weights varied from about a billionth of a pound to more than 100 pounds.²⁰⁰ In his publications he always mentioned the many possible applications of his designs. For instance, the vacuum ultracentrifuge could be used to study the strength of materials, as an alternator, for mechanically making or breaking electrical circuits, to spin rotors, at either high or very low temperature, to spin mirrors at high speeds, to spin rods or other rotors for the study of gyromagnetic phenomena, for moving two surfaces past each other at very high speeds, for rotating drums, and in general in the study of phenomena which occurred in intense centrifugal fields.²⁰¹ It might also be used in

studies of the adhesion of films to surfaces. Such experiments consisted in determining the centrifugal force necessary to throw the film off the periphery of the rotor. Since the peripheral velocity of some of the air-driven, vacuum-type centrifuges might exceed twice the velocity of sound in air, interesting studies of the friction of different gases at reduced pressures on rapidly moving surfaces were also possible.²⁰²

Since Beams was highly interested in having his ultracentrifuges used by other scientists he wrote many review articles giving an overview of his various design. In these articles he always stressed the importance of his machines and the variety of possible applications. Some examples:

"It is general historical fact that, following each improvement in experimental technique, rapid progress has been made in the fields of science to which it was applicable. Therefore it may be worth while to review a few of the recent advances made in the production of high rotational speeds because of their possible use in many different types of research."²⁰³

"The applications of high-speed centrifuges are so wide and varied that it will be impossible to discuss them here in detail. However, it might be of interest to mention some of the researches in which they have been used. Perhaps their widest and most important use up to the present time has been in the fields of medicine and biology. A great many biological and medical substances have been purified and their molecular weights and sizes studied. Svedberg and his collaborators, as well as Bauer, Pickels, Wyckoff, McFarland, Williams, Stern, Dietz, Severinghaus, Chiles, and others, have shown that most of the easily soluble native proteins are composed of homogeneous molecular species."²⁰⁴

"High-speed rotors have been applied to many different fields of research. As a matter of fact they should be classed with that rapidly growing group of physical apparatus which has made possible so much recent borderline research between the sciences. Already the applications of high-speed centrifuges are too numerous to permit a reasonably complete review in this Report. Instead, a few results will be mentioned to illustrate the types of problems that have been undertaken and briefly to call attention to some data usually considered outside the province of physics, yet which may be of interest to physicists."²⁰⁵

The unlimited range of possible applications made that the development of ultracentrifuges might go on forever, which in fact it did as far as Beams is concerned. There was always some aspect of some type of design Beams could improve further. There was also one limiting aspect which he was unable to improve - the strength of the materials used. Hoping that someone else might pick up this problem he often mentioned that materials, that would stand higher rotational speeds, were the greatest need in almost every problem undertaken with the ultracentrifuge.²⁰⁶ This because the drives could spin the rotors much faster than the materials could stand. Another approach might be to give a more exact and usable theoretical analysis which would predict the best shapes of rotors, made

from 'actual rather than idealized materials'.²⁰⁷ It was not until ultracentrifugation was seen as a possibility for large-scale uranium enrichment that this problem was seriously dealt with.

Uranium Enrichment

Soon after the announcement of uranium fission by neutrons in March 1939, Beams and L.B. Snoddy, one of his colleagues at the University of Virginia, like many other workers, became interested in the separation of U^{235} and U^{238} isotopes. The centrifuge method appeared to be well suited for the separation of these heavy isotopes since the separation factor depended upon the absolute difference of their masses in the exponent of e rather than upon their relative difference as was the case in other separation methods. Also the separation factor did not depend upon the state of combination of the elements or did it decrease with increase or decrease in concentration of the rare isotope. Furthermore the elementary separation process was quasi reversible and should require a relatively small amount of energy, i.e., most of the energy requirements were for spinning the centrifuges, maintaining the vacuum in the jacket and circulating the gas both inside and outside the centrifuge, etc. which could be reduced by proper design. From a search of the literature at that time they concluded that of all of the uranium compounds, UF_6 was the best adapted for the gas centrifuge process. It was liquid at $69^\circ C$ with a vapour pressure of 2 atmospheres and hence could be used in any of the centrifuge methods which they had developed. On the other hand apparently only a small amount had ever been made and it was not commercially available. The literature further revealed that UF_6 attacked water violently as well as all metals except gold and nickel. In addition it was extremely poisonous. The process of making it was not clear and the estimated yields were small. Consequently they were faced with the task of producing their own UF_6 in order to study its physical and chemical properties. From these early studies they concluded that, if the UF_6 were pure it not only did not attack gold and nickel but it did not appreciably attack stainless steel and duraluminium, the metals used in the centrifuge, when they were dry and at room temperature. Snoddy also confirmed that fluorination of the metals before use was helpful. While this work was getting under way in March 1940 M.A. Tuve of the Carnegie Institution of Washington became interested in the separation of the uranium isotopes and obtained for them a grant in aid from the Carnegie Institution to get the work started. Tuve and his colleagues were among the first workers in the US to experimentally confirm the fission of uranium by neutrons.

The possibility of generating nuclear power attracted the attention of Ross

Gunn, Director of the Naval Research Laboratory. In 1940 Gunn was most anxious to obtain enriched U^{235} in order to construct a nuclear reactor with which to drive a submarine and had some practical ideas on how to do it. He offered assistance to Beams' group and secured funds to help finance the work for a year. He was also helpful in searching for a supply of UF_6 . This financial support allowed Beams and his colleagues to expand their research efforts. By the end of 1940 the support of the work was taken over first by the NDRC and later by the OSRD. The work was supervised by L.J. Briggs, Chairman of the Uranium Committee, who took an active interest in the experiments and who personally not only helped to get special materials, but also made many useful suggestions. Briggs and his committee set up four groups to investigate the feasibility of separating the uranium isotopes by centrifuging as follows: (1) A group at Columbia University under the direction of H.C. Urey whose purpose was to work out the theory in detail and to coordinate the overall program; (2) A group at Westinghouse Electric Company under L.B. Chubb whose objective was to develop and build the centrifuges which were to be used in a pilot plant; (3) A group at the Standard Oil Development Company under E.V. Murphree whose function was to build and operate the pilot plant and to plan a larger separation plant; (4) A group at the University of Virginia whose purpose was to test the theory of separation by experiment. Also it was to make such tests as the other groups might require.²⁰⁸ The war-time research, also in other fields of physics, implied that all development work on ultracentrifuges, except for the purpose of uranium enrichment, was stopped.²⁰⁹

In World War II the Rouss Physical Laboratory contributed in two ways to the American war effort. In the teaching field they trained the Army Premeteorological units and the certain units of the Navy. Concerning research some investigations began about than a year before Pearl Harbor. But from then on they assumed proportions that taxed available space so, that some extra outside space had to be created. The magnitude of these undertakings is suggested by the list of the contracts given below:²¹⁰

Frankford Arsenal	6,000
Naval Research Laboratory, Wash.	10,000
O.S.R.D. Contracts OEMsr:	
Nos. 398 and 140	193,500
Nos. 598	9,000
No. 1082	140,000
Naval Bureau of Ordnance (NOrd-7873)	420,000
Laboratory Building of the Naval Bureau of Ordnance	122,000
	\$ 900,500

The Frankford Arsenal Contract dealt with the development of a quick test for flaws in shells. It obviated the necessity for the usual shooting tests and made it possible quickly to find out if anything went wrong with the process of manufacture. The contract with the Naval Research Laboratory dealt with the early stages of the development of the Atomic Bomb. The specific problem was on the separation of Uranium isotopes. The contracts with the Navy Bureau of Ordnance included work on fire control and guided missiles. The O.S.R.D. Contracts dealt with a number of different projects. The principal ones were as follows:

- 1) The Uranium Separation Problem as related to the atomic bomb. It was part of the work which later became the Manhattan District Project of the Army.
- 2) Research on the development of a very high velocity projectile for anti-tank guns.
- 3) Research and development of gun directors (radar tracking) for anti-aircraft defense of ships.
- 4) Research and development of Guided Missiles. Both research on the propulsion and guidance of these missiles was carried out.²¹¹

According to Brown it was the nearness of Charlottesville to Washington combined with the membership of Beams on several National Committees because of his research reputation which caused the RPL to being offered such a large number of contracts.²¹² Beams was even invited to be present at the first test of the atomic bomb. He declined the offer on the ground that an absence of two months while the university was in full operation would be inadvisable.²¹³ During the war years almost the whole staff was on the navy payroll, including the instrumentmakers. By the late 1930s, early 1940s the demand for good instrumentmakers grew which made the UVA increase their salaries in order to prevent them from taking another job.²¹⁴ The war work further increased the value attributed to their services which was again expressed in a considerable increase in their salaries.²¹⁵

The first attempts to concentrate the U^{235} by centrifuging were held up almost a year because not enough UF_6 could be obtained for the experiments. Late in 1940, Ross Gunn of the Naval Research Laboratory supplied 6 grammes of UF_6 , and the first experiments were made immediately. These experiments demonstrated that the material could be put through the centrifuging process without loss or deterioration; however, the samples collected were not measured. The mass spectrometer available at the University of Virginia at that time was not suitable for determining the isotopic ratios in uranium, so the centrifuged product was sent away for analysis and was apparently lost before being analyzed. After these first experiments were completed, the method was set aside until a sufficient supply of

UF₆ became available. At this time, emphasis was shifted to developing long tubular centrifuges. In 1941 Briggs and Gunn made an ample supply of UF₆ available, and at the suggestion of Briggs the experiments using the evaporative centrifuge were resumed. Also Alfred O.C. Nier not only offered to measure the changes in the isotopic-abundance ratios with his mass spectrometer but later loaned one of these instruments. E.P. Ney, one of Nier's assistants, also assisted in the experiment. In addition, L.F. Curtis and his group at the Bureau of Standard used the alpha-counting technique to analyze some of the centrifuged samples. In Beams' view it would have been impossible to have reached any conclusions at all at that time without the measurements of Nier and Curtis.²¹⁶ The first experimental separations appeared to be in good agreement with a theory on isotope separation developed by K. Cohen. For Beams, this implied that this theory could be depended upon to predict the performance of a centrifuge provided the experimental conditions were the same as those assumed in the theory.²¹⁷

The problem remaining was to determine if the hydrodynamic flow processes could be produced in such a way as to give the separative work expected. This required the development of long tubular centrifuges spinning at as high peripheral velocities as possible. Consequently while the evaporative centrifuge experiments were being carried out and while it was necessary to wait until enough UF₆ would become available for tubular operation the effort was directed to the development of long tubular rotors and testing them on the separation of gaseous mixtures and isotopes other than uranium. As a result as soon as ample supplies of UF₆ became available the tubular centrifuges were ready for the experimental separation tests. Two tubular centrifuges were used for most of the separation work - one 32 inch long with an inner diameter of 3 inch and a second 11 feet 4 inch in length, 8.35 inch outer diameter, and 7.35 inch inner diameter. They were both made of forged Duralumin ST-14. The latter was obtained for them by E.V. Murphree and was as long as could be accurately machined at that time. These tubes were spun by steam or air turbines and were operated above their second critical speed. The first tube operated at 1020 ± 0.3 r.p.s. and the second tube at 350 ± 0.3 r.p.s. They both operated stably and without appreciable wear for many days. The above centrifuges were used in both concurrent and countercurrent operation. However, it soon became evident that the countercurrent operation in practice gave the highest separative work per unit length of tube. Also this was in agreement with the theory of Cohen for the practical case. Murphree, Urey, Briggs and others strongly emphasized to Beams group that the principal objective of their experiments was to test the Cohen theory so that it could be used to design a pilot plant. The actual magnitude of the separation was secondary. It appeared that the experiments were in good agreement with this theory.²¹⁸

While this work was being carried out, the Westinghouse Company was

designing and building the centrifuges which were to be used in the pilot plant to be operated by the Standard Oil Development Company in Bay Way, New Jersey. They started designs in 1941 and delivered two machines in Bay Way; one in May and one in September, 1943. The cylindrical centrifuge bowls of these machines were 42 inch long, 7.2 inch inner diameter and 8.2 inch outer diameter with a rated speed of 28,200 r.p.m. They operated at subcritical frequencies and were driven by electrical motors. In addition to developing and constructing two of the above centrifuges, Westinghouse developed a dynamic model of a 132 inch long centrifuge with the same bowl diameter. This was assembled and tested at 28,200 r.p.m. in December 1943. The over-all length of the machine was 188 inch and the total weight 3,200 lbs. This machine was finally wrecked in tests but the experience indicated that successful design and operation of a production centrifuge of this length was feasible. However, since the over-all project was terminated in January 1944, the tests were not continued.

Originally, the Standard Oil Development Company had planned to operate a pilot plant of 24 identical centrifuges, but the delivery of the machines was much delayed and only one was used for any length of time. This centrifuge was operated a total of 99 days of which 93 days were with UF_6 feed. During this period, the longest time of uninterrupted UF_6 operation was 69 days. The operation was finally interrupted by a leakage of UF_6 from the bowl seals into the casing space. Since this occurred on 23 January 1944, and the work was terminated on 31 January 1944, it was not repaired. The single centrifuge operated amply long to give valuable information. A total of 1,000 lbs. of UF_6 was passed through the centrifuge of which 800 lbs. had its average composition in U^{235} reduced by about 1 percent while 200 lbs. of the product had the U^{235} isotope enriched by an average of about 5 percent.²¹⁹ In their report to the Atomic Energy Commission they wrote:

"The operating experience with the single-centrifuge unit led to the conclusion that the unit is adaptable to commercial plant operation of long duration. No insurmountable problems were recognized in connection with the operation of the centrifuge itself, or the various auxiliary systems or the UF_6 system".²²⁰

Nevertheless, as mentioned above, on 31 January 1944 the decision was made by OSRD and the Manhattan District U.S. Army to proceed with the diffusion method and to terminate all work on the gas centrifuge project. Although the work was halted abruptly, it had proceeded far enough to enable Beams and his colleagues to draw the following conclusions concerning the gas centrifuge method: (1) The method proved to be an effective method of separating the uranium isotopes; (2) The experimental values obtained were in close agreement with the separation theory and sufficient operational data were collected to make it possible to design

a pilot plant; (3) Centrifuges could be built and made to operate for long periods of time while separating the uranium isotopes in UF_6 ; (4) Tubular centrifuges could be satisfactorily operated both subcritically and supercritically while separating UF_6 . It was demonstrated that rotors over 11 ft. long could be satisfactorily operated. (5) The limiting factor in the gas centrifuge was clearly the strength divided by the density of the rotor material. If this ratio could be increased the effectiveness of the method would be increased accordingly.²²¹

In the decade following the termination of the gas centrifuge project in the U.S.A., the work lay dormant primarily because of the strict classification of the project. During that time in Germany and Russia some groups had also been working on developing ultracentrifuges for uranium enrichment. Learning of this work, the US AEC made a reappraisal of the gas centrifuge project. As a result of from other projects stronger rotor material became available, which should enhance the effectiveness of the method. P.W. McDaniel and G.A. Kolstad of the AEC Research Division became interested in the project and modest funds were provided to reactivate the project on a small scale at the University of Virginia. A.R. Kuhlthau, who had worked on the wartime project, was given the responsibility of assembling the personnel and getting the work under way. Since much could be gained by increasing the peripheral velocity and length of the centrifuge tube, Kuhlthau and his colleagues started out to maximise both of these factors. In addition to this developmental work, they undertook to evaluate the gas centrifuge reports coming from Europe. In connection with this latter work they became interested in the Russian work described in an interview with Gernot Zippe who had been allowed to return to Germany from Russia. The interview had been carried out by M. Schutte who reported to K. Brewer at the Navy. Brewer had long been interested in the gas centrifuge project and had made an important contribution to the theory.²²² Zippe was invited to come to Virginia and repeat the short bowl experiments which he had carried out in Russia. This work was started in August 1958 and completed in June 1960 when Zippe returned to Europe.²²³ While Zippe was still at Virginia, Ralph Lowry, who was soon to follow Kuhlthau as Director when the latter became Associate Provost of the University, and Alwyn Lapsley joined the Virginia group and together they set about to assemble and utilize all of the advantages of their own, the Zippe and all other known techniques. They believed that the gas centrifuge might possibly eventually become a competitor with the diffusion method. The progress made at Virginia soon persuaded the AEC to add a group at Oak Ridge and one at the AiResearch Company in California to the project. Also to shift the responsibility for the project from the Division of Research to the Production Division.²²⁴ Thus, the further development work of the gas centrifuge for uranium enrichment was to take place outside the university of Virginia.²²⁵

Better Times for Physics - Committee on Growth

The role of physicists in World War II made the social and scientific esteem of physicists go up considerably. Whereas before the war it was often very hard to secure funding this changed rather drastically after the war. It was the time that physicists could get many long-time wishes fulfilled. In the 1947-48 annual report from the Rouss Physical Laboratory Hoxton wrote:

"Our research is (...) handicapped. We need space for equipment facilities and for the students who want to come here for graduate study. Without a new building we must face a decline and even disintegration of what has been painfully built up through the years. The University will become conspicuous for its lack of support of a basic science whose importance for its cultural value and national security is universally recognized.

Attention is directed to the fact that physics has received less support from the University than other natural sciences, some of it justly on account of larger registration in other schools, and yet, I submit, as far as outside recognition for research is concerned, it stand out in front. I should be willing to have a visiting board sit on that question. Our earlier requests were relatively modest. It seemed better to wait till things got done. Things have got done and the time has come to demand attention. Physics should stop trailing. It is not trailing elsewhere. Since I have been here I have seen a chemistry building go up, have known of the biology expansion at Blandy Farm and Mountain Lake and have seen two new Law buildings go up. It looks something like our turn now.

Attention is again directed to the fact that in the last ten years or so, the research accomplished was carried out not so much through State support as from support from without. Government support has already been mentioned, but before that, through the alertness, energy and enterprise of Professors Beams and Snoddy, special grants were secured from the foundations. For two years past research here has been entirely supported by the Navy, although this year that is only partly true."²²⁶

Hoxton's wishes were fulfilled and in the early 1950s a new physical laboratory was constructed at the UVA.²²⁷ Funds for research also went up considerably. More and more, physics became seen as a potential source of social benefits. In 1945 the American National Research Council (NRC), Division of Medical Sciences, established a so-called 'Committee on Growth' (cancer) on the request of the American Cancer Society to administer their research funds.²²⁸ The committee was subdivided in panels of Physics, Chemistry, Biology and Clinical Investigations. Beams became chairman of the panel on physics, some other members being Paul C. Aebersold, Chief Isotopes Branch, Research Division, Field Operations, American Atomic Energy Commission, and Harold C. Urey, a physicist at the university of Chicago, an expert in the field of isotope separation.²²⁹ The physics panel was formed to advise the committee and to investigate what physicists and physics could do to help out with their general attack on the problem of Growth. The total funds of the Committee were in the order of a million dollars per year of which about \$ 100,000 would be allocated to the physics panel. Isotopic tracers

would be one of the fields to be sponsored.²³⁰ Urey suggested some radioactive elements which he thought would be the most promising and also stressed the need for developing mass spectrometers for their detection.²³¹ Beams also asked Aebersold about what field he thought should be encouraged. Aebersold mentioned three main fields, viz. (1) Ultracentrifugation, (2) Radio-autography, and (3) Neutron biology. About ultracentrifugation he stated:

"I am not familiar with this field but it is my impression that as a tool the ultracentrifuge has not been used as much as it should be, mainly because of the lack of a source of suitable instruments and personnel to operate them. Could you undertake the engineering of a simple, rugged, cheap, 'fool-proof' instrument for biological laboratory use (...)? It should be developed to the point where some company would be willing to take over producing it for a reasonable price. In lieu of this, you could be in a position to furnish detailed construction drawings to prospective users.

One thought that came to mind was the combined use of the ultracentrifuge and tracers. With this combination more details of cell metabolism, so important to growth problems, could be determined. For example, metabolic differences between nucleus and protoplasm, differences in utilization, synthesization, etc., of proteins and other large molecules."²³²

At that time, the diffusion of ultracentrifuges still went through Beams' workshop. E.g. late 1945 Beams wrote C.P. Rhoads of the Memorial Hospital in New York and Chairman of the Committee on Growth that his instrument makers were allowed to construct centrifuges for Rhoads in their off hours. Beams indicated that he saw a need for the production of ultracentrifuges on a larger scale. During the war he had been associated for a while with the Research Laboratory of the Westinghouse Company at East Pittsburgh and talked to them about it. L.W. Chubb, director of the laboratory had shown an interest in manufacturing electrically driven ultracentrifuges but was not convinced that there would be a sale for them. Beams tried what he could to convince them but thus far had not succeeded.²³³

Early 1946 the first report of the panel on physics was compiled by Art Solomon, a biophysicist from MIT. He stated that biophysics was a growing subject that, at that time, was barely established. There were two ways in which physics could react upon biology: by introduction of physical techniques and of physical concepts. The most popular example of physical technique was the use of isotopes as tracers. But there were many more: the use of high energy radiation, the electron microscope, and the manifold new applications of spectroscopy and electronics. According to Solomon these demonstrated successes accounted for the fact that many people in the fields both of biology and physics had come to regard physics as a source of instruments, and the physicist, in his biological work, as a 'glorified technician'. Although the achievements were many, instrumentation alone was not the real solution to the integration of physics and biology. Competent physicists would not be attracted with so limited a field. To the physicist the

exciting contribution that physics could make would be conceptual.²³⁴ Nevertheless, instrumentation remained important, especially the diffusion of instruments that had been developed already. In his report Solomon argued for a non-profit organization to provide instrumentation in the fields of biology, biophysics and physics. According, an approach had been made to the Sloane-Kettering Foundation, suggesting that they set up an instrument section whose function would be to engineer laboratory equipment so that it would be robust as well as accurate and also to manufacture certain types of laboratory equipment which would otherwise not be easily available, as for example, the ultracentrifuge.²³⁵ The Sloane-Kettering Foundation was established by Alfred Sloane and Boss Kettering of General Motors Company in 1945 and directed at stimulating medical research, especially in the field of cancer.²³⁶ However, these negotiations had been halted during a General Motors strike. The Physics panel had also done some work on possibilities for publication of biophysical research. One of the results was that in *Biological Abstracts* a scientific instrument section would be included.²³⁷

In 1948, Charles F. Hall, who called himself an inventor, applied with the committee for the sponsoring of a 'continuous flow, cross current, convection-compensating' centrifuge. This should be usable for separating larger quantities of materials like hormones, virus and proteins. It would be useful also for basic research in biochemistry, bacteriology, plant and animal pathology, metallurgy, petrology and other sciences. He had already filed five pioneer patent applications covering his invention. He argued that existing types of centrifuges did not function properly because convectional stirring tended to remix the particles faster than the particles would separate and since the tendency was merely to concentrate the particles around the periphery of the rotor, The Committee asked Beams to give his opinion on the matter. Beams answered:

"While it is difficult to comment on Mr. Hall's ideas without first knowing exactly what they are, I gather from this letter that these ideas are not too terribly revolutionary. Some of the statements that he makes about convection taking place in the present ultracentrifuges of course are false. On the other hand, one can imagine many centrifuge methods that might turn out somewhat better than the ones now in use, but I would guess that to carry out the things Mr. Hall is proposing in a high speed centrifuge would be a tremendous experimental job and it is my off hand opinion that the money which the Committee on Growth now has would be better spent on some other projects."²³⁸

Beams continued that, if there would be an urgent need for better ultracentrifuges for the separation of biological material in large quantities, he would suggest that before the Growth Committee would spend money on this project that an effort should be made to investigate some of the work which should be in the confidential files of the Atomic Energy Commission.²³⁹

Highest Rotational Speeds - Further Development of Ultracentrifuges

After the war Beams and his colleagues continued their quest for reaching the highest rotational speeds. Theoretically, for the production of the highest centrifugal fields the radius of the rotor should be as small as possible. For rotors made of a given elastic material the highest peripheral speed should be obtained when the shape was such that the radial and tangential stresses were of constant value throughout the rotor. If hardened high strength steel were used for the rotor, some considerable pains would be required to grind the rotor to the shape required by the above condition. However, spherical rotors were also commercially available in the form of high strength solid steel balls for use in ball bearings and these approximately spherical rotors were used in their experiments. Also in addition to their availability the calculated critical vibration frequencies of these spherical rotors were well above their bursting speeds.

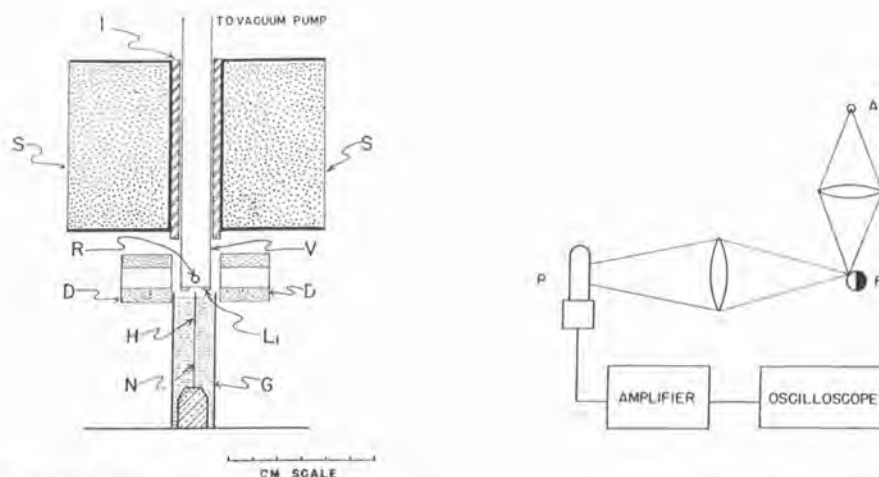


Figure 3.20

Arrangement for spinning steel balls and speed measuring device. A, lamp; P, Electron multiplier photo cell. For further explanation see text. (Beams, Young, III and Moore, 1952, p.886 and 889).

The experimental arrangement is shown in figure 3.20. The rotor R was suspended in the axial magnetic field of the solenoid S and was spun by a two phase rotating magnetic field in the two pairs of coils D. The horizontal position of the steel rotor was maintained by the symmetrically diverging field of the solenoid while its vertical position was maintained by an automatic regulation of the current through the solenoid S. The small coil L_1 was part of the grid circuit of a tuned grid tuned plate radiofrequency oscillator which regulated the current through S. It was so arranged that when the rotor rose the current through S decreased. These current changes were such as to position accurately the rotor

without observable hunting. An iron tube was placed inside the solenoid to increase the field at R. A small iron wire H mounted in a glass tube G filled with a liquid assisted in damping any horizontal motion of the rotor. The glass chamber V surrounding the rotor R was evacuated to values of $1\text{--}2 \times 10^{-5}$ mm of Hg. The arrangement greatly stabilized the rotor and reduced all vertical hunting and oscillations to such an extent that no vertical motion of the rotor could be observed with a 20-power microscope focused on markings of the rotor.

At first some difficulty was experienced in getting a simple accurate method of measuring the rotor speed, but the problem was successfully solved by the apparatus shown schematically in figure 3.20, right. One-half of the rotor was polished and the other half darkened by dipping in dilute H_2SO_4 which had been in contact with metallic antimony. This dark layer was very thin and was not destroyed by the highest centrifugal force obtained. The rotor speeds were believed to be precise to three significant figures. While the above frequency measurements were considered precise enough for the ongoing experiments, they found it highly desirable to have better precision for deceleration measurements. Accordingly, the output of the photo-cell was made to actuate an ordinary scale of 64 counter circuit in such a way that the counter counted the number of revolutions per second directly. This method gave high precision but it was not suited for counting above 5×10^4 r.p.s., even with a counter clock, especially wound for the purpose. But they hoped to extend its range to much higher values. In order to determine the axis of rotation a small flat was ground on each of the rotors. The rotor, the glass vacuum chamber, and the driving coils were surrounded by a wooden barricade which would stop the flying parts of an exploding rotor. Although the rotors used were 'grade A' commercial steel ball bearings and supposedly free from flaws, a number of them exploded at 'abnormally low' rotor speeds. These rotors showed definite flaws when their parts were examined after an explosion. However, most of the rotors required very high stresses to explode them. Table 3.2 gives some of the results obtained just before the rotors exploded.²⁴⁰ The maximum peripheral speed for all rotors was about 10^5 cm/sec. and determined the bursting speed for the steel used. In accordance with their expectations the maximum centrifugal field was obtained with the smallest rotor used and for the 0.795-mm rotor it was 240 million times gravity. Late 1946 they reached 428 million g (633,000 r.p.s.) with a 0.521 mm rotor.²⁴¹ In the 1950s they spun a rotor of 1/100 inch at 1.5 million revolutions per second, generating a field of more than a billion gravity. This rotor had a peripheral speed of some 2,500 miles per hour when it exploded.²⁴² On some of these spinning balls small mirrors were ground without introducing appreciable added friction. Consequently rotating mirrors were available whose rotor speed not only was very high but extremely constant. These could be used to obtain a greater precision for example

in such determinations as the velocity of light. Beams stated that this technique of producing both very high centrifugal fields and very high and constant rotor speeds would open many new avenues for interesting investigations.²⁴³

Diameter of rotor in mm	Rotor speed in r.p.s.	Peripheral speed in cm/sec	Centrifugal acceleration times gravity
3.97	77,000	9.60×10^4	4.71×10^7
2.38	123,500	9.25×10^4	7.20×10^7
1.59	211,000	1.05×10^5	1.43×10^8
0.795	386,000	9.65×10^4	2.40×10^8

Table 3.2

Rotational speeds and centrifugal fields obtained with small rotors. (Beams, Young, III, and Moore, 1946, p.890).

In these experiments, the air pressure surrounding the rotor as measured by an ionization gauge was maintained between 10^{-5} and 2×10^{-5} mm of Hg. With the 1.59-mm rotor spinning freely at about 120,000 r.p.s. with a pressure of about 10^{-5} mm Hg it required roughly two hours to lose one percent of its speed. On the basis of theoretical considerations they attributed the main part of this deceleration to gas friction on the rotor. Other factors could be that the rotors were slightly non-homogeneous magnetically and that the supporting field was perhaps not strictly symmetrical. Also, in addition, other small factors such as oscillations in the pick-up coil probably added up to give a small residual drag. However, in practice, since the major portion of the drag was due to gas friction, the deceleration could be made very small. With proper coupling between a rotating magnetic field driven by a piezo-electrically controlled oscillator an almost constant speed rotor should be obtained. Consequently many experiments requiring constant rotor speed as well as high centrifugal fields were made possible.²⁴⁴ The Committee on Manufacturing Problems of the American Iron and Steel Institute showed their interest in the method.²⁴⁵

Searching for the highest rotational speeds did not mean that Beams had lost his interest in problems of centrifugation. Comparing the air-driven and the electrically driven types Beams concluded that the electrically driven centrifuges were not used extensively because there had been no adequate source of supply. On the other hand, the air-driven self-balancing ultracentrifuges were widely used principally because of their greater availability and ease of construction. However, with the latter usually considerable trouble was encountered in holding their speed

constant enough for the experiments unless the air pressure valves were controlled manually or by 'quite an elaborate' automatic mechanism. Also, there was always the danger that the centrifuge would over speed and explode the rotor. Pointing at this problem Beams developed a device which maintained the speed of the air-driven centrifuge constant to the order of 0.1 percent for as long as would be desired. It was based directly upon some work of Thomas Davis carried out in their laboratory ten years before. It consisted in removing the excess driving energy electrically when the desired rotor speed was attained, and thus maintaining the speed constant. A magnet attached to the centrifuge shaft induced an alternating current in a series inductance capacity resistance circuit whose frequency was equal to the frequency of rotation of the centrifuge. If this circuit was tuned to resonance at just above the desired running speed, the circuit would absorb a negligible amount of energy until the rotor speed reached the frequency where resonance began. At this speed, the current in the circuit would rise abruptly with increase in speed, and hence would hold the speed constant if the driving pressure to the air turbine would be greater than necessary to maintain the speed.²⁴⁶ The arrangement worked very satisfactorily and Beams concluded that it might also be used as a source of alternating power or that it might be applied to any type of rotating machinery where constant rotational speed would be required.²⁴⁷

The use of ultracentrifuges for the separation of gases and isotopes was based on the theoretical consideration that particles in centrifugal fields experienced forces whose magnitude was proportional to their mass. The same consideration led Beams to the idea to use ultracentrifuges for the determination of masses of particles. The very same reasoning had led Svedberg to start the development of centrifuges for sedimentation purposes in the early 1920s. However, whereas Svedberg wanted to study suspensions of colloidal particles, Beams now set out to determine the masses of particles in their gaseous state. For this purpose he developed a cylindrical rotor 2 cm high and 4.4 cm radius which was spun in vacuum by an air drive. The particle mass could be determined by measuring the pressure of the gas at the axis of the hollow spinning rotor at various rotor speeds. Using nitrogen, oxygen and CO₂ gases he found particle masses which agreed to the accepted values within considerably less than one percent. He indicated that the method could also be used to determine the molecular weight of radioactive gases or vapors in which case the mass might be determined by measuring the amount of radioactivity at the axis of the rotor as a function of the rotor speed. The advantage of this centrifuge method for determining the molecular weights of radioactive gases or vapors would be that only an extremely minute amount of the radioactive material was required, especially when the material could be mixed with a gas such as CO₂, nitrogen or helium.²⁴⁸ But not only could his vacuum ultracentrifuge be used for mass-determinations, this was also the case for

the apparatus which spun steel balls. In 1949 he spun a 1/64" rotor to an estimated speed of 800,000 r.p.s. which gave a centrifugal field in excess of one-half billion times gravity. He indicated that the apparatus might also be used as an analytical balance for weighing materials inside a vacuum chamber. It would detect changes in mass of from 10^{-8} to 10^{-9} gramme.²⁴⁹ He also indicated that these spinning balls could be used for testing the strength of adhesion of films deposited on them.²⁵⁰

Coaster

The speed control Beams had developed for the air drive was not yet considered the ultimate in constant rotational speeds. Especially in the case of Svedberg-like sedimentation equilibrium measurements, which often lasted in the order of days, very constant rotational speeds were desirable. To this end Beams developed the ultracentrifuge shown in figure 3.21.

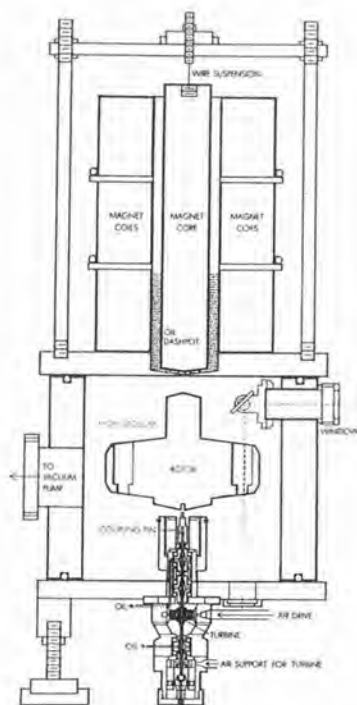


Figure 3.21

Ultracentrifuge with freely suspended rotor. The magnetic support system lets the rotor coast freely after it is spun up to full speed and disengaged from the drive shaft, as is shown here. Unless forcibly decelerated, the rotor would spin for years. A magnetic core in an oil dashpot supports the rotor and damps drift. A window permits observation of the sedimentation sample in the rotor. (Beams, 1961, p.138).

The rotor R of this ultracentrifuge was constructed of steel and Duralumin ST-14 weighed 4.93 kilograms. It had a radius of 65 mm to the centre of the standard centrifuge cell, which contained the material to be centrifuged. The rotor R was freely suspended inside the brass vacuum chamber V (pressure less than 10^{-5} mm Hg) by the solenoid F above the chamber and was accelerated to operating speed by the air turbine T below V. The shaft S which connected the air turbine with the rotor fitted into a 'screw driver slot', in the rotor and was disconnected and pulled down by the lever J when the rotor had reached the desired running speed. At operating speed the rotor was freely suspended and coasted without being driven during the period of observation of the sedimentation. When spinning freely, the rotor lost less than a 0.1 r.p.s per hour. The ultracentrifuge was used both for rates of sedimentation measurements and for sedimentation equilibrium measurements, but was especially suited for the latter.²⁵¹ Beams foresaw numerous possible applications of this apparatus. E.g. in 1954 he wrote in *Science*:

"Space does not permit the further review of many more uses of the magnetically supported, high-speed rotors; but it is believed that their use should be seriously considered whenever high or constant rotor speed is required or the bearing friction must be low. Finally, for some cases where the control circuits are not feasible, the diamagnetic properties of superconductors may be used for supporting spinning magnets. When magnetic fields cannot be used electrostatic suspensions are probably feasible."²⁵²

After Beams had greatly increased the constancy of the rotor speeds, in sedimentation experiment a limiting factor had become the distortion in the sedimentation cell. He tried to limit this distortion by developing a so-called 'double cell'. This cell consisted of two sector shaped cells side by side having the same quartz windows and cell housing. It was similar to the one they had used in the equilibrium ultracentrifuge method. One of the sectors contained the solution to be investigated, the other only contained the solvent. Light passing through the latter gave an indication of distortions due to the solvent and the quartz windows while light passing through the other sector gave information on the sedimentation process superimposed on the cell distortions. Comparing the two signals gave more accurate information on the sedimentation process itself.²⁵³

From the mid 1950s onward Beams' work was mainly²⁵⁴ directed at the further development of the magnetically suspended equilibrium ultracentrifuge, also called 'coaster'. He decreased the pressure in the vacuum chamber to 10^{-6} mm Hg which made the rotor loose about 1 r.p.s. per 3 days when coasting freely in the vacuum chamber. He indicated that, from the two possible methods for determining molecular weights from sedimentation experiments, viz. the sedimentation equilibrium method and the rate-of-sedimentation method, the first was more sound

thermodynamically. Nevertheless, in cases where the molecular weights were large enough to give measurable rates of sedimentation in the centrifugal fields available, the rate-of-sedimentation method was more widely used. According to Beams, the primary reason for this lack of popularity of the equilibrium method was the difficulty of maintaining the rotational speed and temperature of the centrifuge rotor sufficiently constant for long periods of time.²⁵⁵ In his 'coaster' these problems were overcome. Thanks to the very low pressure in the vacuum chamber the rotor hardly heated up and the temperature was maintained constant to at least one part in ten thousand. Actually, the rotor cooled down somewhat because of stretching. Since the precision of the rotor speed could be obtained to about one part in 10^6 and that of the temperature to roughly one part in 10^4 , the method of measuring the concentration as a function of the radius became the factor which limited the accuracy of the results obtained at least during the centrifuging process. In practice a fringe shift of between 0.03 and 0.05 was about the best they could measure with reliability. This gave a precision of about three significant figures for substances with molecular weights from about 100 up to the largest values known. It was usually possible to work with both relatively low or high concentrations of a substance, since the total fringe shift (and hence, the accuracy) was increased by increasing the rotor speed. Fortunately the rotor speeds required usually were well below those obtainable with the apparatus. Nevertheless, Beams considered it highly desirable especially for measurements in extremely dilute solutions to have a more precise method of determining the concentrations in the centrifuge cell. He indicated that greater precision should be obtained if a multiple beam interferometer could be used. They therefore started to develop this technique for the ultracentrifuge.²⁵⁶

The fact that the rotor speed decreased very slowly appeared to be very favorable for the overall method because this caused equilibrium to be established faster than in the case of constant rotor speed. Svedberg had based his experiments on the theory of Mason and Weaver who had assumed a constant rotor speed. In Beams' case it appeared that equilibrium established much faster than they expected on the basis of that theory. After this observation, Archibald, who had studied with Beams, treated the theory for the case where the speed decreased slowly and indeed found a considerable decrease in the time required to reach within 0.1% of equilibrium. With their slowly decreasing speed the equilibrium times in some cases were reduced from the order of weeks to days.²⁵⁷ Beams and his colleagues believed that this centrifuge provided an excellent equilibrium method of getting molecular weights, since it gave good precision and the data were obtained in a relatively short time. Also, it was about equally useful over the entire range of molecular weights above 100. However, there were several 'rather obvious improvements' which they had under development that should make the apparatus

more widely adaptable. For example, it would be of much interest to investigate the methods of obtaining molecular weights by measuring the approach to equilibrium as suggested by Archibald. This required a very rapid acceleration of the rotor followed by an extremely constant speed. The air turbine drive gave the rapid acceleration without rotor heating but did not give the constant speed required. They could also use an electrical drive but the principal problem would then be to produce rapid acceleration without excessive rotor heating.²⁵⁸ However, because the air-drive was very 'noisy' and required auxiliary air compressors, etc. for most experiments they replaced this drive by an electric motor drive which could be operated from the standard power lines. Both the motor and speed regulator could be obtained commercially. Furthermore, the drive was made easily interchangeable with the air turbine drive.²⁵⁹

The main factor causing deceleration of the rotor while spinning as a coaster was the drag of the residual gas in the vacuum chamber. With his latest designs a rotor spinning at 300 r.p.s. would lose one r.p.s. in 3 days. Beams succeeded in bringing down the residual gas pressure by freezing out the residue with liquid helium. Now a number of other factors were limiting the constancy of the speed. In an article published in 1963 in *Review of Scientific Instruments* Beams listed 15 such factors, including eddy current drags produced by the magnetic fields, vibrations of building and the earth, variations in the rotor temperature, creep of rotor material, pressure of light on the rotor, etc. Taking care of all these factors he succeeded in bringing down the deceleration factor f/f to approximately 10^{-9} sec^{-1} where f was the change in rotor speed f per unit time while the rotor was coasting.²⁶⁰ This meant that a rotor spinning 300 r.p.s. would lose about one r.p.s. in forty days. Theoretically he expected that the main limiting factors were now due to the fact that the supporting magnetic field was not rotating while the rotor was. Therefore, his next step was to rotate the supporting field and the surrounding vacuum chamber with about the same speed as the rotor. He did so by spinning a first rotor as he did in his coaster scheme. Inside this first rotor spun a second rotor which was suspended by a magnetic field produced by the first while the first rotor also served as a vacuum chamber to the second. Although in June 1963 Beams had only tested the scheme at atmospheric pressure, and relatively low rotor speeds he found it worthwhile to describe it already because of the 'potential use of the double magnetic suspension in other types of experiments'.²⁶¹ His next step was to extend the technique to a magnetic suspension in which more than two rotors were suspended, one above the other. Concerning possible applications he wrote in 1965:

"Often it is important to measure very small torques or changes in the forces on bodies located at different vertical positions in an experimental system. In

gradient problems it is important that the measurements be made in at least three position simultaneously. This requires a triple suspension. In addition to determining small torques the magnetic suspension systems can measure minute changes in the forces on the suspended bodies. Consequently very small viscous, density, and diffusion, gradients in gases, vapors, and solutions can be determined."²⁶²

In the mid 1960s Beams was also still working on ultracentrifuges for sedimentation experiments. Although the deceleration of his coaster was very small he indicated that for certain experiments, especially in the measurements of very large molecular weight compounds, it was desirable if the speed were more constant. He therefore devised an electronic speed control which held the speed of the rotor constant to the order of one part per million.²⁶³

Beams' Later Years - Broad Interest in Science

All of his academic career Beams kept a broad interest in the fostering of research and its applications. He was a member of numerous societies, boards and committees. In 1958 he became president of the American Physical Society. In the early fifties he was on the board of the physics division of the National Science Foundation and from 1954-1960 he was a member of the General Advisory Board of the US Atomic Energy Commission. From 1948-1954 and again from 1960-1970 he was member of the board of directors of the Oak Ridge Institute of Nuclear Studies. After his retirement in 1969 he also continued to work with the gas centrifuge program as a consultant to the overall program of the AEC, as well as to the project at Virginia. In April 1977, three months before Beams' death, president Carter authorised the construction of a large-scale gascentrifuge plant for uranium enrichment in order to enrich uranium for nuclear power generation. However, in the early 1980s, after huge investments had already been made, the plans were cancelled again. This because the nuclear power growth had been much less than anticipated and because it was concluded that laser enrichment was superior to the gas centrifuge technology.²⁶⁴ For his many contributions to research Beams received a number of awards, including the National Medal of Science in 1967.²⁶⁵ In his own research he remained primarily an experimental physicist, interested in answering all kinds of questions regarding the physical world, although in his later years he laid more emphasis on the investigation of biological problems. He helped to create an interdisciplinary program in biophysics at the UVA and from the early 1960s onward worked closely with Donald W. Kupke, professor of biochemistry, on aspects of protein and virus research. After his retirement Beams continued to stay at the 'work bench' 6 days a week. During

these latter years, he also developed terrestrial methods to test for any change in the gravitation constant with time and on mass creation, and started to develop a method for reducing the radionuclide pollution from burning coal. But he spent the bulk of his laboratory effort on magnetic methods for furthering the study of biomacromolecules. In one of the schemes he superimposed a horizontal rotating magnetic field in order to obtain the viscosity with high precision while measuring the density. Thus, it became convenient to determine both the thermodynamic and hydrodynamic volumes of biomacromolecules on the same sample simultaneously. During his retirement he produced yet another application of magnetic suspension in order to increase the power of the osmotic pressure method.²⁶⁶ This new instrument, a magnetic-suspension densimeter-viscometer measured simultaneously and with quickness and precision the density and viscosity of a fluid system. The density was measured to one part in a million and the viscosity to one part in ten thousand. In the method a small cylindrical buoy was magnetically suspended in the fluid.²⁶⁷ The analogy with the magnetically supported ultracentrifuge easily comes to mind. Beams worked on the refinement and application of the densimeter-viscometer up to the time of his death. In fact, on 23 July 1977, the day he died, Kupke came on Beams' request to his bedside to complete their latest collaborative paper on the application of this instrument.²⁶⁸ This paper reported modifications of the magnetic suspension densimeter-viscometer that made possible continuous and accurate recording of the variations in viscosity and density of solutions undergoing change.²⁶⁹

Notes

The meaning of the various abbreviations used is explained in the notes to Chapter 2.

1. Gordy (1983), pp.3-6.
2. Brown (1967), Ch.IV, p.8.
3. Brown (1967), Ch.II, pp.2-3.
4. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1947-1948, pp.22-23.
5. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1947-1948, pp.15-16.
6. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1947-1948, p.9.
7. Brown (1967), Ch.III, p.2.
8. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1947-1948, p.10 and Brown (1967), Ch.IV, p.2.
9. Brown (1967), Ch.IV, p.2.
10. Brown (1967), Ch.IV, pp.5-6.
11. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1947-1948, p.21-22.
12. Brown (1967), Ch.III, pp.7-10.
13. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1924-1925 p.6.
14. Brown (1967), Ch.IV, pp.7-9.
15. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1924-1925, p.3-4.
16. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1925-1926, p.7.
17. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1926-1927, p.9.
18. Beams and Allison (1927).
19. Beams (1927).
20. Lawrence and Beams (1927).

21. Beams and Lawrence (1927), p.207.
22. Lawrence and Beams (1928b).
23. Lawrence and Beams (1928a).
24. Beams (1928).
25. Henriot and Huguenard (1925 and 1927).
26. Lawrence, Beams and Garman (1928).
27. Brown (1967), Ch.III, p.3.
28. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1926-1927, p.13.
29. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1927-1928, p.9.
30. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1947-1948, p.12.
31. Brown (1967), Ch.V, pp.1-2.
32. Brown (1967), Postscript No.2.
33. Brown (1967), Ch.V, pp.2-3.
34. Brown (1967), Ch.X, p.9.
35. (UVa:Rg-2/1/1.381), 'Annual Report of the School of Physics', 1929-1930, pp.3-4.
36. (UVa:Rg-2/1/1.381), 'Annual Report of the School of Physics', 1929-1930, p.13.
37. Beams (1930a).
38. Beams (1930b).
39. Beams (1930c), p.667.
40. Beams (1930c), p.671.
41. Beams and Weed (1931) pp.44-45.
42. Beams and Weed (1931), p.46.
43. Beams (1932).
44. Garman (1933), p.450.
45. (UVa:Rg-2/1/1.381), 'Annual Report of the School of Physics', 1933-1934, p.5.
46. Dr. Edward G. Pickels, private communication.
47. Dr. Edward G. Pickels, private communication.
48. Pickels (1935), pp.1-2.
49. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1932-1933, p.5.
50. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1933-1934, p.4.
51. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1934-1935, p.7.
52. Beams Weed and Pickels (1933), p.339.
53. Beams Weed and Pickels (1933), p.339.
54. Beams Weed and Pickels (1933), pp.339-340.
55. Pickels (1935), p.32.
56. Pickels (1935), p.32.
57. Pickels (1935), pp.31-32.
58. Beams Weed and Pickels (1933), p.338.
59. Beams Weed and Pickels (1933), p.340.
60. Pickels (1935), pp.10-11.
61. Dr. Edward G. Pickels, private communication.
62. Beams, Pickels and Weed (1934).
63. Pickels (1935), pp.34-35.
64. Beams, Pickels and Weed (1934).
65. Beams, Pickels and Weed (1934).
66. Anon. (1934a).
67. Dr. Edward G. Pickels, private communication.
68. Pickels and Beams (1935).
69. Pickels and Beams (1935).
70. Beams and Pickels (1935), p.299.
71. Beams and Pickels (1935), pp.299-301.
72. Beams and Pickels (1935), p.302.
73. Beams and Pickels (1935), p.303.
74. Beams and Pickels (1935), p.304.
75. Pickels (1935), pp.46-47.
76. Beams and Pickels (1935), p.304.
77. Pickels (1935), p.50.
78. Beams and Pickels (1935), pp.304-306.
79. Beams and Pickels (1935), p.306.

80. Pickels (1935), p.50.
81. Beams and Pickels (1935), p.307.
82. Beams and Pickels (1935), pp.306-307.
83. Beams and Pickels (1935), p.308.
84. Pickels (1935), pp.42-43.
85. Beams and Pickels (1935), p.308; and Pickels (1935), pp.51-52.
86. Pickels (1935), pp.8-9.
87. Pickels (1935), p.52.
88. Pickels (1935), pp.53-55.
89. Pickels (1935), pp. 55-56.
90. Pickels (1935), p.56.
91. (RAC:1.1/252/1/10) Newcomb (UVA) to Weaver, 16 December 1936; annexed research project.
92. (RAC:1.1/252/1/8) Weaver to Beams, 31 January 1934.
93. (RAC:1.1/252/1/8) Beams to Weaver, 2 February 1934.
94. (RAC:1.1/252/1/8) Weaver to Beams, 7 February 1934.
95. (RAC:1.1/252/1/8) Richtmyer (NRC) to Weaver, 19 February 1934.
96. (RAC:1.1/252/1/8) Hanson (RF) to Newcomb (UVA), 23 March 1934.
97. (RAC:1.1/252/1/8) Weaver to Beams, 7 June 1935.
98. (RAC:1.1/252/1/8) Beams to Hagemeister (Weaver's secretary), 10 June 1935.
99. (RAC:1.1/252/1/8) Weaver's diary, 17 October 1935.
100. (RAC:1.1/252/1/10) Beams to Weaver, 27 June 1936.
101. (RAC:1.1/252/1/10) Beams to Weaver, 31 August 1936.
102. (RAC:1.1/252/1/10) Beams to Weaver, 9 September 1936.
103. (RAC:1.1/252/1/10) Beams to Weaver, 9 September 1936.
104. (RAC:1.1/252/1/8) Weaver's diary, 17 October 1935.
105. (RAC:1.1/252/1/10) Weaver to Beams, 11 December 1936.
106. (RAC:1.1/252/1/10) Newcomb (UVA) to Weaver, 16 December 1936.
107. (RAC:1.1/252/1/10) RF-37008: 'Grant appropriation to the University of Virginia (Beams)', 15 January 1937.
108. (RAC:1.1/252/1/10) Weaver to Beams, 11 May 1937.
109. Holmes and Beams (1937).
110. (RAC:1.1/252/1/10) Beams to Weaver, 14 May 1937.
111. (RAC:1.1/252/1/10) Beams to Weaver, 21 September 1937.
112. (RAC:1.1/252/1/10) Beams to Weaver, 15 December 1937.
113. (RAC:1.1/252/1/10) Beams to Weaver, 15 December 1937.
114. (RAC:1.1/252/1/10) Weaver to Beams, 21 December 1937.
115. Archibald (1938a).
116. Archibald (1938b).
117. (RAC:1.1/252/1/10) Beams to Hanson (RF), 28 March 1939; annexed report, p.9.
118. (RAC:1.1/252/1/14) J.W. Beams, 'Progress Report on the Development of the Ultracentrifuge', report to the Natural Science Division of the Rockefeller Foundation, 1937, pp.6-7.
119. Hoxton and Beams (1937).
120. Beams and Linke (1937b).
121. Beams and Snoddy (1937a). An abstract of this article was published in 'Physical Review': Black, Beams and Snoddy (1938).
122. (RAC:1.1/252/1/11) Weaver's diary, 10 December 1938.
123. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1932-1933, pp.3-4.
124. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1933-1934, p.8.
125. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1934-1935, p.6.
126. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1934-1935, p.12.
127. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1936-1937, p.1.
128. Brown (1967), Ch.V, p.6-7.
129. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1938-1939, appendix, pp.2-6.
130. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1947-1948, p.9a and Brown (1967), Postscript No.2.
131. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1936-1937, p.10.
132. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1937-1938, p.12.
133. (UVa:Lib:7265-b/2) Beams to Alford, 22 December 1933.
134. (RAC:1.1/252/1/10) Newcomb (UVA) to Weaver, 16 December 1936.

135. (RAC:1.1/252/1/10) Beams to Weaver, 9 September 1936.
136. (RAC:1.1/252/1/14) J.W. Beams, 'Progress Report on the Development of the Ultracentrifuge', report to the Natural Science Division of the Rockefeller Foundation, 1937, p.8.
137. Beams (1935).
138. Snoddy, Workman and Beams (1936).
139. Gilmer (1937).
140. Chiles (1937).
141. Pickels to Beams, 15 April 1969 (EGP). Beams himself was once seriously injured by an exploding rotor. Shortly after his retirement a fragment of a rotor pierced his throat, and only the fast action of younger colleagues in rushing him to the hospital saved his life. (McShane (1978), p.46)
142. Quoted in Beams (1937b), p.801.
143. Beams (1937a).
144. Beams and Linke (1937b); see also Beams (1937a)
145. (RAC:1.1/252/1/8) Beams to Hanson (RF), 28 March 1939; annexed report, p.4.
146. Beams, Linke and Skarstrom (1937), p.293.
147. Beams, Linke and Skarstrom (1937).
148. Beams (1938b).
149. Beams (1940), p.251.
150. Beams and Snoddy (1937b), p.993.
151. Beams and Snoddy (1937b).
152. Beams and Haynes (1936a).
153. Joly and Poole (1920); Mulliken (1922a and 1922b).
154. Beams and Haynes (1936b), p.491.
155. (RAC:1.1/252/1/14) J.W. Beams, 'Progress Report on the Development of the Ultracentrifuge', report to the Natural Science Division of the Rockefeller Foundation, 1937, p.10.
156. Mulliken (1922a).
157. Beams and Haynes (1936b).
158. Beams and Maskett (1937).
159. Beams and Skarstrom (1939), pp.267-268.
160. Skarstrom, Carr and Beams (1939).
161. Beams and Skarstrom (1939), pp.267-269.
162. Beams and Skarstrom (1939), pp.269-271.
163. Beams (1940).
164. Beams (1939a).
165. Urey (1939).
166. Beams and Skarstrom (1939), pp.271-272.
167. Beams (1937b), p.801.
168. In 1936 a new instrument maker was attracted because A.J. Weed had died early that year of a heart attack while speaking at the Physics Journal Club. He was succeeded by Philip M. Sommer. See Brown (1967), Ch.V, p.9.
169. Beams, Linke and Sommer (1938), p.248.
170. Beams, Linke and Sommer (1938), pp.249-251.
171. Beams, Linke and Sommer (1938), pp.251-252.
172. Maskett (1941).
173. Holmes (1937). See also Beams and Linke (1937a) and Holmes and Beams (1937).
174. (RAC:1.1/252/1/10) Beams to Weaver, 14 May 1937.
175. (RAC:1.1/252/1/11) Newcomb (UVa) to Weaver, 12 December 1938.
176. (RAC:1.1/252/1/11) Hanson (RF) to Newcomb (UVa), 19 December 1938.
177. Beams (1938a), p.253.
178. Beams and Black (1939), p.59.
179. Beams and Black (1939), pp.60-63.
180. Beams (1939b).
181. (RAC:1.1/252/1/14) J.W. Beams, 'Development of the Ultracentrifuge', report to the Natural Science Division of the Rockefeller Foundation, 1940.
182. Beams (1947b), p.231.
183. (RAC:1.1/252/1/11), Weaver's diary, 10 December 1938.
184. (RAC:1.1/252/1/14) J.W. Beams, 'Development of the Ultracentrifuge', report to the Natural Science Division of the Rockefeller Foundation, 1940, pp.4-6; and Beams (1940), pp.255-256.

185. Skarstrom and Beams (1940), p.399.
186. Skarstrom and Beams (1940), pp.402-403.
187. Skarstrom and Beams (1940).
188. Scudder Smith (1941).
189. McHattie (1941a and 1941b).
190. (UVa:7265-b/2: Occupational papers) Beams, untitled paper, 1938.
191. (RAC:1.1/252/1/10) Beams to Hanson (RF), 28 March 1939; annexed report, p.2.
192. (RAC:1.1/252/1/10) Beams to Hanson (RF), 28 March 1939; annexed report, pp.3-4.
193. (RAC:1.1/252/1/10) Beams to Hanson (RF), 28 March 1939; annexed report, pp.5-6.
194. (RAC:1.1/252/1/12) Gray to Beams, 14 November 1940.
195. (RAC:1.1/252/1/12) Beams to Gray, 20 November 1940.
196. (RAC:1.1/252/1/11), 'Excerpt from Trustees Bulletin', December 1950, p.6.
197. Beams (1938a), p.250, Footnote.
198. Beams (1961), p.135.
199. Beams (1940), pp.235-237.
200. Beams (1961), p.142.
201. Beams (1937b), p.804.
202. Beams (1940), p.264.
203. Beams (1937b), p.795.
204. Beams (1940), p.261.
205. Beams (1941), pp. 44-45.
206. See e.g. Beams (1937b), pp.800-801.
207. Beams (1938a), p.250, footnote.
208. Beams (1975), pp.15-16.
209. Beams (1947b), p.233.
210. (UVa:Rg-2/1/1.381), 'Annual Report of the School of Physics', 1947-1948, p.18.
211. (UVa:Rg-2/1/1.381), 'Annual Report of the School of Physics', 1947-1948, pp.18-20.
212. Brown (1967), Ch.VI, p.2.
213. (UVa:Rg-2/1/1.381), 'Annual Report of the School of Physics', 1945-1946, p.6.
214. (UVa:Rg-2/1/1.381), 'Annual Report of the School of Physics', 1940-1941, p.2. and (UVa:Rg-2/1/1.381), 'Annual Report of the School of Physics', 1941-1942, p.1.
215. (UVa:Rg-2/1/1.381), 'Annual Report of the School of Physics', 1946-1947, p.1.
216. Beams (1975), p.17.
217. Beams (1975), p.20.
218. Beams (1975), pp.21-22.
219. Beams (1975), p.26.
220. Beams Hagg and Murphree (1951).
221. Beams (1975), p.29.
222. Quoted in Beams (1975), p.47.
223. Beams (1975), p.31.
224. Beams (1975), p.39.
225. Although these developments were very interesting from the perspective of technology studies they will not be described here because they are heavily interlinked with the development of nuclear power. That means that, from the perspective outlined in Chapter 1, a fruitful study of these developments would only be possible if these developments in the field of nuclear power were also included which is beyond the scope of this study.
226. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1947-1948, p.24-25.
227. Brown (1967), Ch.VIII.
228. (UVa-Lib:7265-a/2/11) Beams to Urey, 6 November 1945.
229. (UVa-Lib:7265-a/2/O) Owen (NRC) to Beams, 6 November 1945.
230. (UVa-Lib:7265-a/2/11) Beams to Urey, 6 November 1945.
231. (UVa-Lib:7265-a/2/11) Urey to Beams, 24 November 1945.
232. (UVa-Lib:7265-a/1/Aebersold) Aebersold to Beams, 5 December 1945.
233. (UVa-Lib:7265-a/2/R) Beams to Rhoads, 10 December 1945.
234. (UVa-Lib:7265-a/2/Solomon) Solomon to Beams, 18 February 1946, annex: 'Report of the Division of Physics to the Committee On Growth', pp.1-2.
235. (UVa-Lib:7265-a/2/Solomon) Solomon to Beams, 18 February 1946, annex: 'Report of the Division of Physics to the Committee On Growth', p.7.
236. Leslie (1983) pp.319-322.

237. (UVa-Lib:7265-a/2/Solomon) Solomon to Beams, 18 February 1946, annex: 'Report of the Division of Physics to the Committee On Growth', pp.7-8
238. (UVa-Lib:7265-a/2/R) Beams to Ray (NRC), 17 June 1948.
239. (UVa-Lib:7265-a/2/R) Beams to Ray (NRC), 17 June 1948.
240. Beams, Young, III and Moore (1946) and Beams and Young, III (1946).
241. Beams and Young, III (1947).
242. Beams (1961), p.135.
243. Beams (1947b), p.241.
244. Beams, Young, III and Moore (1946) and Beams and Young, III (1946).
245. (UVa-Lib:7265-a/3/P) Parker to Young (UVa), 3 June 1946.
246. Beams, Linke and Sommer (1947), p.57.
247. Beams, Linke and Sommer (1947), p.60.
248. Beams (1947a).
249. Beams (1950), p.182.
250. Beams (1954), p.622.
251. Beams, Ross and Dillon (1951), pp. 77-78.
252. Beams (1954), p.624.
253. Beams and Dixon, III (1953).
254. Except for his work on developing the 'gas-centrifuge' for uranium enrichment.
255. Beams, Dixon, III Robeson and Snidow (1955), p.915.
256. Beams, Dixon, III Robeson and Snidow (1955), p.921.
257. Beams, Dixon, III Robeson and Snidow (1955), p.921; Beams (1957), p.68; Beams, Boyle and Hexner (1961), p.650.
258. Beams, Dixon, III Robeson and Snidow (1955), p.921.
259. Beams, Boyle and Hexner (1961), p.647.
260. Beams (1963), p.1071.
261. Beams (1963), p.1072.
262. Beams (1965).
263. Beams (1966).
264. See for an analysis of various uranium enrichment methods: Krass, Boskma, Elzen and Smit (1983).
265. Gordy (1983), pp.35-36.
266. Kupke (1977).
267. Beams and Hodgins (1971).
268. Gordy (1983).
269. Beams and Kupke (1977).

Chapter 4

JAMES WILLIAM McBAIN

Education - Colloid Chemist

James William McBain was born on 22 March 1882, the elder son in a family of five, three sisters and one brother, Clifford, in Chatham in the maritime province of New Brunswick in Canada. He was the son of a Presbyterian minister, James Affleck Frazer and Mary Morrison Quin. A part of his school years was passed in Rhode Island, U.S.A. He entered the University of Toronto at the age of 17, graduating with the B.A. degree in 1903 and the M.A. in 1904, obtaining first class honours in chemistry and mineralogy and the Edward Blake Scholarship in his second year. He was especially attracted to a comparatively new branch of chemistry, viz. physical chemistry, taught there by F.B. Kenrick and W. Lash Miller, to whom he was assistant. By the close of the 19th century they had brought to Toronto the new physico-chemical tradition from Berlin, Göttingen, Munich, and Leipzig. He spent the winter semester of 1904-5 at the University of Leipzig which at that time was at the height of its academic activity in physical chemistry, including on its staff W. Ostwald, R. Luther, H. Freundlich, and K. Drucker. The following three semesters he studied with G. Bredig at Heidelberg, where he obtained the Ph.D. degree in physical chemistry, with mathematics and physics as subsidiary subjects. From student years he passed to his first academic appointment in 1906 as lecturer in physical chemistry at the University of Bristol. There he showed a great interest in the activities of the corporate life of the then young university.¹

McBain's earliest field of research was the physical chemistry of simple soaps, their electrical conductance, extent of hydrolysis, diffusion, transport numbers, and thermodynamic properties. Out of these researches emerged the concept of the 'ionic micelle' as well as of neutral micellar units. He observed that maxima and minima could be identified in the conductivity concentration curves. Since it was possible that this conductivity might be caused by hydrolysis his next

investigation led him to an examination of the degree of hydrolysis for various concentrations of soap. The extent of hydrolysis as revealed by two different methods was found to be small which led McBain to infer the existence of highly mobile negative carriers of electricity which possessed mobilities similar to that of the citrate ion. Thus was born the concept of the 'association ion' or the 'ionic micelle', which later proved to be a valuable guide to the elucidation of the properties of large classes of colloidal systems such as soaps, detergents and dyes.²

McBain developed an experimental technique comparable to that of the moving microtome, the so-called McBain-Bakr spring balance, which was subsequently widely used. This permitted measurements of sorption, within an entirely sealed system, by the extension of a helical spring of fused silica, the extension being determined by the weight of sorbed material on a sorbent in a bucket hanging from the helical spring.³ With Bulton he studied the sorption of nitrogen, nitrous oxide, and ethylene on charcoal at pressures of up to 60 atmospheres, indicating their conformity to the Langmuir formulation of adsorption. The balance proved to be a valuable tool applicable also to mono-layers adsorbed on single crystal faces.⁴ McBain's use of the term 'sorption' dated from 1909 to cover a complex of processes which might include adsorption, diffusion, absorption, and solid solution. The particularized names such as 'adsorption', etc., 'should be restricted to cases in which it has been proven to consist of only one of these'. Phenomena in sorption which proceeded progressively through long periods, even years, he labelled 'persorption'.⁵

After a decade at Bristol McBain had become a well-respected colloid chemist. During his period at Bristol he was a member of several government committees on such topics as adhesion, corrosion and rubber. During World War I he worked for the Department of Explosives Supply of the Ministry of Munitions. In 1919 McBain was offered a Chair and he was appointed as the first Leverhulme Professor of Chemistry at Bristol.⁶ By the mid 1920s he had already published dozens of papers and in 1931 he published a textbook on the *Sorption of Gases and Vapors by Solids* which was very well received.⁷ McBain had become a respected scientist in the field of colloid chemistry and he was considered to be an expert in the field of soaps and soap solutions. In 1926 he was invited as 'the foreign guest of honour' to the American Fourth National Symposium on Colloid Chemistry. The president of the symposium, H.B. Weiser praised McBain's contributions by stating that 'his valued paper, (...) and his scholarly discussions of a number of papers contributed in a large way to the success of the Meeting'.⁸ The paper McBain had presented was on 'the main principles of colloid science'. He held the opinion that the two main problems of colloid science were 'structure' and 'stability': what was the structure which placed matter in this category? Whence would such structures derive such a measure of stability as to constitute nearly all the common materials

which were met with in daily life? According to McBain the answer to the first question was that in most cases the unit of which colloids were built up would not be the mere molecule but a higher organized unit, the particle called by Nägeli the micelle. With respect to stability McBain submitted that there was a class of substances whose most stable state was the colloidal condition. They were thermodynamically stable in the strictest sense, in that the colloid state was for them more stable than the crystalline or crystalloidal.⁹

Ultracentrifuges - Pilgrimage to Upsala

In 1927, after a period of a year as visiting professor, McBain was appointed professor of chemistry at Stanford. Usually he arrived at this laboratory at 8 a.m. and took note of the already growing queue at his door and deal with them first. This was the recognized way that students had of getting hold of him. His research school had overflowed from the main building and had filled all available stables and outbuildings. Each morning, certain research students would find a note on their benches to say that McBain would visit them at such and such a time, thus ensuring that the particular student would not have disappeared at the time McBain had reserved to give him or her attention.¹⁰ At Stanford he got interested in Svedberg's ultracentrifuge work. In 1929 he wrote a letter to J. Burton Nichols, who had cooperated with Svedberg during the development of the first ultracentrifuges and who had by that time returned to the US, showing his interest in ultracentrifuges:

"I am much impressed with the far reaching possibilities of the ultracentrifuge as developed by Svedberg and yourself and of which you gave so striking an account in Toronto last June. I, unfortunately, could not remain for your address as I sailed from New York the second morning of the Symposium. I am therefore writing to ask if you could be so kind as to give me a few details as to costs and sources of supply for any parts of the equipment which do not have to be made in one's own laboratory. I should like to use it in connection with some experiments on soap and would be greatly obliged for any information you can give me."¹¹

Nichols' answer was that the apparatus with microphotometer and auxiliary would cost \$ 5,000 or more and that most of the parts would have to be made in one's own machine shop. He gave some details of construction and enclosed a copy of the paper he had given in Toronto which outlined 'the conditions the centrifuge must fulfill to act properly'. He also advised McBain that Prof. Alsberg of the Food Research Institute at Stanford had asked for information on the ultracentrifuge and that, because of the costs involved, it might be fruitful to join forces with him.¹² McBain replied, stating that 'it seems to me that this new

ultracentrifuge is a much more important method of investigation than the ultramicroscope' and that he would try to acquire an ultracentrifuge together with Alsberg.¹³ Late 1930 he wrote Herman A. Spoehr, Director of Natural Sciences of the Rockefeller Foundation, whether it would be possible to apply for a grant in aid in order to do some studies with the ultracentrifuge in Upsala. Svedberg had placed the ultracentrifuge at the disposal of McBain and his wife, who was also a colloid chemist, for the months of October and November 1931. McBain indicated that Svedberg had only worked with colloids, such as protein and cellulose, of unknown molecular weight. McBain would like to perform experiments with soaps and soap solutions, which he knew very well:

"We wish to test and perhaps standardise portions of Svedberg's theory by means of these standard solutions and it is well, if there is any discrepancy, that the experiments should be carried out under Svedberg's own eyes with his carefully established set of conditions. The theory will then safely follow from the experiments."¹⁴

He hoped that, after examination of Svedberg's 'enormous outfit', he might find it possible to design a much less elaborate instrument with microscopic observation that would serve the same purpose.¹⁵ Spoehr answered that the plans impressed him as being a 'very interesting undertaking' and asked McBain to give him some more details.¹⁶ Early 1931 Stanford University submitted an official request for a grant for McBain. The request stated that the use of the ultracentrifuge had become of vital importance for McBain's work, but the great expense of its construction made duplication practically impossible.¹⁷ Furthermore, Svedberg had advised that anyone desirous of installing an ultracentrifuge would do well first to study the equipment by personal visit to Upsala. McBain's aim was:

"to work out a complete redesign of the ultracentrifuge upon a scale which will avoid the tremendous mechanical difficulties, so elaborately overcome by Professor Svedberg, and yet yield similar results. If this hope is realized, the ultracentrifuge and the varied methods of its employment would be brought within the reach of ordinary laboratories."¹⁸

The Rockefeller Foundation gave him a grant, considering it highly desirable to standardize Svedberg's experimental method and to check the theoretical interpretation underlying these results by experiments with colloidal material of *definitely known molecular weight*. McBain would be the ideal man for this undertaking because, owing to his researches, the family of soaps constituted the best known colloids of well established chemical formula and properties.¹⁹ Shortly before McBain's leave for Sweden, Spoehr advised McBain that he had recently visited Beams who reached 1,000,000 g. 'It occurred to me that this might not be

without interest for you in your consideration of centrifuges for your investigations'.²⁰ McBain replied that he 'was very interested in the information you give about Dr. Beam's supercentrifuge'. Furthermore, on his way to Europe, he intended to visit Harvey at Princeton in order to study his microscope-centrifuge.²¹ (see Chapter 6)

When arriving in Upsala McBain was most surprised that they only worked on proteins while there were so many other interesting substances that could be investigated with the ultracentrifuge. Tiselius argued that indeed there were many more interesting fields of research but that the problem was that they had so little investigators which forced them to limit themselves to a rather narrow field of research.²² In 1933 McBain described the work he had done in Upsala in an article in the *Proceedings of the Royal Society of London* entitled: 'Sedimentation Equilibrium in the Ultracentrifuge: Types Obtained with Soap Solutions'. He argued that, since Svedberg's use of the ultracentrifuge had been largely confined to such materials as proteins, cellulose, and colloidal gold, it might not be generally realised that substances of ordinary molecular weight were also accessible to study by the ultracentrifuge, and in the particularly favorable case of mercuric chloride, even in one of the smaller electrically driven ultracentrifuges. This substance possessed the advantage that it was almost entirely in the form of strictly isoelectric molecules and, therefore, it should be an exceptionally favorable material for testing the operation of any ultracentrifuge.²³ With respect to his experiments with soap solutions a complicating factor was that in these solutions the soap did not exist as a single molecule but as an equilibrium between various constituents which McBain called neutral micelles and ionic micelles. The fact that the latter were charged electrically further complicated the sedimentation process. Therefore, the results of the experiments with the ultracentrifuge could not be interpreted straightforwardly. His main claims in the article were that the experiments had yielded new types of equilibrium and that they had confirmed the independent existence of neutral micelles and ionic micelles in soap solutions.²⁴

Like Beams, McBain saw the ultracentrifuge as an instrument of wider application than Svedberg, though not as wide as Beams. He used the Svedberg apparatus as a 'standard' with which he compared what he wanted. Towards the Rockefeller Foundation he argued that the standard was OK in the scientific sense but that it was too 'high' in terms of what it took to make it. Back in the US, trying to obtain an ultracentrifuge of his own, his main problem was that Svedberg's design was so extremely expensive - in the order of \$ 40,000. The slower electrical type cost about \$ 5,000, but was not suited for most of the researches McBain would like to perform because the centrifugal field generated was too small. He could only solve his problem by using a design that would

basically differ from Svedberg's. Like Beams, he then started with the spinning top principle of Henriot and Huguenard and tried to adapt the scheme for his purposes.

McBain's Approach

McBain's work, however, was severely handicapped for lack of funds. Late 1933 he applied for a grant with the Rockefeller Foundation in order to continue his further investigations:

"Since the funds available at Stanford University for the support of research in the Chemistry Department have been severely curtailed during the present financial crisis, and the residue has to support the work of a large group of investigators, who are publishing forty or fifty papers each year in very varied fields of chemistry, my work in the field of colloids and surface phenomena is gravely handicapped for lack of money. I therefore submit an application for a grant-in-aid of \$ 2000 in the urgent hope that it may receive favorable attention.

My main problems centre in the study of colloids and their relation to other forms of matter, and in the even more fundamental investigation of the structure of surfaces.

Soaps and pure sulphonic acids, of which I now have a unique supply, and pure proteins are the materials being used to study the main problems of colloid science and the bearing thereon of modern developments of the dissociation theory. Towards this purpose we are developing a very simple and inexpensive form of ultracentrifuge, based upon the air-driven spinning top of Henriot and Huguenard, which already shows definite promise of exceeding in scope and performance the enormously expensive ultracentrifuges of Svedberg at Upsala (\$ 25,000 and \$ 41,000 each). We expect to extend work with the ultracentrifuge to ordinary molecules. Many lines of investigation with the ultracentrifuge are opening out in the fields of metallography, oil emulsions, virus and bacteriophage, as well as in colloids. The great interest that is being taken in the possible applications is attested by the numerous letters we receive from all over the country. Dozens of these spinning tops in primitive forms have been set up in laboratories elsewhere after consultation with us or embodying our suggestions. We are seriously handicapped for lack of funds to carry out the necessary tests and to standardize the optimum developments, as well as for the purchase of accessory materials and equipment."²⁵

A few months later he tried to strengthen his request by pointing out to Warren Weaver of the Rockefeller Foundation that the table of contents of the 'Cold Spring Harbour Symposia on Quantitative Biology' showed that quantitative biology was largely colloids and surface phenomena which would include the application of the ultracentrifuge.²⁶ Weaver invited him to elaborate upon the biological significance of his work.²⁷ McBain pointed out that, while the biological significance of Svedberg's work was beyond question, Svedberg's apparatus was far too expensive for others to obtain. Therefore they were developing the air driven ultracentrifuge in a such form that it could be used not only for all the purposes for which Svedberg's was designed but for many other possibilities as well. They

were concerned with developing and standardizing designs sufficiently inexpensive to be afforded by all laboratories. He appended extracts from a letter from C.V. Taylor, Herzstein Professor and Head of the School of Biological Sciences at Stanford, upon some of the purely biological problems already accessible to experiment. Also, Professor Schultz, Head of the Department of Bacteriology, was already applying their designs to the study of virus.²⁸ In the annexed letter Taylor stated:

"The air driven ultracentrifuge set up in 1930 is clearly a most extraordinary device. Its uniqueness lies in its simplicity. One's first impression, therefore, of its possibilities in many fields of science is at once striking and unmistakable. During the time that it has been in operation here at Stanford many observers have expressed this opinion and these who have made preliminary tests with it agree that no one can predict the limits of accomplishments on numerous physical, chemical and biological problems particularly with the improvements in its design that are already made. A goodly share of this development ought to be contributed here at Stanford owing to the number and qualifications of workers with fundamental problems to which this method is definitely applicable.

(...) numerous biological problems, old and new, can be attacked with a certainty of success never before realizable by means of this ultracentrifuge, whose speed of rotation is variable from that countable up to and quite beyond the limits of endurance of living cells and attained with so great acceleration."²⁹

In his next letter McBain specified that he needed \$ 600 for an interferometer and \$ 1800 to secure the services of Laura Krejci who had completed two years of post-doctorate work with Svedberg in 1931-33.³⁰ This grant was awarded to him.³¹ The preceding fall McBain had advised Krejci to apply for a Fellowship in the American Association for University Women. He recommended that she would submit as a subject likely to command attention, 'the use of the air-driven ultracentrifuge in the determination of molecular weights', especially in view of her experience.³² She immediately sent a copy of this letter to Svedberg, remarking 'Nothing could have surprised me more! I have written Dr. McBain that I am applying for the fellowship, but that I plan to use it not to go to Stanford but to return to Upsala.'³³ Two weeks later she sent another letter to Svedberg, telling that in the meantime she had received two letters from McBain. From one of them she quoted:

"I know so very little about proteins and I am not seriously interested in them but I simply have to do a few successful studies with them to demonstrate the possibilities in this direction. You would be simply invaluable for your knowledge of how proteins are prepared and handled. My own interest still lies with such things as HgCl₂, KCl and CdI₂ etc."³⁴

Krejci continued writing Svedberg that she didn't like to go to McBain at all. The idea that his plans would work out before she had news about the possibility of going to Upsala gave her some 'sickening moments'. However, because of the

poor job situation, especially for women, she felt that she could not reject an offer from McBain, if it would come.³⁵ Svedberg answered that he had not much faith in McBain's spinning top proposition, especially since Nichols and Kraemer had tried it some years before and found it impracticable (see Chapter 6). Also for the study of such low-molecular inorganic compounds as HgCl_2 Svedberg argued that their machinery was quite appropriate as was shown by shortly before by measurements by Pedersen.³⁶ April 1934 Krejci wrote Svedberg that she would not get a fellowship to go to Sweden and that McBain had received a grant for his project so she would be going to Stanford soon.³⁷ Although Svedberg was skeptical about McBain's spinning top, he remained interested in possible progress. July 1934 he wrote Krejci:

"If there is any information concerning the progress of the spinning top ultracentrifuge which you can give without being disloyal to Prof. McBain I should like to have it. What I am interested in is especially what centrifugal field is attained at a certain distance from the centre of rotation and in what height of column of solution. These data: Speed, Height of column of solution, Distance of centre of column of solution from centre of rotation constitute the nucleus of the problem. (and of course freedom from convection.)"³⁸

The Rockefeller Foundation grant to McBain was used for two 'fundamental projects', viz. the 'Structure of Surfaces' for which used the grant to buy an interferometer, and the development of the spinning top. As to the latter he developed the apparatus along three different lines which he described in a progress report to the Foundation:

a) Ultracentrifuges for gelatinic or gelatinated systems. This project was approaching complete success. Many of these systems could never be studied in Svedberg's ultracentrifuges because many were not transparent and many were more or less complex mixtures.

b) Ultracentrifuges of extreme power, in which analysis were made by mechanical removal of the successive layers for chemical, physical chemical or biological analysis, as for example by inoculation of virus. Again, this whole project lay outside the possibilities of the Svedberg ultracentrifuges. This project was not yet successful, although highly promising designs were under construction for further test.

c) Comparatively inexpensive ultracentrifuges, with which results similar to those of Svedberg might be attained and extended. Their chief attention was given to this project for developing a transparent ultracentrifuge in which the distribution and movement was photographed *in situ* whilst running. They had a large number of serious obstacles to overcome, but had met them one by one by simple means and appropriate design. Further progress, however, was greatly delayed for lack of an adequate amount of mechanical assistance, so that designs

drawn up over a year before had not yet been completed. They had developed two different designs which, in their view, promised success. In both, light from a very simple but effective monochromater, either visible or in any part of the ultraviolet, was reflected up through a motionless periscope which reached up inside the spinning rotor and passed the light directly through the sectional cell to the photographic camera. In one scheme, they were confined to ultracentrifugal forces which could be withstood by quartz discs in tension; in the other, there were no mechanical stresses greater than those which had been successfully met in Svedberg's latest ultracentrifuges.³⁹ McBain asked the Rockefeller Foundation to continue his grant for another year which was approved.⁴⁰

Early 1934 Arthur B. Lamb, the editor of the *Journal of the American Chemical Society* wrote Svedberg that McBain and others had submitted a draft article entitled 'The Diffusion of Colloids and Colloidal Electrolytes'. In the paper they raised certain important objections to the deductions from data obtained with the ultracentrifuge. McBain had also asked Krejci to comment upon this paper. His objections concerned the use of the diffusion constant for determining the molecular weight by velocity runs. He himself had developed a theory of 'systematic upset' to explain the gradual decrease in concentration of the liquid at the bottom of the cell.⁴¹ Lamb asked Svedberg if he wished to comment on this article.⁴² Svedberg replied that in recent years they had not used the diffusion constant for determining any molecular weights because the method had appeared to be unreliable. Therefore, McBain's discussion of diffusion measurements in the centrifuge were out of date as Svedberg and his co-workers had already attended to this point in several publications from 1930 and onwards. Furthermore, Svedberg argued, the diffusion constants had never been used by them for the calculation of dissymmetry numbers as McBain seemed to assume. Svedberg concluded:

"As recently pointed out (...) it is desirable to use rotors permitting of the study of a column of solution not less than about 12 mm in height and situated at a distance from the centre of rotation not less than about 65 mm in order to be able to follow the movement of the boundary during a sufficiently long time and at the same time have the uniform impoverishment of the solution due to the inhomogeneity of the centrifugal field and to the sector shape of the cell reduced as much as possible. In view of this fact I do not personally believe that the application of the spinning top principle which can only be used to rotate comparatively small objects will be of much value for the construction of ultracentrifuges meant for sedimentation measurements of high accuracy."⁴³

The article by McBain's et.al. was published in May 1934 under the title 'The Diffusion of Colloids and Colloidal Electrolytes; Egg Albumin; Comparison with the Ultracentrifuge'. They had determined the molecular weight of egg-albumin by letting it diffuse through porous membranes of constant properties. Under 'suitable

conditions' this method would become one of the simplest, quickest and most accurate methods of determining particle size or molecular weight of many materials and substances of biological interest.⁴⁴ His results were in agreement with Svedberg's sedimentation *equilibrium* determinations in the ultracentrifuge, as well as with Sørensen's osmotic value. Furthermore, he pointed out that Svedberg's *diffusion* values obtained for the molecular weight of certain proteins were erroneous. However, they continued, 'in recent years papers from Upsala laboratory have laid no weight upon diffusion experiments in the ultracentrifuge.'⁴⁵ But also in the sedimentation velocity method it was necessary to 'measure, estimate or select' a value for the diffusion coefficient. McBain et.al. made some critical remarks about the way Svedberg and Nichols had dealt with this problem.⁴⁶ They concluded stating that these considerations about the role of diffusion in ultracentrifuge experiments were 'of general interest now that the ultracentrifuge developed from the spinning top of Henriot and Huguenard promises to become available in most laboratories.'⁴⁷

The Periscope Ultracentrifuge

In 1935 McBain for the first time published some articles in which he described his ultracentrifuges. In April 1935 he wrote, together with Carroll M. O'Sullivan, S.J., a short note in the *Journal of the American Chemical Society* entitled 'Development of an Air-Driven Ultracentrifuge'. O'Sullivan had taken his Ph.D. in Physical Chemistry with McBain the year before, was a trained mechanic, a fairly good engineer and 'had at least one good idea a week'.⁴⁸ In the article they wrote:

"Up to last summer Svedberg alone had produced convectionless centrifuges whose contents could be submitted to optical observation while in motion. In 1931 we undertook at Stanford the task of developing the air-driven spinning top of Henriot and Huguenard (...) as a Svedberg ultracentrifuge, of equal power and possibilities but at an expense so low as to make it fairly generally available. (...)

We envisage four different fields for the air-driven ultracentrifuge. First, that of Svedberg above, applicable to all molecules. Second, immobilized systems in the hollow spinning top perfected by Henriot and Huguenard (...). Third, sedimentation of the Bechold type in the hollow top. This is presumably the kind of sedimentation we have observed with haemoglobin, methylene blue, etc., during the past few years. Fourth, convectionless sedimentation in a mechanically immobilized liquid of any kind (including for example virus, phage or sucrose)".⁴⁹

They had made various designs, two of which were mentioned. They mentioned that 'a fortunate accident' enabled them to observe the sedimentation velocity of a boundary in aqueous solution of mercuric chloride. The sedimentation constant

measured was: $s = 0.891 \times 10^{-13}$ cm/sec/dyne; theoretically it should be: $s = 0.890 \times 10^{-13}$. Included in the article was a photograph of the sedimentation of the respiratory protein of the blood of the earthworm taken at 2020 r.p.s. and 22.5°. The sedimentation constant was: $s = 72 \times 10^{-13}$. The photo showed all four characteristic features of such measurements'. They also mentioned that an 'elegant alternative solution' was the vacuum ultracentrifuge Beams and Pickels had communicated to *Science* shortly before.⁵⁰

In December 1935, McBain and O'Sullivan gave a comprehensive description of these ultracentrifuges in the *Journal of the American Chemical Society*. In the introduction to the article they wrote:

"An ultracentrifuge is any centrifuge of low or high power in which convection does not occur, and in which it is possible to measure any redistribution of the contents.⁵¹ Up to last year, Svedberg alone had developed such convectionless ultracentrifuges. Further, the contents could be submitted to optical observation while in motion. Svedberg and his collaborators have extended their application from the largest respiratory proteins down to the smallest molecules in aqueous solution. To observe sedimentation equilibrium with the former, a very low power is obligatory since sedimentation outward must be exactly balanced by diffusion inward. For sedimentation equilibrium of ordinary molecules, powers ranging from 100,000 to 1,000,000 times gravity are essential. Still higher powers will be required for observing their sedimentation velocity.⁵²

The remarkable results obtained at the Upsala laboratories in the last few years have made abundantly evident the important place the ultracentrifuge now occupies in chemical research. Unfortunately, the enormous cost of these elaborate high-powered machines has, up to now, necessarily confined them to one laboratory. The urgent need of a far less expensive type of ultracentrifuge, which would yet completely duplicate the achievements of those of Svedberg, impelled us to attempt during the past four years the task of developing the air-driven spinning top of Henriot and Huguenard as a quantitative ultracentrifuge. One of us has elsewhere called attention to the almost unlimited possibilities in applying their original top to the study of systems which are inherently convectionless, such as jellies, curds and liquid crystals.

The essential features of the air-driven spinning top itself have already been sufficiently described in the literature.⁵³ The modifications that we have introduced in order to convert it into an ultracentrifuge and the auxiliary apparatus that we have used in the problem can all be discussed under seven heads: Stability, Speed, Transparent Rotor and Stator, Cell, Temperature Control, Light Source and Optical System.⁵⁴

They developed two types of transparent rotors. Each consisted of two parts, the upper, cylindrical part, containing the cell for the liquid, and the lower, conical part which was the air-turbine proper. In both types the lower part was truncated and hollow and had a 13-mm threaded hole through the truncated bottom. When the rotor was running, a stationary periscope projected up through the hole into the hollow rotating cone (figure 4.1, left). The head of the periscope was a single quartz prism whose cross section at right angles to the light beam was a square 4 mm on a side, and whose cross section parallel to the light beam was a 45° rhomboid with an over-all length of 13.5 mm. The distance from the

centre of the rotor to the average radius of the liquid of the column in the cell was 9.5 mm. The purpose of the prism was to offset the lightbeam passing through the cell at this point to the centre of the rotor. The head of the periscope had a minimum clearance of 2 mm inside the hollow cone of the rotor. The presence or absence of the periscope had a very minute effect on the speed and temperature of the rotor, provided the under side of the upper half of the rotor was smooth. This was insured by inserting a disk of celluloid between the halves or a disk of cellophane when light of a wavelength below $3000 \text{ \AA}$ was used.⁵⁵

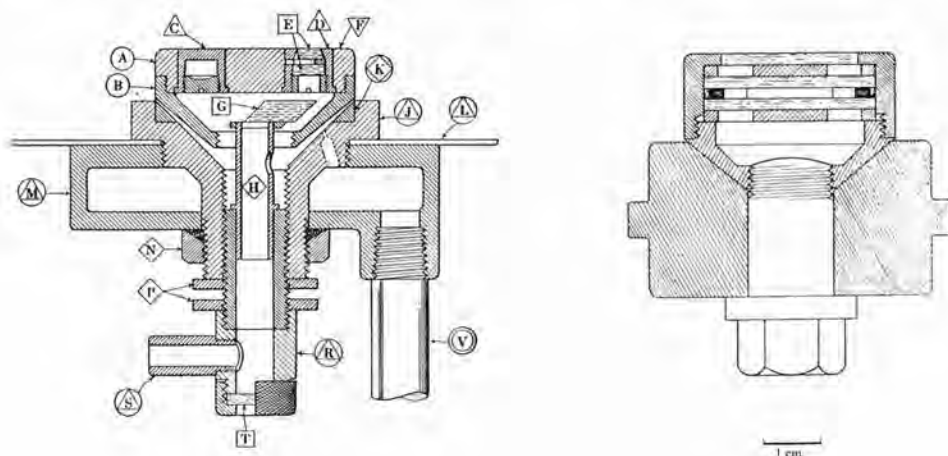


Figure 4.1

Rotors for periscope ultracentrifuge. A, cell-holder; B, rotor cone; C, dummy cell; D, cell; E, quartz disks; F, hard rubber separator; G, periscope prism; H, periscope tube; J, stator; K, bronze insert; L, disk to which baffle strips are fastened; M, manifold; N, packing nut; P, lock-nuts; R, holder for central air inlet and window; S, connection to central air inlet; T, window; V, high pressure supply tube. The symbols indicate the materials of construction. The rotor at the right is shown with the jig which was used to hold the cone of the rotor while the rotor was being assembled. (McBain and O'Sullivan, 1935b, p.2633 and 2635).

In the first type of transparent rotor the cell was composed of two quartz disks 30 mm in diameter and 2 mm thick, fitting into a steel shell which could be screwed on the lower part of the rotor (figure 4.1, right). Giving the disks a special polishing treatment greatly increased their strength. This facilitated an additional increase in the speed at which they broke of nearly 50%, or an increase in the acceleration of nearly 125%. Thirty-millimetre crystalline quartz disks so polished and supported against hydrostatic pressure by the two steel disks could spin 3000 r.p.s. without breaking giving a maximum field of 540,000 times gravity. Despite that fact, however, this type of cell could not be safely used above 1500 r.p.s. No matter how carefully the quartz disks were handled, it seemed impossible to avoid scratching them slightly, thus lowering their breaking speed enormously.

Disks that had made many runs at 2500 r.p.s. would unexpectedly burst at 1700 r.p.s. Disk failures were costly because they generally caused the loss of the periscope also. Even at 1500 r.p.s. the factor of safety was low. The second type of cell was quoted to be somewhat similar to the cells in Svedberg's latest oil-turbine ultracentrifuges (figure 4.1, left, and figure 4.3). The upper half of the rotor was a solid steel cylinder 37 mm in diameter and 8.2 mm high. Near the bottom it was reduced in diameter and threaded to screw into the rotor cone. The steel cylinder had two vertical holes on a diameter, each 8.6 mm in diameter and 10 mm from its centre to the centre of the cylinder, which held the cell and a dummy cell for counter balance. The 6° radial slot which formed the cell proper was 4 mm long. The cell was quickly taken apart for cleaning and reassembled. No trouble had ever been experienced from leaking, or from breaking of the quartz disk. This rotor, being lower than the previous type, ran 17% faster.⁵⁶

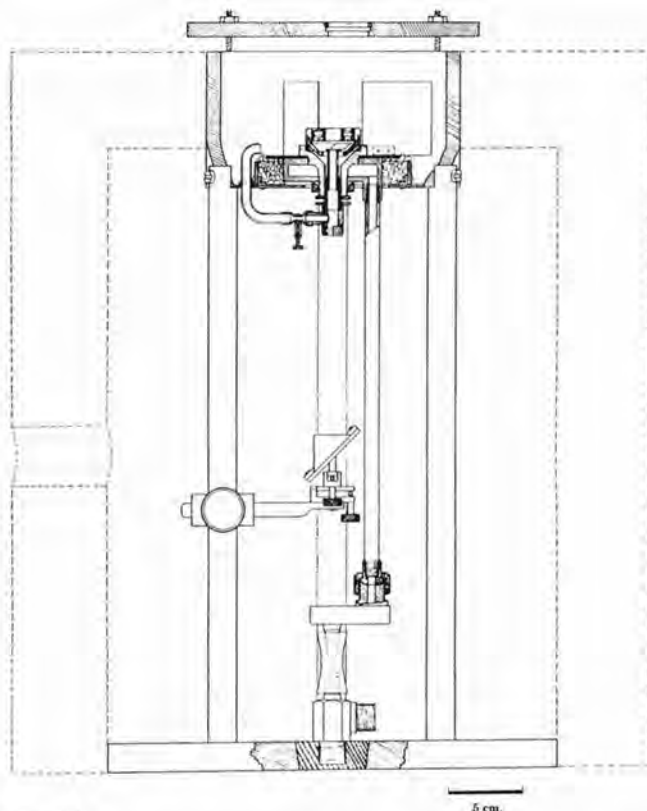


Figure 4.2

Periscope ultracentrifuge. The dashed lines indicate the position of the wool-filled insulating cover. (McBain and O'Sullivan, 1935b, p.2634).

Figure 4.2 gives a complete sketch of McBain's periscope ultracentrifuge. Various thermocouples were used to determine approximately the temperature of the two walls of the cell. If the air used to spin the rotor was allowed to expand from room temperature, it was found that when the rotor was being run at 100 lb. pressure the air in contact with the top of the rotor was about five degrees warmer than the air inside the hollow cone, and about seven degrees warmer than the stator. Such a temperature gradient between the two walls would cause convection currents and make sedimentation impossible. They eliminated the temperature gradient in the following way. To protect the top of the rotor from the slowly descending current of room air caused by the expanding outflow, the guard was covered with an asbestos lined metal plate having a quartz window directly over the part of the rotor to be photographed (figures 4.2 and 4.4). The plate rested on three screws which raised it about 10 mm above the top edge of the guard. Less clearance caused instability in the rotor. The high pressure supply was thermally insulated from the stand and guard at the only point where they came in contact, viz., at the base, by a large bakelite bushing. The stand and guard were further insulated from the room air by a thick hood filled with lamb's wool which slipped over the whole assembly, its top being flush with the top edge of the guard. The driving air was heated by being passed through a large coil of 9.5 mm copper tubing immersed in a water thermostat. By varying the room temperature, or the temperature of the water thermostat, or the driving pressure (and therefore the speed), it was possible to bring the temperatures above and below the cell to exact equality and to hold them thus indefinitely with a variation of less than 0.1° . With the room at 26° , the driving pressure at 100 lb./sq.in. they found that the water thermostat should be at 27° . About 70 watts were required to maintain the driving air at this temperature. From the standpoint of uniformity of temperature, the second type of rotor described above had two decided advantages over the first type. (1) In the second type, the cell was as entirely surrounded by metal as the exigencies of transparency would permit. This tended to short-circuit any temperature gradient existing between the top and bottom of the cell. (2) When the disk of celluloid or cellophane was inserted between the halves of the rotor, a dead air space 3 mm high and 4 mm in diameter was formed immediately below the lower quartz disk. This helped to insulate the quartz from temperature fluctuations in the cone of the rotor.⁵⁷

One of the problems they encountered was that at high speeds the vacuum under the rotor became great enough to overcome the supporting effect of the outflowing air and caused the rotor momentarily to touch the stator. This could be solved by simply admitting a little atmospheric air into the space between the rotor and the stator through a valve connected to the apex of the cone of the stator. The method of adjustment was to open the valve rather too much at first,

then, when the rotor had attained the desired speed, to close it slowly until the vibration just begun to be heard (or felt in the stator with the hand), at which point the valve was opened again very slightly. This adjustable arrangement was preferable to the uncontrolled opening adopted by Beams and his co-workers because the admission of more air than was actually needed slightly reduced the speed and noticeably increased the horizontal wobble.⁵⁸ Horizontal wobble was the name they had given to a form of instability in which, while the axis of rotation remained perfectly vertical, the whole rotor moved horizontally in spasmodic jerks. The phenomenon was not periodic and was ascribed to two causes. The first resulted from the fact that the rotor rotated not on its centre of figure but on its centre of gravity. Since these centers did not, in general, coincide, the periphery of the rotor necessarily revolved eccentrically. If the stator was rigidly mounted, this eccentricity became cumulative, causing the rotor finally to touch the stator and leap out. If the stator was flexibly mounted it was able to follow the eccentric running of the rotor and the danger of the rotor's jumping out was eliminated. However, the customary slightly flexible stator mounting still left another horizontal wobble of smaller amplitude and higher frequency. They found that greatly increasing the flexibility of the stator mounting and reducing the mass of the stator and manifold as much as possible reduced the wobble to about 0.02 or 0.04 mm (as measured with a low power microscope) a few times a second. The second cause of the horizontal wobble was turbulence in the outflowing air, which became quite noticeable when higher pressures and greater volumes of air were used. The turbulence could be eliminated by mounting on the stator three vertical, radial metal strips which they called the 'baffle strips'.⁵⁹

As to speed, contrary to their first expectations, they could not achieve unlimited rotational speed with an air-driven spinning top of given diameter by indefinitely increasing the air pressure, because the velocity of air flowing through an orifice quickly approached a limiting value. The pressure between the stator and the rotor could be reduced and the velocity of the air through the air-ports correspondingly increased by increasing the ratio between the angle of the stator cone and the angle of the rotor cone. However, this resulted in an increase in vertical vibration which could only be eliminated by permitting more air to enter through the central air inlet valve, which in turn increased horizontal wobble. They found the best values for these angles to be 100 to 102° for the rotor cone and 90° for the stator cone. Since for a given pressure the velocity of the air through the air-ports was constant, it followed that the angular velocity of different rotors would be in inverse proportion to their diameters. For ease of experimentation they chose the 'comparatively large' diameter of 37 mm.⁶⁰ A final factor influencing the speed of the rotors was their skin resistance. To reduce this to a minimum, the rotors should be made as low as possible, be free from

anything like eccentric open holes or radial slots and should be highly polished. With a 37 mm rotor made of high tensile strength alloy steel, which could stand higher gravitational forces than rotors made of Duralumin⁶¹ they reached 3,000 r.p.s. Because for any given set of experimental conditions the speed of the rotor was a function only of the air pressure, the attainment of the speed constancy so important in an ultracentrifuge was merely a matter of achieving constant air pressure. With their arrangements the speed variation was generally much less than 0.1%.⁶¹ Photographs of the arrangement are shown in figures 4.3 - 4.5.



Figure 4.3

Rotor for periscope ultracentrifuge. From left to right the parts are: the rotor cone, the cell-holder, the shell of the cell, the upper (conical) quartz window, the hard rubber separator with the sectorial slot, the lower (cylindrical) quartz window, the brass washer and the hollow screw. (McBain and O'Sullivan, 1935b, p.2639).



Figure 4.5

Stator and manifold of periscope ultracentrifuge. (McBain and O'Sullivan, 1935b, p.2637).



Figure 4.4

Periscope ultracentrifuge and optical system before the wool-filled cover and the thermostat for the driving air had been adopted. (McBain and O'Sullivan, 1935b, p.2638).

Without heating the air or attempting in any way to control the 'natural' temperature gradient existing in the rotor, the second type of rotor sedimented at every trial such heavy molecules as the respiratory protein of the earthworm. With the first crude air heating arrangement tried (manually adjusted electric heater inside the air supply tubing) which enabled them to keep the temperatures above and below the cell at the same value to within $\pm 0.3^\circ$, the same rotor easily sedimented molecules as the hemp seed protein edestin (molecular weight about 208,000). With the driving air arbitrarily thermostated to within $\pm 0.02^\circ$ and the room temperature controlled, the same rotor would sometimes sediment molecules as small as purified egg albumin (molecular weight about 35,000). More remained to be done before the instrument would be uniformly reliable for the smallest molecules. The authors were confident that once the exact relations between the temperatures recorded by the cell walls had been determined, the problem would have been solved completely, for it was comparatively easy to maintain any desired temperature gradient between the air above and below the cell. Devices were contemplated which promised to make the temperature of the air above, within and below the rotor, wholly independent of the room temperature.⁶²

May 1935 McBain published a short note in *Nature* where he stated:

"Since no measurements have so far been published, from any country, on colloidal systems using the air-driven spinning top of Henriot and Huguenard, it is evident that the great importance of this remarkable tool has escaped the attention of most laboratories. This is especially surprising in view of the fact that any good mechanic can make the necessary simple equipment (a stator and a hollow rotor) for a cost of about two or three pounds, and that for most purposes no special precautions need be taken as to constancy of temperature or control of pressure. With much less than the pressure of air available in an ordinary garage, the top may spin at several thousand revolutions per second, producing centrifugal forces of the order of 10^5 - 10^6 times gravity."⁶³

In this article they discussed apparatuses which did *not* include photographic registration of the sedimentation. With respect to that scheme they referred to their periscope ultracentrifuge and Beams' vacuum ultracentrifuge which constituted a 'beautifully simple and elegant means of eliminating the most serious difficulties of ultra-centrifuge design'.⁶⁴ In the much simpler scheme they now described convection was avoided because 'convection does not occur in an immobilised system'. The sedimentation could be observed by eye, by callipers, by a scraping pipette, or by pouring off supernatant liquid and weighing. Evaporation was minimised by a solid cover or by a thin piece of cellophane which could be perforated by a hot wire without disturbing the spinning top. They found that the best method of preventing interaction between steel tops and their contents was to bake on several thin coats of bakelite lacquer. This scheme might be applied to a number of investigations, such as:

(a) Measurement of rate of sedimentation of jellies and curds. Examples studied: agar, silicic acid, and sodium palmitate in water; soap jellies in non-aqueous solvents.

(b) Purification of gelating colloids. Examples studied: agar, where half of the agar would not sediment with the rest of the agar jelly.

(c) Measurement of swelling pressure of jellies. When the jelly refused to sediment further, it was in equilibrium with its swelling pressure.

(d) Replacement of ultra-filtration. Supernatant liquid or mother liquor might be removed from a sedimenting system, avoiding all effects of pore-size or adsorption.

(e) Measurement of bound or combined water in colloidal or biological systems using a reference substance separated as in (d) for analysis.

(f) Bound water, by increasing the density through addition of indifferent substances until sedimentation just ceased to occur. Then the reciprocal of the density of the system would be identical with the partial specific volume of the non-sedimenting structure. The composition corresponding to this partial specific volume might be read from a table or graph of densities against composition. The simplest graph to read was that for the jelly itself, as for example agar in pure water.

(g) Determination of sorption. Example: methylene blue, which was strongly adsorbed by most materials, using method (d).

(h) Observation of sedimentation equilibrium within any immobilised system.

They concluded stating that all chemical, biological, metallographic and applied science laboratories might well employ one or more of these simple devices, which had already proven their usefulness in many physical laboratories.⁶⁵

Early 1936 McBain and R.F. Stuewer, one of his colleagues at Stanford, published a similar article in the *Kolloid Zeitschrift*. They stated that the simple hollow spinning top could be one of the most important quantitative tools for the colloid chemist. The fact that any good machinist could make them for 15-20 dollars and that for most applications no special precautions for temperature control were necessary made these apparatuses widely applicable. With a simple garage compressor forces of more than a million g would be possible. They indicated that these machines would probably soon be manufactured and sold by the Sharples Specialty Company in Philadelphia.⁶⁶ Figure 4.6 shows these simple ultracentrifuges. The rotor used most had a 2 cm outer diameter within which a circular hollow room was machined about 1 mm below its surface and 3 mm deep. The outer radius was 0.805 cm and the radius of the top opening was 0.476 cm. The rotor could hold $0.397 \pm 0.001 \text{ cm}^3$ of liquid.⁶⁷ The scheme would be most applicable to the study of systems which contained gellies or other materials with a high resistance against motion. In such systems, which he called immobile or immobilized, diffusion and convection would hardly play a role.⁶⁸ It could also be

used to determine the amount of 'bound water' in a solution. This related to a problem, 'fundamental in physical chemistry and even more in biology', as to the amount of solvent which might be considered as existing as such in a solution, as distinguished from the solvent which was chemically or otherwise combined with the dissolved substance. Most methods used until then relied either upon an interpretation of an observed deviation from ideal behaviour or upon the assumption that a particular reference substance did not dissolve in, or in any way react with, the dissolved substance or its water of hydration. McBain described how his simple ultracentrifuge could be used to give a more reliable determination of the amount of bound water in such solutions.⁶⁹

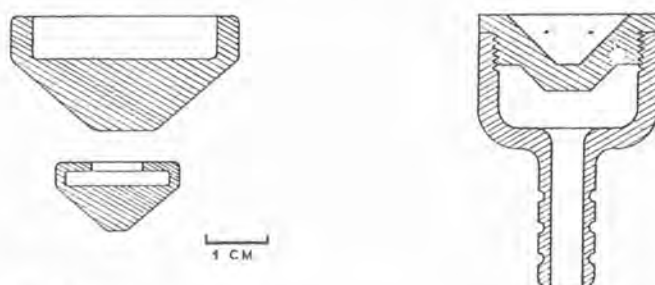


Figure 4.6

One-piece spinning top ultracentrifuge (McBain and Stuewer, 1936, p.14).

Relation with the Rockefeller Foundation

The Rockefeller Foundation was much interested in McBain's work. The Foundation had formulated a new science policy in the late 1920s which implied that for further progress in the 'life sciences' it seemed worthwhile to apply the experimental procedures which had been so successful in the physical sciences (see Chapter 1). For this reason they had supported Svedberg with large sums of money. However, the problem was that Svedberg's apparatus, though in the scientific sense very successful, was too complicated and expensive for almost any laboratory wishing to work with it. Although Svedberg was most willing to let other investigators use his apparatus in Upsala this provided only a solution for a limited number of researchers for a limited period of time - artefacts should come to the investigator, not the other way around. For the Rockefeller Foundation, the McBain approach might provide an attractive alternative. Early 1935 Warren Weaver from the Foundation wrote McBain that he had been interested in developing 'these enormously simpler and less expensive mechanisms' to the point where they would be an effective substitute for Svedberg's 'elaborate machines'. He expressed

some doubt, however, as to whether this would be possible because he supposed that the one perhaps essential argument for Svedberg's procedure would turn out to be the necessity (or at least the desirability) that the acceleration field would be reasonably uniform over the length of the cell. In order to obtain this uniformity, one presumably would have to locate the cell a considerable distance away from the axis of rotation. This geometrical demand would then force one to large rotors and hence essentially to Svedberg's design.⁷⁰

McBain replied including a photograph of the sedimentation of a protein and giving some technical details: they could read the plate accurately to 0.001 mm; they used 121,200 r.p.m., giving 150,000 g at the periphery (10.889 mm from the axis). He argued that this photograph showed all four relevant characteristics of the Svedberg recordings. Moreover, their apparatus was more precise than Svedberg's because the variation of the forces along the length of the cell was only 14% instead of Svedberg's usual 20%. The reason for this was that they could use a proportionally smaller size of cell because they used a very accurate comparator and microphotometer which read 1 mm to an accuracy 0.1%. McBain expected that still smaller rotors should ultimately be used to exploit the fullest possibilities of the ultracentrifuge.⁷¹ Furthermore, he wrote that he intended to extend his investigations to the centrifugation of living protoplasm. No measurement of this had been attempted before and he indicated that this could not be done with Svedberg's machines because they required 40 to 45 minutes to start and half an hour to stop, while the protoplasm would be killed in less than 10 minutes. Their own rotors could be brought to full speed in a fraction of a minute. This would open up a wholly new field of investigation.⁷²

April 1935 McBain was visited by Frank Blair Hanson from the Rockefeller Foundation and showed him his small ultracentrifuges which could be carried in a pocket. Hanson considered them as an adaptation of the Beams 'air pocket centrifuge'. The simplest McBain model cost \$ 20 to construct and the periscope model would cost about \$ 200. McBain claimed that these two ultracentrifuges would do practically anything that the Svedberg centrifuge would do.⁷³ Half a year later, when he was visited again by one of the Foundation's officers, McBain repeated this claim adding that they were also performing studies on the sedimentation of living protoplasm which would be impossible with Svedberg's apparatus.⁷⁴ So, McBain's claim was not only that Svedberg's work was being 'duplicated' but, moreover, that his ultracentrifuges facilitated investigations which were impossible with Svedberg's. He claimed that his ultracentrifuges was more 'powerful' in two respects - in the sense that they were better as a research tool in science and in the sense that they were cheaper and thus better reachable by more investigators.

Early 1936 McBain submitted another request to the Rockefeller Foundation for

a \$ 2400 grant, including a report of the work done with previous grants and a list of publications. He stated that the Svedberg ultracentrifuge cost \$ 50,000-75,000 while his cost 1% of that while being capable of doing more. He mentioned that they had been developing the air-driven top not merely to duplicate such measurements as Svedberg's, but also to extend them in many directions to which the Svedberg machines were wholly inapplicable, the most interesting of which was the sedimentation of living protoplasm which had never been attempted before. Their determinations could also be made much faster than Svedberg's because it took only in the order of seconds to bring their rotors to full speed while they could be stopped equally rapidly. They had published photographs of the measurement of sedimentation velocity of the respiratory protein of the earthworm which were exactly similar to Svedberg's. These experiments took 3 minutes altogether while with the Svedberg ultracentrifuge the actual experimentation could not begin until after half an hour, when the rotor would have come to full speed. This work was performed in cooperation with C.V. Taylor, head of the school of Biological Sciences at Stanford. McBain divided his ultracentrifuges in three main categories, viz:

a) A 'Transparent convectionless ultracentrifuge' in which the distribution and movement is photographed *in situ* whilst running, exactly as in a Svedberg ultracentrifuge.

b) An 'Ultracentrifuge for gelatinous or gelatinised systems' which only cost about \$ 25 to make.

c) 'Similarly inexpensive opaque ultracentrifuges of extreme power' in which the solution, which might be any fluid (colloid, sugar or salt solution, or a culture containing virus or bacteriophage), was immobilized by mechanical baffles or in certain special cases by addition of a jelly. Analysis were made while the top was running by mechanical removal of successive layers for chemical, physico-chemical, or biological analysis, as for example by inoculation of virus. Again, McBain pointed out, this whole project lay outside the possibilities of the Svedberg ultracentrifuges. This project was still in development but he expected 'ultimate complete success'.⁷⁵ McBain stated that the grant requested would be sufficient 'to ensure completion of the work undertaken, together with all current developments'.⁷⁶ The grant was awarded⁷⁷ but in an accompanying letter Hansen stated that it 'is the third one to be made for this purpose (which) will suffice to enable Professor McBain to complete this project and that Professor McBain does not expect to request further funds for this purpose'.⁷⁸

April 1936 McBain was visited by Warren Weaver who wrote in his diary:

"On his surface chemistry work McB. reports extraordinary progress and luck in last two or three years. Five experimental methods for study of surface films are

in use or process of development (...). McB. has been working chiefly on the development and perfection of these techniques rather than on problems. (...)

In his ultracentrifuge work McB. has developed several new dodges. He puts ten cent store glass beads in the centrifuge held around the outer walls of the cell. This 'immobilizes 80% of the liquid'. McB. never clearly explains the mechanism or usefulness of this procedure. It may be that the small pore size between the beads permits diffusion under the large centrifugal forces, but holds this diffused material in place as the speed is slowed down so that samples can be obtained of the inside layer of liquid. When WW asks if these beads assist in diminishing the effects of temperature connections McB. says yes, but gives no clear explanation. McB. also has a top with a sump into which heavy material can be inserted during rotation so as to bring the lighter material being sedimented up where it can be sampled. He works at about 250,000 g. His rotors are 2 cm in diameter and he says larger ones present greater temperature control problems, cannot give such good speeds, and are moreover quite unnecessary because of the accuracy of the work one can do with the small ones. He says he has 14% radial force gradient as compared with 20% in the case of Svedberg. McB. admits that his one accurate result on mercuric chloride was due to a fortuitously sharp (temp. convection caused?) boundary; and that he cannot repeat the result. He says he has made measurements of temperature conditions in his cells by attaching very small bits of crystals of known melting point and having fixed thermocouples very near. Then when the crystal melts he reads the thermocouple and there after interprets this reading as indicating a cell temperature under that spot equal to the melting point of the crystal. Then he compensates by streams of cooling air directed on the rotor, and claims to have equalized temperatures throughout the rotor to one hundredth of one degree!

McB. has not experimented at all with Beams' later devices, saying they had enough good leads of their own. There is something just a touch queer about this whole situation. McB. has some of the impressive front and the suave, unctuous, over-politeness of H.M. Evans."⁷⁹

Early 1936 a Svedberg ultracentrifuge was installed at the DuPont laboratory in Wilmington Delaware which got a considerable attention in the press (see Chapter 6). Referring to these press reports McBain wrote Warren Weaver that their little instrument was at least 99% as good and capable of doing the same work although they were still simplifying and improving it. Since installing simple thermostats around their air lines, they had had no difficulty in sedimenting proteins of low molecular weight. McBain also reported that about a year before he had offered Stanley, after his crystallization of the tobacco mosaic virus, to investigate this virus in his ultracentrifuge. Stanley wrote back saying he would be glad to send any specimen required, but added that Svedberg had also been very interested. McBain therefore inquired with Stanley whether material had been sent to Svedberg, and finding that it had, agreed that 'it was only fair' that Svedberg should have a reasonable time for his study of this subject. Some time later Stanley wrote McBain that Svedberg had stated that he had run a preliminary experiment, but that considerable time would yet elapse before Svedberg could find time for complete study and report. Next, Stanley sent McBain a small sample to satisfy his 'private curiosity'. Running it in the ultracentrifuge showed Stanley's virus to be monodisperse, and of the high molecular weight indicated. McBain

concluded his letter to Weaver stating that many of these biological preparations could not be kept even for a few days without deterioration, and it would be of real value to have an instrument within reach which would measure them while they were fresh.⁸⁰

September 1936 McBain visited Warren Weaver on a trip to the east coast. He thanked the Rockefeller Foundation for its assistance and enumerated the list of scientific results obtained. According to Weaver McBain was a little like H.M. Evans in several respects, - in the syrupy nature of his respect for Foundation officers, in the confidence and pride with which he described the manifold results of his own activity, and perhaps also in the fact that, in spite of these unpleasant characteristics, McBain might well have an element of genius in his make-up.⁸¹ McBain had met Svedberg at a meeting in Pittsburgh and had subsequently seen the ultracentrifuge equipment at the Rockefeller Institute which was developed by Edward G. Pickels for Johannes Bauer who used it for the study of viruses (see Chapter 5). McBain explained to Weaver that he had a high esteem of Svedberg, saying that, if a Nobel prize were at his disposal, he would unhesitatingly present it to Svedberg for his development of the ultracentrifuge and for the magnificent researches he has carried out with it. He also spoke most enthusiastically of Bauer's equipment, and, according to Weaver, almost modestly about his own air-driven centrifuge. He indicated that his own device was far less powerful, but thought that it was still true that a variety of interesting and important things could be done with his 'simple and cheap equipment'.⁸² McBain raised the point of future support for ultracentrifuge work and also for surface chemistry. Weaver pointed out to him that the grant for the current year, being the third successive grant-in-aid, had to be viewed as a definite termination of that type of assistance. He also told McBain that he was 'at liberty' to approach the Foundation, perhaps approximately in January 1937, with a request for assistance over a period of a few years. Weaver emphasized that he could give no assurance whatsoever concerning such a request, since the decision would 'naturally have to depend upon the nature of the request and upon the competition with other opportunities which it would then meet.'⁸³

'The World' turning against McBain

The Rockefeller Foundation officers also discussed McBain's claims with Svedberg. April 1935 Weaver raised three points that seemed to him would be important in an evaluation of an ultracentrifuge: the first relative to the height of column and the homogeneity of the acceleration field; the second relative to the difficulty of fixing accurately a point in the cell relative to the axis of rotation of

a freely spinning top; and the third relative to the question of temperature control. Svedberg agreed that these were the three essential points and that the first was by all means most important, and the third perhaps next in importance. He expected that the second difficulty might very possibly be met in various ways. The first difficulty was primarily a question of dynamics and geometry. The height of column should be long enough so that the sedimentation time measured was large enough for accurate time measurements. It should also be long enough so that blurring of the sharp boundary due to diffusion would not interfere with the measurement, the serious blurring occurring effectively from reflection from the bottom of the cell. Svedberg mentioned that he had experimented with small rotors, in order to determine what their possibilities were. He had constructed rotors with a diameter of 104 mm which permitted a cell of 8 mm height (see Chapter 2). However, with this rotor he had not been able to obtain satisfactorily accurate results, due to the smallness of size. He agreed that it would be very easy to obtain a larger degree of homogeneity in the acceleration field by using a shorter cell, but pointed out that it was not fair to discuss the situation simply in terms of the degree of homogeneity. His experience had convinced him that the column should be not less than 12 mm in height and that the variation in the acceleration should not be more than 20%. He admitted true that McBain had a variation of 14%, but he accomplished this by choosing a cell height so small that Svedberg was convinced that he could not do accurate work except for exceedingly heavy proteins. Svedberg pointed out that McBain's result on earthworm blood was not convincing, since substances of molecular weight 3,000,000 could be handled with almost any kind of centrifuge. In the case of McBain's result on mercuric chloride Svedberg told that he had information from Laura Krejci that this relatively light substance uniformly gave in McBain's cells too diffuse a boundary for measurement; but that a fortuitous thermo-convection, which occurred only once, happened to produce a sharp boundary whose fall they succeeded in measuring. Svedberg also reported that Krejci got into some difficulties with McBain and suddenly left him, carrying her case directly to the President of Stanford University.

From Svedberg's words Weaver concluded that he respected Beams' work very much. Svedberg thought that the development of Beams' vacuum ultracentrifuge was interesting and should be followed up, particularly since it appeared to meet the problem of temperature control. It was also clear to Weaver that Svedberg did not respect McBain at all, who he clearly thought was using questionable methods in an attempt to discredit the Svedberg technique. He also pointed out that the matter of temperature control was exceedingly important and that he did not see how it could be handled in the case of an air-driven top, except possibly by the Beams method. As an evidence of how important it was to exclude air, he mentioned that recently a very small air leak, which increased the pressure only to

200 mm, heated the rotor so much that its expansion damaged the thrust bearings. Svedberg mentioned the various attempts they had made to use other forms of drive, other materials such as light alloys, and totally other designs, but that in each instance they were forced back to the oil-driven turbine.⁸⁴ A year later Weaver discussed once more McBain's work with Svedberg which made Svedberg repeat his objections. According to Weaver Svedberg remained 'disturbed and probably even a little bitter', relative to McBain's claims.⁸⁵

In 1936 McBain wrote an article 'on the size of cells and rotors useful in the ultracentrifuge' of which he also sent a copy to the Rockefeller Foundation. There, McBain wrote:

"Surely in scientific circles it is possible to overtake a canard. An opinion appears to be in current circulation that a radius of rotor of 65 mm and a depth of cell from 10-15 mm, such as was chosen by Svedberg for his work, is excellent, whereas there is some inherent fatal defect if these dimensions are reduced by three- to five-fold. It is evident that the principles involved have not been thought through, since all these magnitudes are gross in comparison with molecular dimensions, and since with suitable equipment they may be observed to a very high degree of accuracy, provided of course that unnecessary extraneous errors are not introduced by unsuitable technique or equipment. In principle the phenomena of sedimentation cannot be so precariously dependent upon an arbitrary choice of numerical dimensions.

Thus, Biscoe, Pickels and Wyckoff in a recent otherwise excellent paper state⁸⁶, 'One such air-driven machine for molecular sedimentation has already been described; it has the disadvantage that it uses much smaller rotors and is accordingly incapable of yielding results of equal accuracy.' Then they proceed to publish in the same paper photographs in which they themselves follow sedimentation velocity down to the bottom of their own cell."⁸⁷

McBain argued that, although in the Svedberg rotor the absolute distance, over which the sedimentation could be observed, was four times greater, this was unimportant when the distances could be read with any desired accuracy. They could determine the distance accurate to 0.001 mm on a total depth of the cell of 3-4 mm. He continued:

"The only other theoretical error to which the authors quoted can have reference is that possibly appreciable progress takes place towards sedimentation equilibrium during the observation of the velocity, so that the latter values are noticeably affected. As regards sedimentation equilibrium, the classical experiments of Nobel Laureate Perrin were measured in hundredths of a millimetre, and hence it was demonstrated once and for all that for sedimentation equilibrium a cell of this height was ample, provided that suitable exact photography and microphotography were available to measure the equilibrium actually set up in such a cell.

The cell of Biscoe, Pickels and Wyckoff is only three times longer than that of McBain and O'Sullivan which they condemn on supposed principle unsupported by any quantitative examination of the well-known theory (Mason and Weaver, 1924 onwards) or even of their own experiments.

In their experiments the error in the lower part of their cell is as a first approximation three times greater than in ours owing to the fact that three times as much material is accumulating at the bottom. Again as a first approximation, their error is once more three times greater because their sedimentation has at least three times as far to travel and therefore three times as long is allowed for the deleterious back or reflex diffusion from the concentrated layer at the bottom of the cell. Together their errors are therefore six to nine times bigger than in our cell which they on a priori grounds dismiss in principle.

Yet even with their greatly magnified error their photographs do not show any abnormality, and they mention no disability in their microphotometer curves. Hence their own evidence does not support their allegation that a cell of their size is fully valid but ours, one-third of the length, is not.

It would have been more scientific, however empirical, if they had filled their cell to the height of ours, plus the distance which their meniscus travels before their or a Svedberg ultracentrifuge attain full speed, and then see if their results were invalidated. It must be remembered that our cells are unique in that measurement actually begins within a fraction of a minute after beginning to spin, because full speed is so rapidly attained, whereas all other existing ultracentrifuges require a large fraction of an hour to arrive at full constant speed.

This error, in so far as it exists, must invariably appear in all measurements with all ultracentrifuges, past, present, and future. Yet it has not been shown in the microphotometer records published by Svedberg from 1927 onwards for the standard proteins.

It is possibly because of the disability in such extremely slow starting, inherent in all Svedberg and Beams type of transparent ultracentrifuges, that Svedberg has run into difficulties in using smaller cells. The upper part of his cells, like those of all workers except ourselves, is wasted because of the slow starting."⁸⁸

McBain summarized:

"It is shown that there is no difference in principle between the dimensions for the ultracentrifuge chosen by Svedberg and others, and ourselves. Any errors introduced must be due to unsuitable manipulation or choice of centrifugal field, and the latter error must be magnified very many fold in all measurements made with cells and rotors of the usual Svedberg size, although even so this has not been apparent in any published work."⁸⁹

Late 1936 John W. Williams and Charles C. Watson, who both worked with Svedberg for some time, published a note in the *Journal of the American Chemical Society* in which they expressed their doubts about McBain and O'Sullivan's claim that they had recorded for the first time the sedimentation velocity of an ordinary molecule (mercuric chloride). They had undertaken an examination of this 'extremely important claim', which was made more striking because of the remarkable agreement between theory and observation (about 0.1%) which was reported by McBain and O'Sullivan. Such an examination, however, was difficult because definite information was lacking on many relevant parameters. But from information given they concluded that McBain-O'Sullivan's sedimentation power could not over have been over 350,000 times gravity. For a molecule of weight and density of mercuric chloride in water at ordinary temperatures, they calculated that in that case the sedimentation rate with such centrifugal force would have

been of the order of 1 mm per hour. Next Williams and Watson stated that with the apparatus described and with the assumption of technique and evaluation of the data according to the methods developed by Svedberg, it was highly improbable that such a rate could be measured with the precision claimed. Also, a serious difficulty was that the back diffusion would so blur the boundary that the distance of travel of the latter in any ordinary interval of time would be hard to estimate. Furthermore, they found it most surprising that the theoretical sedimentation velocity constant for mercuric chloride molecules in aqueous medium was expressed to three significant figures when no temperature was specified. The value of the constant varied considerably with temperature because the viscosity of the solvent was involved. The variation amounted to approximately 2% per degree in aqueous solution at ordinary centrifuge temperatures. They concluded that, since the records of the McBain-O'Sullivan experiment and the calculation for the corresponding theoretical specific sedimentation velocity for mercuric chloride were so incomplete, they were impelled to suggest that a further account of the work be presented before it could be given serious consideration as the first measurement of the sedimentation velocity of an ordinary molecule.⁹⁰

In the same issue of the journal McBain replied that he did not consider that the note by Williams and Watson called for any detailed comment. The two sentences published by himself and O'Sullivan, one sentence in a preliminary communication and the other single sentence in a footnote in a paper of eleven printed pages, still appeared to be ample notice of the physical phenomenon that was observed on 15 November 1934 with the old circular cell whose use was discontinued that year. The cell contained pure water and a crystal of mercuric chloride. Sufficient of the latter dissolved in the lower portion of the cell and then through an accident of convection currents. The absorbing material (HgCl_2) was sedimented downward again with a fairly sharp boundary as shown by the photographs and microphotometer photographs. The sediment moved 0.102 cm in 8400 seconds at 108,600 r.p.m. with an average radius of 1.054 cm, giving an observed sedimentation constant $s = 0.890 \times 10^{-13}$, which, as a 'mere scientific curiosity', agreed with the value predicted.⁹¹ McBain continued that the precise agreement was of course fortuitous and should not have been expressed to three significant figures, as would be obvious to anyone who had any knowledge of an ultracentrifuge. He and O'Sullivan had stated that this result was an accident and that in the ordinary course, where convection would not occur, a higher order of magnitude of centrifugal force than that in 'any existing ultracentrifuge anywhere today' would be required to obtain sedimentation velocities of such small molecules regularly. According to McBain it would be entirely a matter of individual opinion as to whether any significance whatsoever was attached to this photographed and microphotometered observation, and Williams and Watson were convinced on the

basis of their experience that none did. McBain still thought that it did offer an actual 'semi-quantitative measurement'. As regards the last paragraph of the note of Williams and Watson, which was devoted a discussion of the state of development of McBain's ultracentrifuge, McBain argued that their statements were carefully made and stood accordingly as referring to the 'now superseded models' as developed at that time. Appreciable modifications and the 'very simple temperature control' in the later model had resulted in uniform success in sedimenting smaller protein molecules such as carbon monoxide haemoglobin. To McBain, there appeared to be no reason why any sedimentation velocity or equilibrium observable in the Svedberg ultracentrifuges, or the equally good air-driven models developed at the time at the Rockefeller Institute for Medical Research, or the model supplied by the Sharples Specialty Company of Philadelphia should not also be capable of quantitative study in the their transparent ultracentrifuge. All parts of their cell were easily kept at any desired constant measured temperature within 0.02°. Furthermore, all forms of the air-driven ultracentrifuge appeared to be in process of still further rapid improvement.⁹²

Williams informed Warren Weaver that he thought McBain's claims were exaggerated. Furthermore, he argued, McBain's critique of Svedberg was largely built on quicksand. McBain had stated that one effect neglected in Svedberg's calculations could result in errors of 'many hundreds of percent'. However, as Williams told Weaver, Kraemer of DuPont (see Chapter 6) had calculated the factor in question which could, in the most extreme case imaginable, cause an error of less than one percent.⁹³

Early 1937 McBain submitted a request to the Rockefeller Foundation for a \$ 16,000-grant for a four-year period for 'investigations in the field of colloids and surfaces, including the ultracentrifuge'. His greatest need was for senior assistance. His experience with graduate students, however capable, was that only a fraction of their energies and attention could be devoted to their investigation owing to 'minor' and course requirements, etc. A post-doctorate assistant would accomplish many times more than any graduate student, as well as being able to complete the work of graduate students. The primary purpose of his application was therefore to obtain two such assistants with a small balance for other expenses beginning September 1937. For the running year he had already secured the services of an assistant, Dr. Lindquist. McBain considered himself 'sufficiently capable and productive to merit support'. He remarked that the June 1936 Proceedings of the Royal Society considered part of his earlier work as being 'classical'. His investigations at that time were not only interesting by themselves but were 'fundamental in quantitative biology'.⁹⁴ With respect to ultracentrifuges and their applications he distinguished four general fields:

a) The transparent ultracentrifuges. As examples he mentioned Svedberg's, the two (air-driven) which then were recently manufactured by the Sharples Company in Philadelphia, and the air-driven ones set up that year in the Rockefeller Institutes for Medical Research at New York and Princeton, respectively, in addition to the smaller model already worked out in his own laboratory which was 'greatly improved' by a simple temperature control which held the whole rotor at any desired temperature within 0.02° and which would be the only one that promised to be of value in studying the constituents of living protoplasm *in situ*.

b) The centrifuge *with* convection with pervious bottom, which had yielded data for the particle size and density of some viruses.

c) The 'very simple' one-piece or two-piece opaque spinning tops costing \$ 15 - 25 with which he claimed to be able to obtain measurements of ordinary sucrose molecules correct to 5%.

d) The 'very simple and inexpensive' air-driven equipment for studying naturally immobile systems such as jellies. One of these was demonstrated in September 1934 at the Leipzig meeting of the Kolloidchemisches Gesellschaft.⁹⁵

Early 1937 McBain was visited again by Warren Weaver who wrote in his diary about this visit:

"(McBain) seems to have curiously complicated and formal ways of keeping in contact with all of the men who are working with him or under him. WW notices on his door a schedule of appointments for the week, giving a detailed listing of ten-minute interviews two different times in a week with every member of his staff.

(Aside from) one piece of equipment and the optical devices which supplement it, the remainder of the equipment for surface chemistry appears to be simple, if not indeed actually crude. All of the rooms in which McB. has work going on are dirty and confused. WW sees the remarkably precise and efficient automatic recording microphotometer which has been developed by one of McB.'s colleagues. This instrument is an essential part of McB.'s centrifuge work, since the accuracy with which it records density curves for the photographs of sedimentation taking place in McB.'s minute ultracentrifuge cells furnishes McB. with one of his chief arguments for the practicality of the small top as compared with the Svedberg type. WW sees several of McB.'s tops, including his so-called 'transparent' centrifuge. (...) The whole device occupies only a couple of square feet of a work table, and, including the optical device, camera, etc., can doubtless be produced for a few hundred dollars.

McB. does not offer to show WW any of the quantitative results. When WW asks to see some, McB. says that the man who files their plates is not there that day, and that he may have difficulty in finding interesting ones to show WW. As he is thumbing through a box of plates, WW picks one out at random, mentioning that any one of their results would give him a general impression of the way the instrument works. McB. goes on to explain that the particular plate which WW has selected represents a piece of work which 'for personal reasons' they have not yet published. He goes on to say that Stanley sent him some of the crystalline protein virus of the mosaic disease of tobacco. A little later S. informed McB. that he had also sent some of this material to Svedberg. McB. says that he realized that his instrument can produce results within a few hours after the receipt of such

material, while Svedberg's more pretentious technique requires a very much longer time. He, therefore, thought that it was only sporting for him to give Svedberg several months, or even a year of time, to complete his examination of this material, McB. implying that he did not wish to take any unfair advantage of Svedberg by rushing into print with his own determination. This episode is a disturbing one, since it appears to be clearly recognized by Stanley, Wyckoff, Svedberg, and the other interested persons that McB. withheld his results on this virus simply because of the fact that the preliminary runs by the other men indicated that McB.'s results were in error by a factor of two, or even three. In as much as this virus has a molecular weight of something like 15 million, it is clear that McB.'s procedure should give an accurate result for this material, if it is ever to have any success at all, since the case of the determination of molecular weights of sedimentation processes depends directly upon the magnitude of the molecular weight. Svedberg also has evidence that this virus is not homogeneous as regards molecular weight, a fact which McB. undoubtedly realizes his device can not possibly reveal. WW's whole impression from this visit is a poor one."⁹⁶

The following day Weaver visited Linus Pauling, also asking his opinion about McBain. Pauling indicated that he distrusted McBain. He had spent some time in the same chemistry department and had sensed there that the rest of the department did not trust or respect McBain either. Pauling thought that McBain attempted too many things, and that he was too careless with the ideas of others.⁹⁷ A month later McBain was informed that his grant request was rejected, the motivation being that there were 'many interesting and important things which we are unable to aid'.⁹⁸

In November 1937, Tiselius, Pedersen and Svedberg published a 'Letter to the Editor' in *Nature* on 'Analytical Measurements of Ultracentrifugal Sedimentation'. They described that they had made several attempts to take out samples of the ultracentrifugal solutions after concluding an experiment, but the arrangements had not been sufficiently perfect to allow quantitative application. To avoid mixing the layers of the centrifuged solution when stopping the rotor, and especially when pipetting out the samples, they had divided the contents of the cell into two parts separated by a thin wall of bakelite with a large number of fine holes, supporting a piece of hardened filter paper. This arrangement effectively prevented mixing for a time sufficient to remove the cell and to pipette out the contents of the two parts.⁹⁹ In the publication, they did not mention McBain's work which made McBain write Tiselius a letter to point them to this omission. Tiselius replied that they had not mentioned the various papers McBain was referring to, because:

"(...) this in our opinion would have necessitated a detailed criticism of the procedures suggested. We do not consider any of these a solution of the problem of analytical determination of sedimentation velocity in an ultracentrifuge. Such a criticism of a number of different papers would, however, have been far beyond the scope of a note in 'Nature'. - A detailed discussion of this and related questions would be included in the monograph 'The Ultracentrifuge' which is soon to appear in print."¹⁰⁰

Further Development of Ultracentrifuges

McBain saw his air-driven top as a 'device everywhere available for accurately measuring sedimentation equilibrium of particles of all sizes from the smallest molecules in solution to the largest colloids or filter-passing organisms'.¹⁰¹ In 1937 McBain and Alvarez-Tostado described a rotor 'for universal use' consisting of two pieces of steel and a rubber sac in which was laid a pile of 100 ordinary annular washers of coin silver containing 10 per cent copper and each 0.003 inch thick (figure 4.7). The washers were alternately wide and narrow, the outside diameter being the same in all cases. They were held pressed together so that the liquid between the wide washers was immobilized in annular layers, 0.003 inch thick and several millimeters deep.

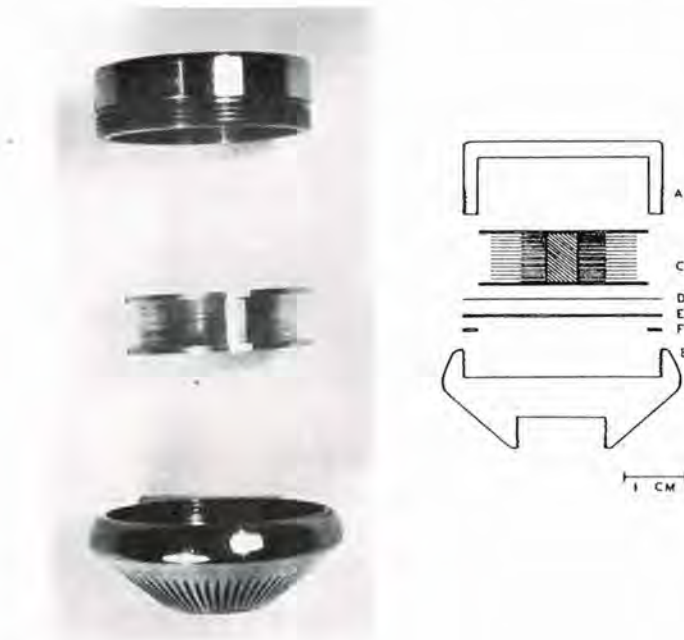


Figure 4.7

Rotor with insert for immobilising liquid. (McBain, 1939, p.294).

Sedimentation equilibrium was set up in this immobilized liquid in any desired centrifugal field up to a few hundred-thousand times gravity. However, the immobilized liquid was inaccessible. A simple device for studying it was to have a thin layer of excess liquid completely mobile and convecting, lining the cylindrical space within the pile of washers. This liquid would necessarily be identical in composition with the most dilute portion of the sedimented liquid. Knowing the speed, the composition of the liquid originally put into the rotor, and the

dimensions of the latter and of the washers therein, it was only necessary after the rotor was stopped to withdraw a sample of the supernatant mobile liquid for analysis in order to determine the molecular weight of any molecules or particles of uniform size. Applying the apparatus to sucrose gave a molecular weight 331 and 339 instead of the theoretical 342. Another variant in design permitted sampling of the liquid in contact with the outside radius of the immobilized liquid as well, to test whether the molecules of particles were all of one size.¹⁰² While passing through New York on his way to a conference in Europe McBain also informed Warren Weaver about the development of this ultracentrifuge.¹⁰³

In 1938 McBain tried to reach a large audience for his spinning tops by publishing an article in *Science*. There, he wrote:

"The great importance of the ultracentrifuge as developed by Svedberg and his collaborators at Upsala is universally recognized, whether for applications in colloid science, in biology, in medicine or in industry. Such equipment has, in spite of its extreme costliness, been installed in a number of laboratories outside Sweden; and similar transparent rotors, run in vacuo, although still distinctly expensive, are being used at several other centers. A less expensive but smaller transparent ultracentrifuge has been developed in the author's laboratory.

It may not be generally realized that there now exists for every laboratory a choice of methods using either commercial centrifuges or still less expensive air-driven ultracentrifuges. With these, quantitative measurements may be made of particle size or molecular weight for every kind of solution or of suspension. They possess the great advantage that the substances or materials measured are withdrawn for direct chemical or physical analysis, or for estimation by biological inoculation, etc.

The descriptions of these various methods are scattered through journals in quite different fields of science, and it is worth while to list them here."¹⁰⁴

He continued discussing his various designs including the latest in which convection was prevented by 'simple mechanical design'. This scheme was most general because the solution was uncontaminated in any way, and it was equally good for aqueous and non-aqueous systems. It also ranged equally well from the smallest molecules to the largest particles. For sedimentation equilibrium of any mono-disperse system, one pile of annular washers would be sufficient. For determination of sedimentation rate or for poly-disperse systems a number of concentric piles of these loose washers, each set held together by vertical pins fastened only to the top and bottom of the pile, were placed in the rotor so that after stopping the rotor each set could be lifted out and the contents analysed to determine rate, equilibrium, true density and number of particle sizes. He concluded the article stating:

"It is evident that the problem of obtaining exact quantitative data on one or all of the quantities mentioned has been completely solved by simple means within the reach of every scientific laboratory."¹⁰⁵

In June 1938, McBain presented a paper at the Fifteenth Colloid Symposium held in Cambridge, Massachusetts, June 9-11, 1938. At the symposium, eight different designs of his new, so-called 'opaque ultracentrifuges', were exhibited in addition to his transparent rotor. His presentation was published shortly thereafter in the *Journal of Physical Chemistry* under the title 'Opaque Ultracentrifuges for Direct Analysis'. In a footnote to the title he stated that he would not discuss his transparent ultracentrifuges but mentioned that their original air-driven ultracentrifuge had been so improved that it was available for every purpose; for example, the sedimentation velocity of haemoglobin was found by A.H. Lewis to be 4.65×10^{-13} , in agreement with the value 4.63×10^{-13} published by Steinhart, rather than the previous value of 4.5×10^{-13} obtained at the University of Upsala.¹⁰⁶ In the introduction to his paper he stated:

"Upon a recent occasion Kraemer stated that nowadays a first instrument which any colloid laboratory should acquire is an ultracentrifuge. This must have seemed to many listeners and readers a counsel of perfection unattainable without special financial resources. It is the purpose of this presentation before the Colloid Symposium to exhibit some of the inexpensive alternatives which are now available to any scientific laboratory that has only modest means, but yet is not satisfied with anything less than the highest degree of accuracy so far attained in this field."¹⁰⁷

McBain continued discussing nine types of rotors which had been developed by him and his co-workers, including the rotor with annular washers used for sedimentation equilibrium (figure 4.7) and a rotor for sedimentation velocity or equilibrium using solid circular disks. When it would be inconvenient to make a two-piece rotor, or where (with a non-aqueous solvent) a suitable seal could not readily be found, the simplest one-piece rotor might be used for sedimentation equilibrium by simply inserting sectorial baffles, cut radially from annular washers, piled like open brickwork (figure 4.8).

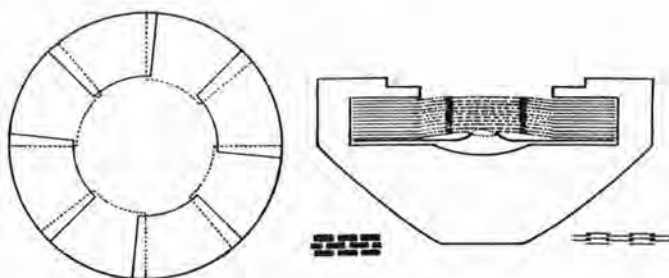


Figure 4.8

One-piece steel rotor with window and with sectorial baffles. To the left: view from above. To the right: cross-section through the axis of rotation. (McBain, 1938a, p.1067).

For sedimentation velocity it was necessary first to place in the rotor a circular distributing disk. When platinum was used for this purpose the rotor should not be more than 20 mm in diameter, since larger pieces of such pure soft metals as silver and platinum would flow freely in the centrifugal field. In a two-piece rotor any strong metal or plastic might be used and in the upper part a window had to be left. The platinum disc inserted in a one-piece 20-mm rotor folded like an umbrella and then opened out. Through its centre there was a smooth hole with upturned edges. Upon this distributing disc the annular circle of sectorial baffles was piled. To make a measurement of sedimentation velocity, only sufficient liquid was put in to fill the spaces between the baffles. After the top had been spinning for a suitable time, the cellophane window was opened with a flame or a razor without stopping the rotor. Then a heavy liquid such as carbon tetrachloride was inserted through the hole in the platinum, would be sedimented outside underneath this disc immediately and be distributed outside the baffles, displacing an equal volume of liquid inward. This was collected with a glass capillary scraping pipet. This method, however, was inferior to the one with circular discs.¹⁰⁸ He concluded the article stating:

"A number of simple and very inexpensive opaque rotors are now available with which measurements both of sedimentation equilibrium and of sedimentation velocity have been made with an accuracy at least as great as that obtainable with the best transparent ultracentrifuge."¹⁰⁹

McBain and Leyda used this opaque ultracentrifuge for measurements of sedimentation velocity of egg albumin in a 37 mm rotor driven at 120,000 r.p.m. Each of fifteen attempts was been successful. In the last five the ultracentrifuge was held at constant known temperature to within 0.1 °C by passing the driving air through a copper coil in a thermostat. Any desired temperature might be selected and held constant to within 0.01 °C. The results were expressed as sedimentation velocity in water at 20°. Analysis of the outer liquid gave $s_{20} = 3.68, 3.69, 3.40, 3.59, \text{ and } 3.64 \times 10^{-13}$. Analysis of the inner liquid gave $s_{20} = 3.35, 3.61, 3.42, 3.89 \times 10^{-13}$, respectively; mean 3.57×10^{-13} . They mentioned that Svedberg's most recent result was 3.55×10^{-13} . Their observations showed that there was no wall effect upon velocity of sedimentation or diffusion where the spaces were as small as 0.01 mm, as would be expected from hydrodynamic theory. The protein particles or molecules were 20,000 times smaller than the capillary spaces.¹¹⁰ McBain and Leyda wrote that with the development of their simple devices 'the time would seem to be approaching when experiments with the ultracentrifuge might be included in practical courses in biochemistry, colloid and physical chemistry.'¹¹¹

In 1938 McBain submitted a request to the Rockefeller Foundation for a \$ 2000

grant in order to buy a precision lathe. It should be used by an 'exceptionally qualified' instrument maker, Joseph Grebmeier. Grebmeier had been mechanic of the Chemistry Department of Stanford University since 1930 and had made all of McBain's ultracentrifuges and various other equipment.¹¹² Their equipment could not meet the demands of their program of research with its emphasis on apparatus of 'the highest precision in design and workmanship', as well as in speed of production. Concerning their ultracentrifuges it would be merely a question of time before their new designs would have been so fully demonstrated that they would be generally available at low cost. They had successfully measured sedimentation velocity of egg albumin with their simple new design of opaque ultracentrifuge without any optical system whatever, and their rotors were already being adopted elsewhere.¹¹³ Two weeks later he tried to support his request by informing the Rockefeller Foundation that he felt 'deeply grateful at the culmination of eight years of work in developing a completely universal form of ultracentrifuge of equal power and accuracy with those of Svedberg, but more universally applicable'. He pointed out that his apparatuses cost less than \$ 50 to make and required no elaborate equipment, whereas those of Svedberg still cost between \$ 17,000 and \$ 20,000, and the simplified form with only glass equipment instead of equipment for ultraviolet put on the market by the Sharples Company under license of the Svedberg/Nichols Patent cost over \$ 3,000 (see Chapter 6). Furthermore, their simple forms were the only ones that could be held accurately at any desired temperature. McBain was 'profoundly thankful that the problem has been so completely solved'.¹¹⁴ He enclosed a copy of an article he had submitted for publication to *Nature*.¹¹⁵ However, McBain's request for a grant was rejected because it was found to 'lie outside our possibilities'.¹¹⁶

June 1938 McBain paid a visit to the Rockefeller Foundation about which Warren Weaver wrote:

"Calls to express his appreciation of RF assistance and to report that the surface chemistry and the centrifuge projects were both carried, under RF assistance, beyond the point which he had hoped for and promised. McB. has with him a small leather sack, which would go in a coat pocket, which contains one mounting and five or six different models of his tiny opaque centrifuges. He says that the transparent centrifuge is now essentially perfected and that it will do everything that a Svedberg or Beams-Pickels-Bauer will do. If a laboratory already has a microphotometer and a source of air pressure up to 100 pounds per square inch, a complete equipment can be installed for \$ 250. An ordinary garage pump, costing \$ 175, is entirely satisfactory as a source of compressed air. The opaque centrifuge can be produced for \$ 50 or less. Using one of the models in which closely spaced (0.003") washers are used to immobilize the solvent liquid, he recently obtained 341 for the molecular weight of sucrose rather than the accurate value of 342. He says that these models can have their temperature controlled to within 1/100° centigrade, by thermostating the air with which they are driven, and that accelerations up to 300-400,000 times gravity are attained without any difficulties."¹¹⁷

For McBain, ultracentrifuges were centrifuges of low or high power containing a fluid in which convection was avoided, so that molecules or particles might sediment and diffuse undisturbed.¹¹⁸ In September 1938 he presented a paper at a 'Symposium on the Physical Chemistry of the Proteins' held in Milwaukee, Wisconsin, under the auspices of the Division of Physical and Inorganic Chemistry and the Division of Colloid Chemistry of the American Chemical Society. There he distinguished transparent ultracentrifuges in which these processes might be followed by measuring the absorption of light or the index of refraction, and analytical ultracentrifuges in which all optical accessories were dispensed with. Instead, at any given time, a whole or a portion of the contents of the ultracentrifuge was removed for analysis by any suitable chemical, physical, or biological method. This analysis determined what movement of each component of the fluid had occurred through a definite cross section of definite radius in a definite field of force. In the analytical ultracentrifuge the one factor, sedimentation velocity, might be isolated for exact measurement, uninfluenced by the other factor, diffusion. In contrast to the transparent ultracentrifuge, according to McBain, it was a matter of complete indifference as to whether or not there was a moving boundary somewhere in the immobilized portion. The precision of the result depended upon the quantitative analysis, the measurement of the radius, temperature, and speed, together with the precautions taken in design and manipulation to eliminate the disturbing effects of convection and diffusion. The analytical method was therefore potentially the most accurate and would still be applicable where, owing to the absence of a boundary, the transparent ultracentrifuge would fail.¹¹⁹

McBain also described a scheme, used before by W.J. Elford, J. McIntosh and F.R. Selbie,¹²⁰ in which glass, silica, or metal tubes, of 1 to 3 mm internal diameter, were immersed in his spinning tops (figure 4.9). The tube was closed at one end and held in position with a cork. With a 70-mm rotor they observed a sedimenting boundary, where with the same tube inserted in a 37-mm rotor a boundary was not formed. McBain mentioned that when the tubes were sufficiently narrow and the centrifuge sufficiently free from vibration and thermal gradients, Elford had found that his tubes resembled an ultracentrifuge, in that a definite boundary appeared, which could be seen with the naked eye by scattered or fluorescent light and the position of which could be measured after stopping the centrifuge. Furthermore, the boundary moved within the experimental error with the same velocity as that observed in the Svedberg ultracentrifuge. McBain indicated that this seemed at first surprising, because the cell was cylindrical, not radial, and some of the sedimentation had to be directed obliquely against the walls of the tube. Thus a sheath of liquid in contact with the walls of the tube should move steadily downward and correspondingly elevate the central contents,

including the boundary. It was this very same phenomenon that had led Svedberg to the development of the sector-shaped cell in 1923. McBain's explanation of the fact that correct results were obtained with the cylindrical tubes was that the movement along the walls was slow and controlled and confined to a layer next to the walls, which was only a few molecules or particles thick and was therefore of a volume negligible in comparison with the contents of the tube.¹²¹ This 'simplest transparent ultracentrifuge' permitted photographic recording of the contents without a camera being needed. A piece of photographic film was placed below the tube, holding the sedimenting liquid. The run was made in dim light or with a cover placed over the guard around the rotor until a record was desired, whereupon a distant light or a collimated beam was flashed on for about one second. This placed upon the photographic film a spot representing the reference point, a boundary for the top of the tube or edge of the window, another for the liquid meniscus and a graduated image showing any boundary or optical inequality in the liquid from top to bottom. They made only one record for each run, but indicated that it should be easy to arrange a slit or opening which could be moved outward to successive positions, and exposed in each. The arrangement was developed for the study of petroleum products in non-aqueous solution, but they also used it for determining the sedimentation velocity in earthworm blood. Such determinations could be made at the rate of several an hour, owing to the fact that the direct air-drive brought the rotor to full speed almost immediately. The duration of each sedimentation was 5 minutes. The values of sedimentation constant ($s \times 10^{13}$) obtained, ranged from 55.9 to 63.4 which was in close agreement with Svedberg's values which ranged from 56.4 to 64.3. Further modifications possible were that, instead of one tube, two to six could be measured simultaneously in the same rotor. Also, if desired, the usual type of radial sectorial cell might be used. McBain concluded that this type of ultracentrifuge could now be made available for undergraduate classes in biochemistry and colloids.¹²²

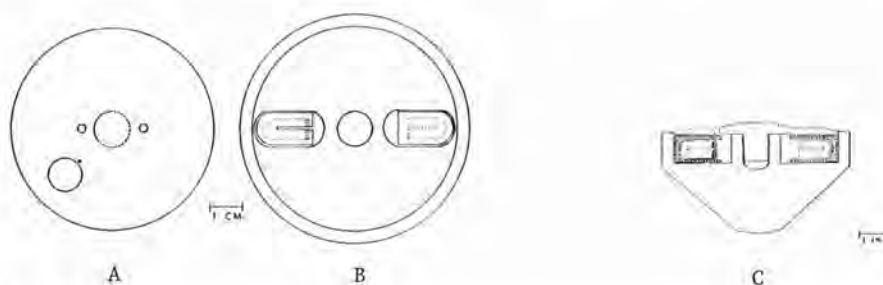


Figure 4.9

Rotor with non-sectorial cells. A, cover-view from above; B, rotor containing cell and dummy; C, cross-section through assembled rotor. (McBain and Lewis, 1939b, p.611).

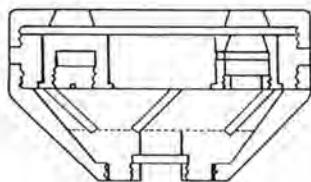


Figure 4.10

Modified rotor for analytical experiments (McBain and Lewis, 1939a, p.1199).

At the 1939 Colloid Symposium, held at Stanford, McBain again presented a paper on his ultracentrifuges, this time focussing on the transparent type. He started stating:

"Different forms of the centrifuge and ultracentrifuge possess great value in the study of the composition and size of the particles. These comprise the batch-concentrating centrifuge of Wyckoff, the continuous-flow concentration process of Beams, the ultracentrifuge of Svedberg, the similar but much less expensive ultracentrifuge of Beams and Pickels, the powerful and versatile opaque ultracentrifuges of McBain, and even the simplest air-driven hollow rotor, or top, extensively used in France and Belgium. There is still, however, a place for directly air-driven transparent ultracentrifuges because (a) they are by far the least expensive, (b) they may be run at any desired constant temperature by first passing the driving air through a thermostat, (c) they may be adapted for use with very small quantities of material, and (d) starting and stopping require but a few seconds."¹²³

In comparison with their earlier design they had introduced a number of modifications most of which were aimed at obtaining a more uniform temperature in the cell (figure 4.10). Above the cell was an enclosed air space made by screwing on a lid with two conical quartz windows cemented in place. Furthermore, the stationary periscope was eliminated by building in polished metal mirrors and closing the bottom of the rotor with a window.¹²⁴ The scheme was used for the sedimentation of haemoglobin. The values for the sedimentation constant $s_{20} \times 10^{13}$ ranged from 3.80 to 5.61 with an average of 4.67. The most accurate series of measurements with the oil turbine ultracentrifuge ranged from 4.54 to 4.70 with an average of 4.63. Measurements on egg albumin with this rotor gave values from 3.33 to 4.10 with an average of 3.64 which was compared with Svedberg's value of 3.55. These results showed that the new rotor was 'completely successful'.¹²⁵

The Death of the McBain Ultracentrifuges

Early 1939 McBain once more approached the Rockefeller Foundation for a grant, asking \$ 4000 for a two-year period in order to appoint a post-doctorate

assistant. In an enclosed letter he stated that 'the study of colloidal electrolytes has been and is the main part of my scientific lifework'. These colloidal electrolytes combined the properties of colloids and electrolytes because they existed partly in colloidal form and partly as simple ions. This was a very large field of research, comprising for example all the soaps, dyes, proteins and biocolloids. McBain stressed the importance of the field and pointed out that, with the cooperation of an assistant, he would be able to resolve a fundamental problem of colloidal electrolytes that had arisen in the preceding years. In the request his ultracentrifuge work was not mentioned at all.¹²⁶ After he had been visited by Warren Weaver shortly thereafter this request was also declined because of 'present demands on our budget and present emphasis within our program'.¹²⁷ Late 1939 McBain wrote the Rockefeller foundation that the Royal Society had awarded him the 'Davy Medal'. He included an overview of 7 research fields in which they were engaged, including: 'Ultracentrifuges; development, theory, applications to soap solutions and many other problems, some in collaboration with others at Stanford and elsewhere'. The letter was meant to reassure the Foundation that his previous grant application, although it was refused on 'completely proper grounds', was for a worthy project.¹²⁸

For McBain the development and use of the ultracentrifuge was one of his many scientific undertakings. For example, in the years 1935-1941 he published 16 articles on ultracentrifuges on a total output of some 75 articles.¹²⁹ This large output was made possible by the fact that he had two secretaries, one a general secretary, and the other a chemist whose duty it was to make first drafts of papers from students' reports so that McBain himself could dash off the finished article quickly.¹³⁰ In the late 1930s, early 1940s less and less time was devoted to work on ultracentrifuges and his latest article appeared in a Russian Journal in 1941.¹³¹ Although he had always stressed that his 'simple, cheap designs' could be used for a variety of applications and that ultracentrifuges could even be made available for undergraduate classes in biochemistry and colloids there is hardly any evidence that his ideas were picked up by fellow scientists. In his own articles he hardly ever referred to other authors using his schemes. One example is given by F.M. Jaeger from the Department of Chemistry from Groningen University in the Netherlands who published an article in 1938 on the application of the analytical ultracentrifuge to the study of filterable viruses. He mainly discussed Svedberg's apparatus and method but also some words were devoted to the Beams and McBain types. A sketch of the latter was included which was presented as a serious, and cheaper alternative to the Svedberg apparatus.¹³² Another example is given by a paper entitled 'An Air-Driven, Air-Floated Capillary Tube Ultracentrifuge', presented by T.F. Ford et. al. at the McBain Memorial Symposium, organised by the

Colloid Section of the American Chemical Society in 1953.¹³³ Ford had cooperated with McBain in the late 1930s on the development of the opaque ultracentrifuges.¹³⁴ The general impression is that McBain's ultracentrifuge work was hardly known or regarded important although McBain as a person was rather well known in the broader chemical community, especially for his work on surface chemistry.¹³⁵

McBain retired in 1947 being still a respected colloid chemist. On the occasion of his retirement the 21st National Colloid Symposium was called the 'McBain Colloid Symposium'. After his retirement he engaged for two years in researches for the U.S. Office of Naval Research and then, on the invitation of Prime Minister Nehru, he accepted the position of Director, to complete and staff the Indian National Chemical Laboratory, at Poona, India.¹³⁶ At Poona he completed a monograph entitled 'Colloid Science', published in 1950. This monograph also comprised a chapter on ultracentrifuges and centrifuges, focussing mainly on his own work done ten years before.¹³⁷ A few months after his return to Stanford McBain had an acute heart attack and three weeks later, on 12 March 1953, died of cerebral haemorrhage.¹³⁸

Notes

The meaning of the various abbreviations used is explained in the notes to Chapter 2.

1. Rideal (1953), p.529 and Taylor (1956), p.1918.
2. Rideal (1953), p.532.
3. McBain and Bakr (1926).
4. McBain and Bulton (1930).
5. McBain (1909a and 1909b).
6. Rideal (1953), p.530.
7. McBain (1931). A full bibliography of McBain's work is given in: Rideal (1953), pp.535-547.
8. Weiser (1926), 'Foreword'.
9. McBain (1926), p.7.
10. Rideal (1952), pp.530-531.
11. McBain to Nichols, 8 February 1929 (HML). The meeting in Toronto, McBain referred to, concerned the sixth national colloid symposium.
12. Nichols to McBain, 19 February 1929 (HML).
13. McBain to Nichols, 26 February 1929 (HML).
14. (RAC:1.1/205/9/119) McBain to Spoechr (RF), 28 November 1930.
15. (RAC:1.1/205/9/119) McBain to Spoechr (RF), 28 November 1930.
16. (RAC:1.1/205/9/119) Spoechr (RF) to McBain, 3 December 1930.
17. (RAC:1.1/205/9/119) Swain (SU) to Spoechr (RF), 2 January 1931.
18. (RAC:1.1/205/9/119) McBain to Spoechr (RF), 15 December 1930.
19. (RAC:1.1/205/9/119) RF-29095: 'Grant appropriation to Stanford University (McBain)', 15 January 1931. (emphasis in original).
20. (RAC:1.1/205/9/119) Spoechr to McBain, 6 May 1931.
21. (RAC:1.1/205/9/119) McBain to Spoechr, 13 May 1931.
22. Tiselius to Nichols, 15 December 1931 (HML).
23. McBain and Laing-McBain (1933), pp.26-27.
24. McBain and Laing-McBain (1933), p.37.
25. (RAC:1.1/205/9/119) McBain to Weaver, 5 December 1933.
26. (RAC:1.1/205/9/119) McBain to Weaver, 24 February 1934.

27. (RAC:1.1/205/9/119) Weaver to McBain, 12 March 1934.
28. (RAC:1.1/205/9/119) McBain to Weaver, 20 March 1934.
29. Letter from C.V. Taylor; annexed to (RAC:1.1/205/9/119) McBain to Weaver, 20 March 1934.
30. (RAC:1.1/205/9/119) McBain to Hanson, 5 April 1934.
31. (RAC:1.1/205/9/119) Hanson to Wilbur (SU) 13 April 1934.
32. McBain to Krejci, 30 October 1933 (UUp-Lib).
33. Krejci to Svedberg, 4 November 1933 (UUp-Lib).
34. Krejci to Svedberg, 17 November 1933 (UUp-Lib).
35. Krejci to Svedberg, 17 November 1933 (UUp-Lib).
36. Svedberg to Krejci, 5 December 1933 (UUp-Lib).
37. Krejci to Svedberg, 21 April 1934 (UUp-Lib).
38. Svedberg to Krejci, 31 July 1934 (UUp-Lib).
39. (RAC:1.1/205/9/119) McBain to Weaver, 31 December 1934.
40. A copy of the original appropriation was not found at the RAC. It is mentioned in (RAC:1.1/205/9/119) RF-35179: 'Grant appropriation to Stanford University (McBain)', 11 February 1936 and (RAC:1.1/205/9/121) Hanson (RF) to Wilbur (SU), 14 February 1936.
41. Krejci to Svedberg, 17 November 1933 (UUp-Lib).
42. Lamb (JACS) to Svedberg, 17 January 1934 (UUp-Lib).
43. Svedberg to Lamb, undated (UUp-Lib).
44. McBain, Dawson and Barker (1934), p.1021.
45. McBain, Dawson and Barker (1934), p.1025.
46. McBain, Dawson and Barker (1934), pp.1025-1026.
47. McBain, Dawson and Barker (1934), p.1026.
48. McBain to Krejci. Quoted in: Krejci to Svedberg, 7 December 1933 (UUp-Lib).
49. McBain and O'Sullivan (1935a), pp.780-781.
50. McBain and O'Sullivan (1935a), pp.780-781.
51. In a footnote they said: 'The term is due to T. Svedberg who has carefully discussed its definition. It has been used loosely by others.'
52. In a footnote they said: 'Only one such measurement has ever been recorded: J.W. McBain and C.M. O'Sullivan (1935a) with mercuric chloride'.
53. Reference is being made to Henriot/Huguenard and to several publications by Beams and co-workers.
54. McBain and O'Sullivan (1935b), p.2631.
55. McBain and O'Sullivan (1935b), pp.2636-2637.
56. McBain and O'Sullivan (1935b), pp.2637-2639.
57. McBain and O'Sullivan (1935b), pp.2639-2640.
58. McBain and O'Sullivan (1935b), p.2631.
59. McBain and O'Sullivan (1935b), pp.2631-2632.
60. McBain and O'Sullivan (1935b), pp.2632-2633.
61. McBain and O'Sullivan (1935b), pp.2635-2636.
62. McBain and O'Sullivan (1935b), p.3461.
63. McBain and O'Sullivan (1935b), p.3461.
64. McBain (1935), footnote 2.
65. McBain (1935).
66. McBain and Stuewer (1936), p.10, footnote 3.
67. McBain and Stuewer (1936), p.14.
68. Craigie and Wishart (1934), pp.10-11.
69. McBain (1936a).
70. (RAC:1.1/205/9/120) Weaver to McBain, 20 March 1935.
71. (RAC:1.1/205/9/120) McBain to Weaver, 26 March 1935.
72. (RAC:1.1/205/9/120) McBain to Weaver, 26 March 1935.
73. (RAC:1.1/205/9/120) Hanson's diary, 26 April 1935.
74. (RAC:1.1/205/9/120) Mason's diary, 24 September 1935.
75. (RAC:1.1/205/9/121) Wilbur (SU) to Weaver, 7 January 1936, annexed research report.
76. McBain to Rockefeller Foundation, 27 January 1936; quoted in (RAC:1.1/800/7/75) RF-37008: 'Grant appropriation to Stanford University (McBain)', 11 February 1936
77. (RAC:1.1/205/9/119) RF-35197: 'Grant appropriation to Stanford University (McBain)', 11 February 1936.
78. (RAC:1.1/205/9/121) Hanson to Wilbur (SU), 14 February 1936.

79. (RAC:1.1/205/9/121) Weaver's diary, 12 March 1936.
80. (RAC:1.1/205/9/121) McBain to Weaver, 23 May 1936.
81. (RAC:1.1/205/9/121) Weaver's diary, 14 September 1936.
82. (RAC:1.1/205/9/121) Weaver's diary, 14 September 1936.
83. (RAC:1.1/205/9/121) Weaver's diary, 14 September 1936.
84. (RAC:1.1/800/7/76) Weaver's diary, 27 May 1935.
85. (RAC:1.1/800/7/76) Weaver's diary, 27 June 1936.
86. Reference is made to Biscoe, Pickels and Wyckoff (1936b).
87. (RAC:1.1/205/9/121) J.W. McBain, 'On the Size of Cells and Rotors useful in the Ultra-centrifuge' 1936, p.1.
88. *ibid*, pp.2-4.
89. *ibid*, p.5.
90. Williams and Watson (1936).
91. McBain (1936b).
92. McBain (1936b).
93. (RAC:1.1/200/164/2013) Weaver's diary, 11 August 1936.
94. (RAC:1.1/205/9/122) Wilbur (SU) to Fosdick (RF), 4 January 1937; annexed proposal, pp.1-2.
95. (RAC:1.1/205/9/122) Wilbur to Fosdick, 4 January 1937; annexed proposal, pp.3-4.
96. (RAC:1.1/205/9/122), Weaver's diary, 27 January 1937.
97. (RAC:1.1/205/9/122), Weaver's diary, 28 January 1937.
98. (RAC:1.1/205/9/122) Weaver to McBain, 20 February 1937.
99. Tiselius, Pedersen and Svedberg (1937).
100. Tiselius to McBain, 11 January 1938 (UUp-Lib).
101. McBain and Alvarez-Tostado (1937).
102. McBain and Alvarez-Tostado (1937).
103. (RAC:1.1/205/9/122), Weaver's diary, 21 May 1937.
104. McBain (1938b), p.93.
105. McBain (1938b), p.94.
106. McBain (1938a), p.1063, note 2.
107. McBain (1938a), p.1063.
108. McBain (1938a), pp.1067-1068.
109. McBain (1938a), p.1069.
110. McBain and Leyda (1938a).
111. McBain and Leyda (1938b).
112. Grebmeier to Hakansson, 3 January 1946 (EGP).
113. (RAC:1.1/205/9/122) Wilbur (SU) to Weaver, 29 March 1938.
114. (RAC:1.1/205/9/122) McBain to Weaver, 13 April 1938.
115. The article was published six weeks later: McBain and Leyda (1938).
116. (RAC:1.1/205/9/122) Hanson to McBain, 3 May 1938.
117. (RAC:1.1/205/9/122) Weaver's diary, 6 June 1938.
118. McBain (1939), p.289.
119. McBain (1939), pp.289-291.
120. McIntosh and Selbie (1937). McIntosh and Selbie designed them for the study of viruses and bacteria. They referred Henriot/Huguenard and to Beams concerning the design and use of a spinning top.
121. McBain (1939), pp.298-300; see also McBain (1940).
122. McBain and Lewis (1939b).
123. McBain and Lewis (1939a), p.1197.
124. McBain and Lewis (1939a), pp.1198-1199.
125. McBain and Lewis (1939a), pp.1203-1204.
126. (RAC:1.1/205/9/122) Wilbur (SU) to Weaver, 11 January 1939.
127. (RAC:1.1/205/9/119) Weaver to McBain, 20 February 1939.
128. (RAC:1.1/205/9/122) McBain to Weaver, 14 November 1939.
129. Rideal (1953), bibliography on pp.535-547.
130. Rideal (1953), pp.531-532.
131. McBain and Leyda (1941).
132. Jaeger (1938).
133. Ford, Ramsdell and Klipp (1955).
134. McBain (1938a), p.1066.

135. Prof. John T. Edsall, private communication.
136. Taylor (1956), p.1918 and Rideal (1952), p.530.
137. McBain (1950), pp.218-239.
138. Rideal (1953), p.530.

Chapter 5

EDWARD GREYDON PICKELS

The IHD Laboratories

At the invitation of Johannes Bauer from the International Health Division (IHD) of the Rockefeller Foundation, Pickels spent the summer of 1934 at the IHD laboratories in New York (see Chapter 3). The IHD had laboratories in several parts of the world, including the one in New York, and was primarily concerned with the study of epidemic diseases. The IHD scientists typically worked 'in the field' for a few years and then again for a few years in New York. Bauer was a yellow-fever researcher, a former member of the Foundation's team in West Africa which had identified the virus of yellow fever. Nothing was then known of the weight, shape or other physical characteristics of the yellow-fever virus, and Bauer was interested in any device that might throw light on these properties. He visited Beams and Pickels in order to inquire whether the ultracentrifuge could be useful for his purposes. Beams and Pickels demonstrated their spinning tops, pointed out the limitations and suggested possibilities. At Bauer's invitation Pickels came to the IHD laboratory in New York in the summer of 1934. He spent two months there getting acquainted with the particular requirements of virus research. This convinced him that the spinning-top technique was impractical because the spinning tops were too small to provide sufficient distance for virus sedimentation to take place at a measurable rate. Moreover, since the spinning top whirled in the open air, enlarging its diameter would cause it to heat up substantially and would require a prohibitively large increase of power, due to the increase in air friction.¹

When back in Virginia, Pickels wrote Bauer that that summer marked the beginning of making a practical application of air turbines. After he had developed the concept of the vacuum ultracentrifuge he believed that before many months he could develop a practical apparatus, closely resembling Svedberg's. Friction, convection currents and dust in the air would cause little trouble because the main body of the rotor would be rotating in a partial vacuum. He expected to get his

Ph.D. degree for this work in June 1935.² In November he wrote Bauer that he had obtained results surpassing even his own expectations. He now had what he believed to be a centrifuge ideal in every desired respect. With the air-driven vacuum centrifuge he had reached 900,000 times gravity. The only reason they did not do better was that the rotor had exploded and had wrecked the outfit. The apparatus was being rebuilt with arrangements for photographing sedimentations. Centrifugal concentration of small particles on a fairly large scale should also now prove practical.³ Bauer responded that this development sounded very interesting but that he could not visualize how you could run a rotor in vacuum using compressed air for driving power. He was still very much interested in the centrifuge but had not accomplished much since Pickels left. Bauer had constructed a very large spinning top, about 8" in diameter, in order to arrive at the same dimensions Svedberg was using. He had placed some test tubes in it in order to use it for the separation of viruses. It was, from the spinning top perspective, an enormous thing that practically took a whole power house compressor to run it.⁴ Pickels sent him a paper on the new ultracentrifuge which stimulated Bauer's interest. He remarked that with this type of apparatus one could easily replace the air in the chamber with hydrogen and get conditions identical with those in Svedberg's centrifuge. But he would hate to be in the vicinity when the piano string would snap.⁵

Late December Bauer was pleased to learn that Pickels obtained good separation of haemoglobin in his new centrifuge. He himself also obtained fairly good separation a couple of months before in a cell made of very thick glass discs at each end and a hard rubber centerpiece. This arrangement ensured enough insulation so that the temperature change in the cell took place very gradually and did not cause sharp gradients which would set up convection currents. At the time his centrifuge was being completely dismantled in order to have larger rotors built to conform with Svedberg's measurements. He hoped to resume the work some time in January, when a new more powerful air-line would be installed.⁶

Pickels had indicated to Bauer that he would like to work with him again after he would have obtained his Ph.D. Bauer was also interested and in March 1935 Wilbur A. Sawyer, associate director of the IHD, invited Pickels to work for a year as assistant to Bauer in developing and applying the ultracentrifuge to biological work.⁷ Pickels responded that he was seriously interested. He indicated that, although he could understand that the job was only for a year, he would also like to give some consideration to what might happen afterwards:

"If promising results are soon obtained (...) I should think that it would take quite a few years' research to exhaust the applications of the air-driven ultracentrifuge in biological work that would interest you. I should think that the services of a trained experimental physicist would be useful in such work. Briefly,

if I 'deliver the goods' next year can I feel some assurance that I will be invited to continue work with the Foundation if, of course, budgetary considerations, etc., allow such an invitation? Or, are you specifically interested in my assisting in developing and adapting the apparatus to just such a point that the main body of the work could be carried on by your present staff, which would seek to untangle both the physical and biological implications of the problem which will necessarily arise? Or, again assuming that favorable results are gotten early in the work, is it your present plan not to outline a fairly extensive field of related investigation but to simply attempt one or two specific problems that may be completed in a year or two? And if you should feel that there is little possibility of being retained by the Foundation for more than a year or two, do you think there is a fair chance of being relocated favorably with the assistance of the Foundation, assuming of course that my work has warranted decent recommendations?"⁸

Sawyer replied that for them the present occasion, and thus the justification of an intensive study of the ultracentrifuge, was the need for a more accurate knowledge of the physical nature of yellow fever virus and for methods of concentrating suspensions of this virus. Incidental to the yellow fever studies, other viruses might be investigated for purposes of comparison and because they might become of special interest to the International Health Division in the future. It would be quite possible that the actual studies with the perfected apparatus could be completed and published rather rapidly and that the centrifuge would become another useful apparatus for intermittent use as needed. From their viewpoint, the need was for the more rapid development of the centrifuge in its biological application. In the course of a year, in view of the work that had already been done, Sawyer would hope that Bauer and Pickels would be able to publish jointly a descriptive paper which would enable other laboratories to make and use the apparatus in biological chemistry or the study of viruses. The mention of a year in Sawyer's previous letter was not intended to be a definite maximum or minimum limit to Pickels' service, or a contract for a year, but rather a prediction that the work would take at least that long. Sawyer expressed his belief there would be a demand for persons in biological studies with the experience Pickels had with the centrifuge. They were already getting inquiries as to when a satisfactory centrifuge would be available for virus and chemical work. Sawyer could not hold out any probability of a permanent position in the International Health Division of the Rockefeller Foundation, as the highly specialized work they were doing with the centrifuge was 'in its nature temporary'. Ordinarily, they worked intensively in a narrow field as long as the work yielded high returns and then considered changes of program.⁹

Pickels accepted the job and started working with Bauer on the first of August 1935. Shortly before he was invited by the AAAS to give a demonstration of his high speed rotor at the 'annual science exhibition'.¹⁰ Bauer, however, advised him to decline the offer because it was the policy of the Rockefeller Foundation not to participate in any exhibits which would involve a considerable amount of publicity

and which were not strictly scientific in their nature. Furthermore, Bauer did not think that the work with the centrifuge had reached a stage at which its practical application could be demonstrated.¹¹

At the Rockefeller Foundation Pickels was the only physicist on the staff. There was one chemist and all the other researchers were medical men. The IHD-laboratories were housed in the Laboratories of the Rockefeller Institute for Medical Research. The installation of the ultracentrifuge implied that some of the laboratory rooms had to be made available for the purpose and for this reason the instrument shop was moved to the basement.¹² The ultracentrifuge work was aided greatly by the skill and ingenuity of Josef W. Blum in the instrument shop. The shop had been created in 1920 and was expanded and modernized in 1935 because the rapid expansion of research in physical chemistry created an ever growing need for experimental apparatus. Blum had joined the staff in 1935, at first as a temporary worker, assisting Bauer and Pickels in ultracentrifuge development. In 1939 he was made head of the instrument shop.¹³

Viruses - Quantity Ultracentrifuge

Johannes Bauer wanted to use the ultracentrifuge for the sedimentation of viruses in order to obtain them in a pure form. Late 1936 Bauer and Pickels published a long article in the *Journal of Experimental Medicine* entitled 'A High Speed Vacuum Centrifuge Suitable for the Study of Filterable Viruses'. In the introduction they wrote:

"The study of filterable disease-producing agents has been much handicapped by the lack of suitable apparatus. The microscope, the ordinary laboratory centrifuge, and culture medium, all of which are invaluable in the study of disease-producing bacteria, are of no assistance in the study of viruses. Viruses associated with disease in animal and man are also always associated with a large amount of extraneous protein matter originating from the host, and no satisfactory method has yet been developed by which these pathogenic agents can be induced into a pure and concentrated state so that their specific antigenic properties and physico-chemical characteristics can be properly investigated. Recently Stanley reported success in the preparation of the virus of tobacco mosaic in crystalline form by the extraction and salting-out process, but as yet this method has not found wide application in the study of animal and human viruses. As is well known, most of the viruses pathogenic to animal and man are rather labile and become easily inactivated by the processes involved in chemical and physical investigations, and since the presence of a virus in a given substance can be demonstrated only by its specific action in a susceptible animal, these methods have proven of little value."¹⁴

Bauer and Pickels quoted a number of workers who had tried to use centrifuges for the separation of viruses. Craigie, and Parker and Rivers had used it for the

study of vaccinia virus, showing that the 'elementary bodies' could not only be separated from the associated protein matter but washed and concentrated as well. Similar application of the centrifuge to a considerable number of other viruses had not yet yielded equally satisfactory results. In the early 1930s, Elford, and Bauer and Hughes had developed a method for the preparation of finely graded collodion membranes of uniform porosity. By the use of these membranes the particle size of a number of viruses had been measured by various investigators. The results of these investigations showed a wide variation in their size.

Most of the preceding centrifugation experiments with various viruses had not been successful because the fields obtained were too low. Although there were a number of commercial centrifuges available which gave fairly high rotational speeds most of them had a relatively short effective radius. Moreover, as they were generally designed to rotate in air, their speed was necessarily limited by the air resistance. Furthermore, in such centrifuges, with the increase of speed a corresponding greater amount of frictional heat was developed in the rotating head. This heating was not only responsible for convection currents which interfered with effective separation, but the temperature frequently rose to such a critical degree that denaturation and inactivation of the material during centrifugation might result.¹⁵

Bauer and Pickels first used the air-drive to spin a rotor in air which worked rather well for the sedimentation of the larger viruses. The rotor was machined from a solid block of duraluminium and weighed 21.5 pounds. It had 48 flutings, each 3 inches long and 1/8 inch deep. The total height of the rotor was 7 inches. Eight holes, each measuring 1/2 inch in diameter and 3 inches deep, were bored in the top portion an equal distance apart and at an angle of 40° from the axis of rotation. Containers of celluloid composition fitted into these holes. Each container had a capacity of 7 cc. and was transparent and flexible. These containers weighed 80 per cent less than the usual glass ones and withstood high centrifugal forces. The material to be centrifuged had to be covered with a layer of oil to prevent evaporation. The highest speed obtained was 16,000 r.p.m., which corresponded to a centrifugal force of 20,000 times gravity in the central portion of the containers. An air pressure of nearly 200 pounds per square inch was required to attain maximum speed.¹⁶ However, for the yellow fever virus, in which they were particularly interested, sedimentation was not obtained because the field obtained was too low to sediment this relatively small virus. Next, when they spun their rotor in vacuum the difficulties were entirely overcome.

The rotor, which is shown in figure 5.1, was machined from a solid block of duralumin alloy commercially known as ST 17. It was given a pear-shaped form having a maximum diameter of 8 inches, tapering off at the top to 3½ inches. This form was chosen in order to reduce the weight of the rotor as much as possible

without sacrificing its strength materially. At the top of the rotor there was a cavity (C, figure 5.1) cut to the depth of $1 \frac{9}{16}$ inch. At the bottom edge of this cavity were drilled sixteen equally spaced holes, each $\frac{1}{2}$ inch in diameter and $2 \frac{7}{8}$ inches deep, to accommodate the celluloid containers described below. The holes were inclined at an angle of 45° to the axis of rotation, and their bottoms were rounded, fitting the shape of the containers. The distance from the inner edge of each hole to the axis of rotation was 3.8 cm at the top, and 8.5 cm at the bottom, where the outside supporting wall reached a minimum thickness of $\frac{1}{4}$ inch. This wall was made considerably thicker at the top where the holes were close to each other and additional strength was needed. In figure 5.1, one container, is indicated as being in position (T).

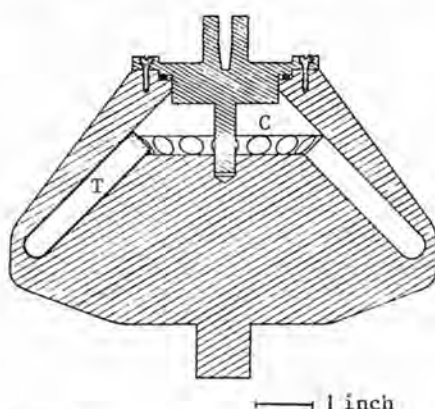


Figure 5.1

Rotor for sedimenting viruses. (Bauer and Pickels, 1936a, p.511).

The sixteen containers, each holding 7 cc. of fluid, gave the centrifuge a total capacity of 112 cc. which could be centrifuged in one run. At the base of the rotor there was machined out a stem 1 inch in diameter and in length, which was used for fastening the rotor in the milling machine chuck while the holes were being drilled. When assembled it weighed, without containers, 6,460 gm. The usual glass containers could not be used in this centrifuge, as they would be crushed under the centrifugal force necessary to separate viruses. The containers were made of a celluloid composition and were transparent and flexible. When filled with fluid, these containers would withstand centrifugal forces over 95,000 times gravity at the bottom portion without breaking or leaking. The containers remained unaltered when run for several hours at a speed of 25,000 r.p.m. But when the speed exceeded 27,000 r.p.m., the empty portion at the top bent and folded over the surface of the fluid, sealing it completely. When used only half filled, the empty portion of the tube usually collapsed. One serious disadvantage of the

containers was that they could not be sterilized in an autoclave or in a hot air sterilizer. They could be sterilized in a more laborious way, either by boiling or by soaking in 75 per cent alcohol and subsequently by rinsing in sterile distilled water. They cost a little over one cent apiece and after being used once were usually discarded. It was not necessary to balance the containers by accurate weighing. Bauer and Pickels found it sufficient to measure accurately with a pipette an equal amount of fluid into any two of the containers and to place them in the rotor in positions opposite to each other.¹⁷

Successful operation of the centrifuge depended upon having approximately constant pressures in all the air lines supplying the various parts of the driving mechanism. Since the head pressure in their laboratory was subject to considerable variation, the air was first passed through a two-stage reducing system of adjustable regulators. The first regulator dropped the head pressure from 150-225 pounds per square inch (psi.) to about 100 psi. The second regulator reduced the pressure to 50 psi. and held it constant at that value as long as the setting of the control valve for the driving line was not varied over too wide a range. The speed attainable with the apparatus was limited only by the strength of the rotor, and since the explosion of a rotor run at excessive speed was both costly and dangerous, it was important to measure and control the speed accurately. It was also important to know approximately what speeds could be regarded as safe for routine operations. The experiments of Biscoe, Pickels, and Wyckoff, described below, on tensile strength and fatigue endurance of duralumin rotors furnished a practical basis for such approximate guidelines. Bauer and Pickels estimated that their rotor would perhaps explode in the neighborhood of 40,000 r.p.m. They considered prolonged operation at a speed not exceeding 30,000 r.p.m. comparatively safe if there were no serious flaws in the metal of which the rotor was made. They never exceeded this speed in their experiments. The speed was measured frequently with a stroboscope, which was of the so-called 'motor-driven, slotted disc type.' The turbine was first painted a dull black on its top surface and then had a white mark placed near the edge of this dark background. This mark appeared to be stationary (although blurred) when synchronization between the centrifuge speed and the speed of the stroboscope was obtained. In this scheme the same pattern was obtained when the turbine speed was one, or three times the frequency of vision interruption. With practice, they could easily make distinctions by noting the amount of blurring. About 35 minutes of acceleration were required to attain a speed of 30,000 r.p.m. Most of their centrifugation experiments with the yellow fever virus were carried out at a speed of 27,300 r.p.m. Because the rotor had a rather high inertia it responded very slowly to small changes in the driving pressure and, therefore, the speed was very constant. A rapid stopping of the centrifuge was accomplished by opening the valve controlling the reversing

mechanism and readjusting the driving pressure to the desired value; 35 psi. was sufficient to stop the rotor in about 20 minutes. If the reverse drive was not applied, and the rotor was allowed to coast until it came to a standstill, it usually took over 2 hours to decelerate from a speed of 30,000 r.p.m. to a full stop.¹⁸

This centrifuge was successfully applied for the separation and concentration of yellow fever virus. The major portion of the virus was sedimented out of the suspension when centrifuged for 3 hours at a speed of 25,000 r.p.m.; in fact, it became so firmly packed to the bottom that the supernatant fluid could be poured off and the sediment resuspended in fresh diluent without appreciable loss of the virus activity. This would seem to indicate that the centrifuge could be applied for the washing and purification of the virus. At the speed of 25,000 r.p.m. the centrifugal force equaled approximately 34,800 times gravity at the top of the fluid column and 66,000 times gravity at the bottom. However, a complete sedimentation of the virus was not obtained even when greater centrifugal forces were applied over a considerably longer period. A certain small proportion of the virus remained persistently in the supernatant fluid even when haemoglobin which was present in the virus suspension had been effectively separated. They were unable to find a satisfactory explanation for the failure to secure a complete separation of the virus under the conditions described, although they felt that this failure was not caused by convection currents or by stirring during deceleration. They intended to investigate the phenomenon further.

Bauer and Pickels expected that their centrifuge would prove a useful instrument in the study of filterable disease-producing agents, including the smallest known. It could be operated with comparative safety at speeds up to 30,000 r.p.m., giving a centrifugal force of approximately 50,000 times gravity at the top of the fluid columns and 95,000 times gravity at the bottom. Although the maximum hydrostatic pressure exerted by the fluid at this speed equaled more than 600 atmospheres, the celluloid tubes had withstood this pressure well. The construction of the centrifuge was relatively simple and it could be built by any first class machinist. The cost of construction of the centrifuge itself, exclusive of the vacuum pump and other accessories, should not exceed the price of a standard laboratory centrifuge. In view of the fact that its air consumption was small and high pressures were not needed even for rapid initial acceleration, it could be operated in any laboratory where there would be a supply of compressed air available.¹⁹

October 1936 Bauer wrote W.A. Sawyer, director of the IHD, that he expected that they would soon receive outside requests from medical colleges and universities for their 'high-speed vacuum centrifuge'. The same had happened with a metal filter apparatus Bauer had developed and described about a year before. Bauer used to turn these requests over to W.R. Flinn, assistant business manager of

the Rockefeller Institute. In many instances the filters were made in the Institute instrument shop and customers were charged cost price of material and labour only. Concerning centrifuges, the IHD could not handle such demands as they lacked adequate machinery, but they considered the possibility that the Rockefeller Institute would be willing to build vacuum centrifuges in its workshop. If it should be willing to do so, there might, however, be a problem: Ivan Sorval, who marketed Angle Centrifuges in the US, had protected by US patent all angles up to 50° . In Bauer's design this angle was 45° but he was informed that when laboratories built equipment for their own use utilizing principles covered by patent rights, it did not constitute infringement, as long as such apparatus was not made for sale. Bauer wondered if making a centrifuge for other institutions, charging only for costs made, would constitute an infringement to Sorval's patent.²⁰ According to the lawyer Thomas Debevoise even the manufacture and use of a patented object for one's own purposes would constitute an infringement. Sawyer therefore suggested Bauer to find out whether angles over 50° were not equally satisfactory. The forces involved in their centrifuge were so much greater than those contemplated by the makers of the patented Angle Centrifuges, that it might well be that the larger angles would be equally satisfactory, or more so.²¹ In his answer Bauer raised the point that laboratory apparatus obtainable from commercial dealers was usually designed for only standardized laboratory procedures which had already passed through the experimental stage. In tackling new research problems, the scientists at the Rockefeller Institute, as well as in other research laboratories, often found it necessary either to modify existing apparatus or to design new equipment into which some patented features were frequently incorporated. Bauer indicated that from that common practice a belief might have grown that such a procedure was proper from the viewpoint of patent laws. Flinn also was most surprised that their activities would be an infringement; the Institute had quite often built and fully described apparatuses including some patented principles and they had never had complaints from patentees. Nevertheless, in accordance with Sawyer's suggestion, Bauer changed the angle of their centrifuge to 52° .²²

At the IHD Pickels had pretty much of a free hand. With the restriction that his work should be relevant to the Foundation's interests he could choose the problems he would like to work on himself. He had the assistance of a draftsman, a machinist, a junior scientist and a technician. In the experiments Pickels always did all the ultracentrifuge work, recorded the results, made the computations, etc. The other scientists just supplied him with the materials. In operating the apparatus he learned where it could be improved with the effect that he was continually changing it.²³

Analytical Ultracentrifuges - Wyckoff

Besides with Bauer, Pickels also collaborated closely with Ralph W.G. Wyckoff from the Rockefeller Institute. Wyckoff was the head of a subdivision of biophysics at the Institute which had opened in 1927. He had started to determine the structure of complex organic substances, including proteins, by using X-ray crystallography. When he learned that Pickels was cooperating with Bauer in the development of the air-driven ultracentrifuge he became highly interested in using the apparatus for his own research.²⁴ However, whereas Bauer was primarily interested in an ultracentrifuge for preparative purposes, Wyckoff would like to have an analytical type for his studies of the structure of organic substances. Developing the ultracentrifuge further for their purposes Wyckoff and Pickels started to investigate what the 'best' material for the rotor would be. Their goal was to 'develop an ultracentrifuge for molecular sedimentation which would combine the simplicity of an air turbine drive with the accuracy attainable only with large rotors'²⁵ They started an investigation of light metal alloys for rotor construction because there were two ways in which the use of such alloys would reduce the cost of ultracentrifugation. In the first place they could be easily and rapidly machined on an ordinary lathe; steel rotors had to be heat-treated after turning, and since they should be very well balanced this treatment had to be followed by a final grinding operation. As a consequence they cost about six times as much to make as duralumin rotors of the same size. Another important difference was that, when they failed during use, as both steel and duralumin might do, the destruction to other parts of the equipment wrought by steel rotors was very much greater. This greater destruction by steel was due to the fact that, being heavier, it carried much more energy at a given speed while, because of its greater hardness, its fragments also cut into barricading metals in a way impossible for softer metals. They investigated two types of light alloys with tensile strengths high enough to warrant test: duralumins and high magnesium aluminum alloys. Two sets of experiments were carried out with rotors made from these alloys. In the first set, the speed at which the rotors exploded was stroboscopically determined. In the second set, similar rotors were run below this explosion speed for several hours to establish the approximate maximum at which they could safely be operated. As a driving mechanism the air-turbine, which Pickels had developed during his research for his dissertation, was used. The top and bottom ends of the vacuum chamber were of half-inch boiler plate while the central cylinder had a one-inch wall of heat-treated chrome vanadium steel. Within this cylinder was inserted a shorter ring of cast lead 1½ inches thick. This lead lining, intended to absorb some of the energy of the disintegrating rotor, had to be renewed after each explosion. Figure 5.2 shows the state of the apparatus following the explosion

of a rotor (shaped as no. 3 shown in figure 5.3). The cylinder A was bulged and warped, the concentrate block C was cracked in two and the entire driving mechanism including the top plate B was driven through the ceiling of the room.²⁶



Figure 5.2

The apparatus after the explosion of a rotor. The bottom plate of the vacuum chamber can be seen still in place on the concrete block C. Some of the lead lining is still within the Cylinder A, other pieces are labeled D. Fragments of the rotor are at E. (Biscoe, Pickels and Wyckoff, 1936a, p.247).

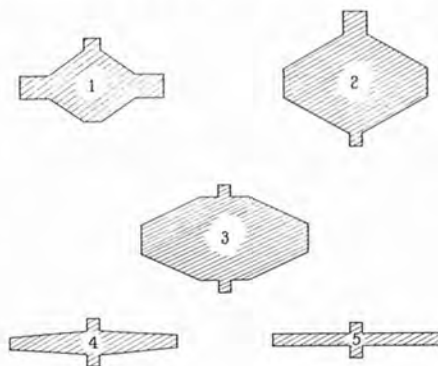


Figure 5.3

Cross sections of tested rotors (Biscoe, Pickels and Wyckoff, 1936a, p.247).

Because their experiments were designed to find out whether light metal rotors could be used for molecular sedimentation, all test rotors were drilled for cells of standard size. During all runs dummy cells were inserted which had an outside diameter of $7/8$ inch with the centre 6.5 cm from the axis of rotation. In almost all rotors there was $1/2$ inch of metal between the cell and the periphery of the

rotor. Failure of the test rotors derived from strains about these cell holes so that the explosion speeds found were probably considerably less than would be given by solid rotors of the same size and shape. In order to fix the extent to which light metal rotors could be employed in the ultracentrifuge, they wanted (1) to select a suitable shape for them and (2) to determine the most satisfactory alloy. As a first approximation they tried to find a theoretically optimal shape of the rotor. However, since failure was largely determined by strains developed about the cell holes, an accurate calculation of the breaking point was difficult.

Besides being easy to construct, the most desirable rotor should be as strong as possible without being unnecessarily heavy. They calculated the bursting strengths of a variety of rotor-shapes shown in figure 5.3. From these calculations and from explosion experiments they chose for future work the shape illustrated in figure 5.3, number 2. Tests with a number of alloys and shapes showed that duralumin 14 ST was most suited for their purposes. Rotors of their 'standard' shape could be run indefinitely at 48,000 r.p.m. and probably, under optimum conditions, somewhat above 54,000 r.p.m. At 48,000 r.p.m. the field at the centre of the cell of such a rotor would be 180,000 times gravity; at 54,000 r.p.m. it was 215,000 times gravity. With these fields the rate of sedimentation of molecules having weights of a few thousand could be measured. However, to obtain more intense fields it would be necessary to reduce the diameter of the rotor or to replace the duralumin by special steels.²⁷

Early 1936 Biscoe, Pickels and Wyckoff published an article in the *Journal of Experimental Medicine*. Referring to Svedberg's ultracentrifuge they stated that his machine was so elaborate and costly both to build and to maintain that no duplicates of it had been put in operation. However, the development of usable air-driven turbines for high rotational speeds had opened up the possibility of making comparatively inexpensive ultracentrifuges. Referring to McBain's ultracentrifuge (see Chapter 4) they considered it to be at disadvantage to Svedberg's because it used much smaller rotors and was accordingly incapable of yielding results of equal accuracy.²⁸ The apparatus they described was developed to provide data needed in studying viruses and crystalline proteins. It was built in their own shop and the materials necessary for its construction, including the lenses, had cost less than one thousand dollars. In designing this ultracentrifuge they had sought to utilize, to the greatest possible extent, the experience embodied in the publications of Svedberg. They had therefore copied his optical system directly and had employed large rotors capable of giving the 6.5 cm distance between cell centre and rotation axis which he had adopted for his most accurate measurements. The liquid to be centrifuged was contained in a cell that was essentially the same as Svedberg's. It differed mainly in that, being fillable from the end during assembly, an oil seal was unnecessary. Temperature measurements indicated a maximum rise in

temperature for runs at 48,000 r.p.m. of the order of 2°C. This temperature rise was ascribed to friction developed in the shaft bearings and to frictional interaction between the rotor and the small amount of gas remaining in the evacuated chamber. In order to check the operation of the ultracentrifuge before using it upon proteins of unknown molecular weights, a series of determinations was made of the sedimentation constant of horse haemoglobin. The results indicated that the apparatus operated satisfactorily. Next they wanted to use this ultracentrifuge to analyze several systems consisting of viruses and of crystallizable proteins.²⁹

After the testing of their analytical ultracentrifuge Biscoe, Hercik and Wyckoff applied it to the determination of the size of so-called 'antibodies'. Recent work had demonstrated that at least some of the antibodies in the blood of immunized animals were proteins or were intimately associated with proteins. Thus arose the question of the relation between these bodies and proteins found in the blood sera of normal animals. In order to investigate this problem Wyckoff applied a method of analysis which was first used by Von Mutzenbecher and later McFarlane in Svedberg's laboratory except that he used an air-driven ultracentrifuge whereas they used Svedberg's oil-turbine type. Wyckoff concluded that the sedimentation constants from the ultracentrifugal analysis of several concentrated antibody preparations were of the same order of magnitude as those of the globulins of normal sera. If these antibodies were proteins or were associated with proteins and if concentration had proceeded till such proteins were a major constituent of these preparations, then it followed that antibody properties were not necessarily associated with exceptionally large molecular size.³⁰ Next, he applied his ultracentrifuge to the study of so-called pneumococcic antibodies. His earlier analysis of concentrates of the Type I pneumococcic antibodies from horse serum had shown that their proteins consisted mainly of molecules with a sedimentation constant of about 16×10^{-13} cm/sec/dyne. This, together with the presence of such molecules in the untreated anti-pneumococcic horse serum and their complete or almost complete absence from normal serum, provided evidence that they were the 'real bearers' of the antibody activity. Further support for this view was supplied by the observation that after ultracentrifugation, most of the antibody activity appeared at the bottom of the cell. Wyckoff centrifuged 'considerable quantities' of serum and commercial antibody preparations in his vacuum centrifuge turning at 25,000 r.p.m. In these experiments two kinds of commercial Felton antibodies and an untreated anti-pneumococcic horse serum were centrifuged for several hours in a maximum field of about 40,000 gravity. After stopping, the top and bottom fractions were withdrawn and investigated further. On the basis of these investigations he formulated two hypotheses on the agent of the antibody activity which would have to be investigated by other means.³¹

Wyckoff not only used the analytical ultracentrifuge but also the 'quantity ultracentrifuge' developed by Pickels for Bauer. Collaborating with Corey, one of his colleagues at the Rockefeller Institute, he applied it to the crystallization of tobacco mosaic virus (TMV) protein. Shortly before, Wendell Meredith Stanley, a scientist at the Department of Animal and Plant Pathology of the Rockefeller Institute at Princeton, had been the first to crystallize the TMV protein, using chemical means. This had roused considerable interest in the scientific world.³² Using plant materials obtained from Stanley, Wyckoff centrifuged the clear juice pressed from plants infected with tobacco mosaic virus at 25,000 r.p.m. (maximum field=40,000 gravity). At the bottom of the tube a pellet separated which, under the polarizing microscope, appeared to be crystalline. Tests showed it to contain all but a small fraction of the virus initially present in the juice. The X-ray patterns of this crystalline material and of the protein prepared from the juice by chemical means were indistinguishable. This made them conclude that the two substances had to be substantially identical and that thus, the ultracentrifuge could be used to obtain a crystalline virus protein.³³

Shortly thereafter Stanley started collaborating with Wyckoff on ultracentrifugal studies of virus proteins. Earlier studies had indicated that the protein carried all the virus activity while no way could be found of obtaining this activity separate from the protein. This stimulated their interest in studies of its physical properties. They investigated the rates at which virus proteins, obtained from several different plant hosts diseased with distinct strains of tobacco mosaic virus, sedimented in an intense gravitational field. A striking result of the ultracentrifugal examination of solutions of mosaic virus proteins was their very large sedimentation constants. Of the order of $s = 200 \times 10^{-13}$ cm/sec/dyne, these constants were the largest yet found for any protein; they referred to molecules with molecular weights probably in excess of 10,000,000. By contrast, the proteins of healthy plants, prepared by the same procedure as used in extracting the virus proteins, did not contain a demonstrable amount of molecules with weights as large as 30,000; there was no observable sedimentation from a solution of normal plant protein maintained in a field of 180,000 times gravity for 90 minutes. These observations indicated that the virus proteins of the various strains of the tobacco mosaic disease consisted of a group of related but definitely different molecular species. However, any simple relation that might exist between molecular shape and size and biologically specific characteristics could only be assessed after the possible virus strains had been more completely studied and standardized.³⁴ Working with another plant disease causing agent, the so-called Tobacco Ring Spot virus, they encountered the problem that this virus was unstable and became almost completely inactivated on merely standing at room temperature for one day. Hence it was necessary to keep the preparations cold during the entire

manipulation. This was accomplished by working with the material in a room held at about 20°C. and by carrying out the ultracentrifugation in a quantity head precooled to about 0°C. Since the centrifuge head spun in a vacuum, it absorbed little heat, and during a 3-hour run usually warmed up less than 5°. In the analytical ultracentrifuge a solution of this protein gave a sharp boundary characteristic of a single molecular species with sedimentation constant equal to 115×10^{-13} cm/sec/dyne.³⁵

In these experiments it proved very fruitful to first use the quantity ultracentrifuge for the purification and isolation of the virus and next to use the analytical machine for its subsequent analysis. In Stanley's view it was a great advantage of using the two types together. Because of their widespread application he thought that every school and institution of any size would have them within ten years.³⁶ He was therefore very pleased when Wyckoff moved to Princeton in 1936 and brought along an analytical ultracentrifuge. Shortly thereafter they also secured a quantity ultracentrifuge, manufactured in the Institute's workshop.³⁷

One of the disadvantages of Wyckoff's driving mechanism was the absence of a device for quickly stopping the ultracentrifuge once it had been set in motion. In early experiments braking was achieved by pressing a piece of cloth against opposite sides of the top of the turbine. This procedure was tedious and for the higher speeds decidedly dangerous. When the heavy rotors needed for quantity ultracentrifugation were used, it should not be attempted. Therefore they modified the driving mechanism by constructing a set of backwardly directed jets in the stator and air buckets around the rim of the turbine. When a centrifuge employing this driver was to be stopped, the forward driving pressure was lowered as much as was safe and a reverse pressure of 60-70 psi. was applied. In this way the rotating system could be brought smoothly to rest in 10 to 20 minutes without temperature rise and without stirring the liquids contained in the rotor. Still, with very heavy rotors care had to be taken in applying the reverse pressure; otherwise the supporting shaft might break.³⁸ Wyckoff and Lagsdin described this apparatus in *Review of Scientific Instruments*, stressing other features also. One of the great advantages of their air-driven ultracentrifuge lay in the fact that, having a vertical axis of rotation, it was easily adapted to the handling of large volumes of solution.³⁹ For the sedimentation and purification of virus proteins a field not exceeding 50,000 times gravity was sufficient. Antibodies, enzymes, protein-linked hormones and the like were smaller and therefore needed higher fields for their concentration. Quantity heads made of duralumin would run well between 250,000 and 300,000 g although their transparent containers had not withstood forces higher than 200,000 g. However, as long as a liquid was not corrosive it could be placed directly in the head and successive layers could be pipetted off after a run.⁴⁰ Wyckoff and Lagsdin also made some improvements in the procedure for

registering the process of sedimentation in their analytical ultracentrifuge. Essentially, they had copied Svedberg's optics but had added a remote control which made it possible to shift filters without coming close to the ultracentrifuge after it had attained full speed. They had also applied a new type of light source giving a more uniform luminosity. Furthermore, they had automated the process of taking photographs at predetermined, successive intervals of time. This made it possible to operate two centrifuges simultaneously.⁴¹ Comparing their apparatus with Svedberg's they stated that the cost of their ultracentrifuge was only a few percent of Svedberg's. Furthermore, their apparatus could also be used for centrifuging large volumes of liquid by merely replacing the analytical rotor by a quantity rotor. Their most recent design could hold 150 cc and could be brought to speed, or stopped, in from five to ten minutes, depending on the desired field. If the need should arise still larger volumes undoubtedly could be handled.⁴² According to Wyckoff, the importance of ultracentrifugal study and sedimentation of viruses lay in the fact that the viruses bridged the gap between the simpler, 'dead' protein molecules and the unquestionably living smaller bacteria. This made the viruses attractive to all who were interested in attaching precise meaning to the term 'alive'. By allowing some of these viruses to be obtained in pure form the ultracentrifuge permitted a new experimental approach to this question.⁴³

Seeking to improve their earlier design Wyckoff and Lagsdin considered the following factors: (1) the ease and cheapness of manufacture, (2) the weight of the finished rotor, (3) the best angle of the centrifuge tubes, and (4) the elastic and 'explosion' limits of the finished rotors. The first factor dictated the use of light metal alloys like Duralumin or magnesium-rich alloys. With Duralumin higher fields could be reached and they were less easily susceptible to corrosion but the lower density of the magnesium-rich alloys made them preferable for most work with all but the highest fields. In choosing the angle which the axis of the centrifuge tubes should make with the axis of rotation they considered both the way the efficiency of centrifugation depended on tube angle and the influence of tube inclination on the weight of the finished rotor. Heads were built with tubes making angles of 20°, 25° and 30° with the rotation axis. From their performance it appeared that the choice of angle should be a compromise. By centrifuging standard solutions and analyzing top and bottom fractions, it was determined that the 20° angle gave somewhat more rapid sedimentation than the 25° and decidedly quicker sedimentation than the 30° angle. The rotor weight, however, mounted so fast with decrease in angle that the increased time and driving energy required to start and stop the 20° rotors became to great a disadvantage. Furthermore, for high fields the centrifuge tubes collapsed more readily the more erect they were placed. Based on this experience they chose to make all their following rotors with a 25° tube angle.⁴⁴ The single most costly item that should be purchased in building up a

quantity ultracentrifuge was the thick special steel pot surrounding the rotor. However, after carrying out some explosion tests in an outdoor pit in which some of the needed protection was supplied by the surrounding earth, they concluded that a cheaper centrifuge could be built without apparent loss of safety by making the vacuum pot of brass tubing set in the ground or in a bed of sand.⁴⁵

For Wyckoff, the ultracentrifuge provided a means of investigating a class of macromolecular substances which could hardly be studied by other means. Until the mid 1930s most work on biologically active materials had been upon the 'simpler proteins'. Such substances had molecules with weights up to about half a million and were stable enough to be concentrated and purified by the chemical action of simple organic reagents or salts. A few still larger molecular materials had also been isolated in this way - notably the haemocyanins and the TMV protein by Stanley. But most viruses were severely damaged or destroyed altogether by these comparatively mild chemical procedures so other methods should be used. According to Wyckoff there were two alternatives - ultrafiltration and ultracentrifugation. Both could be and were used for the isolation and purification of macromolecular substances and for their subsequent characterization and study. The advantage of ultrafiltration was that it exerted a minimum of effect on the unstable macromolecules; it had the disadvantage that the amount of material it would yield was severely limited. In this respect quantity ultracentrifugation was a very attractive alternative. But ultracentrifugation was not a goal in itself but part of a way of gaining more information on the biological activity of certain substances. The main reason for developing the quantity ultracentrifuge was the desire to get macromolecular substances in crystalline form for X-ray diffraction study.⁴⁶ Also the results of experiments with the analytical ultracentrifuge were not a goal in itself. These too were part of a way of gaining more insight in biological processes. Ultracentrifugal studies thus were always followed by other studies of the same material - it was a way of preparing materials for other investigations. This implied that as soon as it could supply materials and information in sufficient quantities, its further development could stop, which was the case around 1937/38. Furthermore the driving person behind the development at Princeton, Wyckoff, left the Institute in 1938 to join the staff of Lederle Laboratories.⁴⁷

Analytical ultracentrifuges - Bauer and Pickels

Pickels and Bauer had started with the development of the quantity type of ultracentrifuge. Over time, Bauer got also interested in the analytical type, and after Wyckoff had left for Princeton, taking along his apparatus, Pickels built

such a machine for Bauer.⁴⁸ Early 1937 Bauer and Pickels published a comprehensive description of their analytical ultracentrifuge in the *Journal of Experimental Medicine*, describing also a number of modifications. One change introduced was a reduction of the diameter of the driving turbine to 35 mm in order to minimize air friction. The apparatus is shown in figures 5.4 and 4.5.

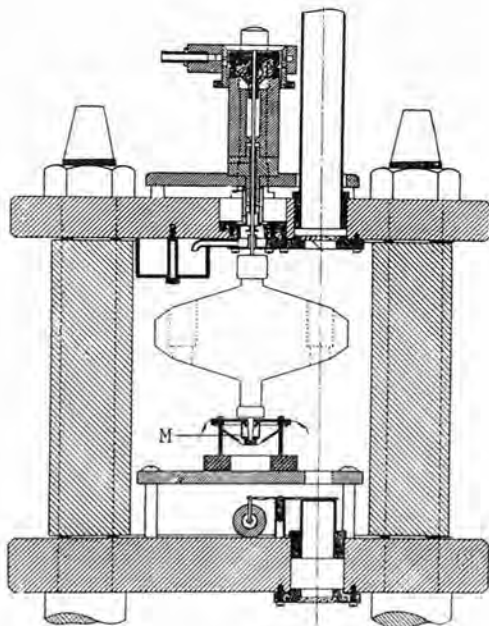


Figure 5.4

Analytical ultracentrifuge. (Bauer and Pickels, 1937, p.569).

Referring to their own experience and to Svedberg's they concluded that ultracentrifuge rotors with transparent cells could be made to withstand considerably greater centrifugal force if they were made oval rather than circular in shape. The two holes cut into the rotor opposite each other to accommodate the transparent cell and its counterbalance resulted in an asymmetrical distribution of stresses during rotation. The danger of rupture was much diminished and the maximum speed obtainable materially increased if the excess of metal was removed from the solid sections along the periphery furthest from the holes. Strength was also added to the rotor if its thickness was progressively increased from the periphery toward the centre as much as the design would permit. From Svedberg they had also copied the cell design and his optical system. The entire centrifuge assembly occupied two rooms. Heavy seamless steel pipes which extended through the wall between the rooms, formed the main body of the cameras. In the room

which housed the centrifuge the ends of these camera tubes were mounted one above the other in a heavy steel support, which in turn was bolted to a large concrete block. In the other room each tube was mounted on a separate hollow steel column; these columns were filled with concrete and their lower ends were embedded in square concrete blocks (photo 9). In order to obviate the transmission of troublesome vibration from the building to the camera systems, all three blocks as well as the centrifuge chamber itself were mounted on soft rubber pads.⁴⁹ Many precautions were taken to keep the rotor from heating up during centrifugation and at various locations thermocouples were fitted to keep a record of temperature fluctuations in various parts of the centrifuge. Successful operation of the centrifuge also depended upon having approximately constant pressures in all the air lines supplying the various parts of the driving mechanism. To this end a system of regulators and controls was developed. With the driving pressure set at 80 psi., about 12 minutes of acceleration were necessary for the rotor to reach a speed of 60,000 r.p.m., and to maintain that speed a reduced driving pressure of about 18 psi. was sufficient. They could keep the speed constant to within a fraction of 1 per cent without any difficulty. To bring the rotor to a full stop from 60,000 r.p.m. required about 20 minutes.⁵⁰

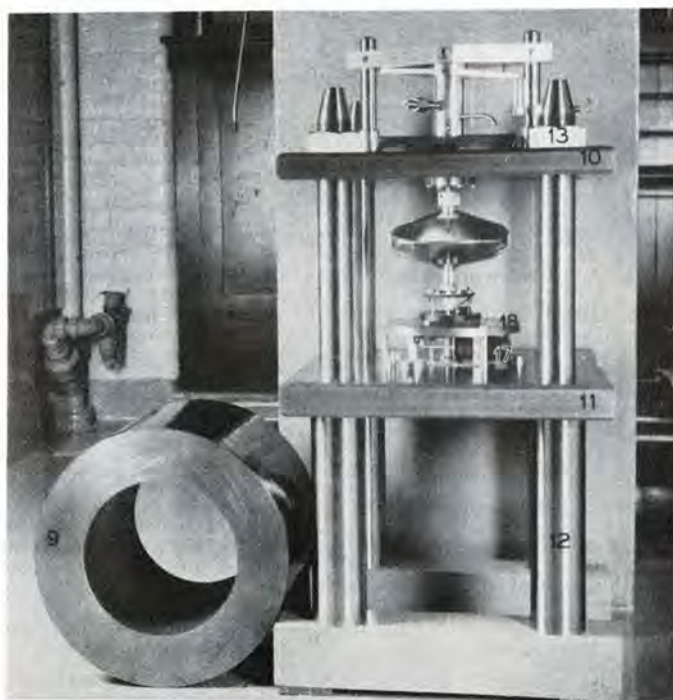


Figure 5.5

Analytical ultracentrifuge. (Bauer and Pickels, 1937, p.570).

After Pickels had left the University of Virginia, Beams had also continued developing the vacuum ultracentrifuge. In 1936 he planned to start working on electrical and steam drives and also planned to start an investigation of the best rotor material. For this work Beams had applied for a grant with the Rockefeller Foundation (see Chapter 3). Weaver consulted Pickels on this proposal, and Pickels response was that the proposal was sound and important, but that Beams' program was too large. Pickels felt that Beams should concentrate on the development of a simple, self-contained steam or electric drive, including accurate speed control, but should not attempt a systematic exploration of materials, designs, heat treatment, etc., for rotors. He felt that the latter problem was too large and complicated to be attempted by Beams under the proposed grant, and also felt that this problem was now well in hand in Svedberg's laboratory and at the Rockefeller Institute. They had recently made a new rotor of elliptical shape, following the suggestion Svedberg made on his visit (see below), and found that it spun perfectly stable. It enabled them to reach speeds about 30% higher than before. At the same time, they had increased the depth of their cell considerably. These two factors now gave them a resolving power effectively equal to that of Svedberg's instrument.⁵¹

The main limitation for the rotational speed was the strength of the rotor. With a seven inch rotor, the same size Svedberg was using, the maximum speed would be about 48,000 r.p.m., giving 166,000 g in the cell. In order to attain greater centrifugal forces with comparative safety they thought they would need to use steel. Before employing steel rotors routinely, they wanted to investigate their breaking points and safety margins. They contacted the U.S. Steel Corporation in order to discuss the point.⁵² One of the main advantages of the light alloys was that in case of rotor explosion the energy released was considerably lower. Furthermore, the light alloy rotors were much softer and much less destructive even at the same energies. Going to steel rotors would mean that they would have to increase the strength of the protective casing considerably. The casing they had was already being considered too thin. They had originally used a 3/4" steel pipe which made Watson, who had worked with Svedberg, remark that somebody would be 'going to be sacrificed to science if they don't fix up a better protection'.⁵³ They now set out to construct a 3" chrome nickel steel protection horizontally and 2" vertically. Svedberg used a 5" protecting case but because he used steel rotors their arrangement was still considered to be considerably safer.⁵⁴ When next the oval rotors allowed them to reach 60,000 r.p.m. they turned away from the idea of using steel rotors.

A problem with the oval shaped rotor compared to the one with a circular cross section was that with the first increases of temperature due to the residual air in the vacuum chamber were found to be considerably more pronounced, mainly because higher speeds were used. However, these temperature rises were not

accompanied by temperature gradients sufficiently great to cause detectable convection currents within the fluids of the cell. Furthermore, they succeeded in bringing down the pressure of the residual air by one order of magnitude by the installation of an additional pump, with which the pressure in the chamber was maintained at less than 1 micron of mercury. Preliminary experiments with the lower pressures had showed temperature rises of only 1 or 2 °C. in the rotor during several hours' operation at high speed.⁵⁵ Except for the use of compressed air for driving the ultracentrifuge they had followed Svedberg's design as closely as possible. They gave full credit to Svedberg by stating:

"The work in developing the air-driven ultracentrifuge is greatly facilitated by the fact that many of the problems involved have already been solved by Svedberg and his associates, and a number of the mechanical features which have been developed by them through years of painstaking research are readily adaptable to the new type of centrifuge described above."⁵⁶

Next Pickels started making some improvements in the experimental set-up of the centrifuges, developing automatic devices to speed up operation, protect the instruments, etc. which he showed to Warren Weaver in October 1937. Weaver was impressed by his simple method of speed measurement based on stroboscopic observation but much more convenient than Svedberg's stroboscopic arrangement. Pickels had also constructed a new photo-micrometer. This instrument was not yet operating entirely satisfactorily, probably due to the fact that the galvanometer was of too long a period.⁵⁷ Pickels was also not satisfied with the set-up of the optical arrangements and would like to be able to use the refractive index method. In order to learn the details of the method and also to see the oil-turbine ultracentrifuge they visited Williams in Wisconsin as soon as his ultracentrifuge was installed.⁵⁸ (see Chapter 6).

In September 1936, Svedberg visited the United States. On this occasion Warren Weaver took the initiative of arranging a meeting between Svedberg, members of the Rockefeller Foundation staff and Americans who were working with ultracentrifuges like Bauer, Pickels, Williams and Wyckoff. Beams could not be present because of other obligations.⁵⁹ During this visit Svedberg also visited the Rockefeller Institute Laboratories where Pickels and Bauer demonstrated the air-driven ultracentrifuges to him. Svedberg was very impressed by what he saw. A few days later he wrote Bauer:

"The morning I spent in your laboratory ranks among the best memories from my last visit in America. You and your group certainly have accomplished wonderful things. The centrifuge drive you have developed is really extremely elegant and I hope you will find it possible to use it to full advantage for the measurements of molecular sedimentation."⁶⁰

Because he thought they had constructed a very good machine he invited Bauer and Pickels to write a chapter on the apparatus for the monograph on the ultracentrifuge which he was editing with Pedersen. While working on this chapter they also continued developing the apparatus. One of their most difficult problems appeared to be to devise a satisfactory method for measuring the rotor temperature during a run. A radiation couple placed in a fixed position very close to the rotor did not work in their centrifuge, as during acceleration the rotor passed through a period of pronounced processional motions at lower speeds. They hoped that a thermocouple brought in contact with the rotor through an electro-magnetic arrangement would eventually prove satisfactory. They were anxious to have this difficulty solved, as they planned to study the working characteristics of their centrifuge from various angles, by carrying through the complete process of molecular weight determination by Svedberg's method on a series of proteins such as egg albumin, haemoglobin, edestin, excelsin, etc., using the data of Svedberg and his co-workers as standards for comparison. They planned using both the absorption method for monodisperse systems, and refractive index method for known mixtures. Concerning the chapter for Svedberg's monograph their original plan was to present actual values obtained along with a description of the apparatus. But appeared that they would not be able to have all this ready in time and they therefore felt forced to limit themselves to giving a description of the apparatus and the sedimentation values obtained by the absorption method alone.⁶¹ Two months later, however, they found a satisfactory method for measuring the temperature. They added an extension to the lower end of the rotor which rotated in a small pool of mercury. The pool was insulated with silk cords and had thermocouple junctions directly connected with it (figure 5.4; m). This arrangement gave accuracy in temperature measurements within two-tenths of one degree.⁶² However, after they had solved this problem they found that there was a considerable amount of heating taking place in the oval rotor during runs. In fact, with a vacuum of about 15 microns mercury maintained in the centrifuge chamber, the rotor temperature rose at times from 10-20° at the end of a three-hour run at a speed of 60,000 r.p.m. They thought of adopting Svedberg's technique of using hydrogen under reduced pressure to provide facilities for conducting heat away from the rotor, but before doing so, they decided to explore the possibility of using a greater degree of vacuum for the purpose of reducing air friction to a minimum and thereby preventing excessive heating of the rotor. To attain such a vacuum, an oil diffusion pump was built and added to the vacuum system. With this arrangement the problems encountered had disappeared. By using the oil diffusion pump, a vacuum pressure in the chamber measuring only a small fraction of one micron of mercury was easily obtained, and as a result of this the rotor temperature rose not more than 2 °C. above that of the chamber after prolonged

runs. On the whole, Bauer wrote Svedberg in connection with his chapter, most of the difficulties in developing the air-driven ultracentrifuge appeared to have been solved and the instrument was now in the stage where it could be used as a practical aid in research. Its development had been greatly facilitated by the fact that many of the difficulties had already been solved by Svedberg and his associates, and most of the accessories adopted for his centrifuge were readily adaptable to theirs. The rotors as described had withstood very well the speed of 60,000 r.p.m. How much more they could stand, they had not tested as they believed that this speed would be sufficient for routine work.⁶³

In the ultracentrifuges he had designed for Bauer, Pickels had used the air-support he had already developed while at Virginia. Although this bearing had been used successfully for several years its optimum performance required a steady flow of air that had to be controlled within relatively narrow limits. As with all centrifuges, the apparatus in which the turbine was employed was subject to appreciable vibrations at certain critical speeds. He therefore designed a new type of bearing, the so-called oil-damped air bearing, which automatically adapted the support to variations in the pressure of the air supply. He first tested the new support in connection with the quantity ultracentrifuge. After its practicality had been demonstrated he simplified and improved the design step by step, with the specific purpose of evolving a convenient arrangement for use with the analytical ultracentrifuge. To distinguish it from other designs the term 'turret drive', suggested by its external appearance, was adopted.⁶⁴ The new drive operated very smoothly. Rotors could be speeded up to 30,000 r.p.m. in 5-30 minutes, depending upon the driving pressure and their weight and stopped again in 7-32 minutes. If there should be a momentary failure of the air supply, the turbine would gently lower itself and ride on a bronze bushing without being damaged. Precession and oscillation of the rotor were absent above 4000 r.p.m. Describing this new drive in *Review of Scientific Instruments* Pickels indicated that the oil-damped air bearing probably could be applied to driving mechanisms of any size. The dimensions did not appear to be critical in any respect, it being necessary only to embody the essential features which were capable of functioning in accordance with the principles he had described.⁶⁵ In the same issue of the journal he also described the speed-measuring device and an automatic timing device for the photography of sedimentation during centrifugation.⁶⁶

Because the new drive was considered a very definite improvement over the earlier type they completely rewrote their chapter for Svedberg's monograph on the ultracentrifuge.⁶⁷ The new drive also eliminated the use of a cross arm which served as the air-distributing chamber. This gave more space on the top of the vacuum chamber and gave more space for the installation of the optical systems for the photographing of sedimentation. They used this advantage to introduce a

second set of windows in the vacuum chamber and to arrange the optical systems so that the refractive index system as well as the absorption system could be used simultaneously in photographing sedimentation in a run. In the study of viruses, which, because of their large size, scattered light and made the application of the refractive index system unsuitable, it seemed desirable to have available an arrangement by which both methods could be employed simultaneously. Because the drive shaft was considerably shorter in the new type of drive there was much less vibration and precessional movement in the centrifuge, especially during the acceleration when the rotor passed through certain critical speeds. The oil-damping feature of this drive made the bearing pressure much less critical than with the old type of drive where variation of a fraction of a pound per square inch in the bearing pressure caused considerable disturbance in the motion of the centrifuge. With this new type of drive the bearing pressure might be varied anywhere from seven to twenty-five or more pounds without causing vibration of precessional motions in the rotor.⁶⁸

Pickels' principal immediate assignment at the Rockefeller Foundation was to perfect high speed angle centrifuges and optical ultracentrifuges which would be suitable for the investigation of filterable viruses, particularly the yellow fever virus. The long-range problem involved the use of such equipment to purify viruses and to study their physical characteristics through the measurements of sedimentation rates. With the passage of time, the scope of his job expanded to include the development and application to virus research of many different instruments and physical methods. He considered his position ideal in many respects, especially as regards the opportunity of enlarging his experience in the practical aspects of designing mechanical and optical equipment. His section of the laboratory was comparatively independent and within broad limits, he was free to choose and direct his own program of research. By 1941, he had several assistants, including an instrument maker, a draftsman and a graduate physicist. At that time there was a considerable demand for their newly developed high speed electrical centrifuges and Pickels was responsible for these being delivered properly. However, Pickels did not feel completely at ease with the Rockefeller Foundation. The overall goal of the Foundation was to do research in the field of experimental medicine. Having developed the physical equipment which constituted his first assignment, Pickels found an increasing proportion of his time taken up with the type of work which was not in line with his experience and 'natural inclinations'. While he appreciated having learned a lot about medical research, his first love had always been the tackling of purely physical problems and the design of physical equipment. He had many ideas on such problems but found that he had little opportunity for testing them out himself or passing them on where they

might be of value, or even discussing their practicability with 'kindred souls'. He therefore applied for a job with the Sperry Gyroscope Company, mentioning these considerations in his letter of application. However, they had no position for him and Pickels, for the time being, remained affiliated with the Foundation.⁶⁹

In the meantime Pickels had spent most of his time 'perfecting' the apparatuses. A problem of the angle centrifuges he had developed that remained, in spite of the numerous improvements in their mechanical details, including the substitution of various electrical drives by Beams, was that these centrifuges were not characterized by the simplicity of mechanical construction and the convenience of operation which had enhanced the usefulness of the lower speed machines. Pickels had therefore developed a scheme in which one of their angle rotors was connected to a commercially available electric motor. This rotor spun in air. A protective housing was recommended because some unforeseen failure might cause a disengagement of the rotor. This centrifuge could be operated routinely at 17,000 r.p.m. Especially with good ventilation the temperature increase of the rotor would be a few degrees which made the scheme applicable to many experiments.⁷⁰

In the beginning a criterion for safety of the rotor was that it should show no permanent distortion during a number of test runs at a roughly estimated maximum speed. Afterwards the rotor was usually operated somewhat below that speed. In practice this appeared not to be a reliable procedure because sometimes after a few hundred or a few thousand runs the rotor might become fatigued and rupture without any obvious warning.⁷¹ Seeking to be able to use high speed angle centrifuges to full advantage in comparative safety, Pickels conducted a theoretical investigation of the magnitude and the nature of stresses developing at various points within rotors of different designs and compared the properties of the materials from which the rotors were generally constructed. To this end he developed a graphical method for determining mechanical stresses in high speed angle centrifuges. He concluded that a properly designed rotor with a diameter of 20 cm and accommodating several hundred cubic centimeters of fluid could operate at speeds up to 50,000 r.p.m. for thousands of runs.⁷²

In 1942 Pickels published a long review article in *Chemical Reviews* entitled 'The Ultracentrifuge - Practical Aspects of the Ultracentrifugal Analysis of Proteins'. In the introduction he wrote:

"Svedberg and Rinde proposed the name 'ultracentrifuge' for the new research tool and recommended that the term be reserved to denote an instrument by means of which sedimentation in a centrifugal field is measured quantitatively. They suggested that an ordinary laboratory centrifuge of high speed might be called a 'supercentrifuge'. However, in recent years it has become the practice of many investigators to associate the term 'ultracentrifuge' with any type of high-speed centrifuge rather than with the original connotation of quantitative measurement."⁷³

He described various aspects of the ultracentrifuge method, including a thorough description of various optical methods for registering the process of sedimentation. The refractive scale method developed by Lamm was subject to less optical errors than Svedberg's original light-absorption method. Another method was the so-called cylindrical lens method developed by Philpot who had obtained an ultracentrifuge made in Svedberg's workshop (see Chapter 6). This method, which was the first to record automatically the refractive index curves with the ultracentrifuge, was optically less sound than the Lamm's refractive-index method, but it was considerably more convenient in operation. Pickels had also used the cylindrical lens method and his experiences indicated that even with comparatively inexpensive optical parts a precision of measurement could be attained which was quite sufficient in view of the many minor uncertainties involved in the ultracentrifugal method. There did not exist one best method for all situations. For instance, since the precision of the refractive method depended on the magnitude of the concentration gradients present rather than on the concentration itself, the absorption method was sometimes more applicable, e.g. with unusually ill-defined boundaries or with very inhomogeneous preparations.⁷⁴

In sedimentation experiments it was necessary to know the diffusion constant of the material in the cell. In the earlier experiments of Svedberg, determinations of the diffusion constant were attempted upon the material under study while it was sedimenting in the ultracentrifuge. An argument in favour of the procedure was that the environmental conditions were identical for both sedimentation and diffusion measurements. However, in later years it was found that the diffusion values obtained in this manner were not very reliable and for later experiments Svedberg determined the diffusion constant in a separate diffusion apparatus. For this procedure the material had to be obtained in pure form which was not always possible. To solve this problem, Pickels had developed a method with which he hoped that reliable diffusion measurements could be made in the ultracentrifuge under certain conditions. It would offer great advantages in the study of mixtures the individual components of which could not conveniently be isolated in pure form for diffusion measurements. With the vacuum-type ultracentrifuge it was possible to decelerate the rotor to very low speeds without disturbing boundaries that had been created at high speed. The boundaries were then allowed to diffuse, and diffusion constants were determined from measurements taken at the low speed. With insignificant centrifugal force, the migration of the boundary became negligible and the principal objections to the determination of diffusion constants in the ultracentrifuge cell were avoided. For the sectorial shape of the cell minor corrections could be applied.⁷⁵ Pickels also improved the cell to avoid leakage, distortion, breakage of quartz windows, and lack of facilities for proper alignment. He investigated these difficulties and provided some remedies, particularly through

the strengthening of cell parts, the use of a specially coated Duralumin centerpiece, the provision of a key for alignment, and an arrangement for always orienting the windows in the same manner to prevent reversal of stresses.⁷⁶

During the war years Pickels and the IHD laboratories were assigned various duties for the armed services. They got involved in the large scale production of yellow fever vaccine and altogether made some 25 million doses. Pickels designed various arrangements for handling this large scale production and, for the purpose, also had to become acquainted with the freeze-drying technique. Before the war he had three rooms plus a shop in the basement of the institute but for the vaccine production they got a whole extra floor. He published a joint paper with Bauer on this work. During the war the armed services also had problems with processing and freeze-drying blood-plasma. There were different companies charging a variety of different prices and they wanted to know what was needed and what it should cost. Thereupon, the surgeon-general set up a group to make a survey, of which Pickels was made the scientific adviser because of his experience with the yellow fever vaccine. Pickels was also appointed to the National Defense Research Committee.⁷⁷

At the end of the war Bauer was assigned to European duty. A few months later Pickels resigned from the staff of the International Health Division.⁷⁸ Bauer's work with the ultracentrifuge was continued by Duncan MacInnis and Alexandre Rothen. Their primary interest was in determining molecular weights as accurately as possible. To improve the sharpness of separations, Rothen provided freezing coils so that his centrifuge could be operated at 0 °C in vacuum. The errors that remained in determining molecular weights were due largely to the difficulty of measuring accurately and controlling the temperature of the centrifuge rotor. It proved very difficult to solve this problem. Because in general the apparatus performed very satisfactorily it was hardly developed any further. Subsequent modifications largely came from the outside, for example Beams' scheme for electromagnetic speed control, which was applied to their ultracentrifuge by Blum in their instrumentshop soon after it had been published by Beams.⁷⁹

Notes

The meaning of the various abbreviations used is explained in the notes to Chapter 2.

1. Gray (1951); and Dr. E.G. Pickels, private communication.
2. Pickels to Bauer, 16 October 1934 (EGP).
3. Pickels to Bauer, 26 November 1934 (EGP).
4. Bauer to Pickels, 1 December 1934 (EGP); and Dr. Edward G. Pickels, private communication.
5. Bauer to Pickels, 17 December 1934 (EGP).
6. Bauer to Pickels, 18 December 1934 (EGP).
7. Sawyer (RF) to Pickels, 5 March 1935 (EGP).

8. Pickels to Sawyer, 9 March 1935 (EGP).
9. Sawyer to Pickels, 12 March 1935 (EGP).
10. Brown (AAAS) to Pickels, 18 June 1935 (EGP).
11. Bauer to Pickels, 28 June 1935, (EGP).
12. (RAC:1.1/100/10/80) Sawyer (RF) to Gasser (RI), 21 January 1936.
13. Anon., 'The making of Instruments for Scientific Research' (RAC).
14. Bauer and Pickels (1936a), p.503.
15. Bauer and Pickels (1936a), pp.503-504.
16. Bauer and Pickels (1936b).
17. Bauer and Pickels (1936a), pp.510-512.
18. Bauer and Pickels (1936a), pp.516-520.
19. Bauer and Pickels (1936a), pp.526-527.
20. (RAC:1.1/100/10/80) Bauer to Sawyer (RF), 5 October 1936.
21. (RAC:1.1/100/10/80) Sawyer to Bauer, 17 October 1936.
22. (RAC:1.1/100/10/80) Bauer to Sawyer (RF), 23 October 1936.
23. Dr. Edward G. Pickels, private communication.
24. Corner (1964), pp.183-185.
25. Biscoe, Pickels and Wyckoff (1936a), p.246.
26. Biscoe, Pickels and Wyckoff (1936a), pp.246-248. Biscoe was one of Wyckoff's students.
27. Biscoe, Pickels and Wyckoff (1936a).
28. Biscoe, Pickels and Wyckoff (1936b), p.39.
29. Biscoe, Pickels and Wyckoff (1936b).
30. Biscoe, Hercik and Wyckoff (1936).
31. Wyckoff (1936), pp. 291-292.
32. See for a historical description of Stanley's Crystallization of the Tobacco Mosaic Virus and its reception in the among bio-scientists: Kay (1986).
33. Wyckoff and Corey (1936).
34. Wyckoff, Biscoe and Stanley (1937).
35. Stanley and Wyckoff (1937).
36. Stanley to Svedberg, 26 March 1937 (UUp-Lib).
37. (RAC:1.1/800/7/76), Weaver's diary, 28 August 1936.
38. Wyckoff and Lagsdin (1937a), pp.74-75.
39. Wyckoff and Lagsdin (1937a), p.75.
40. Wyckoff (1937a), p.391.
41. Wyckoff and Lagsdin (1937a), pp.76-77.
42. Wyckoff (1937b), p.92.
43. Wyckoff (1937b).
44. Wyckoff and Lagsdin (1937b), p.427.
45. Wyckoff and Lagsdin (1937b), p.428.
46. Wyckoff (1938), p.361.
47. Anon., 'The making of Instruments for Scientific Research' (RAC).
48. (RAC:1.1/800/7/76) Weaver's diary, 28 August 1936.
49. Bauer and Pickels (1937), pp.567-577.
50. Bauer and Pickels (1937), pp.578-583.
51. (RAC:1.1/252/1/10) Weaver's diary, 7 December 1936.
52. (RAC:1.1/100/10/80) Bauer to Johnson, 16 September 1936.
53. Watson to Svedberg, 10 August 1935 (UUp-Lib).
54. (RAC:1.1/100/10/80) Weaver's diary, 22 December 1936.
55. Bauer and Pickels (1937), pp.583-584.
56. Bauer and Pickels (1937), pp.584-585.
57. (RAC:1.1/100/10/81) Weaver's diary, 14 October 1937.
58. (RAC:1.1/252/1/12) Bauer to Williams, 25 January 1937.
59. (RAC:1.1/800/7/46) Weaver to Svedberg, 25 August 1936.
60. (RAC:1.1/800/7/76) Svedberg to Bauer, 25 September 1936.
61. (RAC:1.1/800/7/76) Bauer to Svedberg, 8 October 1936.
62. Bauer to Svedberg, 16 December 1936 (UUp-Lib).
63. (RAC:1.1/800/7/77) Bauer to Svedberg, 4 February 1937.
64. Pickels (1938b), pp.358-361.
65. Pickels (1938b).

66. Pickels (1938a).
67. (RAC:1.1/100/10/81) Bauer to Svedberg, 27 April 1938.
68. Bauer to Svedberg, 28 July 1938 (UUp-Lib).
69. Pickels to Sperry Gyroscope Company, 28 November 1941 (EGP).
70. Pickels (1942a).
71. Pickels (1942b), p.101.
72. Pickels (1942b).
73. Pickels (1942d), p.341.
74. Pickels (1942d), pp.347-352; see also Pickels (1944).
75. Pickels (1942d), pp.353-354.
76. Pickels (1942c).
77. Dr. Edward G. Pickels, private communication.
78. (RAC:1.1/252/1/13), 'Excerpt from Trustees Bulletin', December 1950.
79. Anon., 'The making of Instruments for Scientific Research' (RAC).

Chapter 6

WIDER USE OF ULTRACENTRIFUGES

6.1 SVEDBERG ULTRACENTRIFUGES

James Burton Nichols - DuPont Experimental Station

After Svedberg had left Wisconsin in the fall of 1923 Nichols continued working with the optical centrifuge they had constructed there. One of the main problems he encountered with this apparatus was that it developed considerable vibrations and that he wanted to increase the speed. Seeking to solve these problems he made some inquiries with the Sharples Specialty Company in Philadelphia, one of the leading manufacturers of centrifuges. L.D. Jones from the company replied that it would be practically impossible to obtain really high speed with rotating systems even very slightly out of balance, when those systems were supported in rigid bearings. It would also be almost impossible to secure approximately perfect balance in any rotating system except one consisting of rather small diameter shaft. Therefore, he argued, all high speed centrifugals were run in spring supported bearings, or were supported on flexible spindles. Jones enclosed blue prints of turbine wheels they used in their centrifuges, including also the nozzle.¹ In 1924/25 Nichols used the optical centrifuge primarily for the study of paint pigments comparing samples from various manufacturers. He wanted to relate their distribution of particle sizes to the 'physical constants' of these samples - such as hiding power, covering power, resistivity, etc. Some of the materials studied, however, were very sensitive to mixing with his 'crude' machine.²

After his first experiences with the optical centrifuge Nichols thought that the possibilities of general use of the centrifuge as a tool in determining particle size of colloidal material seemed rather good. It then occurred to him that a patent on the device would aid him in obtaining a desirable position with some company when he had finished his work for the doctorate.³ Svedberg was rather reluctant to take

out a patent. He thought that there was not much money to get out of it in its then 'undeveloped' state and that it would take a lot of development to get a type that could be brought on the market. He was convinced that the thing had 'a very high scientific value' but there were so many details to be considered that he could not see when it would be sold. In the meantime they would only be losing money.⁴ However, Svedberg did not push his objections too hard and finally let Nichols have his way. Nichols was anxious to have Svedberg's name with his under the patent which was finally granted on both names in 1927 under the name 'Analytical Centrifuge'.⁵

In 1925 Nichols went to Upsala under a grant from the 'American Scandinavian Foundation' to finish his doctoral dissertation. His research mainly concerned the application of the newly developed ultracentrifuge for the study of egg albumin (see Chapter 2). During his second sojourn in Upsala in 1927 he was offered a job by the Experimental Station of the Chemical Department of DuPont DeNemours & Company. DuPont was established in 1802 as a manufacturer of gun powder and had subsequently developed to one of the important manufacturers of all kinds of explosives. In the first part of the twentieth century DuPont was trying to break away from the focus on explosives and trying to become a manufacturer of all kinds of chemical materials. Part of this policy was to start a new program on fundamental research in several fields in the mid 1920s. Elmer O. Kraemer, who was also at Mathews' laboratory in Wisconsin when Svedberg and Nichols developed their first optical centrifuge, was appointed the head of the physical-chemical/colloid section of this new program. The researchers at the Experimental Station were allowed to do a type of 'basic research' which was not directly linked to the products the company was manufacturing at the time. The research covered in a more general sense the field DuPont was working in with the philosophy that some basic new findings would come out every now and then which would be exploitable by the company. Kraemer suggested that they should obtain an ultracentrifuge and that Nichols would be the perfect man to work with it. It could be used for the study of colloidal materials like paint, photographic emulsions, rubber, etc.⁶ DuPont followed Kraemer's suggestion and offered Nichols a job, at the same time asking Svedberg to manufacture an equilibrium ultracentrifuge for them with which Nichols was expected to work in Wilmington. Mid 1927 they inquired whether Nichols could already give them some instructions concerning the constructions of the ultracentrifuge which could be carried out by their machinist before he would arrive in January 1928.⁷ Nichols replied that Svedberg was willing to supply the blue prints but that these were not at all up to date because many changes had been made. Making new ones would cost about \$ 100,-. The Baltic Cream Separator would cost \$ 50,- and Svedberg's mechanician

could cut off the bowl and make a special rotor for it. The actual separator represented only one of the minor costs; the quartz windows would be about \$200,- whereas the microphotometer would cost between \$ 500,- and \$ 600,-.⁸ DuPont gave Nichols a free hand to buy the necessary parts. They also indicated that if their present laboratory would not be suited for the ultracentrifuge they would construct a separate building for it.⁹

During the first part of his job at DuPont Nichols mainly worked on the further development of the ultracentrifuge itself, keeping closely in touch with Svedberg on the latest developments in Upsala. One of the important problems for Nichols was to develop cells which could withstand organic solvents because of the type of substances he was investigating, like cellulose.¹⁰ Because of the basic nature of the research at the Experimental Station Nichols was also allowed to continue his research on egg albumin. Furthermore, they sometimes performed experiments for third parties, like investigating a certain pigment for the 'Krebs Pigment & Chemical Company'.¹¹

Starting to work with the newly arrived ultracentrifuge Nichols faced a number of problems. One problem, in Nichols view, was that the theoretical background for ultracentrifugal determinations was only poorly developed. De basics were founded on a theoretical analysis by Max Mason and Warren Weaver from the mathematics department of the University of Wisconsin on sedimentation equilibrium in a uniform gravitational field. The field in an ultracentrifuge, however, was non-homogeneous. Nichols approached Weaver whether he could extend his analysis to sedimentation in a centrifugal field and sent him the required data for such an analysis.¹² The analysis, however, appeared too complicated for Weaver to treat mathematically. A year later Nichols also approached Weaver with the problem of the diffusion constant which appeared to be too low in certain cases.¹³ Furthermore, like Svedberg, Nichols encountered problems with the ultracentrifuge based on the Baltic cream separator, especially with respect to vibrations. When he learned in 1929 that Svedberg had developed a new type, based on a Siemens electrical motor, he also tried to obtain such a type. This machine with the auxiliary equipment would cost about \$ 5,000.- It would take some time, however, to construct such a machine for Nichols, because it performed so well that Svedberg was constructing three of them for his own laboratory.¹⁴ Nichols, however, would like to have some modifications introduced because he would like to have the camera in a horizontal position whereas Svedberg used it in a vertical position because he considered it more convenient to have the plate holder within reach of the floor. This necessitated the introduction of an additional prism above the centrifuge and also required to modify the support for hanging the camera.¹⁵ Svedberg preferred to have the camera in an upper room which saved space in case

several centrifuges would be running. The total length of the optical arrangement would be about 6 m.¹⁶ Svedberg advised Nichols to buy certain parts in the US like the lamp and the filters because they might break during shippage. He also gave some instructions for the arrangement of the apparatus which might necessitate some rearrangements in the available in the laboratory space.¹⁷ Another problem was that the power mains at Wilmington were not suited for the Siemens Drive Svedberg was using. So a special frequency generator had to be built which, according to Svedberg's experience, might take 6 months before it could be delivered.¹⁸ The ultracentrifuge arrived in Wilmington in July 1930.¹⁹

Because the DuPont Experimental Station was considered somewhat like a scientific laboratory it was quite natural for Nichols to publish in scientific journals. For instance, in 1931 he gave an overview of the ultracentrifuge work in the newly created *Physics* journal. He described the direct drive sedimentation equilibrium ultracentrifuge, which they had at the Experimental Station, and also Svedberg's oil turbine type.²⁰ In 1932 he published an article entitled 'The Ultracentrifuge and its field of Research' in *Industrial and Engineering Chemistry* in which he also discussed both types.²¹ However, the laboratory was arranged in a specific type of industrial setting which implied that there were limits as to what counted as relevant research. For instance, when Farrington Daniels from the University of Wisconsin proposed a cooperative research on the particle size of filterable virus²² Nichols replied that such would not be possible in terms of the company's interest. Also, because they were about to go on a five-day week, it became imperative to select their work more carefully. He gave Daniels some suggestions on how to pursue his work, one of which was to ask Svedberg to cooperate with him.²³

In the first years Nichols and Kraemer ran a lot of pigments for the pigments department. Later they worked on neoprene solutions which was then seen as a possible synthetic rubber. All sorts of requests came in from within DuPont. During that time the synthetic polymers became ever more important which also leant themselves for study in the ultracentrifuge. As the demand for runs grew they got ever more irritated by the time consuming character of a sedimentation equilibrium experiments which took in the order of days, or sometimes even weeks. As long as they were dealing with colloid particles or suspensions the low-speed was adequate and if they didn't have too many runs on the neoprene or the cellulose they could handle it. But when DuPont got a whole group of chemists working on polymers it became too much for the low-speed arrangement to handle.²⁴ Therefore, Nichols and Kraemer became interested in also obtaining a high speed ultracentrifuge in order to be able to make sedimentation velocity runs which would only take some hours. When Nichols saw Beams' article in *Science* on the spinning top he started

playing with the idea of adapting it to his needs. Beams obtained centrifugal forces of the order of 1,000,000 g with his spinning top and Nichols wondered if they could arrange the rotor to measure the concentration changes optically by making the bottom of the cell a mirror, and reflecting light through the liquid and back in the same direction. He suggested to Svedberg that if this arrangement could be used for their purposes it would furnish a very simple machine.²⁵ Svedberg, however, did not have much faith in it. In Brussels and Paris he had seen such spinning tops based on the principle of Henriot and Huguenard, on which Beams had based his arrangement, and, to him, it appeared 'extremely difficult' to adapt them to their purposes.²⁶

July 1931 Nichols wrote Beams a letter showing his interest. He would like to visit Beams, in order to get a better idea of 'the mechanical problems involved in the construction of such instruments, the operating characteristics, and the general performance'.²⁷ Beams answered that he would be happy to show Nichols various types of centrifuges. However, shortly before he had let the centrifuge rotate a little too fast and it 'blew up'. Weed, their instrument maker, who did the machine work would be away until late August so Beams would not be able to demonstrate this type until Weed would have had time to make another. Nevertheless, he could show the simple type full of liquid rotating at full speed anytime. They were doing some biological experiments and were using a simple hollow rotor every day. He could also demonstrate how it was used to rotate a mirror.²⁸ A few days later Nichols and Kraemer visited Beams laboratory and were very satisfied with what they learned. Nichols planned to start the preliminary work immediately on a 'little toy rotor' to make sure that they would be capable of making the rotors run.²⁹ Svedberg and Nichols had already considered Henriot and Huguenard's principle in the 1920s because they were struck by the extremely high speeds that could be reached with it but at that time had decided that its application to the principle of the ultracentrifuge was doubtful because the diameter of the rotor was so small that the optical system would be difficult to arrange. When they saw Beams' description of a continuous flow type of centrifuge the idea occurred Kraemer and Nichols that the rotor could be hollowed out suitably so that the walls of the well would form part of the cell, the bottom surface could be made a mirror of Stellite or simply silver, and this cell could be made tight by screwing on a glass or quartz plate on the top of the rotor, using a suitable gasket to hold the liquid in at the outer end. A beam of light would then be directed down through the cell and be reflected from the bottom mirror, pass through the cell again, and either be photographed or measured directly by some means so that they would obtain a record of the concentration along the length of the cell during the time the centrifuge was in motion. After their return from the visit to Beams they started developing the 'air-bearing ultracentrifuge' for centrifugal forces 100,000 times

gravity or greater in which the sedimentation process could be viewed optically. Because this was not possible in the apparatus Beams had described Nichols called the 'Simple Ultracentrifuge',³⁰ as Beams had called it, a misnomer.³¹

Early 1932 they had found that the rotors could be made to run remarkably steady under proper conditions. The models Nichols had tried, however, showed considerable precessional motion but, as he wrote in a letter to Svedberg, he thought that could be eliminated.³² Svedberg still did not have much faith in the spinning-top principle. It might be that it would be of service in equilibrium measurements at high speed but in velocity measurements he considered it important to have a rather big distance from the centre of the cell to the axis of rotation. This because the centrifugal field should not be too inhomogeneous, and also the column of solution should be rather high. From this it followed that the rotor should have an outer diameter of at least 15 to 18 cm. It then would become too heavy for the spinning-top principle. After all, according to Svedberg, the mechanical properties of the rotor limited the centrifugal field which could be reached and that would not be any better with the spinning-top machine.³³

Another possible route for reaching higher rotational speeds was trying to make their equilibrium ultracentrifuge rotate more rapidly. Lansing, who worked at the Experimental Station on cellulose and its derivatives, wondered if the Siemens motor could be speeded up to 20,000 r.p.m. rather than 12,000 r.p.m. He hoped that this could be done by using a proper frequency transformer giving 300 or 400 cycles a second. He asked Svedberg if he could give some advice on this matter³⁴. Svedberg answered that he had already approached Siemens with the same question but that they had recently given up the manufacturing of that type of motor. They had developed a modified type which could be run normally at a speed of 15,000 r.p.m. This motor, however, would not fit in their ultracentrifuge. Nevertheless, Svedberg had ordered one in order to find out whether it would be possible to change the design of the centrifuge so as to allow of the using of it. He had also ordered a frequency generator for 300 cycles per second from a Swedish electrical firm. He hoped to be able to run the Siemens motor up to 18,000 r.p.m. with it.³⁵ Another problem with respect to the drive was that because of a variation of the voltage in Wilmington they got variations in the rotational speed of the centrifuges of several hundred r.p.m. In order to solve problem Lansing developed a 'differential gear' type of speed controller which kept the rotational speed almost as constant as the frequency of the power line.³⁶

Cellulose could only be studied in the ultracentrifuge using the index of refraction method. Therefore it could only be investigated with their second ultracentrifuge because the first was made in the time that only the light absorption method for registering the sedimentation had been developed. As they started working more and more with substances that did not display sufficient light

absorption they reconstructed the first ultracentrifuge so that it could also be used in connection with Lamm's index of refraction method. Nichols asked Svedberg to send him some photographic scales for this new arrangement. At the same time they also applied a new photographic lens which made it possible to shorten the distance from lens to photographic plate by nearly one half to about three meters.³⁷ The problem of Lamm's method was, however, that it was quite laborious. But as their main portion of the work was now on substances like cellulose and its derivatives and resins which either did not absorb ultraviolet light strongly or gave better results with the refractive index method, they saw no alternative. They would however be much interested in making the registration easier and wanted to discuss this matter with Svedberg when he would be coming to Wilmington in the summer of 1933.³⁸

During Svedberg's visit to Wilmington a number of items were discussed concerning problems they had with their ultracentrifuge. Their main wish was to obtain higher rotational speeds. With the spinning top it appeared very difficult to arrange the optical parts in a proper way and Svedberg kept emphasizing that the resolving power would be bad because of the small diameter of the rotor. The best way, according to Svedberg, would be to have an oil-turbine ultracentrifuge made by him. The DuPont researchers doubted, however, whether the company would be prepared to finance such an expensive project. They wondered whether it would also be possible to drive Svedberg's large ultracentrifuge with an electrical motor.³⁹ However, after some further consultation with Svedberg they came to the conclusion that it would be cheaper to buy an oil-turbine ultracentrifuge from him than to design and build an electric drive. In addition, they knew the oil-turbine would run while they were not sure of the electric drive.⁴⁰

During Svedberg's visit to DuPont they also visited Miss Seibert at Philadelphia who was working on tuberculin. Sometime after that she visited Nichols' group and saw their ultracentrifuge. She was in close connection with Dr. White from the National Tuberculosis Association who, in November 1933, gave a talk at a luncheon in Wilmington at which Dr. Stine, one of the directors of DuPont was also present. White spoke in complimentary terms of the attitude that industry took towards more academic research, and mentioned the relations between Nichols' group and Miss Seibert as an example. Stine thereupon brought him out to the Station to see the centrifuge, and a considerable part of the conversation with the researchers there dealt with the very much increased possibility for effective work if they had higher centrifugal speeds available of the order that Svedberg had in Upsala. Thereupon Stine told them to make a rapid estimation of what it would cost to buy such a machine as the budget would be made up the following month. Kraemer wrote up a project for the construction of an oil-turbine ultracentrifuge and soon thereafter the project was authorized.⁴¹

Svedberg sent them an estimation of the costs of the various parts of the ultracentrifuge which is given below:⁴²

1. Chromium-nickel steel rotor with turbines (tested at 70.000 r.p.m.)	\$ 700.00
2. Three solution cells (3, 6, 12 mm) and index cell of duraluminium and electron metal with tools	400.00
3. Centrifuge casing with bearings, turbine chambers, bolt system for mounting, thermocouples, shutters, etc.	2000.00
4. Oil Compressor (without motor)	1000.00
5. Two oil-containers with valves	700.00
6. Oil-cooler with valves	500.00
7. Oil-filter with valves	200.00

Kraemer wanted Svedberg certainly to furnish the first three items and quite possible they should also decide to take (4) to (7). However, they would like to withhold decision on the last four temporarily because they might have to pay a rather high duty on some or all of them. In addition, in connection with servicing and repairs, a domestic manufacturer could be of considerable help in saving time and money. Since their Engineering Department had a good deal of experience in handling liquids under pressure, Kraemer wanted to find out with their aid whether they could obtain one or more of these items in the US. In connection with this he asked Svedberg to send him the necessary data.⁴³ This, however, was very difficult for Svedberg. He did not doubt at all that the Wilmington people could construct the necessary items as well as he could do himself, but he simply had not got the data. The compressor had been changed several times to get it to fit their requirements. A series of measurements on the machinery would have to be carried out in order to collect this information and that would mean stopping their investigations for some time. Svedberg had planned to publish a description of the new type of oil-turbine ultracentrifuge but this had been postponed in the hope that still more improvements could be made. For this publication he would need exactly the kind of data Kraemer wanted and they would therefore have to collect them sooner or later but it would take a considerable time which they did not have because of other work that was going on. Furthermore, concerning the oil pumps Kraemer planned to buy in the US, Svedberg had tried several kinds without success. He did not think there was a pump on the market filling their requirements. The compressor which they used was designed especially for the purpose and had given excellent results. Svedberg did not think it was the only solution possible but he was anxious to get the DuPont equipment so that it would

work and, therefore, he thought it would be better to stick to the well known machinery which had proved satisfactory during several years intense work rather than to start experimenting with unknown things. One of the important points about the compressor for the centrifuge was that it should not let in any air and their construction was quite safe in this respect. In connection with this they had had endless trouble with a domestic pump which was used for the first high-speed ultra centrifuge. Svedberg expected that, after Kraemer et.al. had gotten to know the equipment through handling they would be able to introduce improvements but for the time being he was inclined to think that it would be better to copy their installations as closely as possible.⁴⁴

On the basis of these considerations Kraemer et.al. decided in the summer of 1934 to buy almost all of the apparatus from Svedberg. Its construction would take at least six months. At that time Svedberg was also heavily involved in finding an optimal rotor. He therefore advised Kraemer not to decide upon the rotor yet. Their present type reached 300,000 g but they had one under construction which might reach 600,000 g.⁴⁵ After some further experimentation Svedberg believed that the bigger rotor would, on the whole, be more efficient although the centrifugal field would be a little lower. Further improvement might then come from increasing the length of the column of solution in the cell.⁴⁶ Svedberg at that time had also come to the conclusion that balancing the rotor was quite essential and that each time, after recementing of a cell, rebalancing should take place. He was going to furnish the rotor and the cells satisfactorily balanced but it seemed to him that the Wilmington people would also have to get a balancing machine for checking the cells after repair, e.g. after putting in a new quartz-plate. Also they might wish to make new cells themselves later on. Svedberg therefore offered them to furnish a balancing machine of the type he had specially constructed for the purpose. It would cost around \$ 600. The commercial balancing machines cost about double that sum and, according to Svedberg, the accuracy they gave was not 1/5 of the precision they attained with their arrangement.⁴⁷ Kraemer replied to postpone the decision on a balancing machine to a later date when they had actually demonstrated the functioning of the machine in their laboratory. It might then be easier to ask funds for additional accessories.⁴⁸

During the further development of the rotors Svedberg et.al. had changed both design and material hoping to be able to increase the centrifugal field in two ways. They considered new construction quite good but the steel-material, although very satisfactory when tested in shape of test-rods had been a disappointment when used in big pieces for rotors. They found it impossible to remove inner strain completely and as a cause of this deficiency two rotors had exploded during the test runs - one in December 1934 and one in April 1935. These accidents caused

them considerable losses both in time and money. A new rotor of the same design but of a material similar to the one previously used was under construction at the time the stationary parts of the Wilmington apparatus were about finished. But, even if it turned out a success in the test runs it would take time to collect sufficient experience with it. Svedberg did not like to furnish Kraemer things that had not been tested and used for about a month in one of their centrifuges. After that it would have to be tested finally in Kraemer's centrifuge casing. In order to make it possible for Kraemer et.al. to acquire later on a rotor of the new type they were manufacturing at the time Svedberg had made an extra pair of turbine- and bearing-chambers and an extra pair of steel parts which fitted into Kraemer's centrifuge casing. Svedberg kept those in Upsala, without charging for them, and in case they would want a new rotor they would be furnished together with the rotor. In this way they would be able to exchange rotors easily. The price for the new rotor together with these parts would be \$ 965.⁴⁹

In order to install the ultracentrifuge Svedberg suggested that they should ask Charles Watson to help them who at that time was working at Upsala. In this respect, Nichols experience in working with the oil-turbine, gained in 1927, would be of little use because the apparatus was modified drastically since.⁵⁰ Kraemer followed this suggestion and also asked Watson to prepare a kind of manual for the operation and installation.⁵¹ In the summer of 1935 Watson came to Wilmington and started supervising the work on the foundations. The concrete work took much longer than he had expected, owing to the hard rock which had to be dug out, and the complicated procedure for waterproofing the outer walls to keep ground water out of the pit. Because of some other local conditions Watson wondered if it would be practicable to operate the centrifuge with the oil at say 25-28 °C. instead of 18-20°. In that case they could use the city-water for cooling water and keep the oil below that temperature in summer; and 8 months of the year they could do as well as 20°, he thought. However, this might cause trouble with the vacuum, unless they had an oil of extremely low vapour pressure. This might necessitate the installation an ice-box to cool the water in summer. Watson asked Svedberg if there would be any serious difficulties with lubrication, or with the determination of the temperature difference between the cell and the casing, - for the higher oil temperature. Another problem was that they were not able to locate the 'Lovis Oil' Svedberg was using. Texaco Co. claimed they had never heard of it. Watson suggested that it might be a Swedish name for the oil sent from America in bulk. He therefore asked Svedberg to ask the concern he purchased the oil from where they had obtained it. Meanwhile they were going about testing other similar oils, and comparing them with the samples.⁵² Svedberg did not see any fundamental problem in increasing the oil temperature. A problem might be that proteins often tended to deteriorate at those temperatures. For the Wilmington people this might

not be relevant however, as they were interested in other, more stable substances. Concerning the oil it appeared that the type Svedberg used was taken out of production.⁵³ Svedberg had stored enough oil to keep them supplied for a couple of years but this situation prompted him to start testing new types as well. He therefore was also very interested in knowing the type they would decide upon in Wilmington.⁵⁴

In the fall of 1935 the ultracentrifuge at the DuPont Experimental Station was installed and tested. The apparatus performed very well. By May 1936 they had made about 40 runs and things were gradually getting down to a routine basis.⁵⁵ They kept in close touch with Svedberg on further improvements but hardly developed any further modifications themselves because they had no serious troubles with the performance of the apparatus. They bought a balancing machine from Svedberg and were also interested in a new magnetic speed measuring device he had developed.⁵⁶ They also asked Svedberg to send them a sketch of a new arrangement for measuring the cell temperature.⁵⁷ Furthermore Svedberg sent them a new scheme for tightening cells.⁵⁸

Concerning the application of the ultracentrifuge Nichols and Kraemer continued working on substances they had been working on before and also sometimes cooperated with other researchers who were interested in ultracentrifugal analysis. For instance, early 1936 E.B. Sanigar from the 'Cancer Research Organization' came to Wilmington to study a number of proteins.⁵⁹ But usually such work for outside organizations was not appreciated by the company management. For instance, when some scientist asked Nichols to do a run with tobacco mosaic virus, shortly before Stanley crystallized it (see Chapter 5), the management did not approve of this service and argued that it would take too much time.⁶⁰

Although the researchers involved considered their work very innovative the DuPont Company Management held a different view. On the basis of ten years experience it was decided in 1937 that fundamental colloid and physical research of the type carried on by Kraemer's group did not pay for itself and therefore should be discontinued. This decision did not come as a big surprise to the group as there had been some indications before. This change in program did not mean complete discontinuance of their ultracentrifuge work but a very definite reduction in the amount and a change in objective. In the future, the objectives of their colloid and physical work were to be more definitely tied to immediate practical problems with no emphasis on publications and work of that sort.⁶¹ Nichols kept working with the ultracentrifuge on an incidental basis until 1942 when he was made head of the Physics Section of the Chemical Department of the DuPont Company.

Various Scientists

In 1927 R.O. Herzog from the Kaiser Wilhelm Institute in Berlin wrote Svedberg that he considered securing an ultracentrifuge. Svedberg considered Herzog to be a very good researcher in the field of macromolecular substances and wrote him that he would be very pleased if an ultracentrifuge would be set up in Herzog's laboratory. Svedberg stressed that he did not seek a monopoly in the field of ultracentrifuges; on the contrary, the more people would be working with ultracentrifuges, the better. However, the method had not yet been standardised so that it was necessary to use a number of smaller tricks in order to obtain good results. These tricks could hardly be explained in writing and would have to be learned while doing.⁶² Herzog thereupon asked Svedberg to be allowed to send a machinist to Upsala in order to learn the technique of construction.⁶³ This proposal was welcomed by Svedberg because he thought that a machinist would comprehend the details of construction more easily than a physico-chemist.⁶⁴ On the basis of this visit Herzog concluded that the construction of an ultracentrifuge was much more complicated than he had anticipated.⁶⁵ When they had finally constructed the apparatus they had a lot of problems with the cells. Their cells had to be different from Svedberg's because they wanted to investigate cellulose which necessitated the use of organic solvents. These cells, however, appeared to be very difficult to make tight.⁶⁶ Svedberg wrote him that they had encountered the same problem and that, furthermore, the light-absorption of cellulose was rather small whereas the absorption of the solvent was considerable. This implied that a new method for registering the sedimentation would be needed.⁶⁷ Late 1929 Herzog wrote Svedberg that he would discontinue his work on ultracentrifuges because he doubted whether his samples were sufficiently chemically pure.⁶⁸ Furthermore other methods became ever more important to him and, despite the efforts he had made, he found it quite impossible to work with the apparatus.⁶⁹

The Cellulose Company from Japan was also interested in obtaining an ultracentrifuge⁷⁰ but this probably did not work out into the actual construction of an apparatus.⁷¹ Hermann Staudinger from the Chemical Laboratory of Freiburg University, Germany, was also interested in obtaining an ultracentrifuge. Staudinger had proposed the concept of macromolecule in the early 1920s at a time that most chemist did not believe that such large molecules existed. This gradually changed in the succeeding years and by the early 1930s Staudinger's ideas became generally accepted. In 1931 he wrote Svedberg that in the preceding years he had come to the conclusion that colloidal particles of many macromolecular natural products constituted of long, thread-like molecules. The length of these could be determined by means of viscosity determinations. Staudinger wondered, however, whether Svedberg could determine the molecular masses of these particles by means

of his ultracentrifuge.⁷² Because Svedberg was unable to perform such experiments Staudinger asked whether one of his co-workers, Rudolph Signer, could be allowed to investigate the matter in Svedberg's Laboratory.⁷³ Signer would be welcome but Svedberg warned that determination on cellulose implied working with organic solvents which might create considerable trouble with respect to the cells.⁷⁴ Thereupon Signer worked at Upsala during two intervals in 1932 and 1933. When he returned to Staudinger's laboratory Staudinger was impressed with the results he had obtained. Staudinger was therefore most interested in obtaining an ultracentrifuge for himself in order to be able to check the results he had obtained using other methods.⁷⁵ As he failed, however, in raising the necessary funds, the plan never worked out.

Shortly thereafter Signer moved Switzerland to work at the Chemical Institute at the university of Bern. He wanted to start some new investigations for which he needed new instruments. Svedberg advised him to inquire whether the Rockefeller Foundation would be prepared to fund the purchase of the apparatus.⁷⁶ Svedberg recommended Signer to the Rockefeller Foundation for such support which was subsequently given. Svedberg had also mentioned to W.E. Tisdale from the Foundation that it would be very desirable if Signer would be able to obtain an ultracentrifuge. Signer was most pleased with this advice and thought that this would also be welcomed by his colleagues from the medical department who mainly worked on problems in protein chemistry.⁷⁷ However, H.M. Miller from the Foundation's Paris office, thought that there would be little prospect of funding an ultracentrifuge for Signer until they had a better understanding of the line of work Signer was developing in order to be able to determine whether it fell within the Foundation's program.⁷⁸ In the fall of 1937 the matter was taken up again and on the basis of Signer's progress in the preceding years the Foundation was now seriously interested in giving support. It appeared, however, that the installation of an ultracentrifuge necessitated an extension of the existing institute which caused the cost of the total project to exceed the price of the actual apparatus a number of times. The Rockefeller Foundation had shown its preparedness to fund part of these additional cost on the condition that the Swiss state would guarantee the remainder. The latter, however, was not prepared to do so which killed the plan. Early 1938 Signer again explained the Foundation officers how far his research would have been speeded up if he would be able to make use of an ultracentrifuge but the officers were not prepared to consider the matter again if the state would not contribute.⁷⁹ Because Signer felt in much need of ultracentrifugal support of his experiments he applied with the Foundation for a grant in order to have an assistant go to Upsala and pursue his experiments there. The Foundation awarded his request which facilitated Signer to appoint an assistant in Svedberg's laboratory for a period of three years.⁸⁰

Arthur Sproul McFarlane - Lister Institute of Preventive Medicine

In 1933/34 Arthur Sproul McFarlane from Glasgow worked in Upsala using the ultracentrifuge for the study of blood serum (see Chapter 2). McFarlane had been able to determine more accurately the weight of serum globulin and serum albumin. He had made some interesting observations on blood serum which had been subjected to injections of other sera or to infections. He had also found that molecular structures in blood in the case of cancer differed from normal. Both Svedberg and McFarlane were most interested in continuing this research and Svedberg found that it offered most promising opportunities for the future. After his stay in Upsala McFarlane would go to England to work with J.C.G. Ledingham, director of the Lister Institute of Preventive Medicine in London. In April 1934, Svedberg was visited by W.E. Tisdale and D.P. O'Brien from the Rockefeller Foundation. Svedberg stressed the importance of McFarlane's work for medicine and suggested to set-up an ultracentrifuge at the Lister Institute with McFarlane in charge. Svedberg would be pleased to manufacture it at cost-price which would be about £ 2,000.⁸¹ When O'Brien suggested this possibility to Ledingham he was very much interested. At Lister they had already used centrifuges at 13,000 r.p.m. for the study of viruses which had given them valuable information. Apart from continuing the work McFarlane had done in Upsala Ledingham was also interested in studying bacterial proteins and virus fractions in the ultracentrifuge. This would supplement the studies on virus they had done with their own centrifuge.⁸²

Mid 1934 McFarlane came to the Institute on a Beit Fellowship. He planned to start with electrophoretic studies on serum proteins as a supplement to his ultracentrifugal studies on these proteins he had done at Upsala.⁸³ June 1934 D.P. O'Brien and A. Gregg from the Rockefeller Foundation's Paris Office visited Ledingham and, given the research Ledingham proposed to do and given the investment the Institute was willing to make itself, came to the conclusion that an installation of an ultracentrifuge at the Institute would be desirable. Beside McFarlane's salary the Institute was prepared to pay the costs of operation and maintenance and up to \$ 5000 from the cost of procurement. The Rockefeller Foundation was expected to pay \$ 15,000.⁸⁴ After some further consultation with Svedberg this amount was raised to \$ 18,000 facilitating the Institute to obtain both an equilibrium and an oil turbine ultracentrifuge for approximately £ 4000,-. This was a rough estimate as Svedberg did not know the actual cost of the apparatus. Ledingham had also expressed the desire of creating a department of bio-physics at the institute to be used by themselves and qualified outside people. An ultracentrifuge could be an important stimulus for such a development.⁸⁵

In the application it was argued that they were interested in the possible application of the ultracentrifuge to virus work and modern serological problems

such as the ultimate nature of antitoxins and the mechanism of antigen-antibody combinations. In consultation with biomedical colleagues, it emerged that a tool of this kind would likely prove of 'immense importance in the investigation inter alia of ferments and hormones in organic fluids.'⁸⁶ In the event of an equipment being installed they were prepared to invite McFarlane to resign his Beit Fellowship and become one of their own Research Fellows. These posts were usually held for two or three years at a salary of £ 500 per annum. Such an appointment might lead to a permanent post on the research staff. Given the quality of the work McFarlane had done this would be a serious possibility. In the application they also quoted from a letter by Svedberg:

"I feel that important things might result from a continuation of McFarlane's work on the serum and it would be a pity if this opportunity to have a man so remarkably well qualified for investigating this problem, as he undoubtedly is, is not taken care of. Personally it would be very gratifying to know that the ultracentrifugal methods on which I have been working now for about ten years were to become of real service to the medical science. It has always been my dream to be able to do something towards the development of methods for medical investigation."⁸⁷

November 1934 the Institute's request of a \$ 18,000 grant is awarded by the Rockefeller Foundation. The motivation for the award stated:

"The studies of Svedberg on the size of molecules of substances of biological origin constitute a new and promising application of physics to medical research, and are thus related from the side of the Medical Sciences to the program described as vital processes. So numerous have been the demands from medical investigators upon the existing equipment in Svedberg's Laboratory at Upsala that it is quite inadequate for medical as well as the physical research appropriate to the Institute. There are good reasons to expect valuable contributions to our knowledge of the physical nature of body fluids from this technique: such results have been obtained already in connection with blood pigments and serum proteins. A large field in immunology as well as the physical chemistry of normal blood awaits investigation by this method."⁸⁸

In English currency this amount represented £ 3400.- and it was awarded on the condition that the Institute would contribute an additional £ 2000 for laboratory building and drainage, special foundations, light, water and gas installations, etc.⁸⁹ Svedberg could now start the construction of the apparatus. Because of the type of anticipated research Ledingham would like to have some larger cells to hold quantities up to 5 cc of fluid. These would permit pipetting of supernatant and deposit for subsequent examination and titration.⁹⁰ In a letter to Svedberg in November Ledingham emphasized the importance of being able to demonstrate that the biological activity may be removed from the supernatant fluid after centrifugation of certain active solutions at high speed and for prolonged periods.

Other types of semi-quantitative experiments would also be important for many of the scientists.⁹¹ Svedberg thought that the manufacture of such cells would be very problematic. In his reply he wrote Ledingham:

"The cells which are used in the ultracentrifuge at present are the results of extended series of trials. One could hardly tell offhand what difficulties might arise from cells of the type you indicate. On the other hand, using our accumulated experience, it does not seem unlikely to me that cells of the types you want could eventually be worked out.

I should like to point out, however, that my primary interest is to supply methods for accurate quantitative studies of high molecular compounds such as the proteins, and that I have always been a little suspicious of such qualitative and semi-quantitative methods as you suggest in your letter. For instance in cells holding large quantities of liquid convection currents might arise, and unless the process of sedimentation can be followed by optical measurements, you are entirely in the dark about what happens in the cell during centrifuging. All-metal cells, therefore, are rather hazardous unless you know from observations with similar, but transparent, cells that regular sedimentation actually does take place.

The types of ultracentrifuges which we have worked out here are not meant for the separation 'in substance' but for optical observations. It has taken us many years of hard work to arrive at the present types, and it may very well take much time and labour to modify the machines for the purpose you indicate. We have often found that even a slight change may cause much unforeseen trouble.

All I can say, is this: I can offer to supply you with ultracentrifuges of the best types which we have worked out so far, but we cannot just now promise to undertake the experiments necessary for the modifications you indicate. On the other hand, if McFarlane wishes to come here for some time to work along these lines, I am quite willing to put our experiences and the resources of our workshops at his disposal. For the present, though, I think it would be wise to concentrate upon installing in your institute machines of the types we have worked out and the function of which we know and to regard the modifications you suggest as possibilities for the future."⁹²

Ledingham agreed with Svedberg's offer and Svedberg started the manufacture of a copy of his own apparatus which was installed at the Lister institute in the summer of 1936.⁹³ This ultracentrifuge was used extensively thereafter and performed very satisfactorily. Except for some minor modifications⁹⁴ the apparatus did not undergo much further development. As Ledingham had anticipated the ultracentrifuge attracted also foreign researchers, including Frank Horsfall, Edwin Cohn and John Edsall. It was mainly used for the study of viruses which made Svedberg invite McFarlane to write a chapter on this field of applications for the monograph he was editing on the ultracentrifuge in the late 1930s.⁹⁵

John Philpot - Oxford University

Rudolph A. Peters from the department of Biochemistry, University Museum, in Oxford was also very interested in obtaining an ultracentrifuge from Svedberg. He had had first hand information on it from John Philpot who had worked at Upsala

for some time. Philpot had told Peters that an oil-turbine ultracentrifuge would cost approximately £ 2,000. Peters applied for such a grant with the Royal Society which was awarded to him early 1935.⁹⁶ On his request Svedberg informed him that an amount of £ 2,000 for the purchase of the apparatus was approximately right but that a number of additional provisions and the installation of the apparatus would be needed. What would be needed also depended on local conditions with respect to kinds of electric energy available, organization and type of construction of the laboratory space, etc.⁹⁷ John Philpot was hired by Peters in order to supervise the installation of the apparatus and to subsequently work with it. About the same time McBain had started publishing on his air-driven spinning tops, also criticising Svedberg's work. When Peters learned of McBain's work he asked Svedberg what he thought about this development. Svedberg replied:

"1. The primary point is that in order to get sufficient accuracy in sedimentation velocity measurements the height of column of solution has to be not much less than about 12 mm, if less (a) the path of sedimentation is too small, (b) the backward diffusion (reflexion) from the bottom of the cell is too large and disturbs the measurement of sedimentation velocity. From the above statement it follows that 20 mm is the absolute minimum of diameter of the cell.

2. The column of solution must not be situated too close to the centre of rotation, otherwise the 'constant part' of the sedimentation curves falls too quickly because of the inhomogeneity of the centrifugal field and the divergent paths of the sedimentary particles. We have tried the following distances from centre of cell to centre of rotation: 65 mm, 50 mm, 32.5 mm. The last one is quite too short, the second can be used, but the first is decidedly the best. This is the distance we use in our standard rotors (outer diameter 180 mm).

3. From 1. and 2. it follows that the rotor has to have a fairly large diameter, about 180 mm and as far as I know a rotor larger than about 90 mm cannot be used with the spinning top, as stated by Beams in his last Science-paper. In order to reduce the weight on the spinning top he has to make his rotor of duraluminium instead of steel and this reduces his centrifugal field.

There are some other points in favour of our model too, but I need hardly mention them, (the temperature control is easier and the stability better). On the whole I think one could say that the spinning top may be used for preliminary experiments and demonstrations, but an ultracentrifuge built on that principle will not permit very accurate measurements of sedimentation velocity."⁹⁸

July 1935 Peters formally ordered an ultracentrifuge. He would like to have it constructed in such a way that the design could anticipate any improvements in rotor and speed. The reason was that he had been hearing of some major improvements in connection with the Beams centrifuge. Though he did not feel that this had reached the stage yet of a sound engineering proposition, Peters should like to be able to disarm any possible criticism in advance.⁹⁹ Peters ordered the complete apparatus but dispensed with the balancing machine. He hoped to be able to use the one Svedberg was constructing for the Lister Institute, if the occasion would arise.¹⁰⁰ Peters would like to use less laboratory space by using reflecting prisms so that the optics could be 'folded'. Svedberg stated, however, that he

would not advise to do so because this would cause too much loss of light-intensity and the whole adjustment would also become complicated. All in all a room length of 30 feet would be needed.¹⁰¹

Peters had no idea of what would be needed to manufacture an ultracentrifuge and how various parts should be arranged and assembled. He therefore asked Svedberg to supply everything he would need. Svedberg, however, informed him that it would be easier and cheaper to order certain parts in England. Svedberg also stated that they had developed a much more convenient method of speed measurement using a magnetized rotor. This arrangement would cost £ 136 whereas the 'old' stroboscopic arrangement cost £ 93. The cost, however, especially if some less necessary features in the control board would be omitted, would be amply compensated by the work saved through the use of the new speed measuring arrangement.¹⁰² This proposal was readily agreed by Peters. Peters also informed Svedberg that the architect wished to move the centrifuge 75 centimeters because of structural arrangements. He also wondered if it would be possible to place a motor generator in the same room as the centrifuge.¹⁰³ Svedberg had no objections against moving the ultracentrifuge a bit but thought that it would not be wise to place the generator in the same room as the ultracentrifuge because it would be very difficult to damp out the vibrations created by it. Svedberg also warned Peters that it would be necessary to take up negotiations at an early date with customs in order to get a permission to import the equipment free of duty. In this connection it would be essential to avoid such parts that could be purchased and mounted in England. Because some of these items, like the control panel, would be included Svedberg suggested to send these separately so as to avoid influence from them on the possibility of getting the other parts duty-free. The alternative would be to cancel the order for the control panel altogether and get it manufactured in England after the model of McFarlane's arrangement.¹⁰⁴

The apparatus arrived in England in August 1936. Philpot 'spent a happy afternoon with a very young and conscientious customs officer, who examined every single part as it was unpacked'.¹⁰⁵ It took considerable time before the apparatus was installed because some goods ordered in the UK took a long time before they were delivered.¹⁰⁶ 27 February the Oxford ultracentrifuge laboratory was opened with Svedberg being present as a guest of honour. On this occasion Svedberg was also conferred an honorary doctorate by Oxford University.¹⁰⁷ After the installation the ultracentrifuge in Oxford worked quite satisfactorily. Some minor problems, like a slightly leaking vacuum pump,¹⁰⁸ could easily be solved.¹⁰⁹ Another problem came up when they wanted to centrifuge a substance that was only soluble in organic solvents. Philpot asked Svedberg if this could be done in their own cell or if they would need a special cell. Also, they would like to use higher speeds with the ultracentrifuge and Philpot wondered if

this could not be reached by making the cell holes oval rather than circular.¹¹⁰ Svedberg replied that using organic solvents had proven very difficult but that they had constructed special cells for the purpose which would cost about £ 7. Basil Record had worked with these and Svedberg had asked him to respond to Philpot directly. Concerning the oval cells Svedberg wrote:

"Already in 1933 we made calculations about the gain to be expected with oval cells and we made detailed construction drawings. For a cell with the long diameter 2 times the short one would gain 20% in centrifugal force. It turned out impossible to construct such a cell with quartz plates owing to the tightening difficulties. The best one could hope to be able to carry out was a cell having the long diameter 1.5 times the short one. This would mean a gain of only about 10%. The scheme, therefore, was never carried out. Last autumn we took up the problem again and tried on our round cells a tightening arrangement similar to the one suggested by you. It was found unreliable. There is at present so much work to do in the shop that I don't think it wise to take up the oval cell question again."¹¹¹

Record gave Philpot extensive information on what he should and should not do when using various organic solvents.¹¹² This made Philpot decide not to use organic solvents and to continue the investigation of various proteins. In connection with this work he had also developed a new method for direct photography of ultracentrifuge sedimentation curves.¹¹³ Because this method was much more convenient than the scale-projection method Svedberg had supplied Philpot did not intend to use the latter anymore. When Svedberg heard this he proposed to buy their scale-projection apparatus. Philpot was most surprised and said that he would be glad to sell the it¹¹⁴ but in his next letter Svedberg advised Philpot to reconsider this offer because, even if his new methods should prove useful in routine work, there would always be cases where the accuracy needed would necessitate the use of the scale apparatus. Furthermore the Hilger company was considering a recalculation of the whole optical system (scale-projector and photographic objective) with a view of shortening the total optical path and placing in the objective some of the corrections now located in the projector. Svedberg wanted to have the result of these calculations before he would consider buying Philpot's arrangement.¹¹⁵ When the third ultracentrifuge was installed in Svedberg's laboratory early 1939 Svedberg once more inquired about Philpot's willingness to sell his arrangement¹¹⁶ and next agreed to buy it for £ 80.¹¹⁷

John Warren Williams - University of Wisconsin

December 1935 Frank Blair Hanson from the Rockefeller Foundation visited R.A. Gortner at Cornell University who was considered to be one of the big men in

Colloid Chemistry. During this visit the name of Svedberg came up and Gortner offered the first criticism Hanson had heard of Svedberg. The famous number 34,000 which turned up repeatedly in Svedberg's results was to Gortner but a mystical number which did not exist in nature. Gortner's chief criticism was that there was no place in the world where Svedberg's results could be checked. One either accepted them or one did not. Hanson told Gortner about the two ultracentrifuges to be set up in England and the one at DuPont which made Gortner ventilate his criticism of former International Education Board and present Rockefeller Foundation activity in Europe in erecting magnificent buildings and giving large sums for equipment as compared with similar activity in the US. As an example he told when one of his former students, George D. Burr, visited the University of Leiden, he found they had nine Hilger quartz spectrographs and none in use. Burr inquired how they could afford 9 Hilgers and was told that when a Rockefeller Foundation grant was made they just laid them in against possible future needs.¹¹⁸

January 1936 Hanson visited John W. Williams from the university of Wisconsin. Williams was continuing his work on dielectric constants of proteins on which he had worked in Svedberg's laboratory shortly before. He had checked Svedberg's recurring number 34,000 by electrical methods and had gotten the same results secured by Svedberg. During this visit Williams mentioned that he would like to obtain a Svedberg ultra-centrifuge. It would cost about \$ 15,000 to set up this apparatus at Wisconsin. Svedberg would be prepared to make the essential parts at actual cost. Williams thought that there should be at least one ultra-centrifuge in an American university. He did not count the one at the DuPont's, as that would be used commercially. Williams explained that with him and Watson at Wisconsin, both having worked with Svedberg, and Watson having installed the DuPont equipment, Wisconsin would be the natural place for an ultra-centrifuge. He remarked, however, that there would seem to be no possibility of Wisconsin providing the money. He did not press the matter further and did not ask the Rockefeller Foundation for assistance.¹¹⁹

March 1936 Warren Weaver wrote a 'wholly personal and informal' letter to Edwin Fred, Dean of the Graduate school of the University of Wisconsin, whom he had known since he worked in the department of mathematics at the university in the 1920s. Weaver explained that at the time ultracentrifuges were set up at the Lister Institute and at the DuPont Experimental Station. He explained that he was unhappy with the fact that there was no installation of this equipment in the US which would be used on the study of fundamental scientific problems as DuPont's apparatus would be used primarily for commercial applications. He thought that the University of Wisconsin would be most suited for such an installation because of the presence of Williams and Watson. Weaver did not write to them directly in

order not to generate any possible false hopes. He asked Fred to enquire whether such an installation would fit in the general work of the chemistry department, whether space could be made available and whether the university would be prepared to undertake the maintenance of the apparatus. If such were the case, Weaver thought, there would be a good chance that the Rockefeller Foundation would furnish the sum necessary for the purchase of the apparatus.¹²⁰ Fred replied that they had been thinking for a number of years about ways and means to enrich their Physical Chemistry department. The procurement of an ultracentrifuge would very well fit into these ideas. It could be of interest in 'the study of serum fractions, of antitoxins, of hormones, of viruses; in fact of a wide variety of substances now under study at this institution.'¹²¹ Shortly thereafter Williams and Watson were informed about the plans and in May 1936 an official grant application was sent to the Rockefeller Foundation. The application included research plans for a period of five years and a possible way of funding these researches. The Rockefeller Foundation was asked to contribute \$ 25,000 for the procurement of the apparatus while the Wisconsin Alumni Research Foundation and the University of Wisconsin would pay \$ 21,500 and \$ 24,750 respectively towards the maintenance and operation of the apparatus for the five year period. The \$ 25,000 from the Rockefeller Foundation would cover the following costs:

Sedimentation Velocity Ultracentrifuge	\$ 8,000
Sedimentation Equilibrium Ultracentrifuge	4,000
Transportation and Duty	6,000
Installation	4,000
Accessories	3,000

The accessories included things like lenses, balancing machine, stroboscope, miscellaneous instruments, etc. The proposed researches covered both proteins and carbohydrate colloids like starches, glycogens, etc. Furthermore, cooperative researched might be induced in fields of medicine (diagnosis of disease), hormone researches, virus researches, ferments and enzymes, cellulose and other wood substances.¹²²

Because of budgetary considerations Weaver thought it unlikely that the proposal could be considered by the Foundation's Trustees before October or November. In the meantime Weaver would be seeing Svedberg and would ask his opinion on the matter. As he wrote Williams:

"Although I do not have the slightest reservations as to what his recommendations will be, my position here will certainly be much stronger if I can state that this proposal has been carefully gone over with Svedberg and that it has his unqualified backing. Our Trustees have had long association with Svedberg. They recognize his scientific standing and would be, I am sure, considerably affected by his recommendations."¹²³

Williams, however was somewhat disappointed because he had hoped that a decision could be made before the summer. In that case the construction of an addition the chemistry building and the simultaneous preparation of foundation for the heavy machinery could be started and possibly completed during the warmer months which would be much more convenient. Furthermore, apart from the additional expense involved, it would be a matter of some risk to the eventual success of the installation to undertake this work during the winter months; so much that Williams would greatly prefer to begin the work before November, if possible. Having an early decision would have the added advantage that they could be more certain of having the services of Watson. He planned to complete his degree work at the end of the summer and Williams' chances of keeping him would be much improved if a decision on the ultracentrifuge would be made before that time.¹²⁴ Thereupon Weaver cabled Svedberg to ask his opinion on the installation of an ultracentrifuge in the US and whether he thought that Wisconsin might be the place best suited for the installation.¹²⁵ Svedberg replied the same day:

"ultracentrifuge installation american university very desirable and important stop consider wisconsin best opportunity stop staff and plans excellent"¹²⁶

On 1 June the proposal was discussed between Weaver and Appleget from the Rockefeller Foundation. Weaver explained that present information on heavy molecular weights depended on Svedberg's findings alone. The experiment was complex, and while there was no doubt as to Svedberg's accuracy the findings should be verified elsewhere. Appleget questioned whether later developments might not replace the Svedberg centrifuge. Weaver admitted that other centrifuges attained speeds equal to those which Svedberg got and could probably produce the same size rotor. The difficulty, however, was in temperature control. He explained that everybody but McBain believed that the Svedberg centrifuge was not going to be replaced for many years and meanwhile it would earn its keep.¹²⁷ Weaver put the proposal before the trustees and on 12 June 1936 it was agreed. It was considered that programmes dealing with the applications of techniques of physics and chemistry to the solution of important biological and medical problems had received proportionately large support and that in accomplishment and promise it probably ranked as the Foundation's Natural Sciences Division's leading opportunity for effective support. Several 'prominent investigators' had suggested the high desirability of having an ultracentrifuge set up in some American University in view of the widely acclaimed results obtained with it. Furthermore no other institution in America offered such excellent conditions for the operation of the ultracentrifuge as Wisconsin did. Therefore a grant was awarded of \$ 27,500 or as much thereof as might be necessary.¹²⁸ The 1936 annual report stated that 'the

success of the apparatus has been such that in a comparatively few years the physical chemistry of the proteins has been largely revolutionized.¹²⁹

Williams was very keen on having the best arrangement he could get and on having the latest developments included. They wanted to have a Siegbahn micro-photometer because it was the one most suited to their purposes. On the basis of Watson's experience with the Wilmington installation they tried to work out some improvements themselves and tried to work out a different speed measurement arrangement as they found the stroboscopic method very inconvenient and Svedberg's new magnetic arrangement rather expensive. Furthermore, in connection with the equilibrium apparatus, they would like to have the optics in a horizontal position because it would be practically impossible to go through one of the floors above.¹³⁰ They were also interested when Svedberg started working with thinner rotor journals which were expected to produce less bearing friction. This appeared to be a very marked improvement. The energy consumption in the compressor motor was only about 1/3, the necessary cooling water corresponding smaller, the heat-production in the bearings less and the general behaviour of the centrifuge better. The only drawback was that it necessitated a higher oil-pressure for the speeding up of the rotor than for maintaining it at the desired speed and this meant that the speed had to be watched carefully during the speeding up period so as not to pass the speed limit. Svedberg had had no trouble in doing this but he advised Williams to install some sort of safety arrangement, e.g. an alarm-clock, to make it fool-proof. Svedberg was going to use the rotor with thinner journals for routine work so as to satisfy themselves that it was alright before they would decide upon this change for Williams' centrifuge.¹³¹ The apparatus was completed in the spring of 1937 and it arrived in Wisconsin in two shipments, one at the end of April, and the other late in May. It was provided with the thin journals and twin turbines developed just before which had proven to be able to speed up the ultracentrifuge much faster than the old arrangement. When Kraemer saw this apparatus while visiting Williams' lab he was also interested in applying such modifications to their centrifuge.¹³²

In the grant application to the Rockefeller Foundation Williams had also anticipated the purchase of a 'laboratory centrifuge' to cost \$ 200 and had ordered a small instrument of the angle type from the Sorvall Company. They expected to find much use for this centrifuge in the fractionation and purification of their proteins. However, mid 1937 they anticipated the need of a more powerful instrument of the vacuum type in order to concentrate and separate lighter virus proteins for their later characterization with the Svedberg sedimentation velocity instrument. They had inquired with Fritz Linke, instrument maker for Beams, about the cost of rotor, driving mechanism, and jacket for a centrifuge such as Bauer and Pickels had described. This would cost about \$ 600 and they wrote Weaver that

their balance on the Rockefeller Foundation Grant was such that this amount would be available. Williams therefore asked Weaver if it would be o.k. to order this high speed vacuum centrifuge which they considered a necessary accessory for their work.¹³³ Weaver had no objections against this proposal.

Within the University of Wisconsin, there was also some resentment, on the part of other chemists, of the amount of backing Williams was receiving. As a result the department did not approve the promotion for Williams which Dean Fred had intimated would occur.¹³⁴ Such resentment gradually disappeared as the research with the ultracentrifuge got off the ground. The performance of the apparatus was considered to be a complete success. According to Weaver, who visited them in December 1938, the installation was excellent and undoubtedly superior in several respects to Svedberg's. At that time Harold P. Lundgren, who had also worked at Upsala, was working in Williams laboratory on thyroglobulin. His training and knowledge in biochemistry was considered very valuable in this respect. Thyroglobulin appeared to be not homogeneous and Lundgren was studying the stability of this protein. He purified it by fractional precipitation, electrodialysis, etc., and had discovered, he believed, the factors which governed the splitting up of this protein. He felt that the results were fundamental in character, and that they would shed a good deal of light on the problem of protein denaturation. The work with the ultracentrifuge was going forward very well. From his visit Weaver obtained one rather serious reservation: namely, that the considerable expenditure in equipment justified and necessitated somewhat greater expenditures for competent research assistants. Lundgren, for example, had to take complete responsibility on the mechanical and electrical side, had to go out to the packing plant to obtain his own material, had to do all of the chemical preparation, etc.¹³⁵ In connection with their studies they were also interested in obtaining a diffusion cell developed in Svedberg's laboratory. Furthermore they would like to have some new cells as some of them started leaking after some time. Because it proved very difficult to make them themselves they asked Svedberg to supply them. Also they would like to use organic solvents and wondered how such cells should be constructed.¹³⁶

Williams' group received a number of inquiries from other researchers to investigate certain substances for them. For instance, Edwin Cohn from Harvard asked Williams to analyze serum globulin which Cohn's group had been working on for some time. Williams was very anxious to build up such outside contacts and also tried to enlist the active cooperation of several outlying departments of the University. For this reason he felt it necessary to submerge his own research plans for a while.¹³⁷ Early 1939 their chief activities were: 1) Work on tuberculosis sera, toxins, etc., in cooperation with Miss Seibert of the Phipps Institute; 2) Work with Pappenheimer of Harvard on diphtheria toxins, etc.; 3) Work on nucleo-proteins of

thymus; 4) Continuation of Lundgren's work on thyroglobulin; 5) Effects of trypsin, pepsin, etc., on proteins. Williams had 3 New York Academy helpers, and two full-time computers (people who did the measurement of the sedimentation curves and calculated the results). A medical assistant had been assigned to him for the diphtheria work. For this work they had also secured Tiselius' electrophoresis apparatus.¹³⁸ Warren Weaver was very pleased with this type of approach.¹³⁹ The instrumental equipment at Wisconsin continued to perform very well. The ultracentrifuge (or supercentrifuge as Weaver called it) made two runs a day, six days a week. On the first of each year, Williams had the centrifuge entirely taken down, all parts carefully measured and inspected, the rotor rebalanced, and the machine reassembled. This regular inspection program protected them against any interruptions.¹⁴⁰

On the whole, Williams program was directed at fundamental problems in biochemistry but upon the outbreak of World War II he felt that the work should be directed more at practical problems. As he wrote Cohn in July 1940:

"A large portion of our present work has to do with diphtheria proteins, tuberculosis polysaccharides and proteins, and pneumococcus antibodies, but we are also making dielectric constant and other studies somewhat similar to yours. I have even felt a certain amount of duplication to be desirable because many of our problems are so complicated that if two laboratories working independently of each other come to substantially the same result, the establishment of fact is much more complete. However, under the present day circumstances I feel we ought to do more practical things. Under such conditions it seems obvious duplication is undesirable. I have been thinking that your laboratory, that of Stanley, and our own facilities are very much alike and I have wondered about the desirability of combining and coordinating all our efforts to the most useful end. It may be we ought to start work with sera for tetanus, gangrene, etc. I understand the laboratories of Harvard University are being put on war footing and if you have any things with which we can help I would appreciate suggestions."¹⁴¹

Williams also informed Warren Weaver on these plans. It seemed to him that sedimentation, diffusion and electrophoresis experiments with immunological systems ought to be continued and developed on a larger scale than they were able to do with their staff. That had been his reason for writing Cohn. In this respect Williams wondered if British Scientists, who could not pursue their work because of the war, might temporarily work in the US.¹⁴² The work done in Williams' lab was highly valued by the university and the scientific record was considered to be excellent. During the five years since the Rockefeller Foundation grant was made, the University had actually contributed \$ 33,617 to the project, after having originally agreed to contribute \$ 20,500. The University assured Williams that this contribution would be continued for the future, but that they could not do more than this.¹⁴³ The Madison machine was in almost continuous daily use for a quarter of a century.¹⁴⁴

LKB Produkter AB

As in many other countries during the thirties, Swedish industries had begun to include more fundamental research in their development work and had also taken up closer contact with similar research being conducted at universities and institutes. A good example of this trend is found in the formation in 1942 by three leading Swedish industries in the field of organic chemistry and biochemistry of a joint research laboratory for the study of more fundamental problems of importance for their activities. The name of the laboratory, the Research Laboratory LKB, originated from the initial letters of the founding industries: Liljeholmen (fat processing industry), Kema (manufacturer of detergents) and Bryggerierna (brewery).¹⁴⁵ There was already a close connection between these companies because a number of people were on the boards of two or three of them. In 1938 Svedberg had started a cooperation with the breweries on the investigation of the proteins in the brewing process.¹⁴⁶ When the LKB-Laboratories were formed, Svedberg, already cooperating with one of the companies involved, became a consultant to the laboratory. This was also stimulated because one of the directors of Liljeholmen had been a student of Svedberg. Another of Svedberg's students, Sven Brohult, became head of the new laboratory.¹⁴⁷

Svedberg had had a long term interest in industrial matters and had always found that there should be a closer connection between research and industry than there existed. Such closer ties might work two ways: results of research could easier be exploited commercially while industry could add to the meager research funds provided by the state and various foundations. For instance, Svedberg was sponsored by various cellulose companies for research on cellulose which enabled him to appoint Nils Gralén as an assistant in order to do the actual research. But Svedberg would only accept such grants if the research was free and not bound by industry.¹⁴⁸ Around 1943 a governmental committee was established in Sweden, of which Svedberg became a member, for expanding relations between science and industry. The recommendations of the committee resulted in several industry branch research institutes, like the Textile Research Institute and an institute dealing with food research. The Textile Research Institute in Gothenburg which was established in 1944, supported by the Government and the textile industries jointly. On Svedberg's instigation Nils Gralén became its first director.¹⁴⁹

The outbreak of World War II meant that the supply of many goods from abroad became very problematic. For the groups connected to the LKB-Laboratories some of the major problems were the lack of scientific instruments and special chemicals. It was then decided in 1943 to create a new company, LKB-Produkter AB, that was to manufacture these goods. This development fitted very well in with Svedberg's ideas who had, for a long time, wanted to create a small industry

where scientific instruments, developed in Sweden, could be commercially produced. In this connection, however, he was more interested in making new instruments rapidly accessible to fellow scientists than in laying foundations for a large manufacturing industry.¹⁵⁰ One of his sayings used to be: 'Never produce an instrument, no matter how good it is, if it cannot be used for significant work in the service of science or technology'.¹⁵¹ On the board of this company were representatives from each of the participating firms plus Svedberg and Brohult. Svedberg's word weighed very heavy on the board; without him LKB could not exist. Svedberg had his contacts all over the world with potential customers. He knew the trends with respect to the instruments they would need. Nobody ever challenged his view.¹⁵²

The core of the LKB instrument program was constituted by some new and promising instruments developed by Swedish scientists such as Svedberg's ultracentrifuges and Tiselius' apparatuses for electrophoresis and adsorption analysis. These instruments had already been received with great interest in many parts of the world. During the late 1930s and early 1940s Svedberg got more and more requests from research colleagues to supply them with replica from his instruments which became an irritating load on the institute's workshop.¹⁵³ Also the university got somewhat annoyed by these activities which were seen as a kind of commercial undertaking that did not belong in a university.¹⁵⁴

In both the fields of instrument making and chemical manufacturing, LKB-Produkter was able to make use of the knowhow found among the personnel of the LKB-Laboratory and their advisors. For the development of some of the new instruments, direct contact with the inventors and their workshops was also established.¹⁵⁵ The enterprise started in the basement of Svedberg's institute and, afterwards, for a short while they had a workshop in Upsala under the supervision of Ivar Eriksson, Svedberg's chief mechanician. When the company moved to Bromma, near Stockholm, Eriksson was its advisor during the first few years.¹⁵⁶

The transfer of academic inventions was made rather indiscriminately: It sufficed that an instrument was produced and used in Svedberg's (and also other) research laboratories; then it was more or less taken for granted that LKB would produce it. Moreover, no development department was considered necessary. Why should it be? Nobody could know better than the researchers how an instrument should be designed. Nor was a marketing department needed, because the Svedberg and other Upsala instruments were so well known the world over that it would only be necessary to inform people that they were produced, and orders would be streaming in. No sales literature was produced. Separates were produced of the scientific articles where the new developments were described, and they were used as brochures. Thus the company philosophy was that they did not have to find the customers - the customers had to find them.¹⁵⁷

The company began in a very modest way with a share capital of only 5,000 Swedish Kronor and a staff of less than 10 persons, some of them working only on part-time basis. Temporary premises were made available by one of the founding companies. Harry Brynielsson, who had been with Kema, became the first part-time managing director of the company. Two events of great importance occurred at the outset of the company's life: the founding of the Swedish Textile Research Institute, partly on Svedberg's initiative, and the decision by the Swedish government to develop a process for production of synthetic rubber. The actual production of the rubber was carried out under Svedberg's supervision but the job of developing and manufacturing the catalyst used in the process was assigned to LKB. The Textile Research Institute required instruments for ultracentrifugation, diffusion, electrophoresis, adsorption analysis, and so on. The task of manufacturing these instruments was entrusted to LKB. Most of the parts were made in the company's workshop but the rotor for the ultracentrifuge was made by one of their machinists under the supervision of Eriksson at Svedberg's institute. The company paid a ten percent royalty to Svedberg and had the same type of arrangement with Tiselius on the electrophoresis. In return they helped and allowed LKB's clients to learn the various techniques in the Upsala laboratories.¹⁵⁸ These two orders constituted the main contracts for the company's first two years. In spite of the shortage of skilled manpower, machinery, special devices as optical instruments, quartz parts, electronic equipment, and of raw materials in general, the work was completed successfully. Assistance during this time was received from many collaborators - especially Eriksson's assistance proved to be invaluable.

Late in 1945, LKB was entrusted with the duty of acting as designer and main contractor for the 200-Mev synchrocyclotron for the Gustaf Werner Institute at Upsala, in which Svedberg also played an important role (see Chapter 2). This considerable order gave a real boost to the company and enabled a stronger organization, with regard to both personnel and equipment, to be built up. As normal conditions gradually returned after the war, the production program was revised. The production of analytical reagents was abandoned as well as the manufacture of some standard laboratory articles. In order to give a broader base for the sales efforts, the instrument program was supplemented with distribution and service of some foreign instruments, mainly of US origin, one of which was the Beams preparative ultracentrifuge. In 1948, by which time the staff had reached 70 persons, a new factory was built. At this time, about 70% of the production found its way to laboratories abroad, and the portion being exported has since then been steadily increasing.¹⁵⁹

Among the apparatus manufactured by LKB were ultracentrifuges and accompanying accessories. Below are given the cost of some of these at the time of the incorporation of the company (Skr. 1.00 = \$ 0.20):¹⁶⁰

Oil-turbine Ultracentrifuge (Svedberg)	Skr. 85,000
Equilibrium-centrifuge (Svedberg)	30,000
Preparative centrifuge (Beams)	20,000
Microphotometer (Siegbahn)	12,000

In the early 1950s the price of the oil-turbine ultracentrifuge was Skr. 125,000 and of the equilibrium apparatus Skr. 47,000.¹⁶¹ A rotor for the oil-turbine ultracentrifuge was priced at Skr. 11,500.¹⁶² About 1945 one oil-turbine ultracentrifuge was manufactured for Gralén's textile research institute. This instrument was used for the study of fibres - protein fibres, cellulose fibres, artificial fibres - and polymers in general. But the emphasis was on the fibres because of the goals of the institute. They soon found, however, that it was not of such a big interest to the textile processing and textile field. There were other ways of attacking the problems of dyeing, diffusion of dye-stuff, finishing of textile materials, etc. They changed their approach to these problems and found that they had rather little use of the ultracentrifuge in the future. Thereupon they tried to sell it back to LKB in which they succeeded.¹⁶³ Brohult remembers that LKB-Produkter had over a dozen of inquiries by people from whom they never heard anything again after they had told them what the apparatus cost.¹⁶⁴ Around 1947 LKB engaged upon a production of five oil-turbine ultracentrifuges of which, according to Sven Malmström, two were left in 1951 when he became president of the company. One of those was sold that year and the other was reported to be sold in 1956. One went to the Carlsberg Foundation in Copenhagen and two went to the Soviet Union. It is unknown where the others went. One of the Soviet machines was still in operation in 1969. The Svedberg equilibrium centrifuge was sold at a rate of one or two per year. The last delivery was in 1954. The preparative centrifuge, or 'Beams centrifuge' as it was called by the company, sold at a rate of five per year at a price of Skr. 17,000 in the early 1950s. It was very like the Beams original design, driven by an air-cushioned, air-driven turbine on top, the rotor suspended by a flexible steel wire. LKB only produced it in the preparative version, i.e. it was never equipped with Svedberg's optical sedimentation rate instruments.¹⁶⁵

When Malmström joined the company in 1951 it had never been profitable. It just barely managed to survive, often with very narrow escapes. Malmström found that LKB's Svedberg-inspired policy was less than useful - it was impossible and damaging. Moreover, the classical instruments, among them the ultracentrifuges, were rather dead weights. They realized that ultracentrifuges, both analytical and preparative, would be in great demand, but also that the Svedberg designs, no matter how powerful, were not what the market desired. They were considered too expensive, too clumsy, too difficult to operate. Svedberg, however, was very conservative and opposed important changes in designs. Only some 'cosmetic

changes' were sometimes introduced. Malmström remembered that Pickels, during a stay in Uppsala, had proposed some improvements to Svedberg, whereupon he fell in disgrace.

LKB did not have the means to undertake a major development like what a revised ultracentrifuge would have been. Furthermore, they were in a locked position because they felt they could scarcely undertake a redesign against Svedberg's objection. Instead they decided gradually to drop the classical instrument line and to develop new instruments, still in the same general market section, that of analytical biochemistry, but different ones, adapted to market needs, such that they felt that would be adopted by their clients. This however, would take time, and they had to find ways of surviving. What they did was to fill their workshop with contract production from the aircraft industry, where Malmström had certain contacts. Moreover, they got themselves agencies in the field they aimed at among which was an agency for Spinco Instruments. (see section below). Maurice Hanafin, one of the founders of Spinco, came to Stockholm in 1951 and they soon concluded an agreement whereby LKB granted Spinco licenses for a new optical system developed by them. In exchange, LKB took over the Spinco agency for Scandinavia. This turned out to be a lucky strike for LKB as they made good business with the Spinco ultracentrifuges. In 1958 a Spinco Analytical ultracentrifuge was offered by LKB at a price of Skr. 114,000.¹⁶⁶

It was not until 1958 that LKB had an instrument program large enough to survive on and they were not really profitable until that year. One major point was still left from the Svedberg policy - LKB continued to cooperate very closely with academic institutions. Almost all their instruments came from that source. However, before being introduced to the market they were now redesigned to suit the operators better, to be easy in production and reasonable in price. Sales gradually went up and LKB became a large, profitable company for the manufacture and sale of scientific instruments.¹⁶⁷

6.2 BEAMS/PICKELS ULTRACENTRIFUGES

Beams - Spinning Tops

Numerous scientists became interested in Beams's ultracentrifuges. By the end of 1932 some fifteen to twenty requests for the spinning tops had come in but their shop was not equipped to furnish all of them.¹⁶⁸ However, if he saw a way to do so, Beams did offer his assistance. One of the first persons showing his interest in the Beams centrifuges was James Burton Nichols, who had developed the first 'optical centrifuge' with Svedberg. July 1931, after he had seen Beams' article in

Science, describing his first centrifuge based on the spinning top principle, he wrote Beams a letter. He would like to visit Beams, in order to gain a better idea of 'the mechanical problems involved in the construction of such instruments, the operating characteristics, and the general performance'.¹⁶⁹ Beams answered that he would be happy to show Nichols various types of centrifuges. Shortly before, however, he had let the centrifuge rotate a little too fast and it 'blew up'. Weed, their instrument maker, who did the machine work would be away until late August so Beams would not be able to demonstrate this type until Weed would have had time to make another. Nevertheless, he could show the simple type full of liquid rotating at full speed anytime. They were doing some biological experiments and were using a simple hollow rotor every day. He could also demonstrate how it was used to rotate a mirror. Beams continued:

"I do not think that we have at present developed the centrifuge to its limit and when Mr. Weed returns I hope we shall be able to make some changes that will greatly improve it. However, I believe that at the present time you can get a pretty good idea of its possibilities."¹⁷⁰

A few days later Nichols and Kraemer, one of Nichols' colleagues, visited Beams laboratory and was very satisfied with what he learned. they planned to start the preliminary work immediately on a 'little toy rotor' to make sure that they would be capable of making the rotors run.¹⁷¹ But after some further experimentation they decided to discontinue working with the air-drive (see section 6.1).

Edmund Newton Harvey (Princeton University) and Alfred L. Loomis (Loomis Laboratory, Tuxedo Park, N.Y.) were interested in studying the effects of centrifugal forces on living cells. More specifically they were interested in: (a) determining the relative specific gravity and total volume of granules (which were stratified under centrifugal force) present in living cells, (b) observing the behaviour of mitotic figures and other structures under centrifugal force. These experiments should give a clue to the nature of the structure, that is, whether solid and resistant to deformation or merely the configuration of particles in an electrical field, and (c) measuring the viscosity of the protoplasm, by applying Stoke's law to the rate of movement of granules under the centrifugal force. In the late 1920s they used a procedure in which the cells were first centrifuged in capillary tubes, after which the cells were removed from the tube and observed under a microscope in order to determine what happened. For them, a drawback of this procedure was that they could not observe what happened during the actual centrifugation. To overcome this problem they developed the so-called centrifuge-microscope shown in figure 6.1 which made possible microscopic observation of the cells during centrifugation.

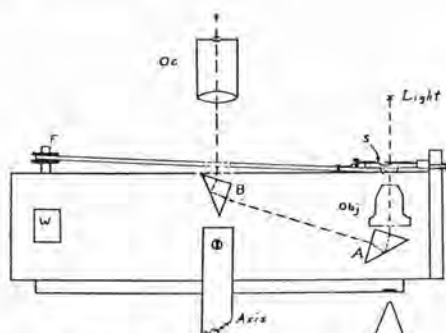


Figure 6.1

Microscope-centrifuge. Obj, microscope objective; Oc, microscope eyepiece; F, focussing screw; W, counter weight; A and B, reflecting prisms; S, slide with life cells. (Harvey and Loomis, 1930, p.43).

In this apparatus the cells were placed at 10 cm from the axis of rotation and the centrifuge could reach 3,000 r.p.m. With high power objectives this image appeared to be remarkably steady. They obtained photomicrographs with the microscope-centrifuge of bacteria and chromosomes in dividing cells which could hardly be distinguished from those taken when the cells were at rest.¹⁷² The dimensions of their rotor, approximately 10 inch diameter and 2 5/8 inch thick, made it impossible to reach rotational speeds over 4,000 r.p.m. Because they wanted to reach higher gravitational fields they tried to diminish the air resistance by using objective lenses only and small right angle prisms mounted either between objective and object or between the lenses of the objective system. In this way the thickness of the head could be reduced to 1/2 inch, and by stream-lining the contours, it was possible to run up to 10,000 r.p.m., giving forces of 12,000 times gravity. This type of head was considered most suitable for general biological work.¹⁷³

When Harvey learned about Beams' spinning tops, reaching gravitational fields of more than 100,000 g, he asked Beams whether these spinning tops could be adapted in order to facilitate microscopic observations. Beams and Weed (his instrument-maker) constructed for him a rotor like the one shown in figure 6.2. In this new scheme no lenses but only mirrors revolved. Two stellite mirrors (M_1 and M_2) were mounted on a Beams rotor in such a position that the image of the object on a special slide (S) was brought to the axis and reflected into a microscope (Mic) mounted above and on the axis of the rotor. W. was a counter weight for balancing the rotor. The illumination was a narrow image of the filament of a straight filament tungsten lamp thrown on the material to be observed parallel to a radius of rotation. While the whole field of view was not perfect, the centre was good enough for all practical purposes. The magnification of this scheme was limited by the working distance of the objectives; 5x to 7x

objectives could be used given with 20x oculars, giving a total magnification of a factor 100 to 140. The centrifugal force attainable by this arrangement was limited only by strength of materials, and for microscopic observations by this method, was determined by the strength of the glass container of the living cells. This facilitated observations up to forces of 200,000 times gravity. According to Harvey, this arrangement would be particularly useful for determining molecular weights of substances by the method of sedimentation, for observing movement of materials in highly viscous cells and for observing the change in shape of living cells due to the stretching forces of light and heavier material.¹⁷⁴ In 1933 Harvey described a scheme which used two cell-holders and which made it possible to observe the simultaneous exposure of two different cells. In this manner he observed a remarkable difference in behaviour under the influence of centrifugal force of unfertilized and just fertilized sea-urchin eggs. This scheme would facilitate a quantitative comparison of the effect of any substance on the viscosity or form of living cells.¹⁷⁵

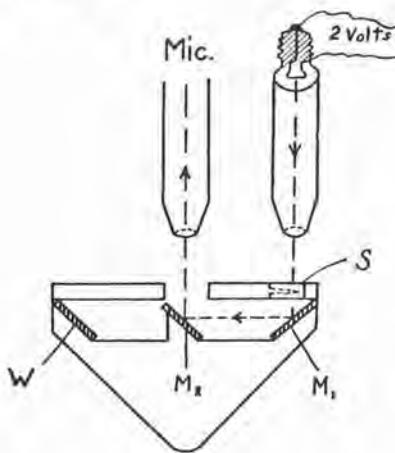


Figure 6.2

Optical system of centrifuge-microscope adapted for Beams rotor. S: slide to hold living cells; M: stellite mirrors; W: counterweight for balancing. (Harvey, 1932, p.14).

Although the air-turbine did a good job for Harvey he still had problems with it. One of the problems was that the living cells might crushed against the bottom of the container by the high forces developed. This could, however, be obviated by suspending the material in a medium of graded density so that it would come to lie in a stratum of equal density which would cushion it against crushing. Another problem was that heating of material occurred due to air friction unless the centrifuge would be run in a vacuum or in hydrogen at low pressure. According to Harvey, such a procedure would introduce complicated accessory apparatus and

would be decidedly objectionable from the biological standpoint.¹⁷⁶

Late 1930 the Bausch & Lomb Company showed an interest in manufacturing and patenting Harvey's microscope-centrifuge. They found that such a patent might infringe the Nichols-Svedberg patent and Harvey therefore asked Nichols to give them a license. Harvey expected that the sale of the instrument would be so limited that practically no profits could be obtained, but it would be of considerable value to a few workers in certain fields of biology.¹⁷⁷ Nichols was willing to give a license on a royalty basis. However, since the microscope-centrifuge only touched partly on the patent, the royalty should be lower than otherwise. About 15% seemed a reasonable figure to him.¹⁷⁸ Bausch & Lomb, however, found this royalty exorbitant. They paid Harvey a 5% royalty. Furthermore, Harvey could not see how the microscope-centrifuge would infringe in any way on the ultracentrifuge patent. He therefore asked Nichols to license Bausch & Lomb without a royalty. He feared that otherwise it would not be possible to put the instruments in the hands of scientific workers.¹⁷⁹ Next, Nichols asked a 5% royalty which was agreed by Bausch & Lomb.¹⁸⁰ The apparatus was put on the market in 1933 at a price of \$ 490 and one was sold that year.¹⁸¹ It probably remained the only one ever sold.¹⁸²

In the early 1930s a brother of Jesse Beams, Harold W. Beams from the Zoology Department of the State University of Iowa, also used the centrifuges developed by J.W. Beams to experiment with live cells. In contrast to Harvey, his main interest was in the way cells recovered after being centrifuged. This implied that he could use the Beams' spinning tops as they were, take out the sample after centrifuging and investigate the cells under a microscope.¹⁸³ When he became interested in observing the cells during centrifugation, Pickels developed for him the microscope ultracentrifuge shown in figure 6.3.¹⁸⁴

According to Pickels it differed from the ones developed for Harvey in the sense that it was more easy to construct. The Harvey scheme was ideal when it was desirable to view the effects of centrifuging from a direction parallel to the axis of rotation and when in addition it was necessary to observe elements of the object more widely separated in that direction than at right angles thereto. If, however, these elements were least widely separated in a direction parallel to the axis, the scheme shown in figure 6.3 gave a greatly improved optical definition.¹⁸⁵ In the Harvey scheme, as the rotor turned rapidly, the image was every time seen in the same position so that the object as seen in the microscope was rather well defined. However, since the light beam had a finite width, the image was slightly blurred by the rotation. The image appeared as if it were suffering a vibration, of very small amplitude, about the axis of rotation. Only one point in the image was 'perfectly' defined. In the new scheme observations were made from the side. The

mirror was so mounted with respect to the cell that the image again appeared at the axis of rotation, but now the axis of rotation lay in the plane of the image. Again the image gave the appearance of suffering a slight vibration about the axis of rotation but since the axis of rotation was perpendicular to the direction of vision, the blurring effect was considerably reduced. At the Marine Biological Research Station, Woods Hole, Ma., Pickels conducted a few experiments with an outfit built by himself which gave very favorable results.¹⁸⁶

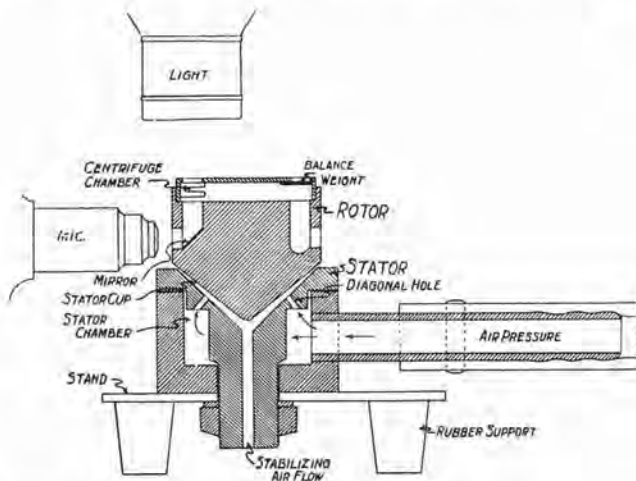


Figure 6.3

Harold Beams' microscope ultracentrifuge (H.W. Beams, 1937, p.574).

Beams' spinning top was also used by J.H. Webb from the Eastman Kodak Laboratories. He wanted to test the equivalence of intermittent exposures of the same average intensity for cases in which the flash period varied over the range 10^{-8} to 10^{-7} second. These exposures were made by means of a mirror mounted on top of a high speed air turbine which was an exact duplicate of a model lent to him by Beams. He mentioned that the turbine performed beautifully throughout all the experiments, being completely stable and free from vibration over the range of speeds 150 to 1675 r.p.s. The line air pressure was 80 lbs. per square inch and the speed of the rotor was varied by means of a fine adjustment needle valve.¹⁸⁷

Beams - Vacuum Ultracentrifuges

When Beams had developed his vacuum ultracentrifuge a considerable number of scientists also showed their interest. Beams' mechanics constructed centrifuges for them by working nights and week-ends. It took them approximately two months to

complete one, and the sale price was about \$ 600 to \$ 800. By 1937 they had already filled several orders and had orders for 8 more centrifuges. December 1938 one of these was shown to Warren Weaver who was very impressed by it. The apparatus had just been completed and would be sent to the Hebrew University at Jerusalem. Others, for example, went to Chicago, Yale and Wisconsin.¹⁸⁸ The latter was used by M.F. Guyer and P.E. Claus from the zoology department to study the growth of cancerous and of embryonic tissues stratified in the ultra-centrifuge.¹⁸⁹ Richard F. Humphreys from Yale used the Beams evaporative ultracentrifuge for the separation of Bromine isotopes. The details of construction and operation followed closely those recommended by Beams. He used it mainly to verify the theory he had worked out for the separation of mixtures and concluded that theory and experiment were in fair agreement.¹⁹⁰

Some researchers picked up Beams' designs and modified it to suit their own needs. James A. Chiles and Aura E. Severinghaus from the Department of Anatomy, College of Physicians and Surgeons, Columbia University, New York, wanted to use the quantity type ultracentrifuge for Hormone studies. They introduced a precession damping device, which prevented the centrifuge rotor from going into disturbing precessional motions at certain speeds during acceleration and deceleration. Together with some other modifications this greatly increased the life of the bearings. Their rotor was patterned after the Bauer/Pickels arrangement with the exception that it was smaller and had fewer test tube holes. This allowed them to operate the apparatus at 51,000 r.p.m. whereas Bauer/Pickels used 30,000 r.p.m. with their quantity rotor.¹⁹¹ Morris Rosenfeld from the Department of Pharmacology and Experimental Therapeutics, Johns Hopkins University, developed analytical cells that could be used in connection with the Quantity type ultracentrifuge. Sieve-like partitions covered with filter paper separated the cell into two or three compartments from which fractions could be removed for chemical analysis or for bio-assay. Referring to McBain and Svedberg he concluded that the cells used in their analytical rotors only held very minute amounts of liquid. He had therefore turned to the Beams arrangement in connection with the Bauer/Pickels quantity rotor. The sedimentation constants measured analytically agreed reasonably well with the values obtained by optical methods. He thought that small amounts of impurities contaminating the proteins might well account for the discrepancies observed in his present work. Agreement between analytical and optical constants was considered close enough to indicate the essential correctness of the theory on which the calculations were based. Rosenfeld indicated that the availability of such an analytical technique would be of particular value in measurements on biological materials. In many instances, enzyme, hormone, and serological activity could not be directly associated with an optically differentiable fraction. Often the active protein was too low in concentration or too greatly

contaminated by impurities to permit optical measurements. When highly purified proteins would be available or when accurate specific methods of analysis were applicable the analytical measurement of sedimentation constants might attain even higher precision than the optical method. At any rate, he concluded, the two methods, optical and analytical, were mutually supplementary and both yielded important information.¹⁹²

Dan H. Moore, a colleague of Chiles and Severinghaus, had also undertaken some modifications of the Beams apparatus. He observed that convection boundaries were caused by small irregularities in the analytical ultracentrifuge cell. He had therefore developed a special method for polishing the cell. A further problem arose from a misalignment of the cell in the rotor. It had been the general practice to align the cell by means of making a stylus scratch on the cell coincide with one on the rotor head. Svedberg had once used a slotted cell hole with matching key attached to the cell so that it was self-aligning. This was in a circular rotor which eventually ruptured at 50,000 r.p.m. He attributed the rupture to weakening caused by the slot. The stresses tending to rupture an oval rotor with cell holes in either end were much less, but since Svedberg's early experience there had been no record of attempts to use a self-aligning cell. Moore had now constructed a rotor with a slot and had provided the analytical cell with a pin made from aluminium and screwed into its shell. The rotor with this arrangement had been in daily use for several months, the usual speed being 50,000 r.p.m., without any indication of failure. Such a self-aligning arrangement would make it unnecessary to remove the rotor from the turbine shaft after each run for realignment of the cell and if properly made would insure high accuracy of alignment, particularly if the cell did not fit the hole tightly.¹⁹³

Beams had many contacts with potential users of the ultracentrifuge and his instrument makers often built special apparatus for other investigators. This usually resulted from consultation between the investigator and Beams concerning the former's problem, and often involved special ideas put forth by Beam as a result of these discussions. These investigators often visited the laboratory as their machines were being built and tested which made it easy to adapt the instrument to their special needs. Thus, the 'customers' were usually quite satisfied with what they got.¹⁹⁴

Sharples Specialty Company

Just before the turn of the century, P.M. Sharples established a company in Philadelphia manufacturing centrifugal cream separators which were used by farmers throughout the nation. One of his sons, Philip T. Sharples, soon after his

graduation around 1910, came to the belief that the cream separator business was a dead end, but that he could sell centrifuges for petroleum and chemical applications. He did just that, buying from his father's company and modifying to suit until he built his own factory, called the 'Sharples Specialty Company'. Under Philip's management his company grew whereas the cream separator company went bankrupt. This latter development followed the shift of cream separation from the farm to the central creamery which was made possible by and stimulated the development of factory size separators. The success of a first few new applications gave the new Sharples Company the ability to attempt to develop newer applications. The company probably spent more, proportionately, on engineering and development than most others at the time. Out of this grew a company belief that it was a premier authority in matters of centrifugals and high speed.¹⁹⁵

In 1924 Lee H. Clark from the Sharples Company presented a paper at the second colloid Symposium entitled 'The effect of Super Centrifugal Force on Industrial Colloid Systems'. He stated that ten years before the centrifuge was practically unknown outside of the dairy industry but that he could now list well over 150 specific applications of the 'Super Centrifuge in various lines of industrial work. Many of these applications concerned the separation of colloidal systems. The Super Centrifuge was an answer to the demand for equipment to handle large volumes of liquids quickly and continuously. Concerning the gravitational force he stated:

"(...) it is quite apparent that the higher the centrifugal force developed by a centrifugal that stays within engineering limits of safe and economical operation, the wider the range of problems over which that centrifugal may be used."¹⁹⁶

The commercial Super Centrifuge operated usually at 15,000 r.p.m., generating a separating force over 13,000 times gravity. They also manufactured a laboratory Super Centrifuge which operated at a maximum of 40,000 r.p.m. generating a maximum separating force of about 42,000 times gravity. The commercial centrifuge operated at a lower speed because in commercial practice work was done on systems having particles usually of a somewhat larger size. Clark stated that the laboratory centrifuge would seem to be an interesting medium for the study of systems, containing very finely divided particles and continued to describe some specific applications.

The Sharples Company was interested in manufacturing anything that rotated, both for industrial and laboratory applications although the bulk of their activities was directed towards industry. The laboratory Super Centrifuge was rather well known in scientific circles. Various supply houses showed the different models in their catalogs. They were available as air turbines, steam turbine and electric

motor drives. The turbine drives had top speeds of 40,000 r.p.m. until about 1935 when it was increased to 50,000 by enlarging the diameter of the collecting covers. The Laboratory Super Centrifuge, which from the design point of view was a repainted, small Sharples' Cream Separator with some extra bowl designs, received a Franklin Institute medal, and there was a widely circulated paper presented at the Institute by Eugene Ayres, 'The Effect of Centrifugal Force on Colloidal Solutions'. Work with this centrifuge was going on a number of laboratories and there was quite a group at MIT working on particle-size analysis.¹⁹⁷ This company background made that they were interested in the ultracentrifuge as soon as they heard of it. In John J. Serrell's words:

"In this atmosphere, the ultracentrifuge was a natural. The name used the magic word. To the self-appointed experts, its very high speed made it obvious as an addition."¹⁹⁸

It was usual for Sharples to look for profitable ideas that had been developed elsewhere and offer to attempt to make them commercial successes, on a profit-sharing or licensing basis. Sharples did little or no development work on it. The basic for such an agreement was anticipated profit for Sharples but there was also the motive in that the company considered itself the purveyor of all things involving high centrifugal force. It looked upon the ultracentrifuge as a means of entering new fields for improved commercial equipment, that might arise out of ultracentrifuge applications. The ultracentrifuge could thus play the same kind of role as the laboratory Super Centrifuge.¹⁹⁹

Soon after Beams development of the spinning top as an ultracentrifuge Sharples offered it for sale and showed it at the fourteenth exposition of chemical industries. It was described in 1934 in *Industrial and Engineering Chemistry* as being able to attain the worlds fastest rotational speed of 20,000 revolutions per second, generating forces of 7,600,000 g. Concerning the applications it was stated:

"The high-speed rotor is not entirely a toy. Some extremely difficult centrifugal separations have been accomplished in units of this type, made in larger size and hollowed out to afford a recess for the liquid. (...)

We see here the genesis of a new physical principle of unusual interest. Its ultimate value to the engineering profession may, in many ways, be revolutionary. For the benefit of posterity, the 1,200,000 r.p.m. centrifugal is being placed in The Franklin Institute at Philadelphia as a permanent exhibit."²⁰⁰

When Nichols learned about this Sharples spinning top he thought that they might be planning to construct a simple centrifuge along those lines for sale among the various research laboratories. Judging from the interest aroused by Beams's work, such a step, Nichols wrote, would seem to be warranted. However, because

Nichols and Svedberg had taken a patent on the optical centrifuge in 1927 some uses and some constructions were subject to licencing by them. Therefore Nichols wrote Sharples early 1934 that if they wished to incorporate optical features as one type of construction of the air-bearing centrifuge, they would need a license.²⁰¹ Sharples at that point, however, was not interested in developing the spinning top as an optical centrifuge. They were only interested in it as a rotational device. One of the original designers of the spinning top, M. Huguenard, at that time acted as consulting physicist for the Sharples Company. He experimented at considerable length with the idea of using this principle merely for its function as an air bearing, rotating the centrifugal by mechanical means. He also did some work on the use of such a device in conjunction with heavy rotors to reduce the load on the thrust bearings by means of the air currents generated through the normal rotation of the rotor.²⁰²

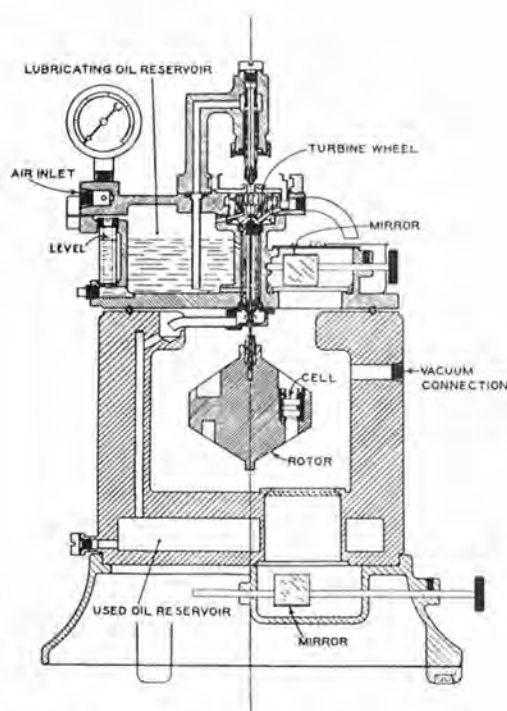


Figure 6.4

Sharples ultracentrifuge (Ayres, 1938, p.18).

When Beams and Pickels had developed their vacuum ultracentrifuge, Sharples was also interested in manufacturing it. Sharples approached Beams and an ultracentrifuge was manufactured for Sharples in Beams' laboratory and tested there by Pickels. Sharples tried to persuade Beams to take out a patent on the

air-driven centrifuge. Failing to convince Beams, Sharples offered a job to Pickels just about the time that Bauer first went to Virginia and invited Pickels to come to the Rockefeller Institute (see Chapter 5). Pickels had to make a choice between a definite and rather attractive offer from Sharples and the chance of a future offer from the Institute. At Beams' rather positive advice, Pickels chose the latter alternative. One of Pickels' considerations for choosing for the Rockefeller Institute was that the Institute offered a much greater challenge in the scientific sense with lots of famous people working there and many others paying occasional visits. Furthermore, it appeared to Pickels that Sharples' Chief Engineer was not as enthusiastic about going into ultracentrifuges as Sharples himself was. The former thought that they should stick to their traditional field of batch processes and not go into specialised instrumentation.²⁰³ Nevertheless, after receiving his Ph.D. Pickels spent a short time in Philadelphia doing some design and development work for Sharples. The apparatus developed at Virginia was transported to Philadelphia and tested by Pickels in July 1935 which led to a few minor modifications. Afterwards the apparatus could be operated for days without any trouble.²⁰⁴ Thereupon, Sharples set out to manufacture this type in a marketable form. The apparatus is shown in figure 6.4.

In connection with this development Sharples was still interested in obtaining patents *en* licenses covering the apparatus. Sharples wrote Beams a few times urging that his company be allowed to take out patents in Beams' name on the air driven ultracentrifuge. In return for this he was willing to turn over to a certain percentage of the returns from sales. The patents Sharples wanted were: First, one on the method of stabilizing the little cone-shaped rotors that spun in air at atmospheric pressure. Sharples had already obtained a patent taken out by Henriot and Huguenard, but this was not of any value without Beams' scheme of stabilization. The second, and the one Sharples most desired, was a patent on the air driven air supported vacuum type of centrifuge which he considered a fundamental patent. Beams, however, did not want to sign over any rights or take out patents on anything connected with the ultracentrifuge. Furthermore, he did not want to accept any pay for consulting work connected with the ultracentrifuge. He took the view that anyone who wanted to construct an ultracentrifuge should be free to do so and that nothing should be done to hold up publication of their or others' work. Furthermore, he felt that, since during the development of the ultracentrifuge he had been employed and supported by the University of Virginia, he had no moral right to take out patents on the apparatus for his personal gain. If patents were taken out, they should be signed over to the University. He explained this viewpoint to Sharples, and further that there was no reason why anyone, including Sharples, could not make the machines until patents were taken out. Beams believed that it would give research a setback if Sharples pushed the

claims of their patents too far or if they would try to prevent people from constructing centrifuges of their own. To Beams, the ultracentrifuge was primarily a research apparatus and could not be completely standardized, and, second, the price charged by Sharples (\$ 3000,-) would limit the use of the machine to laboratories with considerable means. Beams indicated they could not afford such a machine at Virginia. Beams sometimes wondered if it was wise not to take out patents on things as they were developed and then refuse to licence them unless the price was controlled. However, the difficulty under this scheme was that each patent would cost, say, \$ 200, and the scientist would be out of pocket that much.²⁰⁵ Beams wrote Warren Weaver from the Rockefeller Foundation on this matter wondering whether they had developed a certain policy on these matters. Weaver answered that they never took out patents. If others wanted to do so it would be their own matter but if they would do 'bad or clearly selfish' things with it, that would 'probably be reflected in our future relations'.²⁰⁶

After Pickels had left the Sharples company the Sharples engineers ran into difficulties with their machine. They could not get the instrument to run and appealed again to Beams. He invited them to send one of their engineers with the instrument and offered to help them. He found that it required only minor adjustments, and he taught the Sharples engineer the necessary tricks. Beams refused to accept any compensation from the Sharples Company for this service. This machine was to go to Rideal of Cambridge, England, and was priced at \$ 3,000.²⁰⁷ Sharples also contacted Nichols because of his patents and experience with ultracentrifuges. Early 1936 Nichols and Kraemer visited the Sharples laboratories and found that they had made a great deal of progress. They saw the Sharples machine operating at about 2000 r.p.s., using 15 psi. air-pressure for lifting the rotor. They used the latest system of Pickles and Beams having a 10 cm rotor suspended by a piano wire in a vacuum chamber. They had discarded the cone type of turbine, and were using a turbine much like the one they used on their laboratory supercentrifuge. According to Kraemer this accounted for the much greater efficiency. As he recalled, McBain used 100 psi. air-pressure to drive his very small rotors at 1500 r.p.s. Sharples had not yet tried to photograph the sedimentation of anything, and they had not made use of hydrogen in the rotor chamber. Kraemer also observed that the cells were quite small and, according to Svedberg's experience, too near the centre of rotation.²⁰⁸

October 1936 Edward B. Sanigar also paid a visit to the Sharples Company. Sanigar worked at the DuPont Experimental Station with Nichols and Kraemer to investigate the characteristics of the blood proteins in cancer as a continuation of the work that McFarlane started with Svedberg. Sanigar was placed there by a Cancer Research organization to which Kraemer acted as a consultant.²⁰⁹ A.U. Ayres, Chief Engineer at the Sharples Company, demonstrated their ultracentrifuge

to Sanigar. In his report on the visit Sanigar gave some technical data and some characteristics of operation. The rotor was made of duralumin and was about 3" in diameter while the height of the column of solution in the cell was about 8 mm. The rotor operated at 80,000 r.p.m. corresponding to a centrifugal force of 250,000 g while they had also once reached 324,000 g at 90,000 r.p.m. They had made some test runs with haemoglobin in Beams' laboratory the results of which appeared very satisfactory to Sanigar. During the run there was a gradual increase in speed, from 79,000 to 81,000 r.p.m. and in temperature (2 °C rise) over a period of 3 hours. The temperature of experiment was in the neighborhood of 50° C. The molecular weight calculated for haemoglobin differed considerably from that obtained by Svedberg, but the cause of the difference was felt to be in the heterogeneity of the solution used (which was, knowingly, not prepared as carefully as Svedberg's haemoglobin solution) and not in the centrifuge itself. Although the above run employed the absorption method, it appeared to Sanigar that the necessary alterations could be easily and satisfactorily made for the use of the more recently developed and more accurate refractive index method.

The experimental model had been in service for some time and had averaged 6 hours daily continuous running for the preceding three or four months without signs of wear or deterioration. No precautions were taken to rebalance the rotor when the cells were changed. Changes had been made from glass plates of various thicknesses to quartz plates of various thicknesses without causing the rotor to show any signs of unbalance. Ayres stated that he could see no reason why the rotor should develop any unbalance due to use, and any centrifuge supplied would have the rotor balanced, and would be expected to operate satisfactorily, from this point of view, indefinitely. He also stated that he expected the shaft to show very little, if any, tendency to become out of true, or to show appreciable signs of wear, over prolonged periods of use. Moreover, should a shaft become unsatisfactory it could be easily and inexpensively replaced, the only precaution necessary being the proper balancing of the turbine buckets. The cost of the centrifuge was quoted as three thousand dollars. Delivery at that moment, because of the orders ahead, would take about three months, though the actual time required for the manufacture of a centrifuge was considerably less.

Sanigar was 'very favorably impressed' by what he had seen of the performance of this ultracentrifuge and was of the opinion that it would become a definitely useful scientific tool. It would not be possible, without further comparison by means of Svedberg's 'Resolving Power' factor, to state whether it would be applicable to the measurement of sedimentation velocities over as wide a range as the Svedberg ultracentrifuge, but, even if it would not cover as wide a range, it would 'doubtless' prove of value in the range covered. According to Sanigar there was still development work to be done before it could be regarded as

a completed instrument. This included:

- 1) More accurate control of running speed
- 2) More accurate control of temperature, and most important
- 3) Adaptation to the Lamm Refractive Index method of measuring sedimentation velocities since this, as shown by Svedberg and his co-workers, was more accurate and preferable to the absorption method.

Regarding the usefulness of the apparatus for his own Biochemical Research Foundation Sanigar held the opinion that, unless the foundation would be prepared to undertake the necessary development work, the Sharples ultracentrifuge would not be of immediate interest. He suggested, however, that close contact be kept with the development of the instrument so that when the value of ultracentrifugal studies in the Foundation's work would be reviewed, the necessary knowledge would be available to determine the advisability of purchasing such an ultracentrifuge.²¹⁰

The day after Sanigar's visit Weaver L. Marston, Sales Manager at the Sharples Company, wrote Nichols that they had tested the apparatus so satisfactorily that they were about ready to put the equipment on the market. A photograph of the apparatus is shown in figure 6.5. They had built two machines which he would like Nichols to examine and witness their operation.²¹¹ About the same time the apparatus was announced in *Industrial and Engineering Chemistry* in an article on the various types of centrifugals Sharples manufactured. There, Marston wrote:

"A new tool for scientific research is now available in the form of the ultra centrifuge. This unit develops a much higher centrifugal force than even the (laboratory super centrifuge). The laboratory super centrifuge is suitable for continuous inflow and outflow of liquid in quantities measurable in litre per hour, but the ultra centrifuge is particularly developed for the examination of a very small sample, which is placed in a glass cell and rotated for a period of time. The sample can be observed while the machine is in operation. The ultracentrifuge develops a centrifugal force of 300,000 times gravity, and even higher if desired. The rotor is operated in an almost perfect vacuum so that temperature change due to air friction is negligible. The rotor is driven by air pressure and is supported by an air bearing.

This machine can be used for the determination of molecular weights of large complex molecules such as casein. It can also be used for the accurate determination of the particle size of colloidal suspensions such as dyes. The rate of subsidence of the colloidal particles can be watched while the rotor is in operation, and, by photographing this rate, accurate control of a manufacturing process is permitted."²¹²

Although this ultracentrifuge was already offered for sale there were still some problems to be solved which necessitated some changes. Ayres suggested that Nichols would test the effects of these modifications in Wilmington which, however, Nichols found rather impracticable because the optical arrangements in Wilmington could not be easily adapted to a completely different apparatus. Nichols

suggested to make use of a commercial photographer in order to take pictures of the sedimenting process. He also made some other suggestions, e.g. that for proper testing it would be necessary to determine the temperature of the cell more accurately and to operate the apparatus at a lower speed in order to prevent excessive heating of the cell.²¹³ He also made suggestions concerning how to take several exposures on the same photographic plate²¹⁴ which were taken over by Ayres.²¹⁵ Still, Nichols was not satisfied with the performance of the apparatus. A test run on haemoglobin gave a much too low value which Nichols attributed to the optics and the developer. Also the measurement of the temperature was not good enough. Nichols also referred to the 'small' length of the cell available for observation which was 7 mm. He pointed out that Svedberg was using 12 to 15 mm and that he was even arranging to go to 20 mm. Nichols suggested that future developments should be in that direction.²¹⁶



Figure 6.5

Sharples ultracentrifuge. (Alexander and Johnson, 1949, p.266).

Concerning the patent situation Sharples suggested that Nichols would give them an exclusive license with the exception of Svedberg and Nichols themselves and the Bausch & Lomb Company, to whom Nichols had given a license in connection with the centrifuge microscope. Sharples offered Nichols a 5% Royalty based on a sales of 5 Ultracentrifuges a year at a price of \$ 3,000 although Sharples had no idea of whether this estimate made any sense. Sharples furthermore mentioned that there was some infringement on the patent going on and the sooner the license would be given, the sooner the advertisement could start so that people would realise commercial machines were available, the sooner the infringement would automatically grow less of its own accord.²¹⁷ Nichols was prepared to give such a

license only for forces over 20,000 g and demanded an 8% royalty.²¹⁸ It was finally agreed that the first point was taken over and that the royalty be 5%.²¹⁹

Now that the licensing was settled Sharples asked Nichols to write a brief article from which they could quote in their advertising, also allowing them to use his name.²²⁰ Nichols agreed and in the folder based on his text reference was made to a number of people who had worked with ultracentrifuges, like Nichols, Svedberg, Bauer, Pickels and McBain. It was stated that the rotor had been operated at 120,000 r.p.m. giving 485,000 g. However, its safe speed, because of stresses developed in the rotor, was 80,000 r.p.m. giving 250,000 g. At this speed it required 20 to 30 minutes to reach full speed and about 30 minutes to come to full stop. It could, if desired, be supplied complete with light source, light filters, camera suitable for visual light, mechanical vacuum pump, diffusion pump, vacuum gauge, and stroboscope.²²¹ The rotor had a maximum diameter of 3½ inches and was pierced at a radius of 1¼ inches for the transparent cell containing the sample to be tested. The rotor was surrounded by a nickel steel housing 1½ inches thick to protect the operator. Windows were provided at top and bottom of the housing, in line with the cell location. Beyond these were mirrors mounted to direct a beam of light through the cell and then to the lens of a camera. The rotor was first speeded up to approximately 10,000 revolutions per minute after which the vacuum pumps were started to exhaust the housing. The rotor was allowed to revolve at this low speed until the vacuum was established, which took about an hour. This was necessary to prevent a loss of the sample through expansion of air bubbles under the surface. Higher speed tended to increase temperature of sample before vacuum was established. When vacuum was established, air pressure was increased to bring the rotor up to operating speed of 1350 r.p.s. after which the actual experimentation could begin.²²²

Svedberg was rather doubtful about the ability of the Sharples company 'really to make good machines'. On a visit to Oxford taking part in the opening of a centrifuge lab in the department of biochemistry he heard about a Sharples ultracentrifuge delivered to Rideal's laboratory in Cambridge. It was said to be in very bad shape, almost useless. In view of this fact he supported Nichols' suggestion to the Sharples company to employ an ultracentrifuge expert. Svedberg suggested that they should employ Watson who had worked with Svedberg for some time and who had supervised the installation of the oil-turbine ultracentrifuge at the DuPont Experimental Station.²²³ When Sharples tried to find out what was going on in Cambridge Rideal replied:

"I think it is well known that Professor Svedberg sometime ago has expressed the opinion that all air driven centrifuges are useless and I believe that this

statement was made on account of the difficulty of eliminating temperature gradients. This statement however, was made long before our machine was even designed and the statement attributed to Svedberg at Oxford may be nothing more than the usual Oxford-Cambridge competitive spirit combined with this alleged remark of Svedberg. As the machine has not yet been tested, it is clear that Svedberg could not have made this statement at Oxford. I should certainly ignore the whole thing.

The new Compressor and the general set-up will be ready by next week (...). We shall then be able to find out whether the machine is 'in very bad shape - almost useless!' or not."²²⁴

In 1937 the Sharples company contacted some investigators who might be interested in purchasing an ultracentrifuge. For instance they wrote Stanley from the Rockefeller Research laboratories because their latest models of the super centrifuge and the ultracentrifuge would be applicable to the sedimentation of viruses. They invited him to see these instruments at the coming Chemical Exposition.²²⁵ Sharples wrote Nichols that at this Chemical exposition they had had a number of enquiries but had not sold anything yet.²²⁶ Sharples also approached Dr. Ellis from the Cancer Research Organization Sanigar worked for. Although they were interested in obtaining an ultracentrifuge they did not purchase from Sharples but made an arrangement with Beams. As Sharples understood it they were interested in one of Beams' special bowls for isotope separation, and did not build a machine which would infringe the Svedberg/Nichols patent.²²⁷ Beams also referred some people to Sharples, but they informed him that they were not able to pay the \$ 3,000 which Sharples charged and, furthermore, they usually desired to have a different type rotor from Sharples' standard machine. Beams' instrument makers were sometimes also asked to make the same type of apparatus for interested researchers in their off hours from the shop. They charged only for their labour and materials which led to a cost price from \$ 300 to \$ 800 instead of the \$ 3,000 charged by Sharples. Beams furthermore thought that those were better machines than Sharples' because they were constructed with all of the latest improvements while the Sharples machines were still in the Beams/Pickels stage of 1935. Beams furnished anyone with drawings and taught them all they knew about centrifuges whenever they came to Virginia. He encouraged everyone to make their own machines when possible.²²⁸

Late 1937 the Sharples people still had problems getting sedimentation pictures which were meaningless. After a number of tests they found that the trouble was that one of the mirrors was not oriented properly after which the troubles disappeared.²²⁹ Around that time they were also visited by Svedberg at which occasion L.P. Sharples suggested that the Sharples Company should also market the oil-turbine ultracentrifuge in the US. This, however, would imply a considerable increase in price which would make it very difficult for scientific institutions with

limited means to purchase such a machine. Svedberg therefore did not want to consider this proposal. At the same visit Svedberg had also expressed his doubts about the usefulness of the Sharples ultracentrifuge. The most important limitation would be its lower resolving power for mixtures, proteins for example, on account of its smaller diameter than Svedberg's rotors and those of the Rockefeller Institute. Nichols stressed, however, that there surely was plenty of interest in the machines as was evident from the inquiries Sharples had received. The most developed field of use would be the biomedical and medical field but a large number of industrial concerns also needed information it could give on synthetic resins, rubber, protein products, cellulose derivatives, and the like.²³⁰

Sharples wrote Nichols that they would still like to market the oil turbine ultracentrifuge and that it would be necessary to price it somewhat higher than Svedberg did in order to cover the costs of various services connected to it. Sharples argued:

"The service is, I believe, worth more to the customer than he pays for it. By this I do not mean the actual mechanical service, but I mean the well-rounded total which first brings the machine to the customer's attention at a time when he needs it, but perhaps does not know he needs it, afterward gives him the opportunity to find all he wants to know about it in direct conversation with a representative, afterward lets him make certain tests with somewhat similar apparatus to be sure that he is going to need the device after he does order, and finally gives him assurance that a company close to his home will be ready to take care of him promptly on spare parts and on other information.

Perhaps all of the above services are not as necessary on a piece of laboratory apparatus of this nature as they are on a piece of machinery, but I believe general experience has shown that any article of commerce which has a full line of sales services behind it is much more useful to the community at large regardless of the fact that a somewhat higher price always has to be charged for that article.

I do not think we will ever make a profit out of the sales of Svedberg ultracentrifuges that we might make, as the number of sales will probably not be large enough to pay for the amount of time that our organization has to put on the machine. I believe the same is true of our own air-driven ultracentrifuge, although on that we have a chance of making some profit if a considerable number of people purchase it. We entered this ultracentrifuge fields not to make money, although we hope not to make a loss. We entered it because it is a centrifugal field and we wish to keep our position in that field, even though some of the items we have to handle are non-profit items."²³¹

For Svedberg, the fact that the price would go up was a reason for opposing Sharples plans. Furthermore, he argued, that he had planned, and by then partly carried through, a number of experiments aiming at definite improvements and simplifications in the design. He, therefore, preferred to keep the matter entirely in his own hands.²³²

Early 1938 Sharples decided upon a new policy in connection with the sale of their ultracentrifuge which would be in the public interest. They put a special,

reduced price on ultracentrifuges that were desired by non-profit institutions, such as universities or research laboratories that had their income from endowment. Their standard price on the ultracentrifuge with stroboscope was \$ 3,000, and they anticipated offering these same machines to non-profit organizations for \$ 1,800, which was said to be their actual cost. Sharples explained Johannes Bauer that this rather high cost was caused by the fact that they had all of the parts of the ultracentrifuge made for them and only did the final fitting and assembling in their own plant. The bulk of the cost thus consisted in cash outlay to others. Sharples had been informed in one case where an ultracentrifuge was made by an institution that their cost for same was under \$ 600, but upon a closer inspection they found that with the proper charge for labour and overhead the price was above their \$ 1,800 figure. He hoped that their offer of machines to the non-profit institutions would be considered as a really worth-while concession in the interest of science. Furthermore, as he wrote Bauer, they were trying to have it become generally known that they had to pay royalty under the Svedberg/Nichols patent. Having obtained a license under it, and having to pay royalties under it, they felt that others should not be permitted to use it free of charge. Their policy would be to give definite licenses under this patent to those charitable institutions who had already acquired ultracentrifuges provided they could obtain Svedberg's and Nichols' permission to make such gifts. Sharples trusted that Bauer would consider this 'entirely businesslike and ethical and in the general public interest.'²³³ Nichols agreed to this policy²³⁴ but Bauer had some reservations. He contacted the staff of the international Health Division on the matter and also sent a copy of Sharples' letter to Svedberg. Svedberg replied:

"(...) I always thought that one had a right to make and use patented devices for scientific purposes, if no profit motive was involved.

When Nichols suggested the taking out a patent on the general principle of the ultracentrifuge in 1923 I had not the faintest idea that this would in any way injure scientific research. During the following years I quite forgot the existence of this patent until Nichols called my attention to the fact that the Harvey microscope-centrifuge manufactured by the Bausch and Lomb Co. was covered by our patent and that accordingly they should obtain a license from us. I have never heard the question raised about any license being needed for the use of the 'home made' microscope-centrifuges used by Dr. Harvey himself and others (I saw a couple of them at Woods Hole in 1933). Then, later on, Nichols wrote me about the Sharples centrifuge and pointed out that this company too ought to obtain a license from us. I gave my consent never suspecting that the Sharples people would or could interfere with scientific institutions using 'home-made' instruments of this kind.

If there is anything I can do in the way of securing for you (and other scientific institutions) the right of making and using ultracentrifuge for your own work I will be very glad to act. Needless to say I am prepared to grant you a personal licence if that is required, but I would rather see that your right to use this tool were recognised in principle. (...) As things have turned out I am sorry that I ever granted the Sharples people the license for the manufacturing of the air-driven centrifuge."²³⁵

Svedberg also wrote Nichols asking him 'to stop Sharples action against the scientific institutions'.²³⁶ He also wrote Sharples that he regretted ever giving them a license and urged them to change their policy.²³⁷ Sharples replied Svedberg that Bauer had probably misunderstood his letter. He explained:

"If you will carefully note the next to last paragraph in that letter you will see that we offered to obtain for the Rockefeller Institute, as well as for any other charitable institution already owing an ultracentrifuge, an absolutely free license under the Svedberg-Nichols patents. Certainly nothing could be more fair or more charitable on your part and on Dr. Nichols' part than this. Surely no charitable concern, and this, of course, includes Rockefeller, could have any complaint at this policy and could have nothing but good words to say about your goodwill in the matter, Dr. Nichols' goodwill in the matter, or the Sharples Specialty Company's goodwill in the matter.

(...) I would be very loath to have you think that this concern is anything but one hundred percent ethical, as we have a very fine reputation for business ethics throughout the United States. Mr. Rockefeller, of course, also has a reputation for business ethics second to none in this country, and the last thing in the world we would want was for Mr. John D. Rockefeller to feel that the Sharples Specialty Company could in any way be accused of bad ethics in its dealings with that most marvelous foundation that is his and his father's monument."²³⁸

As Svedberg was the partial owner of the patent in question Sharples would like to have his consent for their policy which would enable scientists throughout the United States to make more use of Svedberg's 'pioneer work and of the pioneer work being done by Rockefeller.' Giving an official free licence to charitable institutions would be far better than having them continue infringing the patent without license, which would be 'entirely illegal and would leave the institution in question open to criticism and would perhaps make it very difficult to sell the license to strictly commercial, profit-making institutions who desire to use an ultracentrifuge and should be sold a license under the patent.'²³⁹ Svedberg did not find this answer at all satisfactorily and replied on 9 March 1938 that he renounced, in favour of Nichols, all rights to any profits arising from the license.²⁴⁰ In a letter to Bauer the same day he explained that such an action would not help Bauer much but that it might make Sharples understand how strongly he disapproved his policy.²⁴¹ To Nichols Svedberg wrote that he found it both unethical and stupid if a manufacturer interfered with scientific people in their experimental work. They should be grateful to them for their endeavour to develop further and improve devices which they might have acquired a right to manufacture. It was an established practice in Sweden and also in America, Svedberg believed, to permit scientists to make and change such devices without being granted special licenses. Svedberg asked Nichols to arrange for a new agreement to be drawn up and the old one to be cancelled. Svedberg did not want to have his name on an agreement which, in his opinion, had been misused.²⁴²

Nichols had taken the defense for Sharples position and had written Bauer on

15 February that he saw no objection to a formal recognition of the patent through a licensing agreement. If this would not be done it would render very difficult a future prosecution of some other concern who decided to start the manufacture and sale of a patented device.²⁴³ Nichols had also sent a copy of his letter to Bauer to Sharples. A few days later Sharples wrote Nichols that they were preparing a license for the Rockefeller Foundation which they proposed to give them free of charge, even though Bauer did not particularly want it. Furthermore they were preparing a license for American Cyanamid (Lederle Laboratories) which license they expected to sell to them and transmit twenty-five percent of the proceeds to Nichols and Svedberg, as agreed with Nichols.²⁴⁴ Shortly thereafter this sale was agreed and March 16 Sharples sent a \$ 125,- check to both Nichols and Svedberg.

The Rockefeller Foundation took counsel's advice on the basis of which Bauer wrote Sharples on 15 February that the Foundation had a right to use patented devices, principles or processes when such use was not prompted by a profit motive and when its purpose would be scientific. In case Sharples' counsel would not concur in this opinion Bauer suggested to have the two counsels look into the matter.²⁴⁵ 25 February Sharples replied that, if Bauer did not wish to receive a free license from them, they were prepared to let the matter drop even though it involved some risk with damaging the validity of the patents. Sharples wrote that he did not feel that the matter was of sufficient importance to warrant the expense of a conference of attorneys.²⁴⁶ On 8 March Bauer informed Svedberg that Sharples was prepared to drop the matter.²⁴⁷

Nichols did not feel comfortable about Svedberg's wish to withdraw his name from the patent. He asked Sharples if he had suggestions for making him change his mind.²⁴⁸ Sharples replied:

"I believe the only thing we are doing to which Dr. Svedberg objects is asking profit-making companies to pay a license if they wish to infringe the patents. We have, as Dr. Svedberg knows, offered to give a license to Rockefeller Foundation, and are going to be very liberal with other non-profit technical organizations. With this in mind, perhaps Dr. Svedberg would care to enjoy the benefits of any sales made of our centrifuges just as he enjoys profits made for the sale of his own centrifuges. He might stipulate in the agreement that any royalties collected by us from organizations not purchasing our machine were collected against his desire and he would refuse to participate in the benefits of such royalties.

I am willing to do almost anything you suggest in this matter. I doubt if we will ever make a cent out of the ultracentrifuge. The market is somewhat restricted and the cost of doing business we find is quite high due mainly to the prolonged tests which prospective customers desire that we make for them in our laboratory setup before they are ready to purchase the machine. We do, however, wish to get some goodwill out of the substantial amount of money and time that we have already put behind this ultracentrifuge, and if possible we would like to get enough cash returns to repay this financial investment."²⁴⁹

Mid-April Nichols wrote Svedberg that Sharples had dropped the matter so 'there should be no hard feeling now'. He therefore would like Svedberg to change his mind. If Svedberg would still withdraw Nichols wondered if his continuance of the license would cause him embarrassment. In that case maybe the patent should be dedicated to the public. Nichols, however, would not like such a step for it would seriously restrict Sharples' chances of getting a return on their rather considerable investment.²⁵⁰ Svedberg replied that:

"we are used over here to feel entirely free to use patented procedures for research, education or any work which does not aim at making money. I don't know if this is the strict letter of the Law but it is at least the way these things are handled here. My indignation at Mr. Sharples' way of proceeding was therefore boundless - and is still so.

If however, an agreement could be reached whereby Mr Sharples declares himself willing to uphold the licensing principle only in the case of commercial concerns I would feel free to go ahead with the license. The freedom to use the process and to build analytical air-driven centrifuges would have to include not only the Rockefeller Institutes but other scientific institutions too.

Will you try to put this before Mr Sharples as clearly as possible. Would you mind telling him also that I will leave check for \$ 125:-- uncashed until the matter is settled satisfactorily."²⁵¹

Sharples accepted Svedberg's terms, stressing that they had already adopted a policy of selling ultracentrifuges at a very low price to scientific institutions in case they desired to buy rather than to build their own machines. Furthermore, he wrote Svedberg, in certain cases they had donated the use of their machine, laboratory, and operator, to charitable institutions which wanted work done but had not the funds to buy, build, or even operate an ultracentrifuge. In effect, he stressed, they had constantly been handling Svedberg's patent rights even more liberally than he now requested.²⁵² This letter removed Svedberg's doubts as to the possibility of coming to an understanding satisfactory to all parties and he felt that the invention was now being handled according to his desires.²⁵³

The sales of ultracentrifuges by the Sharples Company were not going very well. April 1938 Sharples wrote Nichols that they had had numerous enquiries for ultracentrifuges, but that actual sales were certainly scarce. Sharples indicated that Dr. Stern of Yale was at that time very much interested.²⁵⁴ About a year later Nichols wrote Sharples that he had already expected to receive a royalty check.²⁵⁵ Sharples replied that they had found surprisingly small response to their sales efforts which, he assured, had been very considerable. According to Sharples there were undoubtedly numbers of people using ultracentrifuges but many of them were using ultracentrifuges that did not come under the patent. Hardly any of them appeared to want what Sharples had to offer, although there had been no criticism of the superior operating characteristics, from a mechanical standpoint, of their

machine. Sharples also complained that the fact that the Rockefeller interests had spread the news of how much it cost for direct labour and material to make an ultracentrifuge, had not helped their end of the business.²⁵⁶ Half a year later Sharples again wrote Nichols, stating:

"As you know, we have not been successful to date in selling a quantity of ultracentrifuges. To be successful I believe we would first have to have a special department for ultracentrifuges that would be prepared to tailor-make machines suitable to the individual needs of each customer, and secondly we might have to sell the equipment at a price that would compete with the equipment now available from one of the universities on a basis that includes no expense for advice and consultation, and in addition no expense for manufacturing overhead.

At the present time we do not believe there is sufficient market or a sufficiently profitable market for us to handle the ultracentrifuge business in the manner indicated above. We would like to continue to offer our present ultracentrifuge equipment through our sales organization as we have in the past. We would also like to hold open an opportunity for us to change our course and install a special department for tailor-making the machines if and when we foresee a market for the machines that will warrant this step.

Meantime, we wish to give you and Dr. Svedberg full opportunity to cancel our exclusive right under your patent if you wish to do so, although, as above stated, it would be our preference to continue the arrangement as it stands at present, leaving the way open to us to expand our activities at any time that we think the market warrants it."²⁵⁷

Nichols found it also desirable to continue the agreement but indicated that, under the present low sales, it seemed to him that a 'token' payment of say 10% of the agreement would be a fair arrangement until such time as Sharples would be able to expand their activities.²⁵⁸ Sharples declined to pay such a token, amounting to \$ 75,00. He indicated that they found themselves unable to even sell their demonstration machine due to the fact that the different persons who came to see it and who heard about it ended up by building their own machines. Shortly before they checked up on Dr. Stokes of the Children's Hospital, and found that after visiting them he had had a machine built by the Pennsylvania Hospital. Sharples felt that there was no profitable business to be had owing to the non-profit competition that seemed to exist. Therefore, until they would see a new light on this proposition, he proposed to let it ride dormant. He assured Nichols that they would keep completely up-to-date on what would be going on in ultracentrifuges and that they would be ready to step in again at any time they found a fair-sized market for any particular type of machine at a reasonable profit.²⁵⁹

September 1939 L.P. Sharples published an article in *Industrial and Engineering Chemistry* an article entitled: 'Which Centrifugal - and when?' in which also their ultracentrifuge was discussed in two sentences.²⁶⁰ It was probably the last time it was publicly offered for sale. During the war the request for industrial centrifuges grew as did the demand for oil purifiers and naval vessels. This so occupied

Sharples that the ultracentrifuge 'business' was completely put aside.²⁶¹ According to John J. Serrell, who came to work in the Sharples sales department in 1937, after the sale to Rideal no ultracentrifuges were ever sold.²⁶² Eirich and Rideal described this ultracentrifuge in *Nature* in 1940. They had introduced some changes into the model as it was made originally by Sharples. Because the problems due to a temperature rise in the cell were too great they spun the rotor in low pressure hydrogen like Svedberg. Some changes were introduced after discussion with Philpot who had worked with Svedberg and who had bought an oil turbine ultracentrifuge from him. One of these changes was that they now used longer cells than Sharples had supplied, 10 mm column of solution rather than 7 mm. In most cases Svedberg had used between 8 and 12 mm columns.²⁶³ So considerable work was done after Sharples had supplied the machine.

According to Ashton T. Scot, who has been working in the engineering department of the Sharples Company, Sharples had had great success in selling tubular centrifuges as integral parts of processes. Conversely, they had no significant success in selling centrifuges 'off the shelf'. The company did not seem to be adapted to manufacturing the tailor made machines that ultracentrifuge researchers needed. They only stepped in to it because it used the magic word 'centrifuge'.²⁶⁴

Edwin J. Cohn - Harvard Medical School

Edwin J. Cohn was a protein chemist at the Department of Physical Chemistry of Harvard Medical School. Cohn had known Svedberg since the early 1920s and in those days had also visited the Upsala laboratory, shortly before Svedberg started his first experiments on haemoglobin. Cohn had been one of the first who believed that proteins were well defined molecules and had argued with Svedberg about what could be expected running them in the ultracentrifuge. Svedberg expected that it would show a distribution of sizes while Cohn argued that a single boundary would appear as indeed turned out to be the case when Svedberg actually performed the experiment. Cohn was very impressed by Svedberg's apparatus and saw it as an important new tool in physical chemistry. However, because the number of existing proteins was essentially finite and because the high cost of the apparatus Cohn held the opinion that there was no occasion for more than one centre for such research in the world and that researchers, who were concerned with protein investigation, could not do better than to supply Svedberg with materials and students so that the molecular weights of the proteins could be established on a firm foundation. In the early 1930s Cohn shifted away from the

proteins to the smaller biological particles like amino acids and peptides. About 1935 J.L. Oncley came to Cohn's lab who had studied with J.W. Williams and mainly had worked on dielectric constants and electric moments of proteins. By that time Svedberg had demonstrated that proteins decomposed and recomposed under a variety of experimental conditions. This implied that the ultracentrifuge could be applied to a much broader range of problems than Cohn had anticipated in the 1920s. Svedberg's new evidence regarding the dissociation of proteins into molecules of smaller molecular weight opened new vistas and rendered it desirable, so it seemed to Cohn, that any laboratory concerned with protein investigations would have to control the size of the molecules under the conditions of their investigation.²⁶⁵ Cohn expressed his interests in obtaining an ultracentrifuge to Warren Weaver from the Rockefeller Foundation. Weaver mentioned to Cohn that Beams was also experimenting with ultracentrifuges, at that time investigating the possibilities of steam and electrical drives. Weaver was inclined to fund Cohn's ultracentrifuge but because of the general demand on the budget it appeared unlikely that such funds would be available within a year. Weaver wondered if it might be possible to supply Cohn with one of Beams' ultracentrifuges. Cohn had visited Beams in the spring of 1937 and subsequently had also seen the Pickels/Bauer equipment in the IHD laboratories. When Weaver asked Beams whether steam or electrical drives might soon be available he also mentioned to Sharples ideas about infringements on patents by institutions that built their own ultracentrifuges and wondered if these patents in any way applied to the air drive Beams had developed. Weaver stated that he could understand Sharples' reasons for their policy but mentioned that the Rockefeller Foundation had no interest in the development of an ultracentrifuge industry. They only wished that development in that field could be made freely and economically available.²⁶⁶ Beams replied that he expected the electrical drive would displace the air drive in chemical and biological research because of the precision and ease with which its speed could be regulated. He thought that the Svedberg/Nichols patent in no way affected the air-drive as such. It would only cover the optical arrangement in connection with the ultracentrifuge. Beams also stressed that he personally was against taking out patents because he held the opinion that the results of his research should be freely available for everybody. He was therefore prepared to give his blueprints on the ultracentrifuge to anybody who wished to construct one.²⁶⁷

Because it might take some time before the Rockefeller Foundation might consider a grant application Cohn applied with the 'Commonwealth Fund' in 1938 for the purchase of an ultracentrifuge for their studies on proteins. He argued that almost every method of studying proteins involved some assumption regarding their molecular weight and that the molecular weight seemed to depend largely upon experimental conditions. Thus their studies could not be pursued reliably without

determining the molecular weights which necessitated the purchase of an ultracentrifuge. Concerning the type of ultracentrifuge Cohn stated that the Svedberg type was the most accurate but that the major advantage of the Beams type was that the spinning rotor did not develop a temperature gradient because of its good isolation and the vacuum chamber surrounding it. However, the resolving power of the latter type, as it had been adapted to qualitative studies of proteins by Pickels and Bauer, was inferior to Svedberg's so that it could not as readily distinguish proteins of the smallest molecular weights when more than one was present.²⁶⁸ In the fall of 1938 Cohn was awarded the applied grant for the purchase and installation of ultracentrifugal equipment. This grant was not large enough to buy the Svedberg apparatus but permitted him to combine Svedberg's optical system with the air driven ultracentrifuge as Bauer and Pickels had done.²⁶⁹ Thereupon Cohn approached Pickels who sent him information on their latest developments.²⁷⁰ He also approached Svedberg asking his advice before he would place his major orders.²⁷¹ Svedberg replied that he was pleased that Cohn was allowed to purchase an ultracentrifuge but that he could not understand why Cohn would want his advice. Because he wanted the air-driven ultracentrifuge he should be able to get all the advice he needed in the US. Svedberg suggested him to contact Frank Horsfall of the Rockefeller Institute of Medical Research in New York who had worked with Svedberg for a year. Horsfall thus had had the opportunity to work with both the air-driven and the oil-driven systems. Svedberg continued:

"When we met last time I think I expressed the opinion that the air-driven type is very useful for many purposes, especially for the study of high-molecular proteins such as the viruses where the resolving power need not be very high and where the light absorption method can be used. As I understand it, your work is mostly concerned with 'ordinary' proteins of medium and low molecular weight and their dissociation products. In such cases one is forced to use the refractive index 'scale-method' in its most refined form combined with thick ultracentrifuge cells run at high speed. I therefore doubt that you will be able to obtain reliable results for the dissociation of low-molecular proteins with the equipment you propose to install. After all the difference in cost between the two systems is not large considering that many parts - optics, speed measuring, instruments etc. - have to be the same. I am afraid that you will find it a waste of money to install a system not adequate to your requirements.

This is my personal opinion and, I think, the opinion of my collaborators here in Upsala. We might be prejudiced and our opinion may perhaps not be of much value. You asked for it and I, therefore, have given it frankly. Our monograph on the ultracentrifugal technique will soon be published and there you will find detailed description of the various procedures, such as the different methods of observation, and their merits. Needless to say we will always be glad to give you the advice we can with regard to experimental detail."²⁷²

Cohn replied that this was exactly what he argued in his report to the Commonwealth Fund but that they had nevertheless only given him money for buying the air-driven equipment. They had therefore started installing an

ultracentrifuge which was to be closely patterned after the one at the Rockefeller Institute. Oncley was to be in charge of the apparatus and, like Cohn, had also visited the Institute in order to get an impression of its functioning. The apparatus was made in the Institute's workshop by Cohn's mechanic under the supervision of Pickels' mechanics. Cohn had discussed the details of the apparatus with Bauer, Pickels and Horsefall who had given them a lot of useful advice on the basis of their own experience. Cohn wanted to be sure of any new developments in Svedberg's laboratory, and in that of Williams or of Beams. Although they did not feel as though they could afford at that time the oil driven sedimentation ultracentrifuge, they had been discussing the possibility of adding one of your Svedberg's equilibrium type ultracentrifuges. He therefore asked Svedberg to send him the cost estimate of this type. Furthermore he expressed that he hoped that at some future time Oncley or some other colleague could be sent to Upsala to learn all the details of the technique. Up till then they had been instructed by Horsefall who had given them a lot of practical advice.²⁷³ Svedberg sent him the requested information²⁷⁴ and Cohn replied that he would be in touch again as soon as their plans were further developed. He also stated that he felt certain that putting in the Beams air driven ultracentrifuge with the Svedberg optical system would be the beginning and not the end of their development.²⁷⁵

Cohn's air-driven ultracentrifuge appeared to perform very well. During the war it was run practically every day for sedimentation velocity measurements. They were also fractionating proteins of the blood plasma on a very large scale. The National Defense Research Council gave them a large grant in order to build a very big cold room because the fractionation had to be done in the cold. Every week they got about 60 litres of blood plasma from the Red Cross blood donor centre which would be fractionated. The great emphasis was at first on the serum albumin for transfusion to maintain blood volume. Later on they worked on the gamma globulins for immunization purposes. They constantly varied the preparation procedure in order to find one that could be used on a big industrial scale. The ultracentrifuge was used in order to check what the effect of the method had been. The program was so successful that it was continued after the war.²⁷⁶ After the Spinco ultracentrifuges were produced commercially from the late 1940s onwards (see below) they also bought one of those and there is no evidence that Cohn contacted Svedberg again on the further purchase of his ultracentrifuges.

Pickels - Spinco Ultracentrifuges

Because of his work for Bauer and Wyckoff Pickels became a well-known and respected expert in the field of ultracentrifugation of proteins and other

macromolecular substances. Early 1936 W.T. Salter from the Harvard Medical School asked Pickels to determine the molecular weight of a certain enzyme. Pickels answered that at that moment, in order to make the work safer in case of rotor explosions, their centrifuge was dismantled for removal to another laboratory in the subbasement, and it would take some time before its installation would be complete and the optical system would be lined up in the new location. For this reason they could not cooperate with Salter in testing his enzyme for the next couple of months. However, if this delay should not be a problem they would be pleased to cooperate in this study when the apparatus had again been properly installed.²⁷⁷ Somewhere around 1943 Pickels was invited to write a chapter in a new edition of Alexander's *Colloid Chemistry*, one of the most authoritative sources in the field. The chapter was entitled 'High-speed Centrifugation; Ultracentrifugal Analysis of the Centrifugal Fractionation and Concentration of Molecular Particles'.²⁷⁸ In April 1946, John W. Shakespeare of the Office of Research and Inventions, Special Devices Division, US NAVY, wrote Pickels at the Rockefeller Institute that they would like to procure one or two ultracentrifuges of the so-called oil-damped air-supported air-driven turbine type (the 'turret drive'). Referring to Pickels' various publications he specified their requirements. They would like to have two analytical rotors and 6 preparative rotors.²⁷⁹ Pickels estimated that such an order would cost approximately \$ 6250 for materials plus \$ 1750 for labour.²⁸⁰ During his twelve years with the Rockefeller Foundation, Pickels had often been called in by outside research institutions for advice on construction and operation of ultracentrifuges, and had actively assisted the building of ultracentrifuges in several laboratories. With the return of science to a peacetime basis, requests for such services were increasing.²⁸¹

In 1946 Pickels was visited at the Rockefeller Institute by Maurice Hanafin who was a salesman, associated with the 'Glass Engineering Laboratories' at San Carlos, California. About 1935 Hanafin had started to sell Swedish angle centrifuges, made by the 'Sorval' company, on the American west coast. Selling these machines he encountered the problem that American glassware did not readily fit in the apparatus which inspired him to try and make the glassware himself. Thus, in 1937 the Glass Engineering Laboratories were created which set out to make special glassware for scientific apparatus. The angle centrifuges were widely used and cost about \$ 200,- a piece. This stimulated Hanafin's interest in centrifuging in general and made him study all kinds of publications on the subject, including publications on ultracentrifuges by Beams, McBain, Pickels, and Svedberg.

One of Hanafin's customers had been the University of California Medical School in San Francisco (Hooper Foundation). Dr. Carl Meyer from the school inquired whether Hanafin could obtain for them a preparative ultracentrifuge like

the one Pickels had described. Hanafin made some inquiries and found Joseph Grebmeier prepared to manufacture the mechanical parts of the apparatus.²⁸² Grebmeier had been a mechanic at Stanford University in the 1930s and had made all of McBain's ultracentrifuges. In the early 1940s he had started his own shop and had made some ultracentrifuges for other departments at Stanford.²⁸³ The apparatus manufactured for the Medical School was used by Dr. Walter Mack. At first they had some problems to get the machine running which made them contact Pickels on the matter. Pickels made some suggestions after which the apparatus performed quite satisfactorily. The episode gave Hanafin the impression that there might be a market for these machines. Thereupon, on a trip to the east coast, he made inquiries with about half a dozen potential customers and their reactions made him decide to manufacture ultracentrifuges on a commercial basis. His idea was to start manufacturing ultracentrifuges with an air drive as that had been fully described already, but also to try and apply the Beams electrical drive in order to make them more easy to operate.²⁸⁴

Hanafin also included a visit to Pickels in his trip and asked him whether he would be willing to act as a consultant to his company. Pickels declined the offer because he found it incompatible with his work at the Institute. Instead, he proposed to form a new company with him and Hanafin as directors. Pickels felt that the work at the Institute had become too much routine-like and that the ultracentrifuge had already been developed to a mature instrument. He did not find much scientific challenge in his job and had already tried before to get another job. Starting a business with Hanafin would form a challenge to him although in a field different from what he was used too. However, because he was impressed by Hanafin as a salesman and because he also saw it as a new challenge for getting 'further' with the ultracentrifuge, i.e. making it available on a large scale, he made his proposal. Hanafin readily accepted, and invited Pickels to come to California in order to see what was going on there. Pickels did not think much of the Glass Engineering Laboratories but was impressed with Hanafin and together with two other partners formed the 'Specialized Instruments Corporation' (Spinco) in 1946.²⁸⁵ Pickels was to be the only full time employee and responsible for Engineering, Research, Development and Production. Hanafin was employed half-time and responsible for merchandising and sales. They anticipated that during the first year of operation the corporation would make gross sales of approximately \$ 80,000.²⁸⁶ The banks were not very impressed by their undertaking and they had to invest all the money they had in the new business. Pickels liked the challenge and the fact that, on the technical side, he could 'run his own show'. He left it up to Hanafin to get the show on the road.²⁸⁷

Pickels hired a draftsman and a machinist and started building his first commercial ultracentrifuge in a garage. He first designed an analytical

ultracentrifuge which was supplied with both an analytical and a preparative rotor. Because of this dual purpose they hoped to be able to create sizable market. In order to make it more generally applicable Pickels decided that the air drive should be replaced by an electrical motor. This would eliminate the need for a noisy compressor but created new problems because a special bearing would be needed. Pickels did not want to use Beams' magnetic suspension because he thought the design was too tricky and would be an invitation for trouble. He did not consider it to be fool-proof. Also Pickels did not want to design a special motor but preferred a type which was commercially available and which operated at 14,000 r.p.m. Because he anticipated that ball bearings would give too much trouble Pickels designed a special doughnut type of bearing which performed very well from the beginning.²⁸⁸ The apparatus was equipped with a gear box which allowed the operator to choose thirty speed settings from 12,000 r.p.m. to 74,000 r.p.m. by simply setting a dial on the front panel of the apparatus. In routine use the drive accelerated the standard analytical rotor to 60,000 r.p.m. in 7 minutes with a power input into the motor of 1700 watts. Constant speed operation at 60,000 r.p.m. required about 400 watts input to overcome losses in the drive, the frictional resistance on the rotor being very small. A so-called differential gear speed control kept the speed constant within 0.1%. The control provided also an automatic adjustment for fluctuations in the line voltage and motor efficiency. The apparatus was also equipped with a temperature control. When the pressure in the rotor chamber was less than 1 micron of mercury, frictional heating on the rotor raised its temperature about 1 or 2 degrees Centigrade per hour at full speed. If, however, the surroundings were maintained at a temperature approximately 20 degrees below that of the rotor, the temperature rise could be reduced to zero and the rotor spun indefinitely without any significant change in temperature. Therefore the apparatus had a chilled copper liner which surrounded the rotor within the evacuated chamber and which made rotor temperatures even below freezing possible. Temperature measurements of the rotor and other parts of the machine were made to within ± 0.2 °C by a system of thermocouples. This model, called model E, could also be used for preparative purposes by simply inserting a different rotor. Figure 6.6 shows Pickels with the apparatus.²⁸⁹ Inside the vacuum chamber was placed a second cylinder that could freely rotate, a device which was meant to absorb much of the energy in case of a rotor explosion. During his work at the Institute Pickels had experienced that such explosions could destroy the whole apparatus and with the present arrangement he might just have to replace the cylinder and the rotor.²⁹⁰ Model E was equipped with an optical system which recorded automatically, at intervals, the refractive-index gradient at every level in the column of fluid being centrifuged. On the front panel a viewing screen was mounted which allowed the operator to watch the sedimentation continuously. Two

different analytical rotors could be supplied, one for cells with a fluid thickness from 2-12 mm, suitable for forces up to 260,000 g, the other for cells with fluid thicknesses from 18 or 30 mm which could stand 167,000 g. The housing dimensions were 74 by 27 by 60 inch and the total unit weighed 2400 pounds.²⁹¹ The first model E was completed in 1947 and installed in the Virus Laboratory at the University of California in Berkeley.²⁹²



Figure 6.6

Pickels with Spinco ultracentrifuge. (Pickels, 1949, p.2).

In the meantime Hanafin had been able to sell seven of these machines. They were sold at a price of \$ 13,200 with a 25% deposit. The deposits financed the company in the beginning. The apparatus could also be bought without the optics in case a customer only wanted to use it as a preparative machine. However, as most of the cost went into the mechanical parts, this hardly saved any cost. Only one such machine was ever sold. In 1947 they moved to a larger production facility where they took six machines in production at the time. After some time, however, they had a fire which destroyed all of their drawings although it did not damage the machines. Nevertheless, they had to be taken apart in order to be cleaned.

When the machines were finished Pickels went out with the customers in order to install them. With the first two of these, the shaft broke during the installation, which ruined the optics. After some time Pickels found the source of the trouble, and modified the design. Afterwards they had no more trouble from this source. Although the machines operated quite satisfactorily, the company as a

whole did not. Because of the meager company results in 1947-48 Pickels and Hanafin felt forced to lay off half off their staff.²⁹³

In his sales efforts Hanafin experienced that there were more people interested in preparative machines than there were in analytical machines. Thereupon Pickels set out to design an ultracentrifuge for preparative purposes only which should be about the size of a standard laboratory centrifuge. The machine should be as simple to operate as a washing machine: open up the lid, put in the sample and run it by turning the switch. This led to a design called model B, later to be called model L. The machine was much simpler in design than model E because it did not need any optics and could be equipped with a limited amount of speed regulation (figure 6.7).



Figure 6.7

Spinco model E preparative ultracentrifuge. (Spinco, 1960, p.15).

In model E the speed control was accurate to 0.2 per cent; for the lower speed preparative centrifuge an electronic control unit had been adopted that held rotor speed to about 3 per cent of the speed chosen, close enough for service requirements. In 1950 model L cost about \$ 3000, compared with \$ 14,000 odd for the analytical machine, which was capable of gravity multiplication of 260,000 g at 60,000 r.p.m. The smaller unit produced 144,000 g at 40,000 r.p.m. To make it feasible to use untrained operators, much attention was given to safety devices,

simplicity of control and interlocks to prevent operating errors. With the electronic controls, the machine would accelerate to a preset speed and return to rest automatically. Rapid loading and unloading was achieved by use of interchangeable rotors which could be loaded at the bench while a run was being made. Mechanical coupling was avoided through use of a machined socket in the rotor bottom that mated with a tapered drive-shaft extension. A self-balancing feature in the drive made meticulous balancing of the rotor load unnecessary. Like model E, model L also spun in vacuum and was also equipped with a refrigerating system for the sedimentation of materials that would disintegrate at room temperature. The fully enclosed drive assembly and motor were suspended directly under the rotor chamber. The total equipment measured 27 by 31 by 40½ inch and weighed 735 pounds.²⁹⁴

After they had constructed the first model B, the selling orders soon came rolling in. Within a few years hundreds were sold. This allowed the company to survive its first years. Gradually orders for the analytical type also increased. When the first was sold to the Virus Laboratory of the University of California, Berkeley, in 1947, there were in operation throughout the world about eight oil turbine ultracentrifuges of the Svedberg design and about an equal number of air-driven analytical ultracentrifuges.²⁹⁵ By 1951, more than 70 Spinco analytical ultracentrifuges were sold,²⁹⁶ a number that rose to 300 by 1958.²⁹⁷ About ten years later, number 1000 was built. Like the first, it was purchased by the Virus Laboratory at Berkeley.²⁹⁸ There was a great interest and enthusiasm for the Spinco machines also because Spinco took care of the machinery afterwards. Their maintenance was considered very good and they were very helpful when trouble arose by sending out someone to study the problem and trying to solve it.²⁹⁹

As had been the purpose from the outset, in the early 1950s Spinco also started to manufacture other types of scientific apparatus like, for instance, the Tiselius electrophoresis apparatus. Pickels had learned to operate this apparatus when he was still at the Rockefeller Institute. At Spinco they developed a more compact version of it, again, as with their ultracentrifuge, by folding the optical system so that it could be put in one room. By the mid 1950s the company performed very well. At that time they were visited by a representative from Beckman Instruments, one of the major manufacturers of scientific instruments in the US. Beckman was very impressed with the Spinco achievements and made an offer to buy the company in 1955. They came to an agreement and Pickels became director of research and Hanafin director of sales. Later Hanafin was made head of another division of Beckman and Pickels became acting manager of the Spinco Division. This post he held for about a year after which he decided that the job had not sufficient challenges for him. He acted a short while as a consultant after which he got involved in other business endeavors.³⁰⁰

6.3 USE AND FURTHER DEVELOPMENT OF ULTRACENTRIFUGES

On 14 and 15 November 1941, a conference on the Ultracentrifuge was held by the Section of Physics and Chemistry of the New York Academy of Sciences. Participants were D.A. McInnes, J.W. Beams, W.D. Bridgman, J.W. Williams, W.J. Archibald and A. Rothen. The presentations were published in the *Annals of the Academy* in 1942 in the introduction of which McInnes stated:

"Although the ultracentrifuge is now a most useful tool its development is far from complete, in either its experimental or theoretical aspects, as the papers that follow clearly show. In the near future the precision of the data obtained will be increased by closer regulation of temperature, of speeds of rotation, and by improved optical systems. The interpretation of the resulting data will in certain cases be facilitated by utilization of the more elaborate theory, already at hand, of the instrument."³⁰¹

At the Conference Beams discussed the various types of ultracentrifuges. He remarked that although the highest fields could be obtained with steel rotor's, softer metals would usually be preferable because of safety and because they were more easy to machine. He also discussed the electrically driven, magnetically supported ultracentrifuge. He concluded remarking that although for most problems one had a choice of several methods, he did not expect all the research on high-speed centrifuges had already been done. Due to their growing use, it would be a safe guess that great advances in this technique would be made within the next few years.³⁰² Bridgman and Williams discussed the various optical methods and concluded, depending on the specific needs of the researcher, a choice would have to be made as to which method would be most appropriate. They concluded their paper stating:

"Some of the important modern methods of studying high molecular weight substances have been the result of researches of Svedberg. The ultracentrifuge, developed by him, is the most powerful tool for the study of the mass behaviour of such substances. It is proposed to honour him on this occasion by designating as the Svedberg the unit of specific sedimentation constant, i.e., the rate in centimeters per second at which the boundary moves under unit centrifugal field, multiplied by 10^{13} . It is further proposed that the capital letter S be used as its symbol."³⁰³

This proposal was taken over by the other participants in the conference and has since become a basic unit in the field of ultracentrifugation.

Alexandre Rothen from the Rockefeller Institute treated the 'Present Status of Molecular Weights of Proteins'. Shortly before they had installed in their air-driven centrifuge a cooling coil connected with a Frigidaire unit which had a double purpose: first, to make possible experiments at low temperatures; and second, to

exert a better control on the temperature of the rotor. It also seemed desirable to him to determine the physical properties of proteins at 0 °C. By adding hydrogen at low pressure (about 0.1 mm Hg), it was found that the temperature of the rotor could be kept for 5 to 6 hours easily within the small range of 1 °C when the rotation was 57,600 r.p.m. By carefully adjusting the temperature of the chamber somewhat lower than that of the rotor, the heating of the rotor by the residual air and hydrogen could be exactly compensated by the cooling due to the coil. In his presentation Rothen criticised Svedberg's 'multiple law'. From a chapter by Pedersen in Svedberg's monograph the suggestion arose that it was a well proven fact that molecular weights of proteins were simple multiples of a single unit of a weight of about 17,600, the deviations which occurred being simply explained by the distribution of smaller or larger amino acids in the units. In Rothen's opinion, however, Pedersen's argument was based on insufficient evidence to prove definitely the reality of the unit. Rothen argued that an error as great as 8 per cent in the molecular weight of a protein determined by centrifugal methods could very well occur. This implied that all proteins with a molecular weight greater than 100,000 were unsuitable materials to test the hypothesis of the Svedberg unit, since the experimental error amounted to 50 per cent of the unit and any number greater than 100,000 could be looked at as a multiple of the unit within experimental error. He also concluded from a table given by Pedersen that 50 per cent of the examples disproved rather than proved the rule. When later some other low molecular weight proteins had been studied, the picture looked even worse for the empirical foundation of the unit. Rothen finally argued on theoretical grounds against the unit, quoting from an article by Pauling and Niemann:

"It seems to us, however, very unlikely that the existence of favored molecular weights (or residue numbers) of proteins is the result of greater thermodynamic stability of these molecules than of similar molecules which are somewhat smaller or larger, since there are no interatomic forces known which could effect this additional stabilization of molecules of certain sizes".³⁰⁴

Rothen concluded giving some prospects for the further development of the ultracentrifuge. Of prime importance would be improvements in the direction of better control of the temperature. Another improvement would be to increase the sensitivity of the optical method to make possible the study of systems at very low concentration in proteins. In the case of biologically active substances, the concentration of the active material was very often so small that it was impossible to detect optically its sedimentary boundary. Refractive methods as they were then in use were not expected to become 10 times more accurate without difficulty. Rothen thought that maybe interferometric methods could be adapted for the ultracentrifuge.³⁰⁵

In 1949 a second conference on the ultracentrifuge was organised by the American National Academy of Sciences. Two years before Spinco had started the commercial manufacture of ultracentrifuges and this time about 20 researchers from different institutes participated, including Pedersen from Upsala University. Svedberg had just retired earlier that year. In his report on the conference L.G. Longsworth wrote:

"The discussion of the relative merits of the contemporary air-, oil- and motor-driven centrifuges was overshadowed by the glimpses of the centrifuges of the future given by J.W. Beams. Magnetically supported and driven, the rotors of these machines spin about a vertical axis in sealed containers that permit the attainment and preservation of the best vacuum possible. Consequently the frictional losses are so low that the rotor can be kept, with negligible temperature change, in synchronism with a crystal-controlled rotating magnetic field."³⁰⁶

The most serious problem in connection with these machines was that of acceleration without excessive heating of the rotor. In order to accelerate, some slippage between the rotor and the rotating field had to occur and this lack of synchronism resulted in the generation of heat that could be dissipated only by radiation. Beams was reported to be working on this problem. Beams also worked on an interference method for the detection and recording of refractive index changes in the cell. A number of other researchers were trying to develop an alternative for the Lamm scale method for the observation of the sedimentation. Several schemes had been developed but neither of them was unproblematic. Because the engineering problems connected with the sedimentation equilibrium ultracentrifuge were a lot less than with the sedimentation velocity machine, several researchers preferred to work with the former. Especially since Archibald had developed a method by which it was not necessary anymore to wait for the establishment of equilibrium, the method had become more popular. For this apparatus also new observation techniques were developed which differed largely from the ones developed for the sedimentation velocity apparatus because of the difference in principles involved.³⁰⁷

Because of the growing interest in ultracentrifugal analysis some American publishers got interested in publishing a book on the matter. Pedersen felt that this necessitated a considerable investment in time as the monograph published in 1940 should be reworked considerably. In 1950 he wrote Clarendon Press that he had a strong impression that there was a need for a book about sedimentation and diffusion especially in the USA, where they were then selling 'as many of the Spinco ultracentrifuges as they can produce'. In Europe also the number of ultracentrifuges (of different types) was rapidly increasing.³⁰⁸ During a six weeks visit to the USA he had had many occasions to discuss the problem of such a book and the need for it. Some thought that it ought to come out in the States, but

Pedersen preferred to have it published in Europe.³⁰⁹ However, as other demands on his time appeared to be more stressing, the plan never worked out.

Ten years later the number of researchers working with an analytical ultracentrifuge had risen to be in the hundreds. Some of them just used the apparatus as it was supplied, some tried to modify certain aspects of it in view of the research they wanted to do with it. In 1959 Howard K. Schachman, from the Biochemistry and Virus Laboratory of the University of California, Berkeley, published a monograph entitled *Ultracentrifugation in Biochemistry* in which he described the latest developments. A variety of cells had been developed, sometimes coupled with the exploitation of multicell rotors so that many different samples could be examined simultaneously. Factors hardly considered before, such as the precise measurement of temperature and the effect of pressure, were then either clarified or the subject of active and productive investigation. Analysis of mixtures was made feasible and the effects of concentration had been carefully considered and reliable theories presented.³¹⁰ Because of these developments much of the ultracentrifugal data in the literature required revision either because of improvements in experimentation or because theoretical developments had shown that the results were calculated or interpreted incorrectly.³¹¹ Concerning the apparatus, Schachman stated:

"It is of interest that the apparatus currently being used extensively bears so little physical resemblance to either the oil turbine or air-driven ultracentrifuges which historically form the background for instrumental design in this field."³¹²

The only thing that had remained constant, in Schachman's view, was the distance of the location of the cell at 65.0 mm from the axis of rotation. Furthermore the rotor design and the basic features of cell design had been altered in only relatively minor ways, but the rest of the apparatus had undergone drastic changes. In this respect the measurement of the temperature in the cell represented one of the most important developments. Because of large discrepancies between experimental results obtained on the same materials examined in the oil turbine and electric-driven ultracentrifuge, Shulman had examined this matter further. He concluded that errors in measuring the temperature of the rotor were responsible for the discordant results. In a particularly thorough experimental study of rotor temperature, Biancheria and Kegeles had described a modification of this method, which avoided some of the deficiencies of the melting point method as used by other workers. During careful studies of temperature measurements of the rotor, Waugh and Yphantis observed a decrease in temperature of the rotor upon acceleration from rest to 60,000 r.p.m. This was attributed to stretching of the

rotor at the higher speeds, and a simplified calculation of the temperature change upon acceleration of the rotor to 60,000 r.p.m. gave results in satisfactory agreement with the measured temperature change of -1.0°C . Though this adiabatic cooling effect was contested by Hiatt, it was later confirmed by Biancheria and Kegeles in their melting point experiments and by direct measurement with a thermistor in the rotor by Pickels. Waugh and Yphantis examined that the negative temperature change was linear with the square of the speed of the rotor. By the late 1950s it was generally agreed that the cooling of the rotor upon its acceleration to 60,000 r.p.m. was very close to 0.8°C . Much of the data in the literature would have to be modified because of neglect of this factor. This stretching of the rotor also led to another source of difficulty, because it rendered uncertain the position of the cell in terms of the distance from the axis of rotation. Although the errors resulting from neglect of this effect were small, the demands of greater precision in sedimentation measurements required that allowances for this should be made.³¹³

In the 1950s the cell design had occupied the interest of many workers motivated by problems substantially different from those confronting the workers using the ultracentrifuge shortly after its initial development. As a result, there had been developed a variety of special cells for the study of small molecules, a new type of separation cell for the examination of biologically active materials, a cell for the simultaneous recording of concentration and concentration gradient, a cell in which a base line was automatically recorded along with the pattern of the unknown sedimenting substance, and a cell with a prismatic window for shifting the photographic pattern, thereby permitting analysis of different samples in a single run. There were also cells for measuring the compressibility of liquids, cells with special features for interferometric optical methods, and cells constructed of different materials for solvents which might be injurious to one or another of the cell parts.³¹⁴

Concerning convection Schachman wrote that, despite the important contribution of Svedberg and his colleagues in their design and construction of the sector shaped cell, it seemed likely that convective transport would occur in many ultracentrifuge experiments. This might be due to scratches in the surfaces of the radial walls creating crevices or protuberances which caused both the accumulation and depletion of solute molecules in the vicinity of the imperfection. The orientation of the cell in the rotor was also considered critical, if convection was to be avoided. In the early 1950s the rotors had a key-way cut into the cell hole and the cells possessed a pin which fit the key-way. With this mechanical arrangement, the alignment of the cell was extremely reproducible, but this practice was abandoned when it was found that the key-way appeared to be the site of local stresses which were responsible for the failure of the rotor. Next,

fine lines were engraved both on the rotor and the cells so that the latter were oriented to produce a matching of the inscribed lines. This procedure, however, was not infallible with regard to both the engraving of the lines and the judging as to which orientation would be best. Some misalignment was bound to occur, and when it did, a fraction of the sedimenting molecules would strike the cell wall before they reached the cell bottom. On the opposite side of the cell, there would be a depletion of solute. Both of these effects caused convections, as could be seen readily when the cell was deliberately oriented incorrectly. However, quantitative measures of the amount of convection were lacking and it was difficult to state how serious a given misalignment would be. Another source of convection was caused by the phenomenon that, as the rotor was accelerated, the liquid near the cell bottom was subjected to a pressure of several hundred atmospheres. This led to an elevation in the temperature of the liquid at the cell bottom relative to the temperature near the meniscus. Moreover, the stretching of the rotor produced the greater stress near the rotor centre, and the consequent cooling of the rotor would lead to a temperature gradient within it, the periphery being warmer than the centre. How much of this gradient was transferred to the liquid within the cell was difficult to determine.³¹⁵

Although the Beams ultracentrifuge with a magnetically suspended rotor (UMSR) had aroused strong interest among the ultracentrifuge community at the second ultracentrifuge conference in 1949 the apparatus still was hardly being used a decade later. A number of problems associated with it still were not solved. Thermal gradients which produced convective disturbance could not be tolerated in any type of ultracentrifuge. Since there was no gross heat conduction path in the UMSR it would seem that one of its main virtues lay there. According to McCosham and Williams, however, there would be some heating of the rotor and thermal gradients would be set up, due primarily to the eddy currents. In a practical way, then, the relative merits of the UMSR and the conventional machines were to be judged largely on the relative magnitudes of the thermal gradients. Although intuitively one might feel that the effect was small, nobody had actually paid serious attention to the effect of such eddy current heating of the rotor in the UMSR. This problem was closely related to the problem of the actual measurement of the rotor temperature. With the existing machines at the time this was almost a routine matter. With the UMSR, however, this would be an arduous engineering task. McCosham and Williams felt that monitoring the radiation from the rotor was not the answer, in spite of reports in the literature which suggested that this had been accomplished with remarkable precision. They argued that the techniques involved were not of a routine nature and the practice itself might be adversely affected by many variables. The ideal method was to have a temperature-sensing device buried in the rotor, but still to be explained would be

how one might obtain the information presented by the device. It might be telemetered from the rotor. They reported that they had, in fact, had some encouraging experiences with a device of this kind. On the basis of what was then known, even including the successful achievement of a stable support circuit, McCosham and Williams considered it advisable to regard the UMSR as being yet in the developmental stage.³¹⁶

As more scientists started working with ultracentrifuges the interest in the theory of ultracentrifugation also grew. In 1940 Pedersen-Svedberg had listed all papers on ultracentrifugation up to 1940. Out of approximately 400 references no more than a dozen were devoted to theory.³¹⁷ At the third congress on ultracentrifugal analysis, held in 1962, it appeared that further development of the theory of ultracentrifugation had become ever more important. Progress had been made in the exact theoretical description of sedimentation processes in simpler systems, particularly in describing the sedimentation of heterogeneous and polydisperse solutes, the effects of association-dissociation processes, and of interactions in multicomponent systems. Anomalous effects due to frictional interactions and to hydrostatic instability had been reported and awareness grew on limitations inherent in attempts to measure particle parameters. Furthermore, techniques and theory of sedimentation in density gradients had been developed.³¹⁸ Williams wrote in 1974 that, with a few notable exceptions, the extensions and generalizations of the essential working equations did not begin to appear until the early 1950s. But it was not until the 1970s that theoretical advances had made it possible for the ultracentrifuge to become a tool of quite general applicability.³¹⁹

In the course of time more and more scientists started working with ultracentrifuges. An increasing number of scientists developed new lines of attack, generated new questions and new problems. Ever since Svedberg had published his first results on studies with the ultracentrifuge there had been a considerable interest from the scientific world. But it was not until Pickels started manufacturing the Spinco machines that a substantial spread of ultracentrifuges to other laboratories began. This did not imply that the ultracentrifuge had been fully developed by then. As more scientist started using them for different applications new problems with respect to the apparatus were identified. The development never really stopped.

Notes

The meaning of the various abbreviations used is explained in the notes to Chapter 2.

1. Jones to Nichols, 22 July 1924 (HML).
2. Nichols to Svedberg, 6 April 1925 (UUp-Lib).
3. Nichols to Bauer, 15 February 1938 (HML).

4. Svedberg to Nichols, 15 February 1925 (UUp-Lib).
5. Nichols to Bauer, 15 February 1938 (HML); Svedberg and Nichols, 'Patent on Analytical Centrifuges', US Patent 1648369, 8 November 1927; and Dr. J. Burton Nichols, private communication.
6. Dr. J. Burton Nichols, private communication.
7. Tanberg (DuPont) to Nichols, 17 May 1927.
8. Nichols to Tanberg (DuPont), 21 May 1927 and Nichols to Tanberg, 6 July 1927 (HML).
9. Tanberg to Nichols, 19 July 1927 (HML).
10. Nichols to Svedberg, 22 August 1928 (HML).
11. Pfund (DuPont) to Seguine (Krebs Pigment Company), 17 August 1929 (HML).
12. Nichols to Weaver, 27 June 1928 and Nichols to Weaver, 1 August 1928 (HML).
13. Nichols to Weaver, 17 September 1929 (HML).
14. Svedberg to Nichols, 28 October 1929 (HML).
15. Nichols to Svedberg, 16 November 1929 (HML).
16. Svedberg to Nichols, 11 April 1930 (HML).
17. Svedberg to Nichols, 18 December 1929 (HML).
18. Svedberg to Nichols, 7 January 1930 (HML).
19. Nichols to Svedberg, 25 July 1930 (UUp-Lib).
20. Nichols (1931).
21. Nichols (1932), p.13.
22. Daniels (UWi) to Nichols, 15 September 1931 (HML).
23. Nichols to Daniels (UWi), 10 October 1931.
24. Dr. J. Burton Nichols, private communication.
25. Nichols to Svedberg, 15 July 1931 (HML).
26. Svedberg to Nichols, 13 October 1931 (HML).
27. Nichols to Beams, 16 July 1931 (HML).
28. Beams to Nichols, 20 July 1931 (HML).
29. Nichols to Beams, 29 July 1931 (HML).
30. Beams and Weed (1931).
31. Memo from Nichols to Whitten (DuPont), 16 September 1931 (HML).
32. Nichols to Svedberg, 3 February 1932 (UUp-Lib).
33. Svedberg to Nichols, 28 February 1932 (HML).
34. Nichols to Svedberg, 3 May 1932 (UUp-Lib).
35. Svedberg to Nichols, 19 May 1932 (UUp-Lib).
36. Nichols to Svedberg, 13 December 1932 (UUp-Lib).
37. Nichols to Svedberg, 29 September 1932 (UUp-Lib).
38. Nichols to Svedberg, 23 March 1933 (UUp-Lib).
39. Lansing to Svedberg, 22 September 1933 (UUp-Lib).
40. Lansing to Svedberg, 9 November 1933 (UUp-Lib).
41. Nichols to Svedberg, 15 February 1934 (UUp-Lib).
42. Svedberg to Lansing, 6 October 1933 (UUp-Lib).
43. Kraemer to Svedberg, 1 February 1934 (UUp-Lib).
44. Svedberg to Kraemer, 20 February 1934 (UUp-Lib).
45. Svedberg to Nichols, 26 August 1934 (HML).
46. Svedberg to Nichols, 19 October 1934 (HML).
47. Svedberg to Kraemer, 5 March 1935 (UUp-Lib).
48. Kraemer to Svedberg, 18 March 1935 (UUp-Lib).
49. Svedberg to Kraemer, 9 May 1935 (UUp-Lib).
50. Svedberg to Nichols, 19 October 1934 (HML).
51. Kraemer to Watson, 18 March 1935 (UUp-Lib).
52. Watson to Svedberg, 10 August 1935 (UUp-Lib).
53. Svedberg to Watson (DuPont), 25 September 1935 (UUp-Lib).
54. Svedberg to Kraemer, 25 November 1935 (UUp-Lib).
55. Kraemer to Svedberg, 11 May 1936 (UUp-Lib).
56. Kraemer to Svedberg, 6 April 1936 (UUp-Lib).
57. Kraemer to Svedberg, 11 May 1936 (UUp-Lib).
58. Svedberg to Nichols, 13 May 1936 (UUp-Lib).
59. Kraemer to Svedberg, 13 January 1936 (UUp-Lib).
60. Dr. J. Burton Nichols, private communication.
61. Kraemer to Svedberg, 2 July 1937 (UUp-Lib).

62. Svedberg to Herzog, 11 April 1927 (UUp-Lib).
63. Herzog to Svedberg, 25 June 1927 (UUp-Lib).
64. Svedberg to Herzog, 30 June 1927 (UUp-Lib).
65. Herzog to Svedberg, 31 January 1928 (UUp-Lib).
66. Herzog to Svedberg, 15 May 1928 (UUp-Lib).
67. Svedberg to Herzog, 17 May 1928 (UUp-Lib).
68. Herzog to Svedberg, 26 November 1929 (UUp-Lib).
69. Herzog to Svedberg, 12 May 1930 (UUp-Lib).
70. Svedberg to Nichols, 22 November 1930 (UUp-Lib).
71. Prof. Kai O. Pedersen, private communication.
72. Staudinger to Svedberg, 27 November 1931 (UUp-Lib).
73. Staudinger to Svedberg, 16 December 1931 (UUp-Lib).
74. Svedberg to Staudinger, 26 December 1931 (UUp-Lib).
75. Staudinger to Svedberg, 18 October 1933 (UUp-Lib).
76. Svedberg to Signer, 12 April 1935 (UUp-Lib).
77. Signer to Svedberg, 16 July 1936 (UUp-Lib).
78. Miller (RF) to Svedberg, 12 February 1936 (UUp-Lib).
79. Signer to Svedberg, 14 March 1938 (UUp-Lib).
80. Signer to Svedberg, 13 June 1938 (UUp-Lib).
81. (RAC:1.1/800/7/76) Tisdale's diary, 14 April 1934 and (RAC:1.1/401/18/244), O'Brien's diary, 14 April 1934.
82. (RAC:1.1/401/18/244) O'Brien's diary, May 1934.
83. Pedersen (1983), p.264.
84. (RAC:1.1/401/18/244) Gregg's diary, 9 June 1934.
85. See e.g. (RAC:1.1/401/18/244) O'Brien to Gregg, 5 November 1934 and (RAC:1.1/401/18/244) O'Brien to Gregg, 12 November 1934.
86. (RAC:1.1/401/18/244) Ledingham and Bulloch (LI) to Medical Board of Rockefeller Foundation, 9 October 1934.
87. (RAC:1.1/401/18/244) Ledingham to O'Brien, 18 August 1934.
88. (RAC:1.1/401/18/244) RF-34126: 'Grant appropriation to the Lister Institute of Preventive Medicine', 16 November 1934.
89. (RAC:1.1/401/18/244) O'Brien to Ledingham, 26 March 1935.
90. (RAC:1.1/401/18/244) Ledingham and Bulloch to Medical Board of Rockefeller Foundation, 9 October 1934.
91. Ledingham to Svedberg, 12 November 1934; quoted in Pedersen (1983), pp.264-265.
92. Svedberg to Ledingham; quoted in Pedersen (1983), p.265.
93. Pedersen (1983), p.268.
94. McFarlane to Svedberg, 24 February 1938 (UUp-Lib).
95. McFarlane to Svedberg, 29 July 1938 (UUp-Lib).
96. Peters to Svedberg, 22 January 1935 (UUp-Lib).
97. Svedberg to Peters, 28 January 1935 (UUp-Lib).
98. Svedberg to Philpot, 31 May 1935 (UUp-Lib).
99. Peters to Svedberg, 27 July 1935 (UUp-Lib).
100. Peters to Svedberg, 14 September 1935 (UUp-Lib).
101. Svedberg to Peters, 5 November 1935 (UUp-Lib).
102. Svedberg to Peters, 27 January 1936 (UUp-Lib).
103. Peters to Svedberg, 5 March 1936 (UUp-Lib).
104. Svedberg to Peters, 9 March 1936 (UUp-Lib).
105. Philpot to Svedberg, 26 August 1936 (UUp-Lib).
106. Philpot to Svedberg, 3 December 1936 (UUp-Lib).
107. Svedberg to Peters, 22 February 1937 (UUp-Lib).
108. Philpot to Svedberg, 10 March 1937 (UUp-Lib).
109. Svedberg to Philpot, 13 March 1937 (UUp-Lib).
110. Philpot to Svedberg, 11 March 1938 (UUp-Lib).
111. Svedberg to Philpot, 14 March 1938 (UUp-Lib).
112. Record to Philpot, 15 March 1938 (UUp-Lib).
113. Philpot (1938).
114. Philpot to Svedberg, 18 May 1938 (UUp-Lib).
115. Svedberg to Philpot, 24 May 1938 (UUp-Lib).

116. Svedberg to Philpot, 20 November 1938 (UUp-Lib).
117. Svedberg to Philpot, 11 January 1939 (UUp-Lib).
118. (RAC:1.1/800/7/76), Hanson's diary, 18 December 1935.
119. (RAC:1.1/200/164/2013) Hanson's diary, 11 January 1936.
120. (RAC:1.1/200/164/2013) Weaver to Fred (UWi), 31 March 1936.
121. (RAC:1.1/200/164/2013) Fred (UWi) to Weaver, 9 April 1936.
122. (RAC:1.1/200/164/2014) Fred (UWi) to Weaver, 1 May 1936.
123. (RAC:1.1/200/164/2013) Weaver to Williams, 15 May 1936.
124. (RAC:1.1/200/164/2013) Williams to Weaver, 19 May 1936.
125. (RAC:1.1/200/164/2013) Weaver to Svedberg, 21 May 1936.
126. (RAC:1.1/200/164/2013) Svedberg to Weaver, 22 May 1936.
127. (RAC:1.1/200/164/2013) Appleget's diary, 1 June 1936.
128. (RAC:1.1/200/164/2013) RF-36101: 'Grant appropriation to the University of Wisconsin (Williams)', 12 June 1936.
129. Rockefeller Foundation, 'Annual Report', 1936 p.187 (RAC).
130. Williams to Svedberg, 13 October 1936 (UUp-Lib).
131. Svedberg to Williams, 23 January 1937 (UUp-Lib).
132. Kraemer to Svedberg, 2 July 1937 (UUp-Lib).
133. (RAC:1.1/200/164/2013) Williams to Weaver, 16 June 1937.
134. (RAC:1.1/200/164/2013) Weaver's diary, 3 August 1937.
135. (RAC:1.1/200/164/2013) Weaver's diary, 7 December 1938.
136. Williams to Svedberg, 15 December 1938 (UUp-Lib).
137. (RAC:1.1/200/164/2013) Williams to Weaver, 12 November 1937.
138. (RAC:1.1/200/164/2013) Weaver's diary, 21 January 1939.
139. (RAC:1.1/200/164/2013) Weaver to Williams, 16 November 1937.
140. (RAC:1.1/200/164/2013) Weaver's diary, 15 January 1940.
141. Quoted in (RAC:1.1/200/164/2013) Williams to Weaver, 10 July 1940.
142. (RAC:1.1/200/164/2013) Williams to Weaver, 10 July 1940.
143. (RAC:1.1/200/164/2013) Hanson's diary, 13 November 1941.
144. Williams (1979), p.78.
145. Brynielsson (1963), p.2.
146. Quensel and Svedberg (1938) as quoted in Claesson and Pedersen (1972), p.613.
147. Prof. Sven Brohult, private communication.
148. Sven Malmström to the author, 22 April 1987. Malmström was Managing Director of LKB after 1951.
149. Claesson and Pedersen (1972), p.613 and Prof. Nils Gralén, private communication.
150. Claesson and Pedersen (1972), p.613.
151. Brohult (1987), p.12.
152. Harry Brynielsson, private communication. Brynielsson was the first Managing Director of LKB.
153. Malmström to the author, 22 April 1987.
154. Prof. Sven Brohult, private communication.
155. Brynielsson (1963), p.2.
156. Brohult (1987), p.12.
157. Malmström to the author, 22 April 1987.
158. Harry Brynielsson, private communication.
159. Brynielsson (1963), p.3.
160. LKB-Produkter AB, 'Preliminary List of Apparatus', 1946 (EGP).
161. Malmström to the author, 22 April 1987.
162. Alfeldt (LKB) to Pedersen, 4 September 1950 (UUp-Lib).
163. Prof. Nils Gralén, private communication.
164. Prof. Sven Brohult, private communication.
165. Malmström to the author, 22 April 1987.
166. Malmström to the author, 22 April 1987; and Philip (LKB) to Borgman (UUp), 22 December 1958 (UUp-Lib).
167. Malmström to the author, 22 April 1987.
168. (UVa:Rg-2/1/1.381) 'Annual Report of the School of Physics', 1932-1933, p.5.
169. Nichols to Beams, 16 July 1931 (HML).
170. Beams to Nichols, 20 July 1931 (HML).
171. Nichols to Beams, 29 July 1931 (HML).

172. Harvey and Loomis (1930), p.44.
173. Harvey (1932), pp.10-11.
174. Harvey (1932), pp.11-16.
175. Harvey (1933).
176. Harvey (1934), p.48.
177. Harvey to Nichols, 28 October 1930 (HML).
178. Nichols to Harvey, 12 January 1931 (HML).
179. Harvey to Nichols, 11 February 1931 (HML).
180. Eellestad (BLC) to Nichols, 7 April 1931 (HML).
181. Seebach (BLC) to Nichols, 23 January 1934 (HML).
182. Dr. J. Burton Nichols, private communication.
183. Beams and King (1935 and 1936).
184. Beams (1937).
185. Pickels (1936).
186. Pickels (1935), pp.39-40.
187. Webb (1936), p.348.
188. (RAC:1.1/252/1/10) Hanson's diary, 30 December 1937 and (RAC:1.1/252/1/11) Weaver's diary, 10 December 1938.
189. Guyer and Claus (1937), pp.468-469.
190. Humphreys (1939).
191. Chiles and Severinghaus (1938).
192. Rosenfeld (1942).
193. Moore (1943).
194. Letter from A. Robert Kuhltau (a student of Beams in the 1940s) to the author, 8 July 1985, p.3.
195. Letter from John J. Serrell (development and sales engineer at the Sharples Company) to the author, 29 March 1986.
196. Clark (1925), p.177.
197. T.D. Sharples to the author, 16 December 1985.
198. Serrell to the author, 29 March 1986.
199. Serrell to the author, 29 March 1986.
200. Anon. (1934b).
201. Nichols to Sharples, 21 February 1934 (HML).
202. Anon. (1934b).
203. (RAC:1.1/252/1/11) Weaver's diary, 24 February 1938 and Dr. Edward G. Pickels, private communication.
204. Pickels, 'Notes on the Specifications and the Operation Test of the Vacuum Ultracentrifuge', report to the Sharples Specialty Company, 24 July 1935 (EGP).
205. (RAC:1.1/252/1/10) Beams to Weaver, 21 September 1937.
206. (RAC:1.1/252/1/10) Weaver to Beams, 3 December 1937.
207. (RAC:1.1/252/1/10) Beams to Weaver, 21 September 1937 and (RAC:1.1/252/1/11), Weaver's diary, 24 February 1938.
208. Kraemer to Svedberg, 11 May 1936 (UUp-Lib).
209. Kraemer to Svedberg, 13 January 1936 (UUp-Lib).
210. Sanigar to Kraemer, 15 October 1936 (HML).
211. Sharples to Nichols, 2 October 1936 (HML).
212. Marston (1936), p.58.
213. Nichols to Sharples, 15 October 1936 (HML).
214. Nichols to Sharples, 6 November 1936 (HML).
215. Sharples to Nichols, 18 November 1936 (HML).
216. Nichols to Sharples, 4 March 1937 (HML).
217. Sharples to Nichols, 21 November 1936 (HML).
218. Nichols to Sharples, 16 December 1936 (HML).
219. Agreement between Sharples, Svedberg and Nichols, March 1937 (HML).
220. Sharples to Nichols, 12 February 1937 (HML).
221. 'Sharples Ultra-Centrifuge', the Sharples Specialty Company, Pittsburgh, Pa., 1937.
222. Ayres (1938).
223. Svedberg to Nichols, 6 March 1937 (HML).
224. Rideal to Lutyens, 16 April 1937 (HML).
225. Sharples to Stanley, 15 November 1937 (Rockefeller University Archives).

226. Sharples to Nichols, 4 January 1938 (HML).
227. Sharples to Nichols, 13 April 1937 (HML).
228. (RAC:1.1/252/1/10) Beams to Weaver 21 September 1937; and (RAC:1.1/252/1/10) Hanson's diary, 30 December 1937.
229. Sharples to Nichols, 28 October 1937; and Sharples to Nichols, 19 November 1937 (HML).
230. Nichols to Sharples, 29 November 1937 (HML).
231. Sharples to Nichols, 1 December 1937 (HML).
232. Svedberg to Sharples, 4 December 1937 (UUp-Lib).
233. Sharples to Bauer, 4 January 1938 (UUp-Lib).
234. Nichols to Sharples, 7 January 1938 (HML).
235. (RAC:1.1/100/10/81) Svedberg to Bauer, 26 January 1938.
236. (RAC:1.1/100/10/81) Svedberg to Nichols, 26 January 1938.
237. (RAC:1.1/100/10/86) Svedberg to Sharples, 26 January 1938.
238. Sharples to Svedberg, 12 February 1938 (UUp-Lib).
239. Sharples to Svedberg, 12 February 1938 (UUp-Lib).
240. Svedberg to Sharples, 9 March 1938 (UUp-Lib).
241. (RAC:1.1/100/10/86) Svedberg to Bauer, 9 March 1938.
242. Svedberg to Nichols, 9 March 1938 (HML).
243. Nichols to Bauer, 15 February 1938 (HML).
244. Sharples to Nichols, 19 February 1938 (HML).
245. (RAC:1.1/100/10/81) Bauer to Sharples, 15 February 1938.
246. Sharples to Bauer, 25 February 1938 (HML).
247. (RAC:1.1/100/10/81) Bauer to Svedberg, 8 March 1938.
248. Nichols to Sharples, 28 March 1938 (HML).
249. Sharples to Nichols, 29 March 1938 (HML).
250. Nichols to Svedberg, 14 April 1938 (HML).
251. Svedberg to Nichols, 19 May 1938 (HML).
252. Sharples to Svedberg, 14 June 1938 (UUp-Lib).
253. Svedberg to Sharples, 5 July 1938 (UUp-Lib).
254. Sharples to Nichols, 23 April 1938 (HML).
255. Nichols to Sharples, 10 February 1939 (HML).
256. Sharples to Nichols, 11 February 1939 (HML).
257. Sharples to Nichols, 5 October 1939 (HML).
258. Nichols to Sharples, 29 November 1939 (HML).
259. Sharples to Nichols, 8 December 1939 (HML).
260. Sharples (1939), p.1075.
261. T.D. Sharples to the author, 16 December 1985.
262. John J. Serrell to the author, 29 March 1986.
263. Eirich and Rideal (1940).
264. Ashton T. Scott to the author, 24 April 1986.
265. Cohn to Svedberg, 19 October 1938 (UUP-Lib); and Prof. John T. Edsall, private communication. Edsall worked with Cohn in those days.
266. (RAC:1.1/252/1/10) Weaver to Beams, 13 September 1937.
267. (RAC:1.1/252/1/10) Beams to Weaver, 21 September 1937.
268. Cohn to the Commonwealth Fund; quoted in: Cohn to Svedberg, 19 December 1938 (UUp-Lib).
269. Cohn to Svedberg, 19 October 1938 (UUp-Lib).
270. Pickels to Cohn, 19 October 1938 (EGP).
271. Cohn to Svedberg, 19 October 1938 (UUp-Lib).
272. Svedberg to Cohn, 1 November 1938 (UUp-Lib).
273. Cohn to Svedberg, 30 November 1938 (UUp-Lib).
274. Svedberg to Cohn, 19 December 1938 (UUp-Lib).
275. Cohn to Svedberg, 6 January 1938 (UUp-Lib). The date on this letter is likely to be wrong. It should probably be 6 January 1939 as it is a reply to: Svedberg to Cohn, 19 December 1938 (UUp-Lib).
276. Fujita (1975), p.5 and Prof. John T. Edsall, private communication.
277. (RAC:1.1/100/10/80) Pickels to Salter, 30 January 1936.
278. Pickels (1944).
279. Shakespeare (US-Navy) to Pickels, 11 April 1946 (EGP).
280. Sketch of Spinning top (EGP)

281. (RAC:1.1/252/1/13) 'Excerpt from Trustees Bulletin', December 1950.
282. M. Hanafin, private communication.
283. Grebmeier to Hakansson, 3 January 1946 (EGP).
284. M. Hanafin, private communication.
285. Dr. Edward G. Pickels, private communication.
286. Agreement between Pickels, Hanafin, Boucher and Warden, constituting Spinco, 1946 (EGP).
287. Dr. Edward G. Pickels, private communication.
288. Dr. Edward G. Pickels, private communication.
289. Pickels (1950).
290. Dr. Edward G. Pickels, private communication.
291. 'Spinco Ultracentrifuges', Spinco, 1947 (EGP)
292. Williams (1974), p.5.
293. Dr. Edward G. Pickels, private communication.
294. Pickels and Scofield (1950).
295. Schachman (1959), p.1.
296. Gray (1951), p.5.
297. Schachman (1959), p.1.
298. Williams (1974), p.5.
299. Prof. John T. Edsall, private communication.
300. Dr. Edward G. Pickels, private communication.
301. McInnes (1942), p.175.
302. Beams (1942).
303. Williams (1942), p.210.
304. Quoted in Rothen (1942), p.238.
305. Rothen (1942), p.241.
306. Longworth (1950), p.503.
307. Longworth (1950).
308. According to Zernike the Phywe Company from Göttingen started manufacturing the Beams preparative UC around 1940. Zernike (1941), p.229.
309. Pedersen to the Clarendon Press, 25 January 1950 (UUp-Lib).
310. Schachman (1959), pp.1-2.
311. Schachman (1959), p.4.
312. Schachman (1959), p.13.
313. Schachman (1959), pp.18-19.
314. Schachman (1959), p.21.
315. Schachman (1959), pp.56-58.
316. McCosham and Williams (1962), p.123.
317. Svedberg and Pedersen (1940a), pp.408-423.
318. Ogston (1963), pp.264-265.
319. Williams (1974), p.6.

THE DEVELOPMENT OF ARTEFACTS: PATTERNS AND ANALYTICAL MODELS

In the preceding chapters I have given a description of how various actors developed ultracentrifuges and how these subsequently became used by numerous other actors. To facilitate the use of this material as a case study in sociology of technology I summarize the main findings in section 7.1. In section 7.2 I will compare the various developments, looking for patterns in the differences and similarities. Drawing on these insights, I shall in section 7.3 present an analytical model that will help us gain a better insight in the developmental processes of technological artefacts. In section 7.4 I will argue that this model fits and can be seen as an addition to the new approaches in technology studies.

7.1 SUMMARY OF THE DEVELOPMENT OF ULTRACENTRIFUGES

In 1923 Svedberg and Rinde constructed the first ultracentrifuge for the study of gold sols. About half a century later ultracentrifuges were widely used in biochemical laboratories and in the mass production of enriched uranium. There is a link between the two situations but it is certainly not a linear link that led from innovation to the diffusion of the same innovation. The path of the development of ultracentrifuges was one with many detours, with dead ends, and with junctions where new paths started or other paths crossed the paths of ultracentrifuge development. The original main path has split in two, each of which paths again followed a crooked course. Metaphorically, the development of ultracentrifuges can be seen as an area rather than as a route leading from one place to another. It does not make much sense to talk of the development of 'the' ultracentrifuge.

A number of actors were involved in the development of ultracentrifuges, each with their own backgrounds and goals, and with their 'own' ultracentrifuge. Still,

the various developments influenced one another; actors related their developmental work to that of others and more or less explicitly tried to convince others to copy or buy their ultracentrifuge. Although presented as the work of actors, the emphasis here is on the artefacts: where did the different artefacts come from, in which direction where they modified and why? How did the different developments influence one another and influence each other's course?

In 1923, while in Wisconsin, Svedberg suggested a number of possible projects for research one of which was to develop centrifuges for the determination of distribution curves. This project was taken up by J.B. Nichols and led to a first centrifuge that allowed a photographic registration of the sedimentation of colloids. Although the apparatus still had many problems, Svedberg was convinced that it could be developed further into a useful device for sedimentation experiments. Back in Upsala he developed it further into a new type of centrifuge which used sector-shaped cells and in which the rotor spun in a hydrogen atmosphere. This apparatus finally enabled him to determine the distribution of sizes of colloidal particles and he coined the name *ultracentrifuge* for it. Svedberg was interested in using it for the study of the usual inorganic colloids as well as organic substances like proteins. In those days proteins were considered to be colloids and the general idea was that proteins were aggregates of smaller molecules. However, when Svedberg used the ultracentrifuge for the determination of the particle sizes of haemoglobin, this first results suggested that all particles had the same size. This conclusion was completely contrary to his expectations and, because of the uncertainties of his method, he did not make a firm claim that it was indeed a monodisperse protein. In order to verify this possibility Svedberg saw only one way: to develop another ultracentrifuge, but with a gravitational field of 70,000 to 100,000 g, i.e. 15 to 20 times more powerful than the one he had. But he had no idea whether this could be done. He had to get help from external experts and he assessed that it would cost a lot of money to find out whether it could be done. He succeeded in getting grants from two Swedish foundations for the development of such an apparatus which was designed and made at the Ljungström Steamturbine Company. After half a year of development and testing the original objective of over 40,000 r.p.m. was attained, generating a force over 100,000 g.

In 1926 the Nobel Prize in Chemistry was awarded to Svedberg for his work on 'disperse systems'. There had, however, been some controversy over his award which also made Svedberg have ambiguous feelings about it. He had been awarded the prize more or less for his total body of work while he felt that only his latest investigations, the protein studies with the ultracentrifuge, could really be seriously considered. These were just begun which made him feel that he should have been awarded the prize some years later. He set himself the goal to use the

next ten years to prove that he was really worth the Prize. The Nobel Prize itself turned out to be an important aid in doing so. It gave Svedberg an extra status which greatly assisted him in obtaining funds for further investigations. The Swedish government financially supported the construction of a new research laboratory for physical chemistry at Upsala University, allowing Svedberg to design an entirely new ultracentrifuge laboratory, which opened in 1931. Svedberg also succeeded in obtaining a large grant from the Rockefeller Foundation for instrumentation of the laboratory and the further development of the ultracentrifuge.

After the first surprising results with haemoglobin Svedberg used his ultracentrifuge mainly to study a wide range of proteins. It was a time that an increasing number of scientists started studying proteins from various angles. Increasingly, the study of proteins was seen as a possibility for unraveling the mysteries of life and proteins also became ever more important in medical research. Svedberg's finding that proteins were monodisperse aroused great interest. His results stimulated the interests of other scientists in the field and a large number of them came to Upsala to do research in Svedberg's laboratory. Some of them expressed the desire to obtain their own ultracentrifuge but the apparatus appeared much too expensive for most of them. Svedberg's work also aroused the interest of the Rockefeller Foundation. In those days they were one of the principal foundations that financially supported scientific research. In the early 1930s they had formulated a policy according to which they wanted to stimulate research in the life sciences by using tools and methods that had been so successful in the physical sciences. Svedberg's use of the ultracentrifuge perfectly fitted that policy. However, in order to take full advantage of the apparatus it should be used in many more laboratories; thus the Foundation was interested in the development of a cheaper alternative. One example of this interest is the support given to McBain when he asked them to fund the development of such a cheaper alternative.

James William McBain, like Svedberg, was a colloid chemist who had built up a good reputation as a scientist by the late 1920s. In the first decades of the century he held various posts in Europe but he was also known in the US. In 1926 he was invited as the foreign guest of honour to the US National Colloid Symposium. In 1929 McBain was appointed Professor of Chemistry at Stanford where he remained until his retirement. When he learned about Svedberg's use of ultracentrifuges for the determination of particle sizes McBain also became interested. Unlike Svedberg, however, McBain wanted to use them for inorganic colloids exclusively. He worked with Svedberg for some months to learn the technique and, when back at Stanford, set out to develop his own ultracentrifuge. However, whereas Svedberg was able to raise large sums of money for its

development, McBain had to work with limited funds. His goal, therefore, was to develop a cheaper alternative to Svedberg's 'enormous outfit'. This goal was well in line with the interests of the Rockefeller Foundation which made them support his investigations. McBain based his apparatus on a spinning top design that had originally been developed in the mid 1920s by two Belgian researchers, E. Henriot and E. Huguenard. This, after some years, led to his so-called 'Periscope Ultracentrifuge'.

Although he was not interested in proteins he used them as a test material in order to compare his findings with Svedberg's. He hired Laura Krejci, who had worked with Svedberg, to help him because he knew nothing about proteins himself. These experiments convinced him that he could use his apparatus for sedimentation experiments. Moreover, he could do things with his ultracentrifuges that Svedberg could not because Svedberg's took about half an hour to reach the maximum speed while his speeded up in less than a minute. This made it possible to study the centrifugation of living protoplasm (which was killed in about ten minutes). McBain also started to criticise some aspects of Svedberg's experimental procedure. Svedberg contested McBain's criticisms and also argued that McBain's ultracentrifuge was no good. According to Svedberg's experience, the sedimentation cells should be located at least 65 mm from the axis of rotation which set a lower value of about 18 cm to the diameter of the rotor while McBain's rotors were only 3.5 cm in diameter. Svedberg himself had experimented with a 10 cm rotor in the mid 1930s but had dismissed them on the basis of their inferior resolving power. McBain stated that this requirement did not apply to his scheme because he used an 'extremely accurate' microphotometer in his experimental procedure. This was never contested by Svedberg.

The Rockefeller Foundation faced a problem in that they were interested in a cheaper alternative for Svedberg's ultracentrifuge but that the only alternative, that was actually being developed, was disclaimed by Svedberg. Whether McBain could indeed do meaningful sedimentation experiments with his ultracentrifuge, which he claimed he could, they could not judge. But what good would such a claim be if nobody in the field believed him. The Foundation therefore discontinued supporting him. McBain continued working with his spinning top ultracentrifuges for some years but nobody seemed to take this work serious. Around 1940 he stopped working with them altogether.

Their experience with the McBain apparatus made the Foundation wonder if it would at all be possible to develop a cheaper alternative to the Svedberg ultracentrifuge. As a result they awarded large grants to two other institutions for the purchase of a Svedberg ultracentrifuge in the mid 1930s. Within the restrictions of their budget this seemed to be the best option. However, around 1935 another alternative candidate appeared on the stage, an ultracentrifuge

developed by Beams and Pickels.

In the mid 1920s Jesse Wakefield Beams used rapidly rotating mirrors in the production of extremely short flashes of light for which the onset and duration were measured with a light-switching mechanism which he himself developed. During this work, while collaborating with E.O. Lawrence at Yale, they came across Henriot and Huguenard's spinning tops. Beams and Lawrence used such a design for rotating mirrors in their experiments but found that the mirror was not stable enough for their purposes. They modified the apparatus and were able to solve the problem. In 1928 Beams returned to the University of Virginia where he remained for the rest of his career. He continued using the spinning top in his experiments and also improved its stabilization and ease of operation.

In 1930, following a suggestion already made by Henriot and Huguenard, Beams started using the apparatus as a centrifuge by making the rotor hollow. From this time on his attention gradually shifted from using the apparatus in experiments to the actual development of centrifuges. From being an instrument in his own research in physics it became an instrument that could be used in 'science in general'. Beams developed several centrifuges, which differed in the way the centrifuged material could be extracted from the rotor while rotating at its maximum speed. Yet, in Beams' view much remained to be improved: rotational speed, bearings, strength of materials, vibrations and methods for making the centrifuging continuous. One of the possible applications was to use the spinning top as an instrument for the kind of experiments Svedberg was doing. Edward Greydon Pickels, one of his students, chose to investigate this problem for his thesis research. Pickels tried a number of different schemes, all of which he found unsatisfactory. However, when he finally tried to spin the rotor in vacuum, most of his problems appeared to be solved. It was evident from the first experiments that the rotor turned remarkably smoothly. Careful balancing appeared unnecessary and the maximum rotational speed was limited only by the strength of the materials used in the rotor. A duralumin rotor with a diameter of 8 cm exploded only at 132,000 r.p.m., corresponding to a gravitational field of 900,000 g.

Pickels left after finishing his studies and Beams continued working with the vacuum ultracentrifuge, trying to develop it for various different applications. He decided that the air-drive was a handicap because many potential users did not possess the necessary compressors for generating the air pressure. When he approached the Rockefeller Foundation, indicating that his work might lead to a cheap and easy to operate ultracentrifuge, they were much interested because it might lead to the cheaper alternative to Svedberg's machine that they were looking for. They therefore funded Beams' development of steam and electrical drives. The steam-drive appeared to work alright but was considered rather inefficient and Beams was more satisfied with the electrical drive. The first

electrically driven ultracentrifuges were still supported by compressed air but for this only a small compressor was needed which was easily available and cheap. Shortly thereafter Beams and one of his collaborators eliminated the need for air compressors altogether by developing a magnetic suspension. Although Beams often stressed that his ultracentrifuges for sedimentation experiments were cheap, easy to operate, 'fool-proof', etc., few of them actually spread to other laboratories. The only ones that were actually used elsewhere were made by Beams' instrument makers.

The Rockefeller Foundation also secured Pickels' assistance in the further development of ultracentrifuges. After he had developed the vacuum ultracentrifuge as a student he was asked by the International Health Division of the Rockefeller Foundation to work for them and develop the ultracentrifuge for virus research in their laboratories. Researchers like Bauer and Wyckoff would like to be able to study viruses in the same way Svedberg studied proteins. They also liked to use the apparatus to purify viruses. Pickels started with the air-driven vacuum ultracentrifuge developed at Virginia, finally developing two versions of it. The first, which had cells like Svedberg's, could be used for sedimentation experiments on viruses and was called the 'analytical ultracentrifuge'. In the other a number of test tubes, holding a virus in solution, were placed in the rotor. After a certain time of centrifuging with certain viruses crystals would accumulate at the bottom of the test tube which meant that the virus was obtained in a very pure form. When Svedberg was in the US in 1936 Warren Weaver from the Rockefeller Foundation arranged that he would also visit Bauer's laboratory where Pickels worked. Svedberg was very impressed with what he saw and judged that they had constructed a very good ultracentrifuge which could be of great value for further protein research. At that time he was already working on a monograph on the ultracentrifuge and he invited Pickels and Bauer to contribute a chapter on their apparatus, an offer which they accepted.

Two ultracentrifuges had by then been developed that were generally seen as good instruments for sedimentation experiments but neither of them easily spread to other laboratories. The Beams/Pickels type was manufactured commercially in the US in the late 1930s but it became a commercial failure. In the early 1940s Svedberg's oil turbine ultracentrifuges were also marketed. These were manufactured by a company called LKB-Produkter which was formed during the second world war, partly on Svedberg's initiative, in order to manufacture and sell scientific instruments, one of which was Svedberg's ultracentrifuge. Although the company became quite successful, the ultracentrifuge was a commercial failure. Only a few were actually sold. Svedberg had continued developing ultracentrifuges until the late 1930s but only in the sense that they were better suited for his own research on proteins. Almost everyone in the field agreed that he had been quite

successful in doing so. But developing ultracentrifuges in such a way that they could be used in many laboratories appeared to be quite a different matter. Svedberg continued using ultracentrifuges in his research until his retirement in 1949. All the time, the Rockefeller Foundation kept a great interest in his work and continued to support it. At the Upsala Laboratory, Svedberg's successors continued working with the oil-turbine ultracentrifuge until the mid-seventies.

Whereas Svedberg stopped developing ultracentrifuges in the late 1930s Beams continued developing them all of his life. But for Beams, a Svedberg-type application was just one of the many possible applications for his artefacts. He also started to develop his ultracentrifuges for the separation of gases and isotopes. In 1939/1940, separation of uranium isotopes (uranium enrichment) became an important issue in view of the possible construction of nuclear weapons in the United States. Beams tried to adapt his ultracentrifuges for the purpose and, although the production of enriched uranium in them was very small, it was decided in 1940 to build a pilot plant with these centrifuges. In January 1944 the ultracentrifuge project for uranium enrichment was terminated because another uranium enrichment technology, that of gaseous diffusion, was preferred. After the war, Beams continued developing his ultracentrifuges in various directions. He tried to obtain the highest gravitational field possible, in the late 1950s reaching more than one billion g with a small steel ball rotor of a quarter of a millimetre in diameter. He also set out to obtain rotational speeds as constant as possible and to reduce the loss of speed due to friction. This led him to the development of the so-called coaster, an ultracentrifuge spinning in vacuum that, after it had been speeded up by an air turbine, was disconnected from the drive. Afterwards the rotor coasted without being driven. In the early 1960s he reduced the residual deceleration to the point that a rotor, initially spinning at 300 r.p.s., would lose one r.p.s. in forty days. These apparatuses never found any widespread application.

In the late 1930s, Pickels had developed his ultracentrifuges at the International Health Division to the point that they could be used routinely by other researchers at the institute and no further development would be necessary. Trained as an experimental physicist he was able to assist these researchers, who were usually trained as biological or medical researchers, in other ways, and help them with the use of various instruments. One day in 1946 he was visited by Maurice Hanafin, a salesman from California, who was engaged in the manufacture of so-called angle centrifuges. He had developed a broader interest in centrifuging and had studied all kinds of literature on the subject, including literature on ultracentrifuges by Beams, Pickels, McBain and Svedberg. This made him decide that he wanted to manufacture and sell them and he asked Pickels to become a consultant to his company. Pickels, however, having been looking for another job for some time, suggested that rather than become a consultant he would like to be

in business himself, as a partner to Hanafin, an offer which Hanafin accepted. They formed Spinco, to manufacture various scientific instruments, starting with ultracentrifuges.

At Spinco, Pickels decided that they would not be able to sell the ultracentrifuges as they were because they were too difficult to operate, needed a noisy air-compressor and a large room to house all of the equipment. He wanted to have the whole thing in one casing with a control panel in front from which the whole operation could be directed and followed. It made him redesign the apparatus by using an electrical motor as a drive and a gear box in order to be able to choose different speeds. The gear box could be controlled from the front panel. Furthermore he folded the optics so that they too could be housed in the same casing. Initially they were only able to sell eight of these machines, and at a slow rate, and Spinco nearly went bankrupt. Pickels then decided to forget about the analytical ultracentrifuge for a while and concentrate on the quantity ultracentrifuge. This was a good move as it sold at a high rate from the outset. Gradually, also more orders for the analytical ultracentrifuges came in. In four years time, 70 were sold; after a decade 300 and in the mid 1960s one thousand Spinco analytical ultracentrifuges were spinning around the world.

This was not the only type of ultracentrifuge that finally found wide-spread application. In the 1950s, based on Beams' work in the late 1930s, further developments in ultracentrifuge technology for uranium enrichment were instigated in several countries, including the USA where Beams resumed his earlier work. After a long period of further development, in April 1977, three months before Beams' death, president Carter authorised the construction of a large-scale ultracentrifuge plant for uranium enrichment. The plant would have to be in full operation by 1990 and would have a capacity big enough to fill about one quarter of the world's estimated needs by the time. However, in the early 1980s, after huge investments had already been made, the plans were canceled again. Nuclear power growth had been much less than anticipated and, furthermore, laser enrichment had been developed to the point that it was considered superior to enrichment with ultracentrifuges. In Europe, notably in the UK, the Netherlands and the Federal Republic of Germany, a different policy was followed and hundreds of thousands of ultracentrifuges are actually used there for the commercial production of enriched uranium.

7.2 PATTERNS OF DEVELOPMENT

In the cases described in the previous chapters a number of actors tried to develop ultracentrifuges each of them with their own specific approach. This led to

a whole variety of different ultracentrifuges. But there are also similarities and accountable differences in the various cases which can be linked to characteristic phenomena and patterns. In section 7.2.1, entitled 'Actors and Artefacts', the emphasis is on more or less stable phenomena in the development of ultracentrifuges. In a number of subsections I will discuss the relation between actors and artefacts, hard characteristics of artefacts, and the role of artefacts in relations between actors. In the final subsection I will argue that a combination of SCOT and network approaches can be fruitfully used for characterising the patterns identified. In section 7.2.2, entitled 'Patterns of Change', I will discuss in two subsections how artefacts and relations between actors can change. On the basis of the patterns identified I will argue in the final subsection that 'stabilization', rather than 'success', should be a central concept in understanding processes of technological development.

7.2.1 Actors and Artefacts

Relations between Actors and Artefacts

The general point I want to make in this section is that actors have or develop a certain way of dealing with artefacts which applies to various different artefacts and which may be unaltered for long periods of time. A considerable degree of order can be found in the relations between actors and artefacts although contingencies may also influence these relations. Looking at the development of ultracentrifuges we observe that the different actors have come into first contact with ultracentrifuges in various contingent ways: Svedberg got an idea of using centrifuges in the course of his scientific work; Beams read about spinning tops in a scientific paper; Pickels started with it because Beams had given the development of ultracentrifuges to him as a problem for his thesis research; McBain had read about Svedberg's work; etc. However, once the various actors started working with ultracentrifuges, this fitted their own characteristic pattern of dealing with artefacts. This will be illustrated in the examples below.

Svedberg's idea of using centrifuges was inspired by the use of the sedimentation balance as an instrument in colloid research for the determination of distribution curves. Centrifuges were to be used for increasing the gravitational field used in such experiments. This would make it possible to investigate the distribution of much smaller particles than was possible with the sedimentation balance. In these scientific investigations Svedberg also used a number of other artefacts as instruments. It was quite common that these instruments were usually made and developed by the researchers and their students themselves, sometimes

with the assistance of some machinshop in town. This implied that Svedberg was both the developer and the user of these artefacts which was also true for the way he dealt with centrifuges. When after some time he had developed a centrifuge to the point that he could use it for his scientific experiments he coined the name *ultracentrifuge* for it in order to stress its analogy with the *ultrafiltration* apparatus and the *ultramicroscope* which were used as instruments in the same field where these centrifuges were to be used. Svedberg continued using the apparatus for this work for the remainder of his academic career although there was a shift of focus in the application - from colloids in general to proteins which were considered to be a special class of colloids. For more than a decade Svedberg also remained working on the artefact as its developer until he decided that he had reached the limits of its possibilities.

Beams, in his research on various optical phenomena, often used rotating mirrors. During this work he came across the papers of Henriot and Huguenard in which they described their spinning tops and their application to the rapid rotation of mirrors. Their scheme was most interesting for Beams as it facilitated very high speeds at very low cost which would enable him to increase the accuracy of his experiments. As in the Svedberg case this new artefact fitted the way he usually dealt with artefacts, viz. making them himself and using them as instruments for his research in experimental physics. However, after some time, a notable change took place in the way Beams dealt with his spinning tops. From being an instrument for his own research they were to be used as instruments in science in general, especially if the tops were made hollow in order to facilitate their use as centrifuges. Because the speeds he could obtain were considerably higher than the ones possible with conventional centrifuges at the time, he started to use the name *ultracentrifuge* for the apparatus. The way Beams and Svedberg came to the naming of the apparatus also demonstrates the difference in how they saw the apparatus. Svedberg based the name upon the use of the centrifuges in colloid chemistry; Beams based it upon the speed of rotation. After Beams had started using the spinning top as a centrifuge he developed many different variants of ultracentrifuges which could be used for various scientific applications. Sometimes he, or one of his students, used them as a tool in other research but mostly these experiments were used to demonstrate the capabilities of the artefact in question. Beams' principal relation with ultracentrifuges was that of their developer which he remained for the rest of his life.

It is uncertain how McBain first learned about ultracentrifuges though it is quite likely that, being a colloid chemist like Svedberg, he had read some of the latter's publications. Especially because Svedberg was considered to be one of the most distinguished scientists in the field. McBain wanted to use this instrument in his own work in colloid chemistry but could not afford to buy or copy Svedberg's

machine. He therefore tried to develop a cheaper alternative. Before he actually started working on the problem Herman Spoeher from the Rockefeller Foundation pointed out Beams' recent work on spinning tops to him. Although it is uncertain whether this inspired McBain to use the same principle he actually did use this scheme which finally led him to the development of the *periscope-ultracentrifuge*. This apparatus facilitated his performing of the intended investigations. He also developed a number of other variants which were specially adapted to other experiments in his own research in colloid chemistry. Like Svedberg, McBain was also both developer and user. An important difference between the two was that, in the course of time, Svedberg's ultracentrifuge had become the principal instrument in his scientific work while McBain also used numerous other instruments and different experimental procedures. After about a decade, McBain even stopped working with ultracentrifuges altogether.

Beams gave the ultracentrifuge to Pickels as a problem for his thesis research. Out of two possibilities to develop it for a specific application he chose to develop it for the type of sedimentation experiments Svedberg was doing with his ultracentrifuge. When Bauer learned about this work he wondered whether the Beams/Pickels scheme could also be developed for use in his virus research. After Pickels had constructed the first vacuum-ultracentrifuge he was offered a job by the IHD to develop this apparatus further for Bauer's type of work. This work was finished as soon as Bauer and other researchers at the Institute could do the research they wanted to. An important change in Pickels' relation with the apparatus came when Hanafin asked him to become a consultant to the commercial production of ultracentrifuges. Pickels decided that he would like to be in business himself and therefore proposed Hanafin to become partners. They formed Spinco but, beside ultracentrifuges, they wanted to manufacture and sell other scientific instruments as well. When he found this work no longer satisfactory Pickels quit the business. So, all of the time Pickels remained developing the apparatuses for final use by others although, at the IHD, he was very close to the people who should actually use it. When further development no longer seemed necessary from the perspective of the users, Pickels went to do something else.

The Rockefeller Foundation saw its primary role in the funding of scientific research that fitted their own research interests. For them, artefacts were to be used as instruments by the researchers they funded. Instruments were seen as very important in this work and they were prepared to give large sums for the development of instruments which, in their opinion, might make new promising research possible. It is uncertain whether the Foundation first learned of Svedberg's ultracentrifuges through his published work or through his grant application for the instrumentation of his new laboratory. Anyway, they did learn about it and the promise of this new machine perfectly fitted their own interests.

Especially after it appeared that Svedberg indeed produced important scientific knowledge with its help. This made them conclude that ways should be found to make the apparatus available to many more scientists. All of their subsequent actions towards the apparatus, viz. funding Svedberg, McBain and Beams for the development of the apparatus, and funding Ledingham and Williams for the purchase of one, were guided by this view. They did not stop funding ultracentrifuge work until Svedberg's retirement which was about the same time Pickels started manufacturing them commercially.

When Sharples learned of Beams' ultracentrifuges, probably by one of Beams' publications, he decided that they should manufacture and sell it because they considered themselves to be the principal industry in the field of centrifuges. This attitude also made them approach Svedberg to manufacture and sell his oil-turbine ultracentrifuge. In their view, ultracentrifuges fitted the things they used to do. However, Svedberg declined their offer and they were not able to sell more than one of the type developed by Beams and Pickels. Their relation with ultracentrifuges therefore remained a short one.

Concerning LKB, during the second World War a concern developed in Sweden that the country might be cut from important supplies. Because of this fear, and partly on the initiative of Svedberg, LKB was established in order to make Sweden self-supporting in the field of scientific instruments and important chemicals. The instruments, according to Svedberg's philosophy, should be sold as they were because nobody but their actual developer could know better what they should look like. This philosophy was supported by the fact that he had had numerous requests for his own instruments from various parts of the world. However, the philosophy did not work and the company nearly went bankrupt. When Malmström became director he set on a course of developing a new line of instruments and drop the old one, including Svedberg's ultracentrifuges. Furthermore, they started to establish agencies in the fields they were aiming at, including an agency for Spinco which made them also sell Spinco ultracentrifuges.

These excerpts demonstrate that the relation, that developed between these actors and their ultracentrifuges, was not a contingent one. In all cases there was a gradual shift from not working with ultracentrifuges to working with them. In the cases of Svedberg, McBain, Pickels, Rockefeller Foundation and Sharples, the new artefact fitted a way of working with other artefacts. In the Beams case he perceived new possible applications for an artefact he was already working with. These new possibilities made him also give it a new name. Pickels also perceived new possibilities for an 'old' machine when Hanafin approached him. However, when they established Spinco, they did not see the ultracentrifuge as a single item, but as one of a number of artefacts they intended to manufacture and sell. The same

holds for LKB. Here, after some time, a shift in the relation between actor and artefact took place when the Svedberg inspired philosophy was replaced by a new one in which the company became more active in the development of artefacts rather than just manufacturing and selling them.

Summarizing, the various actors came into first contact with ultracentrifuges either because it was an alternative for an artefact they were already working with or because new possibilities were seen for an artefact they were already working with. If the artefact starts functioning in a way that satisfies the actor, the relation can develop to a long lasting one. In the Beams case this came about quite easily but usually the actor has to put in more effort in order to make the artefact function successfully. The cases suggest that the amount of effort, the actor is prepared to put in, at least depends upon two factors which are the anticipated gain when the artefact does become successful and the range of possible alternatives the actor perceives. For Svedberg, the question whether haemoglobin was monodisperse could only be answered by developing a new ultracentrifuge and the question was so important to him that he invested lots of time and money in their development. McBain had many alternative ways for producing scientific knowledge and he discontinued working with the apparatus when after ten years of working with it on an occasional basis nobody took this work serious. Sharples, LKB and Spinco¹ continued or started manufacturing selling other artefacts when after some time it appeared they were not successful in selling ultracentrifuges.

Hard Characteristics of Artefacts

Let us now take a closer look at the artefacts. In the case histories we sometimes observe that actors were very explicit that certain characteristics of ultracentrifuges should not change. For instance, Svedberg explicitly protested when McBain claimed that meaningful sedimentation could be obtained in small rotors. Svedberg argued that the cells should be located at least 65 mm from the axis of rotation which set a lower value of about 18 cm for the diameter of the rotor. McBain, on the other hand, indicated that he was not prepared to drop the air-turbine or the smaller rotors. When Svedberg first heard about the vacuum ultracentrifuge he claimed that it was better to use a hydrogen atmosphere. Pickels, on the other hand, towards Bauer, defended the vacuum against the hydrogen arrangement. The phenomenon, that for actors certain characteristics should not be changed, may be described by stating that *for the actors* certain characteristics of the apparatus have become *hard*, i.e. not amenable to change. A characteristic is any piece of hardware, technological principle, etc., and its

hardness is indicated when it is mentioned explicitly by the actor in papers, letters, oral communication, etc. For Svedberg, the oil-turbine and the hydrogen atmosphere were hard characteristics; for McBain the air-turbine was hard as was the vacuum for Pickels. For Svedberg, moreover, in the mid 1930s, almost every characteristic of his ultracentrifuge had become hard. This became evident when he discouraged Kraemer and Ledingham from attempting any modification to the apparatus.

Beside the ones mentioned, there were numerous other characteristics that have not been changed either but which the actors have not been explicit about as to whether they were amenable to change.² This may be fortuitous as actors simply cannot change everything and may not have had any opportunity for changing certain aspect. For instance, were Svedberg's thermocouples hard? And what about Beams' flexible shaft or Pickels' celluloid containers in his Preparative Ultracentrifuge? Whether they were hard or not, the least that we can conclude that they were not changed. Obviously the actor was not interested in modifying the characteristic which we may also describe by saying that the characteristic had become normal to the actor. I will use the phrase *presumptive normality*³ to describe that the actor is not interested in modifying certain characteristics. The actor is quite satisfied with their functioning. Hardness would then constitute a special case, a case where the actor has *asserted* the normality of that aspect.

When we take a closer look at the hard characteristics identified above for the various actors we may notice that all of these characteristics, in the past, have solved a problem for the actor. For Svedberg, the oil turbine was an answer to the problem of reaching a twenty-fold increase in gravitational field which was solved after putting in a lot of effort and money. It was an important problem to him - a necessary step in order to be able to answer the scientific question he had posed himself: was haemoglobin monodisperse or not? The hydrogen atmosphere was also an answer to an important problem. Without solving the problem of convection any ultracentrifuge experiment would be meaningless to him. In another example the Hilger Company had proposed Svedberg to use only sector shaped masks rather than a sector shaped cell. Svedberg, however, was very explicit that the cell itself had to be sector-shaped. This hard characteristic was an answer to the problem of convection along the walls of the first optical centrifuge. For Pickels, the vacuum arrangement was the answer to the problem of convection which he developed after having tried other possibilities for about a year. And solving the convection problem was a necessary step in the task he was given for his thesis research which was the adaptation of the spinning top for Svedberg-like sedimentation experiments. McBain faced quite a different problem. The ultracentrifuge had to be cheap or he would have to forget it. For him, the air-turbine was an answer to that problem. These examples illustrate that presumptive

normality is reinforced if the characteristic has solved a problem that the actor has been worried about and put effort into. The effect may be that the characteristic will become hard for the actor.

Beside the hard characteristics described above, there were also other characteristics of ultracentrifuges that were an answer to a problem the actor once had with the artefact. For instance, when Svedberg started thinking about using centrifuges for the determination of distribution curves he had to find a way of registering the sedimentation. As an answer to this problem he developed an optical method which supplied him with photographic recordings in which the pattern of blackening gave information on the distribution of particle sizes. These photographic plates were subsequently analysed with a microphotometer which, after a tedious calculation procedure, gave the distribution curve. This scheme was never changed again. When new problems arose because of the amount of data produced Svedberg did not change the procedure but solved the problem by adding a calculating department to the laboratory. For Beams the vacuum chamber solved the problem that the rotational speeds of his spinning tops were limited by atmospheric drag. Afterwards the vacuum was never questioned by him again. These observations suggest that solving a problem by applying a certain characteristic to the artefact results in a presumptive normality that is not modified again unless something special happens. Many more examples can be found in the cases. Hardness can be an effect of this process of normalising which we can only see if the actor is explicit about it.

An interesting example of a hard aspect of the Svedberg ultracentrifuge in the late 1920s was the cross section of the rotor. Svedberg was very explicit at the time about the fact that this cross section should have a circular shape and so the circular shape had become a hard characteristic of his ultracentrifuge. This example is interesting in two ways: 1) The hardening was *not* caused by solving a problem which indicates that there may be other reasons for hardening than the one I identified above. 2) The aspect was altered after some time and in later ultracentrifuges Svedberg only used rotors with an oval cross section. I will get back to this latter point below. Concerning the first point we see that Svedberg defended the circular shape on *theoretical* grounds. Theoretical considerations made him expect that due to the oval shape of the rotor the exchange of heat between the rotor and the casing was worse than in the case of the cylindrical type and that thus convection currents could set up more easily. And freedom from convection was one of the crucial requirements of his ultracentrifuge - if this would not be satisfied the apparatus would be useless to him. This suggests that an actor's *theoretical knowledge* can also lead to hardening characteristics of artefacts. Another example is Beams' flexible shaft concept. On theoretical grounds Beams expected that rigid shafts would break easily and that therefore the highest

speeds would be obtained with flexible shafts.

In the example of Svedberg's rotor shape, despite his reluctance on theoretical grounds, Svedberg after some time did agree that an oval shaped rotor should be made. When it was tested it showed, as Svedberg had expected, very bad convection currents which made Svedberg even more convinced that they should stick to the circular shape. This suggests a third reason for hardening, notably when the actor has developed an alternative for a certain characteristic but that, upon testing it, the alternative appeared to worsen things. Other examples are that Svedberg did develop smaller rotors with cells closer to the axis of rotation but dismissed them on the grounds of their inferior resolving power. Afterwards he was very decided about the fact that the cells should be located at least 65 mm. from the axis of rotation. Pickels tried a horizontal axis of rotation for his vacuum ultracentrifuges but experienced much trouble with vibrations, heating and breaking of the shaft. Although he indicated that it might still be of use to someone, he himself afterwards stuck to the vertical axis of rotation.

Summarizing, I have identified three reasons for an actor normalising or hardening characteristics of artefacts. We could say that two of these are based on the actor's experience - either the experience that the characteristic has solved a problem or the experience that he got into trouble when he tried to modify it. The other reason is based on the actor's theoretical knowledge. But whatever the causes, we can observe that hardening takes place and plays a role in the subsequent development of the artefact. The characteristic is simply unquestioned by the actor and, moreover, the actor will protest when other actors suggest to modify it.

In the case of Svedberg's circular rotor two reasons for hardness even reinforced each other. Nevertheless, this characteristic was changed after some time. How could this happen? At a certain point, while the request for centrifuge time was very high, all of Svedberg's circular rotors were damaged. At that point he remembered that he still had the oval rotor which he had dismissed two years before because it gave very bad convection currents. He had the choice between not being able to do any experiments at all or trying something he did not believe in. He chose to do the latter and, to his complete surprise, had no problem at all in doing meaningful sedimentation experiments. Because of unforeseen problems occurring while using the ultracentrifuge with circular rotors it appeared that the hardened characteristic did not work anymore. This stimulated Svedberg to try an oval shaped rotor as he had nothing to loose because it was already lying there. So, hardened characteristics may become questioned again if new problems arise. They may also become questioned if an existing problem does not seem to be solvable otherwise. Take for instance Svedberg's rotor size. On theoretical grounds Svedberg had developed the notion of resolving power which made him conclude

that the most reliable results would be obtained with larger rotors. Also on theoretical grounds he expected that higher rotational speeds could be obtained with smaller rotors but, because the resolving power would be lower, he expected that they would perform worse for him. Thus, on theoretical grounds, the larger rotors were hardened characteristics of the ultracentrifuge. Seeking to increase the gravitational field Svedberg started to change a number of characteristics that were not hardened like the type of oil used, the oil compressor, the shape of the rotor (making it thinner towards the periphery), shape of the turbines, etc. Only after he had tried many other possibilities he also tried the possibility of smaller rotors. Hardening does not imply that these characteristics will never be changed. Unforeseen problems or problems that cannot be solved otherwise can still have the effect that the hardened aspect becomes questioned again.

Summarizing, actors may be very reluctant to change certain characteristics of the artefact. Characteristics can become hardened or normalized (Presumptive Normality) if they solved a problem for the actor, if it appeared problematic to modify them or if the actor concludes on theoretical grounds that the characteristic should be as it is. When encountering new problems actors will first consider modifying characteristics of the apparatus that are not hard. The point is not so much that the actor does not have sufficient resources for modifying the characteristic but rather that the actor is not inclined to modify it. If the problem does not easily give way actors will try to find a 'work around'⁴, like mobilising new resources. Only when they conclude, on theoretical or empirical grounds, that this is not likely to solve the problem they may also consider modifying the hard characteristics.

The Role of Artefacts in the Relations between Actors

Of course, actors have numerous relations with other actors. Some of these relations may be incidental, others may be long lasting. In many of these interactions artefacts play a certain role, sometimes very pronounced, sometimes more in the background. The relation can be dominant, and the artefact is intended to play a role in these relations as they are or the relation between actor and artefact is dominant, and this implies that relations with other actors may have to change. The central point I want to discuss in this section is that artefacts can be embedded differently in relations between actors and that the way it is embedded co-determines the chances for survival of the artefact.

Svedberg started working with ultracentrifuges as a colloid chemist and intended to use them in this work. As a colloid chemist he had developed a stable pattern of relations with other scientists in the field. These scientists interacted through

their publications, private correspondence and meetings at conferences and symposiums. The subject of their interaction was scientific knowledge. Knowledge produced by one scientist was judged by the colleagues and, if judged valuable, added to an accepted body of knowledge that was further built upon. Already before he started working with ultracentrifuges Svedberg was quite successful in this field as the knowledge he produced was considered important by his colleagues. He even gained the most prestigious award there existed for this type of work, the Nobel Prize. When Svedberg started using ultracentrifuges for determining particle sizes of proteins, again this work was highly valued by his colleagues. Svedberg's shift to proteins rather than inorganic colloids came in a time that protein chemistry was increasingly seen as important for unravelling the mystery of life and various diseases. Little was known about proteins and Svedberg's ultracentrifuge was seen as an important tool for producing knowledge about them. The ultracentrifuge was seen by many as an apparatus that could produce knowledge about the size of proteins but there were also reservations as to the accuracy of the procedure. The effect was that many scientists in the developing field of protein chemistry were interested in working with the ultracentrifuge themselves. However, the apparatus was much too expensive for most of them to copy or buy and for most of them the only way to work with it was to go to Upsala which many of them did.

Svedberg also developed a long lasting relation with the Rockefeller Foundation in which the ultracentrifuge played an important role. The Foundation was much interested in stimulating the development of the life sciences by the use of procedures and methods that had demonstrated their usefulness in the natural sciences. Svedberg's work fitted this policy very well. The knowledge Svedberg produced was considered so important by them that they continued funding his work for about twenty years until his retirement. Moreover, because Svedberg was so successful in producing knowledge with the ultracentrifuge, the Foundation often expressed their desire that the ultracentrifuge should spread to other laboratories. They also found it problematic Svedberg's results could not be independently verified outside his laboratory. The desire to let the ultracentrifuge spread to other laboratories made the Rockefeller Foundation award various grant proposals that might make this possible, like proposals by McBain, Beams, Ledingham and Williams.

Svedberg also developed a long lasting relation with, first Lysholm, and later Boestad from the Ljungström Steamturbine Company. The ultracentrifuge was the central element in this relation. Because of his scientific interests Svedberg wanted to develop it further in specific directions and used Lysholm's and Boestad's expertise for determining the most fruitful possibilities for doing so. When after about ten years Svedberg had decided that the apparatus could not be developed

further the basis for the relation disappeared as did the relation itself.

McBain, like Svedberg, was also a colloid chemist who wanted to use ultracentrifuges in his colloid research. For him, the ultracentrifuge should play the same role in the relation with his fellow scientists as Svedberg's did. The principal difference between the two was that McBain did not succeed in letting the ultracentrifuge play the role he intended it to - the results he obtained with it were not considered important by his scientific colleagues. In his relation with the Rockefeller Foundation McBain promised to solve precisely the main problem they had with Svedberg's apparatus, notably that it did not spread to other laboratories. McBain promised to create this missing link. However, when after some years the Foundation came to the conclusion that McBain would not create this missing link the basis of their relation disappeared and they stopped funding him. In subsequent years McBain submitted a number of new proposals for grants which were all declined by the Foundation.

Although Beams was working in a scientific discipline very distinct from Svedberg's and McBain's, the role the spinning top originally played in the relation with his fellow experimental physicists was quite similar to the role the Svedberg and McBain ultracentrifuges played or should play in the relations with their scientific colleagues. Beams produced scientific results and the spinning top was used as a new instrument in this work. However, as has been indicated before, at a certain point Beams started seeing the apparatus in quite a different perspective which also implied that the role it was to play in his relations with others was to change. One change was that his work should become relevant to scientists in general rather than just to experimental physicists. The second change was that these relations should now be built on Beams' production of artefacts rather than on his production of knowledge. Beams was quite successful in establishing the new type of relations he intended to. A considerable number of scientists copied his artefacts or asked him for help if they had some specific wishes. The Rockefeller Foundation also became interested in this work as Beams might create the missing link indicated. They gave him some grants but their contacts did not develop into permanent relations. From the Foundation's perspective Beams' ultracentrifuge played the same role as McBain's, viz. as the possible cheaper alternative for Svedberg's apparatus although in the Beams case the Foundation had become more skeptical as to whether this would ever be established. Beams did some work in this direction but also continued working on ultracentrifuges as he had done since the early 1930s which was to develop the apparatus for any type of scientific application he could think of. The role it played in his relations with other scientists did not really change until his death.

Pickels, like Beams, also developed ultracentrifuges for use by others although he aimed at a much narrower group of scientists as Beams did. He always kept

developing them for use by (bio)chemists. But his relations with these scientists changed considerably in the course of time. As a student this relation was comparable to the ones Beams had which was that other scientists should become interested on the basis of Pickels' publications. Furthermore, the ultracentrifuge played the role of being able to demonstrate to Beams that he could do proper engineering work, well enough to be awarded a Ph.D. upon. He was successful in creating relations through publications in the sense that he interested Bauer for this work. This led to his relation with the IHD and the Rockefeller Institute where there was a very direct contact between Pickels as the developer and the researchers as users of the ultracentrifuge. They published some joint papers for a wider audience but the prime purpose of their relation was to develop the ultracentrifuge, and also other artefacts, for use at the Institute itself. When Pickels decided to establish Spinco he had to develop completely new relations with the (bio)chemists, notably trying to make them buy the ultracentrifuges he manufactured. The same goes for Sharples and LKB. The latter two were not successful in creating such relations while Spinco, after some initial problems, did succeed.

The fact that artefacts can become embedded in the relations between actors has some important consequences for their subsequent development. In the beginning the artefact may only be connected to one single actor which implies that, if for some reason the actor does not continue working with it, this will mean the end of the artefact. For instance, McBain's ultracentrifuge, after the Rockefeller Foundation had stopped being interested, did not become embedded in relations between McBain and other actors. When afterwards McBain stopped working with it this also implied the end of the artefact. In the Svedberg case, however, his ultracentrifuge did become embedded in his relations with fellow scientists, with the Rockefeller Foundation and with the Ljungström Steamturbine Company. If at that point he would have stopped working with the apparatus his relations with the Ljungström Company would have ended because the artefact was the sole basis of this relation. The relation actually did end when Svedberg stopped the further development of the apparatus. However, his relations with the Rockefeller Foundation and other scientists might have continued because they were not based on the artefact only. They were based on the production of scientific knowledge which could also be done using other artefacts. Furthermore, and this is the point I want to emphasize here, after the ultracentrifuge had become embedded in his relations with his scientific colleagues and the Rockefeller Foundation, if Svedberg would stop working with it, would not necessarily have meant the end of ultracentrifuges. Because of the embeddedness, ultracentrifuges had started to live a life independent of Svedberg's actions towards them. This

independence from Svedberg's actions becomes evident when we look at McBain's and Pickels' attempts to develop alternatives or by looking at the Rockefeller Foundation supporting such attempts. Furthermore, Sharples, and some years later also LKB and Spinco tried to manufacture them commercially. Except for LKB, Svedberg had nothing to do with these actions. Nevertheless, until the late 1940s the apparatus remained quite vulnerable. Nobody copied McBain's ultracentrifuge and his scientific results were not considered important by the scientific community. The Rockefeller Foundation stopped funding him and McBain himself stopped working with ultracentrifuges after about ten years. They might have remained lying on the scrap heap of history for ever if I had not picked them up. Beams' relations with the Rockefeller Foundation and users of his ultracentrifuges remained incidental which led to the use by a limited number of researchers of the apparatuses for the actual production of knowledge. Sharples and LKB were not able to create the intended markets and forgot about ultracentrifuges although LKB, in a later stage, was successful in selling Spinco machines. Svedberg's relation with the Rockefeller Foundation remained stable as long as he produced scientific knowledge. But this relation was also discontinued when he stopped doing so. It was not until Spinco started to manufacture ultracentrifuges that they became embedded in a relations between actors in a sense that they were actually used for the production of knowledge on a large scale. It seems that, in these cases, any relation in which the ultracentrifuge played a role could only become lasting if the apparatus was eventually used for the production of scientific results which were considered important by the scientific community. If not, the relation was eventually killed and with it the ultracentrifuge.

The point I want to make here is that the relation between the actor and the artefact, which started as a private relation, can develop to relations between actors in which the artefact has become embedded. A kind of reversal can then take place from a situation in which the artefact is the outcome of an individual actors' actions towards it to a situation that it seems to have become 'leading' for subsequent developments - it starts getting meaning for many more actors which will increase its chances for survival in the long run. I will return to this point later.

Combining SCOT and Networks

We have observed in the preceding sections that the actors had different relations with artefacts and that the artefacts were embedded differently in their relations with other actors. Furthermore, for different actors, different characteristics of the artefact had become hardened. The consequence of this was

that the actors developed quite different notions of what the artefact was. For Svedberg an ultracentrifuge was an apparatus in which sedimentation under high centrifugal forces could be observed optically without convection taking place. Although the same was true for McBain Svedberg disclaimed his apparatus as an ultracentrifuge because Svedberg had also hardened the characteristic that the cells should be located at least 65 mm from the axis of rotation. McBain, after some time even dropped the optical observability as a requirement because, as an outflow of his work as a colloid chemist, he wanted to be able to analyze the separated substances biologically or chemically after centrifugation. For Beams, anything that rotated fast and in which substances could be placed constituted an ultracentrifuge. Both the Svedberg and McBain apparatuses were ultracentrifuges to him as he demonstrated in references to their work. For Pickels an ultracentrifuge was either an apparatus for performing sedimentation experiments (the analytical ultracentrifuge) or an apparatus for the separation of particles from suspensions (the quantity ultracentrifuge). Svedberg held the opinion that the first was indeed an ultracentrifuge whereas the latter was not because no optical registration took place. For the Rockefeller Foundation, Sharples, LKB and Spinco ultracentrifuges were those apparatuses which were used by (bio)chemists and called thus by them. They did not have an independent evaluation of their own of what did and what did not constitute an ultracentrifuge. These observations clearly demonstrate that the actors had quite different views on what an ultracentrifuge was. As I have partly demonstrated already this had important implications for the directions in which the various actors tried to develop them. This is also one of the main points that are emphasised in the *SCOT* approach in technology studies.

In the preceding sections I have identified some patterns in the development of artefacts. These patterns illustrate that a certain degree of order can be found in the contingency. I specifically identified three different patterns of order, viz: (1) patterns in the relation between actor and artefact in the sense of how the actor dealt with the artefact and how the artefact was intended to function; (2) patterns in what the artefact should look like in the sense of what, for the actor, were normal or hard characteristics of the artefact; and (3) patterns in the way artefacts were embedded in the relations between actors. The first two patterns were characterised by putting emphasis on factors that are also stressed in the *SCOT* approach in technology studies, notably that actors develop a way of dealing with artefacts that is characteristic for a larger group, the so-called 'Relevant Social Group' and that this implies that for different actors, belonging to different RSG's, the artefact will mean something different (see Chapter 1). The third pattern puts emphasis on phenomena that are stressed in the *network* approach in technology studies, notably that actors and artefacts are parts of heterogeneous networks which have a dynamics of their own. The actions of individual actors

only marginally influence the patterns of development that can be identified at the level of these networks. These observations therefore suggest that a combination of the SCOT and network approaches can be fruitfully used for characterising the order that can be found in processes of development of technological artefacts. This underlines the point observed in Chapter 1 that these approaches can reinforce each other in the analysis of technological development.⁵

7.2.2 Patterns of Change

Defining Problems - Developing Solutions

When an actor first encounters a problem it is very rarely immediately evident what should be done in order to solve it. For instance, trying to determine the molecular weight of various proteins Svedberg found that egg albumin did not give any noticeable blackening on his photographic plate. This constituted a problem for him because it implied that he could not determine the mass of this protein in the same way he did with other proteins. To him, the problem was serious enough to try and solve. (He could also have concluded that this was just too bad and have moved to a next protein.) The problem, as he encountered it, did not tell him very much yet about how it might be solved. He first made a more precise analysis of the problem. Taking most characteristics of the ultracentrifuge as given and using theoretical knowledge from the field of optics Svedberg reformulated the problem as that egg albumin did not have a sufficient light absorption. Thus the problem was tied up closely to the artefact and what he wanted to do with it. *This close link is important because it determines what can and what can not be seen as a solution to the problem.* For instance, Beams and Svedberg both formulated that they wanted to reach higher values of g with their ultracentrifuge. Both used the same theory, indicating that this could be done using smaller rotors. For Svedberg this implied that the radius could not be made too small because that would affect the resolving power negatively. By contrast, for Beams ultracentrifuges and rotating systems could and should be used in science in general and almost each new achievement had a value in its own right irrespective of what it did to other characteristics of the artefact. As the number of possible different applications were so numerous it would always be of use for some purpose. Thus, Beams set out to reach higher values of g by trying to make the rotor as small as he could, finally achieving over one billion g . For Svedberg, however, such an achievement did not have any meaning for the development of ultracentrifuges.

Thus, actors are guided by particular problem definitions, which are structured by their overall perception of how the artefact should function and by the problem

as it was encountered. Sometimes, a problem definition makes the solution seem obvious. For instance, when Pickels had defined the problem of finding the strongest material for the rotor it was immediately clear *to him* what should be done: make rotors of a variety of materials and find out which one will stand the highest speeds. In other cases, the definition of the problem does not offer immediate access to a solution. When Svedberg decided that he wanted to reach 100,000 g it was quite evident to him that he had to reconstruct the ultracentrifuge but he had no idea of what should be modified. In general, formulating a problem definition is bound up with a process in which the actor tries to develop and test ideas of how the problem might be solved, for instance by drawing upon experience and knowledge, searching the literature, working out ideas on paper, discussing possibilities with others, etc. This process can lead the actor to a concatenation of problems. For instance, when Pickels was seeking solutions for the convection problem, he came up with the idea of using a vacuum chamber in which the rotor should spin. This idea, however, not only promised to solve a problem but also created new ones. For Pickels, on the basis of his knowledge of other rotating systems, using an air turbine drive and a rotor spinning in vacuum implied that he had to use a shaft to connect the rotor and the turbine. This shaft should pass through a gland which, on the one hand, should be completely sealed as to maintain the vacuum while, on the other hand, it should leave some clearance as to facilitate rotation. The 'old' problem of convection was reformulated as the problem of designing a gland with specific characteristics. Next, after he had developed the vacuum arrangement Pickels encountered the problem of an exploding rotor. Making an evaluation of the problem in terms of how the artefact should function Pickels identified two questions explicitly: 1) The speed of the rotor should be so controlled as to prevent explosions and, 2) precautions should be taken in order to minimize the damage in case rotor explosions would still occur. The first led to the development of a reliable method for measuring the speed and the second to using a vacuum chamber of soft metal and a heavy barricade around the whole apparatus. The process of problem-solution concatenations may be stopped when the actor has solved all problems in the sequence. But it may also be stopped without a solution to the original problem. After Svedberg had constructed a first ultracentrifuge he encountered the problem of diffusion for which he saw no way of how it could be solved completely. At a certain time it occurred to him that he could also *use* diffusion in sedimentation equilibrium experiments. This led to the idea of using a new type of ultracentrifuge with new problems connected to it. The original problem had now become part of a solution which, however, also had new problems associated with it.

As part of a search for possible solutions the actor may start to manipulate certain characteristics of the artefact. Modification of the artefact quite commonly

happens in a process in which, on the basis of experience gained during the modification, adjustments will be made because things did not work out exactly as anticipated or because new problems were encountered. Svedberg expected that he would obtain higher speeds with harder steels but when he had constructed a rotor of such material it appeared to explode at lower speeds. So, one more step has to be taken before a modified artefact can solve the actor's problem: it has to be tested in order to demonstrate whether it will actually work in the situation it was intended to work in. If it does, the actor will harden the modified aspect of the artefact as has been observed in a preceding section; if it does not, the actor has a new problem and the whole thing may start anew. In Svedberg's case mentioned above he concluded that the speed problem could not be solved with harder steels and he went to try something else in order to solve the problem. The softer steel subsequently became a hardened characteristic of his artefact and was never questioned again. The actor may also conclude that the problem cannot be solved as Svedberg did in the late 1930s when he tried to develop rotors for extra long cells. That was the point that Svedberg decided that he had developed the ultracentrifuge as far as was possible and stopped developing it further. After manipulating the artefact the actor may also conclude that the alteration does indeed solve the problem. It is only then that the artefact is actually developed in a way that has some chance of survival.

Problem definitions contain elements of the problem as it was encountered by the actor but the problem is also structured by the actor's relation with the artefact. Problem definitions can change but, because of the actor's relation with the artefact, they cannot change arbitrarily. In the development of the relation between actor and artefact certain characteristics of the artefact have become hard which is reflected in the problem definition and in what can and what can not be seen as a solution to the problem. Furthermore, problem definitions can also be influenced by interaction with other actors as will be discussed in the following section.

Interaction Processes

An actor may approach another actor in the expectation or desire that the other actor will react in a certain way. For instance, McBain submitting a grant proposal to the Rockefeller Foundation, hoping they would give him the money he asked for. Or Svedberg, going to the Ljungström Company hoping they would be able to manufacture an ultracentrifuge capable of generating 100,000 g. Such 'offers' may be picked up by the actor addressed but they may also be declined. When Nichols asked Svedberg to modify various aspects of the ultracentrifuge in

order to make it cheaper Svedberg said this would be impossible. Nichols asking Beams to visit him can also be seen as an 'offer' which Beams might have declined but which, in fact, he accepted. I use the phrase 'offer' here because there is a parallel between these situations and situations in which two parties negotiate certain issues, like negotiations between employers and trade unions on labour issues or arms-control negotiations between two countries. In these negotiations offers are being made by one actor which often are reacted upon by the other actor by making a new (counter)offer. This process may continue until some agreement has been reached about what to do or it may be discontinued if after a certain time no such agreement has been found. The parallel with the processes in which artefacts are developed is that there too offers can go back and forth until agreement is reached on the course of action to be taken. Also the interaction may be discontinued if such a course cannot be found or if one actor has no interest at all in what the other actor suggested.

Concerning offers made to 'new' actors we may observe that offers are not made 'blindly' but on the basis of the actor's knowledge of the 'social' and the 'material' world. When Svedberg had defined the goal of reaching 100,000 g he knew that there were actors who had specialised in rotating systems and also that it was bound to cost a lot of money to ask their assistance. Concerning the latter, he knew that there existed private foundations that gave money for promising research. On the basis of this knowledge he submitted grant proposals to the Anderssons Foundation and the Nobel Foundation and he turned to the Ljungström Steamturbine Company for technical expertise. Beams and McBain turned to the Rockefeller Foundation because they knew the Foundation was interested in the development of ultracentrifuges. Beams started developing spinning tops as centrifuges partly because he knew centrifuges were used in many different scientific disciplines. So, the actor usually already had some idea of whom to turn to in order to reach his goal or solve his problem. This knowledge, however, gave no guarantee that addressee would react in the intended way as McBain experienced when the Rockefeller Foundation declined his later requests.

In the early 1930s Nichols and Kraemer at DuPont's Experimental Station became interested in doing sedimentation velocity experiments for which they needed high values of g. Nichols had considerable experience in working with Svedberg's apparatus and on the basis of this he knew that it could do the job. He also knew that Svedberg would be willing to supply it at cost price. However, the problem was that it would be very expensive and that, as they expected, the Company would not be willing to furnish the necessary sum. They therefore embarked upon a course of finding a cheaper way of producing high rotational speeds. In their correspondence with Svedberg they asked his opinion about a number of possibilities like using air-turbines or electrical motors. They also

visited Beams when they learned he had made a very cheap ultracentrifuge. Their offers to Svedberg, however, were declined by him. More than once Svedberg told them that the things they wanted were not possible or that he expected that the modifications, they proposed, would not work. This can be understood by looking at Svedberg's relation with the ultracentrifuge and its hard characteristics. The offers made by Nichols and Kraemer implied that part of these hardened characteristics had to change which, as has been argued before, the actor will consider only if this will solve a problem for the actor that is not considered to be solvable otherwise. In this example there was not even a problem for Svedberg so he declined the offer. The same argument makes us understand why Beams accepted Nichols' and Kraemer's offer of paying him a visit because in his view ultracentrifuges should be used by as many scientists as possible. Here was an offer that perfectly fitted that view, something to grasp with your both hands.

In interaction, offers are transformed by the actor addressed on the basis of the latter's relation with the artefact and the characteristics that have become hardened in the process of working with it. Such a transformation implies that at least some aspect of the offer is picked up by the actor addressed as meaningful that should be reacted upon. For instance, the offer made to Svedberg by K.J. Sommerfeld who wanted to use ultracentrifuges for testing air-raid shelter materials, did not make any sense to Svedberg so he declined it in a two sentence letter; interaction did not even start. In the mid 1930s Sharples decided that they wanted to sell ultracentrifuges. In their view they were the principle manufacturers of all kinds of centrifuges so they should also have this one. In order to build up a new market, they wanted to obtain or control some patents in the field. They obtained a license to the Svedberg/Nichols patent and furthermore Sharples asked Beams to take out a patent on the stabilization scheme. But this offer did not make any sense for Beams who held the opinion that no restrictions whatsoever should be made to the use of scientific instruments. He declined Sharples' offer. So, if the offer does not make any sense to the actor addressed the latter will decline it. If the offer is picked up as something meaningful it will be transformed by the actor addressed, sometimes quite radically so. For instance, in 1938 Sharples offered to give free licenses to scientists in non-profit laboratories for making ultracentrifuges. When Svedberg learned about this he transformed this offer to: somebody is trying to interfere with the right of scientists to make scientific instruments. This is the problem Svedberg subsequently tried to solve and which made him do all he could to prevent Sharples from having his way, finally even threatening to withdraw from the patent if Sharples would go on.

For both actors in an interaction, the problem becomes to find a form of action that will serve the goal of both or solve both of their problems. Sometimes, such action was very easily found. For instance when McBain submitted his first grant

proposal to the Rockefeller Foundation (because he wanted to use ultracentrifuges in his colloid research) the Foundation saw this proposal as a possible way of solving their problem that ultracentrifuges should spread to more laboratories. Simply accepting McBain's offer also served their goal. But in many other cases, there was protracted negotiation and compromise at best. When in the late 1920s Svedberg asked the International Education Board of the Rockefeller Foundation for a \$ 75,000 grant this offer seemed to fit the Foundations goals. These goals, identifying promising research worthy of support, implied that actions taken in order to achieve it were always taken under uncertainty because there was no way to assure that the project would indeed yield what it promised. However, for larger grants they wanted to be more sure that it would. This led them to making a counteroffer to Svedberg which differed from the one he had made to them - they were prepared to give him \$ 50,000 if he would succeed in getting the additional funds from other sources. So, in interaction, a process of making offers and counteroffers may take place before 'definite action' is taken. During negotiation, new problems may crop up. In the late 1930s Sharples offered Bauer to give free licenses to non profit institutions. Bauer informed Svedberg about this which made Svedberg define as a problem that Sharples tried to interfere with the right of scientific institutions to make their own instruments. After some correspondence between Svedberg, Nichols and Sharples, Svedberg decided that he would renounce all rights to any profits arising from the license. This created a new problem for Sharples because he was very anxious to be able to use Svedberg's name in the selling of ultracentrifuges. If Svedberg disclaimed what they were doing, he thought their chances for selling the apparatus would become even smaller than they were already. Sharples assessed that this problem, of Svedberg stepping out, was more important than the problem of patent protection which he had based his first offer to Bauer upon. He therefore decided to drop the matter. Because of Svedberg's offers in reaction to Sharples offer to Bauer, Sharples got a new problem. Sharples wanted to sell ultracentrifuges and he assessed that Svedberg's offer would make that more difficult. Trying to settle the patent situation, rather than solving a problem, created a new, and in his assessment, a more severe one. His final decision to refrain from the policy of giving free licenses solved Svedberg's problem of interference with rights of scientific institutions while it also solved Sharples new problem, developed in the interaction, that Svedberg might drop out. The old problem, he assessed, he just had to forget because it appeared not solvable to him without getting in new, greater problems. So, problem definitions can change in a way very similar to the effects of interaction between actor and artefact. Because other actors also have intentions and strategies, the change in problem definition will often take the form of a compromise, or of cutting losses. The latter is illustrated by the Rockefeller Foundation's reaction to

Svedberg's monopoly. In the early 1930s the Rockefeller Foundation defined the problem that ultracentrifuges should be used in many laboratories which was impossible with the Svedberg machine because it was too expensive. They funded McBain as part of a possible way to solve the problem. When they decided that his approach would not work they redefined their problem as that there was not one single place where Svedberg's results could be verified and that the apparatus should at least spread to some other laboratories. This problem could be solved by them by funding the purchase of the apparatus by Ledingham and Williams.

In 1946, Hanafin approached Pickels, offering to become a consultant to a new company for the manufacture and sale of ultracentrifuges. This offer made sense to Pickels because he also wanted ultracentrifuges to spread. But Pickels also had an other problem. He was getting bored with the work at the Rockefeller Institute because there was not much challenge left in the work he did. Up till then, in Pickels' view, ultracentrifuges were apparatuses that were used by the staff of the Institute for virus research. Although he had displayed an interest in wider applications of the apparatus this had not been his primary concern. Hanafin's offer changed that - now, diffusion of ultracentrifuges became his principal concern. This means that, as a result of Hanafin's offer, things shifted in the relation between Pickels and ultracentrifuges. Hanafin approached Pickels because he wanted to build up new relations with other actors, using an existing artefact. Pickels transformed this offer in the sense that, in order to be able to do so, the artefact should change first. Whether or not actual modification will take place will depend upon a number of other factors that have been described before. In this case it led Pickels to developing the Spinco model-E ultracentrifuge.

Summarizing, in interaction a negotiation process may take place in which offers are made back and forth. In this process, problem definitions may change. However, as has been discussed in one of the preceding sections, problems cannot be changed arbitrarily. What the problem is and what can be seen as a solution to the problem is constrained by the actor's perception of how the artefact should function which is different for the different actors. The problem then becomes to find a common course of action that will fit both actors' perceptions of how the artefact should function.

Detours and Stabilization

In this section I want to make the point that success and failure are quite ambiguous concepts which do not yet tell us very much about the development of artefacts. For instance, biochemists now may agree that Svedberg built a very successful ultracentrifuge, but if it had not been for Pickels and Spinco maybe

everybody would have forgotten about ultracentrifuges altogether. Success and failure leave a lot of the story untold. The preceding sections demonstrate that technological development is an interactive process in which many things may happen and in which success cannot be determined unambiguously. Many things can change, like relations between actors and artefacts, relations between actors, problem definitions, artefacts, etc. Success is not something that can be easily identified which also makes it problematic to trace factors that enhance success. There is a large discrepancy between the historical reconstruction made in this study and the 'success stories' in the usual potted histories we find in contemporary books on ultracentrifugation. These books may contain a historical review of the development of the ultracentrifuge in which Svedberg is always presented as the 'Father of the Ultracentrifuge'. Beams and Pickels are only rarely mentioned while nobody seems to remember McBain.⁶ This study shows that present day ultracentrifuges have little to do with the ones Svedberg was using. Of course, there is a route leading from the things Svedberg did to the things contemporary researchers do with ultracentrifuges. This route, however, is not a straightforward one but one with many detours in which many actors played a role.

In his own days, Svedberg was celebrated as the man who produced important knowledge on proteins by using ultracentrifuges. However, if we take a look at how the ultracentrifuges Svedberg worked with actually spread over the world the picture becomes somewhat less glorious. Four of them went to other laboratories through Svedberg's own direct mediation, a few others were sold by LKB and that was it. Although some of them were still in use after several decades this can not nearly account for the present day activity in the field of ultracentrifugation. There is a link between Svedberg's scientific investigations and present ultracentrifugal investigations but the link between the two was not constituted by Svedberg's apparatus. Svedberg did succeed in stimulating other people's interest in ultracentrifuges but it was well known among his scientific colleagues that the apparatus was extremely expensive. Furthermore it was obvious from Svedberg's publications that it was not easy to operate the oil-turbine ultracentrifuge which is also likely to have deterred potentially interested researchers. Some people at LKB thought that the apparatus should be redesigned in order to increase the chances for selling it but they dared not do so against Svedberg's will. If it had not been for Pickels, ultracentrifuges might never have become as popular as they eventually did. When he decided to cooperate with Hanafin in the commercial production and manufacture of ultracentrifuges he started out by concluding that this was bound to become a failure if he would try to sell the machines as they were. He decided that the apparatus should first fulfill certain conditions like, easy to operate, be fool proof, be easy to maintain, etc. It led him to a number of changes compared to the apparatus he made at the IHD. But also this apparatus did not sell at a rate

high enough for commercial production. It remained a complicated and expensive machine with high thresholds for potential customers. Pickels' next step was to manufacture preparative ultracentrifuges which Spinco was able to sell at a high rate from the onset. This created some breathing space for selling analytical ultracentrifuges as well which, after two decades, led to a situation in which thousands of researchers all over the world worked with ultracentrifuges.

As success and failure are such ambiguous concepts they should not be taken as the explananda, as what should be understood about processes of technological development. I prefer to analyze these processes in terms of growing and diminishing degrees of stabilization and apply this concept to various characteristics of the development process, like artefacts, relations between actors and artefacts, patterns of interaction, etc. Stabilization means that characteristics have become normal for the actors and are not easily questioned again. This may happen for individual actors, as in the case of hardening characteristics of artefacts, but it may also happen at a more collective level, for instance patterns of interaction as observed in the preceding sections. The story would then become that, what stabilized in the Svedberg case, were the scientific results he obtained with the ultracentrifuge. This implied that the ultracentrifuge became embedded in a stable pattern of interaction between Svedberg and his scientific colleagues. This increased the chances of survival of the ultracentrifuge but it remained vulnerable as it was not the apparatus itself, that formed the basis of this interaction, but the results obtained with it. Although this embedding did stimulate other actors to become interested in using ultracentrifuges, the thresholds for actually doing so appeared very high. Everybody knew that Svedberg had invested tens of thousands of dollars in it and that it was a complicated machine to operate. Somebody, not having any experience with it, would therefore not easily embark upon a strategy of trying to obtain one. Only some researchers who actually worked with the apparatus at Upsala eventually obtained one themselves. Even when Pickels had constructed the fool-proof, easily operable Spinco machine these thresholds appeared to be very high. They could only be gradually lowered by the demonstration that more and more people could work with the apparatus. That would explain that when Spinco marketed them they were only able to sell them at a slow, though steadily increasing rate. The effect of this was that a new stable type of interaction developed between Spinco, and later also other companies, and biochemists as the users of ultracentrifuges. Contrary to Svedberg's relations with his scientific colleagues, now the ultracentrifuges themselves were embedded in these relations. This made it possible for the artefact to stabilize on a collective level. A large group of actors had obtained a shared view on the apparatus that certain characteristics were OK as they were and should not be changed.

7.3 DYNAMICS OF THE DEVELOPMENT OF ARTEFACTS

In the preceding sections I have identified a number of patterns in the processes in which ultracentrifuges were developed. These patterns can be understood and embedded in a more encompassing whole by postulating in this section a model for the analysis of the development of artefacts. This model is made plausible by the empirical evidence presented in this study and is in agreement with insights that have been developed in the recent sociology of technology (see Chapter 1). Concerning the patterns identified in the preceding section I will now distinguish two different types of patterns, viz:

- 1) Patterns at the level of *search processes* of actors: how do they try to realise goals and solve problems? what does that imply for the development of artefacts?
- 2) Patterns at the level of *interaction* in which what the actor does is also influenced by what other actors do. What role does the artefact play in interaction and what does that mean for its development?

This distinction is reflected in the subsequent sections.

Search Processes of Actors

In order to analyze how actors define problems and try to develop solutions to those problems I will now propose to use, what I will call, the *definition-artefact spiral (DAS)* (figure 7.1). The DAS is intended to analyze the development of artefacts by focussing on the individual actor. When there is a discrepancy between an existing situation and a desired situation, this constitutes a problem for the actor. The phrase 'existing situation' is to be read as referring to the situation from the actor's point of view. So one should attribute to each actor a *definition of the situation (DS)*, which encompasses the perceived problem. An actor's DS at a certain time is the result of preceding interaction, both with other actors and with artefacts. Four distinct elements of the DS, each of which are both the result of preceding developments and the antecedents of further development, account for the structuring of the problem. These four elements are the relation between the actor and the artefact, the social world, the artefact, and knowledge and skills. I want to stress that these elements describe the situation as they are defined by the actor. For example, they denote *how the actor sees* the social world, what knowledge and skills the actor has or how the actor sees the artefact. Concerning the latter this means that the hardened characteristics of the artefact make up this element of his or her DS. The outcome of the DS, applied to a particular situation, is a *problem definition* which is structured by the relation between actor

and artefact and by the characteristics of the artefact that are hardened by the actor as well as by knowledge and skills the actor has and by the way the actor wants it to function in relation with other actors (see section 7.2.2).

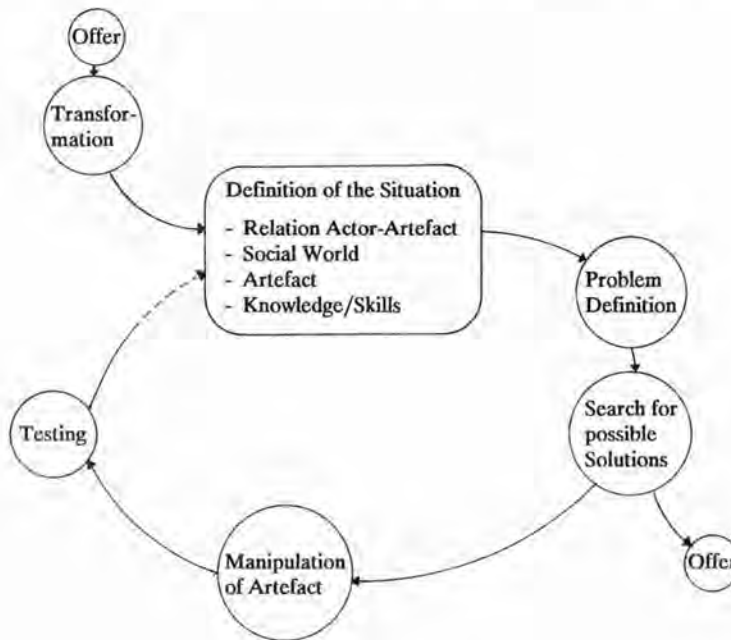


Figure 7.1

Definition-Artefact Spiral. The dashed line is meant to indicate that this figure does not represent a closed loop. A development, triggered by the definition of the situation at a certain time, leads to minor or major changes in the definition of the situation at some later time which makes the model resemble a spiral rather than a loop.

I demonstrated in the preceding sections that all elements of the DS can change in the course of time: characteristics of artefacts can become hard; actors can start to do new things with the artefact; they may start new relations with other actors or discontinue existing relations; they may obtain new knowledge and skills; etc. Just as in the case of the artefacts, I will now propose that the other elements of the definition of the situation can also have 'hard' characteristics for the actor. For instance, the actor's knowledge may range from unreliable to certain. The same goes for the social relations. Some may be beyond question, like in our studies the notion that scientific research is funded to a large extent by private foundations. Other relations the actor may explicitly seek to change like trying to build up *a priori* a market for the sale of ultracentrifuges. Essential is, however, that I do not *a priori* assume that the other elements are causes and artefacts are effects.⁷

The definition-artefact spiral is called a spiral because after each 'stroke' something has changed, like the artefact, other elements of the definition of the situation or a problem definition. I want to stress, that by using the notion of a spiral, I do not mean to suggest that the development has a specific direction. As I have indicated in section 7.2 it is more appropriate to see technological development as an area rather than a route.⁸ The DAS represents both change and continuity. Everything can change in principle but not everything can change all at once. This is because an actor's DS is linked to the DS-es of other actors in networks (see below). As in this study I have focussed primarily on the developers of artefacts, modifications of the artefacts were the changes that occurred most frequently. These modifications were applied in an attempt to solve problems. This part of the development is not simply a matter of finding a solution to the problem. It has been shown that the problem itself often underwent considerable change as it was structured by an actor's DS. And structuring problems also implied structuring possible solutions. If subsequently modifications were applied and tested often this did not simply solve the problem. Sometimes it solved nothing and only created new problems. More frequently it solved part of the problem and also created new ones. A stroke in the definition artefact spiral often already carried the seeds for the next stroke.

The definition-artefact spiral is defined at the level of actors but incoming and outgoing offers may be hooked up to the spirals of other actors and thus the spiral will make it possible to study and describe the interaction between actors as well. For the various actors described these interactions had a different character. Although the four actors, which I emphasised most in this study, all were developers of ultracentrifuges, each of them developed it in a different way. The problems, each of them tried to solve, originated from differences in their definitions of the situation and, because of these differences, there were also differences in what could be seen as a solution to the problem. Svedberg was both the user and the developer of his ultracentrifuges. The developer, however, was subservient to the user. For instance, for the developer an important consideration is often that things should be easy to make (cf. Beams and Pickels) but if Svedberg's anticipated use indicated that it could only be done the hard way in developing then it was done the hard way. McBain was also both developer and user with emphasis on the user. For both, the problems that made them develop their ultracentrifuge originated from using it in their own scientific research. Both unilaterally decided what was problematic and subsequently tried to solve the problem themselves. For McBain, this approach was successful in the sense that it enabled him to do the experiments he wanted to. But, for the scientist the problem also is to get the scientific results accepted. In this respect, except for a short relation with the Rockefeller Foundation, McBain did not succeed in getting any

positive response to his offers. Svedberg, however, was highly esteemed as the great man who developed the ultracentrifuge.

In the Beams case, most of the problems he tried to solve emerged in his own DAS. Because of his definition of the situation almost anything could be seen as a solution. On the other hand he was also sensitive for problems individual scientists had with his apparatuses. He took over the problems as they were defined by them with hardly any redefinition. When Pickels started redesigning ultracentrifuges at Spinco he did so by trying to anticipate problems his potential clients might have with the apparatus. To this end he made use of his own experience in working with the apparatus and of information Hanafin gathered by talking to potential customers. So the potential customers themselves, although in an indirect way, had an influence on what the apparatus came to be.

In the McBain and Svedberg cases there was no way that potentially interested fellow scientists influenced the development. They decided unilaterally what the problems were and interested others would have to adapt themselves to the apparatus as it was. In the McBain case nobody tried to; in the Svedberg case many showed their interest but only few succeeded in adapting themselves. Svedberg usually made his offers to others as a user of the ultracentrifuge - he offered scientific knowledge, not apparatuses. In the Beams case, he also usually unilaterally decided what was problematic about the ultracentrifuge. Beams made his offers to others as the developer of ultracentrifuges but what he offered were not artefacts but only descriptions of artefacts. His potential clients had to make the apparatuses themselves or have them made by a machinist. Especially for the more complicated versions, like Beams' vacuum type sedimentation ultracentrifuge, this appeared problematic for potential users and, because of the amount of work that went into it, would be rather expensive. Like in the Svedberg case, scientists interested in obtaining Beams' ultracentrifuges also in general had to adapt themselves to the apparatus as it was or undertake further development themselves. Hardly anyone is known to have actually done so and only a small number of biochemists succeeded in obtaining the apparatus by buying an ultracentrifuge made by Beams' instrumentmakers. Only Pickels succeeded in making offers in such a way that ultracentrifuges became used by large numbers of scientists. He offered the ultracentrifuges themselves after he had tried to adapt them to his customers as far as he thought possible. Callon and Law have argued that actors need a certain 'private space' in which they can make mistakes before the artefact is exposed to other actors.⁹ This study shows that such a period of uncriticized manipulation of artefacts should not last too long. Otherwise a greenhouse-plant is likely to be constructed that will not be able to survive the harsh circumstances in the 'real world'.

Stable Patterns of Interaction

In the preceding sections I observed that more or less stable patterns of interaction can develop between actors. Svedberg built up long-lasting relations with his scientific colleagues, the Rockefeller Foundation and the Ljungström Steamturbine Company. Beams developed a stable pattern of interaction with 'scientists in general' while McBain had a long lasting relation with colloid chemists and a relation with the Rockefeller Foundation that lasted several years. Spinco built up stable relations with their customers. The stability in these relations can be found in the offers, in the transformation of the offers and in the way the offers were responded to. This implies that in such interactions negotiation is routinised. The interaction has become more or less like a routine for both actors (figure 7.2.b). For the individual actor this means that the responses of the actor addressed have become more or less predictable and a stable pattern of interaction then constitutes a kind of knowledge that can be built upon.

A stable pattern of interaction can only develop and continue if certain characteristic features, that structure the interaction, are not questioned anymore. In other words, certain characteristic features have become normal or hard for the actors. A stable pattern implies that for both parties the interaction has certain benefits or desirable effects. As in the case of hardening of characteristics of artefacts this has the effect that certain characteristics of the interaction will be hardened. Thus, a stable pattern of interaction tends to reinforce itself. As in the case of hard characteristics of artefacts actors will not easily question it. The interesting point about hardening in interaction is that this hardening takes place at a collective level; it applies to both actors in the interaction. Depending upon what the interaction is about, this collective hardening may also apply to the artefact.

How can stable patterns of interaction come about? If an actor makes an offer to a 'new' actor, unless the offer immediately fits the other actor's definition of the situation, negotiations will follow. These negotiations can only lead to agreement if there is a certain flexibility in the DS and the problem definitions of at least one of the actors. Certain characteristics should *not* be hard. On the other hand, for the interaction to develop to a stable pattern, the interaction should be structured by a continuous interest of both actors. In other words, the offers should also be structured by certain hard characteristics of both actors' DS. Otherwise the interaction can never become lasting. Whether such a stable pattern will indeed develop depends upon the content of each actor's DS and also upon a variety of other factors. But a certain degree of compromise over private hardness should be possible to arrive at collective hardness. In the case of McBain and Svedberg too many characteristics of the artefact were hard in order to make it

stable on a collective level. In the Beams case it was just the opposite. Too many characteristics of his ultracentrifuge were soft for arriving at a collective hardness with the protein chemists that were interested. As soon as he had solved a problem he might 'drop' the solution again and go and modify something else. Only in the case of developing ultracentrifuges for uranium enrichment he held on to a specific application, hardening characteristics that did a good job for him and only this ultracentrifuge finally gained widespread importance. In the case of ultracentrifuges for sedimentation experiments only Pickels appears to have found the proper balance between hardening and being flexible. Only his Spinco ultracentrifuges finally spread to a large number of laboratories.

Summarizing, in stable patterns of interaction different actor's definitions of the situation have become linked and embedded in the interaction. Certain characteristics of those DS-es have become hard on a collective level and are not easily questioned again. These hard characteristics subsequently become the starting point for further development. If one of these hard characteristics concerns the artefact we may then say that the artefact has become 'leading' for further developments, i.e. that in subsequent developments these characteristics are taken as given. This situation should be distinguished from the situation to which the Definition-Artefact Spiral was applied. In these situations an individual actor's DS was more or less 'leading' in the development.

Artefacts embedded in Networks

In this section I want to make the point that artefacts can survive in two ways. Either by being fed continuously locally or by being situated in many different locations which increases the chances that there is always someone who feeds it. In either case the artefact has to be embedded in stable patterns of interaction. I propose to use a network approach to analyze the situations in which artefacts have become embedded in stable patterns of interaction between actors. In these situations we do not need to focus on an individual actor's DS but rather on the object of interaction between the actors. The actors constitute the nodes of the network while the links represent the object of interaction that flows between the actors (figure 7.2.c). I will characterise the network by the object of interaction. For instance, Svedberg was an actor in a protein-chemistry network in which the prime object of interaction was scientific knowledge. A continuous flow of new knowledge kept the network going and an established body of accepted (hard) knowledge was the collective hard characteristic that all actors further built upon. The Rockefeller Foundation was also an actor in that network as they played an important role in stimulating the process of knowledge production in specific

directions. McBain was an actor in a colloid chemistry network which in the early decades of this century also comprised protein chemistry. However, during the 1920s and early 1930s the two fields became more and more separate and it is therefore more appropriate to speak of an independent protein-chemistry network in which Svedberg became an actor.¹⁰

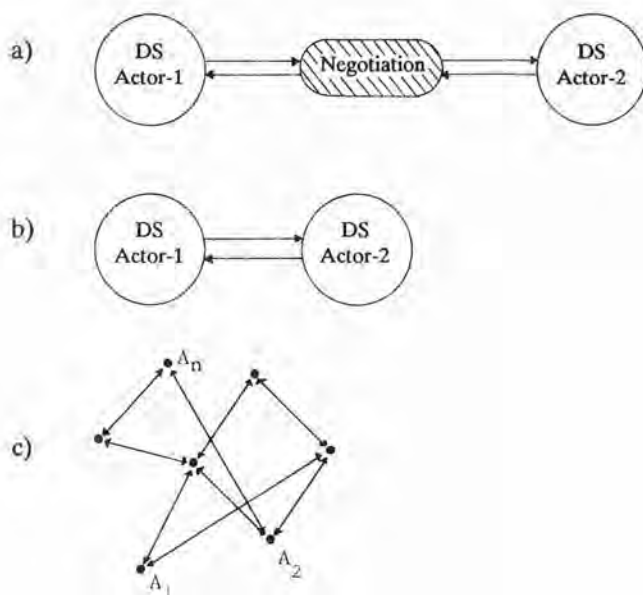


Figure 7.2

Different patterns of interaction. At a) the interaction is not stabilized. In negotiation offers are being made and transformed. Depending upon the result of the negotiation certain characteristics of the artefact may be modified. At b) the interaction has become stabilized. Transformations have become like a routine. The situation can be characterised by the object of interaction between the actors, e.g. scientific knowledge, money, artefacts. At c) many of the patterns in b) have become interlinked in a network. The actors constitute the nodes of the network which is characterised by the subject of interaction, e.g. a protein chemistry or ultracentrifuge network. Individual actor's actions only marginally influence the network as a whole.

Beams was an actor in a physical chemistry network but, after he had developed his first ultracentrifuge, he also tried to establish contacts with other scientific networks. He was partly successful in doing so but not on a basis stable enough for a new network to originate. Although ultracentrifuges played a role in these networks I will *not* call them ultracentrifuge networks. Ultracentrifuges played a role in keeping the interactions in the various networks going but they were not, except in a limited number of individual cases, the object of interaction. Some attempts were made to establish such a network, notably by Sharples and LKB, but both attempts failed. It was not until Spinco marketed them that an ultracentrifuge network came into being. I therefore suggest to distinguish two types of networks

in which artefacts are embedded. In the one type, artefacts are the *object of interaction* between the actors. In these cases, the artefacts can stabilize and become hard on a collective level, as was the case with the Spinco ultracentrifuges. The artefacts themselves are part of offers and go from one actor to another. These networks I will call *artefact networks*. In the other type of networks, which I will call *user-audience networks*, artefacts are primarily used for enabling the actor to make offers. E.g. Svedberg used the ultracentrifuge for producing scientific knowledge which he fed into the protein chemistry network. For Svedberg as a user of ultracentrifuges the protein chemists can then be seen as an audience, hence the name user-audience network.

Whether the artefact is embedded in an artefact network or in a user-audience network has important consequences for its chances for survival. In the latter it will have to be 'fed' continuously by the actor (or few actors) it is depending upon. The actor will only do so if he or she sees the artefact as an important resource for making offers in interaction. This was the case for Svedberg and McBain. However, in the Svedberg case his offers were picked up and responded to positively by his colleagues whereas in the McBain case they were not. So, Svedberg continued feeding his ultracentrifuge whereas McBain let it die after ten years of irregular nourishment. The fact that Svedberg's ultracentrifuge was embedded in a network increased its chances for survival as this embeddedness stimulated Svedberg to continue working with it. Nevertheless, also in this situation the ultracentrifuge remained vulnerable. It remained dependent on the whims of a small number of individuals. About half a dozen spread to other laboratories but each of them died a peaceful death when the respective scientist stopped working with it. In these cases the artefact was embedded in a network but the ultracentrifuges themselves did not flow. Knowledge was the object of interaction and knowledge was hardened in that interaction. For most actors in the network, the ultracentrifuges remained soft. In this type of situation, as compared with an artefact network, the artefact can be changed more easily. The individual actor's definition of the situation is still 'leading' for its development. This also implies that the artefact can more easily be killed.

In an artefact network, the artefact itself has become the object of interaction that flows through the links between the actors. The artefact can then become hardened on a collective scale. Its chances of survival are greatly enhanced as it starts living in many different locations and is embedded in a network in a way that it has many attendants to feed it. As networks tend to reinforce themselves and as the artefact can, because of its collective hardness, become 'leading' in subsequent developments, it is in such situations that artefacts can become 'big and strong'.

7.4 DISCUSSION AND CONCLUSION

I have shown that in the early stages of technological development an individual actor's definition of the situation is the primary source of change in the development of artefacts. Subsequently elements of an actor's DS, including the hard characteristics of the artefact, can in interaction become shared with other actors. This lends support to the SCOT approach in technology studies where actors are seen as representatives of 'relevant social groups' (RSG). The key requirement for an actor to belong to a specific RSG is that all actors in that group share the same set of meanings attached to a specific artefact.¹¹ In terms of the definition-artefact spiral an RSG would be a group of actors that shares a definition of the situation. Starting with individual actors we can then use the DAS to analyze how a DS has become shared, i.e. how a relevant social group has come into being. It may then appear that actors already shared certain characteristics of the DS and that in interaction with other actors and with the artefact they developed a shared definition of the artefact. For example, Ledingham, Peters and Williams were all actors in the protein chemistry network and shared with Svedberg the notion that ultracentrifuges should be seen as instruments in protein research. In interaction with Svedberg they also developed the idea, sometimes after first having asked for modifications, that the ultracentrifuge should be taken as it was developed by Svedberg. Once an RSG has come into being it is more fruitful to analyze the subsequent developments on a more collective level. The fact that an actor's DS is being shared with other actors makes it less likely that the actor will suddenly change his or her definition of the situation and try to develop the artefact according to this new definition or forget about the artefact because it has lost its meaning. On the other hand we have to be aware that developments may start that will make it necessary to focus again on the individual actor. Then the DAS can be used to follow this actor in order to trace developments that, eventually, may even lead to the disintegration of the relevant social group.

In the SCOT approach the development of artefacts is studied by focussing on problems actors have with respect to the artefact. Actors will focus their activities primarily on trying to develop solutions to those problems. Such an approach can be quite fruitful as has been demonstrated in the studies of Pinch and Bijker,¹² Bijker,¹³ and Elzen.¹⁴ In these studies the emphasis is on understanding why something constituted a problem for the actor rather than on understanding how solutions were sought. In this study I have focussed primarily on the developers of artefacts and can therefore shed more light on the search for solutions. I have demonstrated that tinkering and trial and error strategies play an important role in these processes. Nevertheless, patterns can be found by noting that, for the actor,

certain characteristics of the artefact are more amenable to change than others which I described by using the concept of 'hardening' of characteristics of artefacts. A way of analyzing how actors seek solutions to problems is then to identify characteristics of artefacts that have become hard for the actors. That will help us understand why certain routes of development, that are easily embarked upon by one actor, may trigger resistance by another actor. Hardness can also help us understand the range within which problem definitions can change in interaction. This co-determines the possibilities for finding a course of modification of the artefact that will satisfy both actors in the interaction. Thus, using the concept of hardness will help us understand why solutions for problems are more likely to be sought in one direction rather than in another and, therefore, why certain actors develop artefacts in one direction while other actors can choose quite a different course.

Callon, Latour and Law use network approaches for the analysis of the developmental processes of artefacts.¹⁵ In these approaches the focus is on the individual actor. They analyze how actors try to build networks in which they themselves become indispensable. As these authors emphasise, the actors in the network are no fixed, unchangeable entities. They may change continuously under the influence of changes in the network. But in these network approaches no tools are offered to analyze in detail where these changes come from, why certain changes are possible without causing the disintegration of the network while in other situations it may appear impossible to sustain the network. Attributing to each actor a definition of the situation would facilitate such an analysis. The definition of the situation is the result of preceding interaction in the network under study and in other networks in which the actor is an entity. In these interactions certain characteristics of the DS have become hard which implies that they are hardly negotiable, or, in Callon, Latour and Law's vocabulary, 'translatable'.¹⁶ It is quite unlikely that a network can be built up or maintained if for a considerable number of actors this would imply the translation of hard characteristics of their definition of the situation.

Callon, Latour and Law make no distinction between human and non-human actors. The network builder has to translate each of them in order to create a network and each of them is a potential source of trouble because they may revert their actions and drop out again. Both human and non-human actors can constitute nodes in the network. This study shows that there are some interesting parallels between how actors manipulate artefacts and how they negotiate in interaction with other actors. In both cases their offer or manipulative effort is guided by a problem definition and an 'educated guess' of what the result of the action might be. The action may result in a counter offer or in the performance of a modified

artefact. But both will be evaluated in terms of the actor's definition of the situation which sets the (hazy) boundaries for what can and what cannot be considered a solution to the problem. But there are also important differences between human and non-human actors which, in my view, make it necessary to make a distinction between the two. I have shown that it can be fruitful to analyze the development of artefacts by attributing to each actor a definition of the situation. This definition of the situation is both the result of preceding interaction and the antecedent of subsequent interaction. It reflects that actors attribute a meaning to the social and material world which they are part of. This makes it possible to analyze both how actors try to manipulate their environment and how they are manipulated and changed themselves. The analyst can only attribute to non-human actors an 'incentive' for manipulating their environment by assuming that material objects have an independent status of their own. But it was precisely by not doing so, by being impartial to the truth or falsity of scientific claims, that social scientists have been able to demonstrate how scientific facts are being constructed.¹⁷ In the sense of being able to attribute a meaning to what is happening in their surrounding world it thus is necessary to make a distinction between human and non-human actors. This does not have to imply, as I have already indicated, that the non-human actors slavishly do what human actors expect them to do. But it is more fruitful not to ask why the non-human actors do what they do (let 'our' human actors worry about that) but on how the human actors react to what the non-humans do and how the humans try to make the non-humans obedient. What we can observe is that human actors do make a distinction between human and non-human actors. It can further our insight in the development of science and technology to ask why they do so and how this affects subsequent developments.

I have shown that the combination of a number of detailed case studies of technological development can be fruitfully used for developing a better sociological understanding of the development of artefacts. Based on patterns identified in the various cases I have postulated a model of analysis, the *definition-artefact spiral*, that can be used for identifying the relevant factors in the early stages of the development of a new artefact. By attributing to each actor a *definition of the situation* the model makes it possible to analyze how the artefact is modified by focussing how problems are defined and how solutions to the problems are sought.

In interaction, an individual actor's definition of the situation will be influenced by other actors. These interactions can become stable which makes it also possible that artefacts become stabilised on a collective level. Stable patterns of interaction can then be analysed in terms of networks in which the artefacts have become

embedded. The artefact has gained meaning for many more actors which makes it harder to change it, especially if the artefact itself has become the object of interaction. An individual actor's actions towards the artefact then only marginally influences the development as a whole. Because of the embeddedness, many actors take the artefact for granted as it is which has the effect that the artefact has become 'leading' for subsequent developments. It is in these situations that artefacts can become 'big and strong'.

The definition-artefact spiral fits and can be seen as an addition to the new approaches in technology studies. It can be used to analyze how, in terms of the SCOT approach, 'relevant social groups' come into being, remain stable, and may eventually disintegrate again. Within a network approach it can be used to analyze why certain translations are easier to make than others.

Notes

1. Also Spinco started manufacturing a new model when their first analytical ultracentrifuge did not sell.
2. We might also not have the right sources which could demonstrate that the actor has been explicit about certain characteristics.
3. The use of this phrase is inspired by Ed Constant's phrase 'presumptive anomaly' which indicates that an actor presumes that a certain characteristic of an artefact, at some future date, will be seen as a barrier to further progress. Actors may then focus their manipulative effort on developing an alternative to this characteristic. See Constant (1980). This contrasts with the 'presumptive normality' used here which indicates those characteristics the actor does not seek to change.
4. See Fujimura (1987).
5. That these approaches reinforce each other is also implicit in the argument in Bijker, Hughes and Pinch (1987), pp.9-15 (introduction to Part I) and pp.107-110 (introduction to Part II).
6. See e.g. Bowen and Rowe (1970); Lewis and Weiss (1975).
7. As, in this study, I am primarily interested in the development of artefacts I have discussed the hardening of characteristics of artefacts in considerable detail. With respect to the other elements I want to use the scheme as a heuristic device that enables me to trace the relevant aspects for each actor in a rather loose way. Although all elements can change I am more precise in discussing changes in artefacts than in discussing changes in, for example, knowledge. Scholars, being more interested in the latter, would choose to follow that path more precisely and discuss the development of artefacts more loosely. Bringing the two together might further our insight in the development of both but that would be far beyond the scope of this study.
8. I have also considered using the notion of 'cycle' in order to avoid this misunderstanding but I think that the notion of a spiral reflects change more appropriately.
9. Callon and Law (1987).
10. Maybe Svedberg's initial results on the mono-dispersity of proteins were an important stimulus for this separation. A further investigation in the development of protein chemistry would be needed to demonstrate the plausibility of this possibility.
11. Pinch and Bijker (1984), p.414.
12. Pinch and Bijker (1984 and 1987).
13. See e.g. Bijker (1987a).
14. Elzen (1985 and 1986).
15. See e.g. Callon (1980a); Callon and Law (1987); Latour (1987).
16. See for the concept of translation e.g. Callon (1980b and 1986).
17. See e.g. Latour (1987).

Samenvatting

WETENSCHAPPERS EN ROTOREN

DE ONTWIKKELING VAN BIOCHEMISCHE ULTRACENTRIFUGES

In deze studie wordt de historische ontwikkeling van een aantal biochemische ultracentrifuges beschreven. Tegenwoordig zijn er twee belangrijke toepassingen van ultracentrifuges, te weten voor de commerciële productie van verrijkt uranium en voor wetenschappelijk onderzoek aan een brede variëteit van biochemische substanties. Hoewel deze toepassingen weinig met elkaar te maken lijken te hebben suggereert de naam van het artefakt dat er gemeenschappelijke wortels zijn. De ontwikkeling van ultracentrifuges vormt daarmee vanuit techniek historisch perspectief een interessant object van onderzoek. Het eerste doel van deze studie is het beschrijven van die geschiedenis.

Een tweede doel is het verwerven van een beter inzicht in de ontwikkeling van artefakten door het opsporen van karakteristieke verschijnselen en meer algemene patronen in processen van technologische ontwikkeling. Deze patronen zijn geïdentificeerd door de ontwikkelingsprocessen van de verschillende ultracentrifuges met elkaar te vergelijken en daarin verschillen en overeenkomsten op te sporen. Er zijn op het gebied van het techniekonderzoek de laatste jaren een aantal benaderingen ontwikkeld die zijn gericht op het verwerven van sociologische inzichten in processen van technologische ontwikkeling. Deze benaderingen worden in *hoofdstuk 1* kort besproken omdat ze mij hebben geïnspireerd gevoelig te zijn voor bepaalde aspecten van technologische ontwikkeling hetgeen wordt weerspiegeld in de wijze waarop de ontwikkeling van ultracentrifuges is geanalyseerd en beschreven. Deze benaderingen betreffen de systeembenadering, de netwerkbenadering en de sociaal-konstruktivistische benadering.

In het historische deel van de studie wordt de ontwikkeling van een aantal ultracentrifuges beschreven. Ultracentrifuges voor uraniumverrijking worden nu in een aantal landen gebruikt, met name de Duitse Bondsrepubliek, Nederland, het

Verenigd Koninkrijk en Japan. Dit verrijkt uranium wordt vervolgens gebruikt als splijtstof in kernreactoren. Hoewel de ontwikkeling van deze ultracentrifuges vanuit techniek historisch perspectief zeer interessant zou zijn wordt zij slechts summier besproken en heeft deze studie vrijwel uitsluitend betrekking op de ontwikkeling van biochemische ultracentrifuges. De belangrijkste reden daarvoor is dat de mate van gedetailleerdheid, die in deze studie wordt nagestreefd, betekent dat de ontwikkeling van ultracentrifuges voor uraniumverrijking een onderwerp op zich zou vormen. Niettemin zal ik laten zien dat beide ontwikkelingen gemeenschappelijke wortels hebben en zal ik aangeven waar de beide ontwikkelingen verschillende takken aan een zelfde stam zijn geworden.

Hoofdstuk 2 beschrijft de ontwikkeling van ultracentrifuges door de Zweedse chemicus Theodor Svedberg die in het begin van deze eeuw was geïnteresseerd in het bepalen van de grootte van colloïdale deeltjes in een oplossing. Een belangrijk instrument in dat onderzoek was de in zijn eigen laboratorium ontwikkelde sedimentatiebalans waarbij gebruik werd gemaakt van het verschijnsel dat colloïdale deeltjes in een oplossing onder invloed van de zwaartekracht langzaam naar beneden zakken. In een poging de nauwkeurigheid van de methode te verhogen kwam hij vervolgens op het idee één van de konstanten van zijn methode te beïnvloeden, te weten de zwaartekracht. Daarvoor wilde hij centrifuges gebruiken waarin krachten konden worden opgewekt die velen malen groter zijn dan de zwaartekracht van de aarde. Na het overwinnen van een groot aantal problemen slaagde Svedberg erin dit idee tot een praktisch bruikbare experimentele methode uit te werken en de deeltjes bloot te stellen aan krachten tot 5.000 g (5.000 maal de aardse zwaartekracht). In analogie met de ultramicroscoop en de ultrafiltratie methode noemde hij het apparaat ultracentrifuge. Svedberg gebruikte dit nieuwe apparaat voor het bepalen van de distributie curves van zowel anorganische colloïden als van eiwitten. Toen hij aldus hemoglobine onderzocht leek het tot zijn complete verrassing of alle deeltjes dezelfde grootte hadden en dat dit eiwit daarmee een wel-gedefinieerd molecuul zou kunnen zijn. Hij vond echter dat zijn methode niet nauwkeurig genoeg was om daarover definitieve uitspraken te kunnen doen. Daartoe werd een nieuwe ultracentrifuge ontwikkeld, die werd aangedreven met olie turbines, waarmee een veld van 100.000 g kon worden gegenereerd. Op grond van experimenten met deze nieuwe ultracentrifuge konkludeerde Svedberg dat hemoglobine inderdaad een monodispers eiwit was. Vanaf dat moment werd het onderzoek in Svedbergs laboratorium vrijwel uitsluitend gericht op de verdere studie van eiwitten.

Svedberg was een zeer gerespekteerd wetenschapper en in 1926 werd hem op grond van zijn gehele wetenschappelijke werk de nobelprijs chemie toegekend. Dit vergrootte zijn aanzien verder en stelde hem tevens in staat fondsen voor verder

onderzoek te verwerven. Een belangrijk deel daarvan werd besteed aan de verdere ontwikkeling van ultracentrifuges waarbij hij vooral was geïnteresseerd in het vergroten van het veld dat met de centrifuge kon worden gegenereerd. Voor vrijwel ieder onderdeel werd naar een optimaal ontwerp gezocht, b.v. vorm van turbines en turbine kamers, wijze van insputting van de olie, lagering, gebruikt soort olie, balancerings van de rotor, etc. Na ruim tien jaar ontwikkelingswerk besloot Svedberg in 1937 dat hij zijn ultracentrifuge zo ver had ontwikkeld als technologisch mogelijk was. Svedberg zelf bleef met het apparaat werken tot zijn emigratie in 1949. Het eiwitonderzoek werd daarop door zijn opvolgers voortgezet en pas in het midden van de jaren zeventig, een halve eeuw nadat het oorspronkelijk was ontwikkeld, werd deze ultracentrifuge buiten gebruik gesteld.

In *hoofdstuk 3* wordt een tweede lijn van ultracentrifuge ontwikkeling beschreven die in gang werd gezet door de Amerikaanse fysicus Jesse W. Beams. Beams was geïnteresseerd in optische verschijnselen waarbij hij in zijn onderzoek gebruik maakte van snel roterende spiegels die waren gemonteerd op een met perslucht aangedreven konische tol van 1 à 2 cm diameter. Vanaf 1930 ging Beams deze tolleren hol maken waardoor ze als een kleine centrifuge konden worden gebruikt. Vanwege de zeer hoge snelheden die daarmee konden worden behaald noemde Beams ze ultracentrifuges. Hij zag hiervoor een groot aantal toepassingen in wetenschappelijk onderzoek waaronder de toepassing voor het bepalen van moleculargewichten analoog aan Svedbergs methode. Deze ontwikkeling werd vervolgens ter hand genomen door Edward G. Pickels, één van Beams' studenten. Ontwikkeling in deze richting bleek daarbij zeer problematisch te zijn, vooral door het optreden van konvektie stromen die werden veroorzaakt door opwarming ten gevolge van luchtweerstand. Na gedurende een jaar zonder veel succes verschillende concepten te hebben geprobeerd ontwikkelde Pickels een apparaat waarbij de eigenlijke rotor in vacuüm draaide. Deze rotor was via een dunne snaar verbonden met een door perslucht aangedreven kleine tol waarmee de meeste problemen bleken te zijn opgelost.

Beams bleef geïnteresseerd in het ontwikkelen van ultracentrifuges voor een zeer breed spectrum aan toepassingen. Hij streefde er daarbij ook vooral naar om de apparaten zo eenvoudig mogelijk te maken zodat zoveel mogelijk onderzoekers er mee zouden kunnen werken. Hij konkludeerde dat lang niet ieder laboratorium over de nodige perslucht voorzieningen beschikte en ontwikkelde daarom een vacuüm ultracentrifuge met elektrische aandrijving. Verder ontwikkelde hij ultracentrifuges t.b.v. isotopenscheiding, welke hij in eerste instantie toepaste op chloorisotopen. Kort na de eerste demonstratie van het splitsen van uraniumatomen raakte Beams ook geïnteresseerd in de ontwikkeling van ultracentrifuges voor het scheiden van uraniumisotopen. Vanuit verschillende legeronderdelen ontstond er

belangstelling voor dit werk i.v.m. de konstruktie van kernwapens hetgeen leidde tot de bouw van een ultracentrifuge proeffabriek voor uraniumverrijking. Dit projekt werd in 1942 weer beëindigd omdat men meer vertrouwen had in een andere verrijkingstechnologie, te weten gasdiffusie. Het ontwikkelingswerk aan deze ultracentrifuges werd na de oorlog in een aantal landen voortgezet, waaronder de Sovjet Unie, Nederland en de Duitse Bondsrepubliek. Toen dit werk aan het eind van de jaren vijftig vrucht ging afwerpen hervatte ook Beams zijn ontwikkelingswerk aan dit type ultracentrifuges.

Na de oorlog zette Beams zijn werk aan roterende systemen vooral in twee richtingen voort. De ene richting betrof het bereiken van zo groot mogelijke gravitatie krachten. Aan het eind van de jaren vijftig bereikte hij meer dan een miljard g met een rotor van een kwart millimeter diameter. De andere ontwikkelingslijn betrof het bereiken van een zo konstant mogelijke rotatie door het zoveel mogelijk elimineren van remmende invloeden. Beams ontwikkelde daartoe de zgn. 'coaster' waarbij de rotor, nadat deze op snelheid was gekomen, werd losgekoppeld van de aandrijving. Het afremmen was daarbij zover beperkt dat de rotor tientallen jaren zou blijven draaien. Gedurende zijn hele verdere leven is Beams aan roterende systemen blijven werken.

Hoofdstuk 4 beschrijft de ontwikkeling van ultracentrifuges door de Amerikaanse colloïd chemicus James W. McBain. Omstreeks 1930 raakte McBain, n.a.v. publikaties van Svedberg, geïnteresseerd in het gebruik van ultracentrifuges voor zijn eigen colloïd chemisch onderzoek waarbij hij, in tegenstelling tot Svedberg, vooral was geïnteresseerd in onderzoek aan anorganische substanties. Omdat McBain over een zeer beperkt onderzoeksbudget beschikte probeerde hij een goedkoop alternatief voor Svedbergs instrument te ontwikkelen waarbij hij, evenals Beams, koos voor door perslucht aangedreven tolleren. Echter, waar Beams en Pickels uiteindelijk terecht kwamen bij de vacuüm ultracentrifuge, bleef McBain bij de eenvoudige tolleren waarvan hij na een jaar of vier claimde dat ze geschikt waren voor hetzelfde soort onderzoek als Svedberg deed. Daarbij benadrukte hij dat zijn apparaat zeer eenvoudig te maken en te bedienen was en dat het, afhankelijk van de preciese wensen van de experimentator, maximaal een paar honderd dollar kostte. Aanvankelijk was er enige belangstelling voor McBains werk maar deze verdween na een aantal jaren, vooral nadat Svedberg had betoogd dat het apparaat van McBain ongeschikt was als instrument voor eiwit onderzoek. McBain ging nog enige jaren door met het ontwikkelen van zijn ultracentrifuges maar dit werk werd door vrijwel niemand serieus genomen en omstreeks 1940 stopte hij met dit werk.

In *hoofdstuk 5* wordt beschreven hoe de vacuüm ultracentrifuge van Beams en Pickels de aandacht trok van virus onderzoekers in het 'Rockefeller Institute for

Medical Research' in New York. Na zijn afstuderen kwam Pickels bij hen in dienst om dit apparaat voor hen verder te ontwikkelen waarbij hij twee verschillende typen konstrueerde. Het eerste type, de analytische ultracentrifuge, kon worden gebruikt voor het bepalen van deeltjes groottes volgens dezelfde methode als Svedberg. Het tweede type, de preparatieve ultracentrifuge, diende voor het scheiden van een opgeloste stof van het oplosmiddel en werd vooral gebruikt voor het concentreren van virussen.

Hoofdstuk 6 beschrijft hoe een verdere verspreiding van ultracentrifuges in de wetenschappelijke gemeenschap tot stand is gekomen. Beams' instrumentmakers maakten regelmatig ultracentrifuges voor derden waardoor er een beperkte verspreiding plaatsvond. Omstreeks 1937 werd zijn vacuümcentrifuge door een Amerikaanse firma op de markt gebracht hetgeen echter een commercieel fiasco werd. Svedberg was eveneens bereid het apparaat tegen kostprijs aan derden te leveren maar dan kostte het nog steeds enkele tienduizenden dollar, een zeer hoog bedrag in die tijd. Slechts een vijftal zijn op deze wijze in andere laboratoria terecht gekomen. In het begin van de jaren veertig is het apparaat door een firma in Stockholm op de markt gebracht hetgeen eveneens een commerciële flop werd.

Pickels kwam in 1946 in contact met Maurice Hanafin, een ondernemer uit Californië, die het plan had opgevat om op basis van Pickels' ontwerp een ultracentrifuge op de markt te brengen. Pickels stelde hem voor partners te worden waarop de firma Spinco werd opgericht. Omdat Pickels de ultracentrifuge in de toenmalige uitvoering niet geschikt vond voor commerciële produktie startte hij de ontwikkeling van een gemakkelijk te bedienen, 'fool-proof' analytische ultracentrifuge. Deze bleek echter niet voldoende te verkopen en Spinco ging bijna bankroet. Vervolgens concentreerde Pickels zich op de ontwikkeling van een preparatieve ultracentrifuge welke wel zeer goed in de markt bleek te liggen. Dat gaf Spinco voldoende financiële armslag om ook de analytische ultracentrifuge te blijven produceren die daarop eveneens in steeds groeiende aantallen werd verkocht. Langzaam maar zeker ontstond daarmee een groep van onderzoekers die werd gekenmerkt door het gebruik van ultracentrifuges voor biochemisch onderzoek. Deze onderzoekers voelden zich met elkaar verbonden hetgeen onder meer blijkt uit het organiseren van eigen symposia en konferenties. Dit betekende niet dat de ultracentrifuge daarmee volledig was ontwikkeld. Naarmate er meer onderzoekers met het apparaat gingen werken, ieder met een eigen aanpak en interesse, werden er ook steeds nieuwe wensen en problemen m.b.t. tot het apparaat geformuleerd. De ontwikkeling van de ultracentrifuge maakte het mogelijk dat deze groep van onderzoekers ontstond maar het ontstaan van deze groep betekende tevens een stimulans voor de verdere ontwikkeling van het apparaat.

In *hoofdstuk 7* worden de ontwikkelingsprocessen van de verschillende ultracentrifuges met elkaar vergeleken en worden daarin een aantal patronen geïdentificeerd. Daarbij wordt onderscheid gemaakt tussen twee verschillende soorten patronen, t.w. patronen in de relaties tussen actoren en artefakten en patronen van verandering. Allereerst wordt gekonstateerd dat een relatie tussen aktor en artefakt in de regel niet 'uit het niets' ontstaat maar dat er voor alle actoren een graduele overgang was van niet naar wel werken met ultracentrifuges. Die continuïteit zat b.v. in het vinden van een nieuwe toepassing voor een artefakt waar al mee werd gewerkt of in het ontwikkelen van een nieuw artefakt voor een bestaand toepassingsgebied. Wat betreft de verdere ontwikkeling van het artefakt blijkt het dat sommige karakteristieken daarvan meer voor verandering in aanmerking komen dan andere waarbij een karakteristiek betrekking kan hebben op een stuk 'hardware', een technologisch principe, etc. Het gaat er daarbij niet zozeer om dat bepaalde veranderingen op technologische gronden als moeilijk realiseerbaar worden gezien maar meer om het verschijnsel dat sommige karakteristieken als essentieel of 'hard' worden beschouwd en daarom niet voor verandering in aanmerking komen. Een dergelijke verharding kan het gevolg zijn van dat de betreffende karakteristiek een voor de aktor belangrijk probleem heeft opgelost of dat de aktor op theoretische gronden vindt dat de karakteristiek niet mag worden veranderd. Die hardheid is niet absoluut en kan door de aktor weer ter discussie worden gesteld op het moment dat andere modifikaties niet het gewenste resultaat opleveren. Het punt is dat de harde karakteristieken pas in laatste instantie, als andere potentiële mogelijkheden zijn overwogen en uitgesloten, voor modifikatie in aanmerking komen.

Aktoren trachten artefakten te veranderen in antwoord op problemen waarbij het voor de aktor zelden direkt duidelijk is wat het probleem precies is. De aktor brengt daarbij een zekere mate van structurering in het probleem aan die wordt beïnvloed door het probleem zoals dat werd tegengekomen maar ook door de relatie tussen aktor en artefakt. Die structurering van een probleem wordt een 'probleemdefinitie' genoemd. In pogingen dat probleem op te lossen kan een probleemdefinitie wijzigen maar slechts binnen bepaalde grenzen die b.v. worden gevormd door de harde karakteristieken van het artefakt. Probleemdefinities kunnen ook worden beïnvloed door interacties met andere actoren. Voor verschillende actoren kan het artefakt een verschillende betekenis hebben hetgeen in de regel impliceert dat zij ook verschillende probleemdefinities zullen ontwikkelen en ook verschillende visies hebben op wat een oplossing voor het probleem kan zijn. De daarop volgende interactie kan worden gezien als een onderhandelingsproces waarin over en weer aanbiedingen worden gedaan en waarin probleemdefinities kunnen veranderen. De mate waarin de probleemdefinitie kan veranderen en wat als een oplossing voor het probleem kan worden gezien wordt daarbij beperkt door de perceptie van de

aktor op hoe het artefakt zou moeten functioneren hetgeen verschillend is voor de verschillende aktoren. Het punt wordt dan voor beide aktoren om een gemeenschappelijke koers van aktie te vinden die voldoet aan de perceptie van beide aktoren op hoe het artefakt zou moeten functioneren. Doordat er verschillende aktoren bij de ontwikkeling zijn betrokken met ieder een eigen perceptie op waar de ontwikkeling naar toe zou moeten krijgen technologische ontwikkeling daarmee een grillig karakter. Het is dan niet erg verhelderend om technologische ontwikkeling te zien als een lineair proces dat b.v. leidt van innovatie naar diffusie van dezelfde innovatie. In een metafoor is technologische ontwikkeling dan niet zozeer een route die leidt van de ene plaats naar de andere maar meer een gebied met grillige wegen die andere wegen kruisen, nieuwe wegen die ontstaan en doodlopende wegen. Slechts een schets van dat hele gebied doet recht aan de complexiteit van technologische ontwikkeling.

Op grond van de geïdentificeerde patronen wordt in paragraaf 7.3 een model voor analyse van de ontwikkelingen van artefakten gepresenteerd dat de 'definitie-artefakt spiraal' (DAS) wordt genoemd (figuur 7.1). De DAS is vooral bedoeld om te onderzoeken hoe aktoren oplossingen voor hun problemen trachten te vinden. Daartoe wordt aan iedere aktor een 'definitie van de situatie' (DS) toegekend die het resultaat is van voorgaande interactie tussen verschillende aktoren en tussen aktor en artefakt. Aan de definitie van de situatie worden vier verschillende elementen onderscheiden waarvan de inhoud zowel het resultaat is van voorgaande ontwikkeling als antecedent is voor verdere ontwikkeling. Deze elementen betreffen de relatie tussen aktor en artefakt, de sociale wereld, het artefakt alsmede kennis en kundes. Al deze elementen zijn gedefinieerd vanuit het perspectief van de aktor waarbij b.v. van belang is dat de sociale wereld er voor verschillende aktoren zeer verschillend uit kan zien. Indien de aktor met betrekking tot het artefakt tegen een probleem aan loopt zal dat probleem worden gestructureerd door zijn of haar DS en leiden tot een probleemdefinitie. Op grond daarvan kan de aktor ofwel in interactie met andere aktoren treden (een aanbieding doen) ofwel trachten het artefakt te veranderen. Een veranderd artefakt zal na testen de aktors definitie van de situatie weer beïnvloeden, b.v. door het harder worden van bepaalde karakteristieken van het artefakt of door een verandering in de relatie tussen aktor en artefakt. Ook interactie met andere aktoren kan leiden tot veranderingen in de DS. In principe kan de inhoud van ieder element van de definitie van de situatie veranderen maar op grond van de analyse van de ontwikkeling van ultracentrifuges wordt gekonkludeerd dat niet alle inhouden tegelijkertijd veranderen en dat verder bepaalde inhouden van sommige elementen moeilijker kunnen veranderen ('harder' zijn) dan andere. Wat daarbij hard is is verschillend voor verschillende aktoren en afhankelijk van de voorgeschiedenis waarin de DS is ontstaan.

De definitie-artefakt spiraal kan vooral inzicht verschaffen zolang er een relatief klein aantal individuele actoren bij de ontwikkeling is betrokken. In interactie kan het artefakt echter voor steeds meer actoren betekenis krijgen wat kan leiden tot het ontstaan van min of meer stabiele patronen van interactie die de tendens vertonen zichzelf in stand te houden. Het effect daarvan is dat elementen van de definitie van de situatie op een kollektief nivo hard worden. Dergelijke patronen van interactie worden hier netwerken genoemd waarbij een netwerk wordt gekarakteriseerd door het onderwerp van interactie tussen de actoren. In het geval van de ontwikkeling van ultracentrifuges heeft het lang geduurd alvorens er een ultracentrifuge netwerk ontstond. Svedberg was een belangrijke aktor in een eiwit-chemie netwerk waarbij die positie vooral werd mogelijk gemaakt door zijn met de ultracentrifuge behaalde resultaten. Er is echter geen sprake van een ultracentrifuge netwerk omdat de ultracentrifuge zelf, behoudens enkele uitzonderingen, geen onderwerp van interactie was. Dat het artefakt op deze wijze is ingebed in een 'gebruikers-gehoor netwerk' betekent wel dat het artefakt een grotere kans heeft om te overleven omdat de aktor dan meer geneigd zal zijn het te blijven gebruiken. In het geval van McBain is er niet zo'n gebruikers-gehoor netwerk ontstaan en kwam het apparaat, tot ik het er uit haalde, in het vergeetboek van de geschiedenis terecht. Svedbergs apparaat kon veel langer overleven omdat het wel was ingebed maar op den lange duur bleef het toch kwetsbaar omdat het nog steeds verbonden was met een relatief beperkt aantal actoren. Pas toen Spinco ultracentrifuges op de markt bracht ontstond er een ultracentrifuge netwerk waarin het artefakt kon overleven omdat het met een groot aantal actoren verbonden raakte.

In de slotparagraaf wordt betoogd dat het in deze studie ontwikkelde model voor analyse van de ontwikkeling van technologische artefakten kan worden gezien als een aanvulling op de recentelijk ontwikkelde nieuwe benaderingen in het techniekonderzoek. In de beginstadia van technologische ontwikkeling vormt de definitie van de situatie van de individuele aktor de belangrijkste bron van verandering. Het verschijnsel dat elementen van de DS kunnen in interactie gedeeld kunnen worden met andere actoren betekent een ondersteuning voor de sociaal-konstruktivistische benadering in het techniekonderzoek waarin actoren worden gezien als representanten van zgn. 'relevante sociale groepen' (RSG). De DAS kan dan b.v. worden gebruikt om te analyseren hoe RSGs ontstaan. Na verloop van tijd kunnen karakteristieken van een artefakt, dat verder verspreid raakt, op een kollektief nivo hard worden. De ontwikkeling kan dan vruchtbaar worden geanalyseerd door het artefakt als 'leidend' te zien voor de ontwikkeling van een artefakt netwerk. Een netwerk benadering kan dan verder inzicht verschaffen in processen van technologische ontwikkeling.

BIBLIOGRAPHY

- Abir-Am, P. (1982) 'The Discourse of Physical Power and Biological Knowledge in the 1930s: A Reappraisal of the Rockefeller Foundation's 'Policy' in Molecular Biology', *Social Studies of Science*, Vol.12, pp.341-382.
- Adair, G.S. (1925) 'The Osmotic Pressure of Haemoglobin in the absence of Salts', *Proceedings of the Royal Society of London*, Vol.109, Series A, pp.292-300.
- Alexander, A.E., and P. Johnson (1949) *Colloid Science*, Vol.I, Oxford: Clarendon Press.
- Anon. (1934a) '1,200,000 r.p.m.', *Scientific American*, (April), p.208.
- Anon. (1934b) Sharples Ultra-Centrifuge, *Industrial and Engineering Chemistry*, Vol.12, No.3 (10 Feb.), p.56.
- Archibald, W.J. (1938a) 'The process of diffusion in a centrifugal field of force', *Physical Review*, Vol.53, pp.746-752.
- Archibald, W.J. (1938b) 'The process of diffusion in a centrifugal field of force II', *Physical Review*, Vol.54, pp.371-374.
- Arrhenius, S. (1921) 'Speech at presentation Nobel Prize to A. Einstein', in: *Nobel Lectures Physics 1901-1921*, Amsterdam, London, New York: Elsevier Publishing Company, 1967, pp.479-481.
- Astbury, W.T., and H.J. Woods (1931) 'The Molecular Weights of Proteins', *Nature*, Vol.127 (2 Mai), pp.663-665.
- Ayres, A.U. (1938) '80,000 Revs per Minute? Modern Design does it!', *Machine Design*, Vol.10(4), pp.17-19.
- Bauer, J.H., and E.G. Pickels (1936a) 'A high speed vacuum centrifuge suitable for the study of filterable virusses', *Journal of Experimental Medicine*, Vol.64, pp.503-528.
- Bauer, J.H., and E.G. Pickels (1936b) 'A high speed centrifuge for study of virusses', *Journal of Bacteriology*, Vol.31, pp.53-54.
- Bauer, J.H., and E.G. Pickels (1937) 'An improved air-driven type of ultra-centrifuge for molecular sedimentation', *Journal of Experimental Medicine*, Vol.65, pp.565-586.
- Beams, H.W., and R.L. King (1935) 'Effects of Ultra-Centrifuging on the Cells of the Root-Tip of the Bean', *Nature*, Vol.135 (9 February), p.232.
- Beams, H.W., and R.L. King (1936) 'Survival of Ascaris Eggs after Centrifuging', *Science*, Vol.84 (7 August), p.138.
- Beams, H.W. (1937) 'The air turbine ultracentrifuge, together with some results upon ultracentrifuging the eggs of fucus serratus', *Journal of the Marine Biological Association*, Vol.21, pp.571-588.
- Beams, J.W. (1927) 'A study of the lag of the Kerr effect for several liquids as a function of the wave length of the light', *Physical Review*, Vol.29, p.903.
- Beams, J.W., and F. Allison (1927) 'The Differences in the Time Lags of the Faraday Effect behind the Magnetic Field in Various Liquids', *Physical Review*, Vol.29, pp.161-164.
- Beams, J.W., and E.O. Lawrence (1927) 'On the nature of light', *Proceedings of the National Academy of Sciences of the USA*, and pp.207-212.
- Beams, J.W. (1928) 'The time lag of a spark gap', *Journal of the Franklin Institute*, Vol.206, pp.809-815.
- Beams, J.W. (1930a) 'Spectral phenomena in spark discharges', *Physical Review*, Vol.35, pp.24-33.
- Beams, J.W. (1930b) 'The propagation of luminosity in discharge tubes', *Physical Review*, Vol.36, pp.997-1001.
- Beams, J.W. (1930c) 'An apparatus for obtaining high speeds of rotation', *Review of Scientific Instruments*, Vol.1, pp.667-671.
- Beams, J.W., and A.J. Weed (1931) 'A simple ultra-centrifuge', *Science*, Vol.74 (10 July), pp.44-46.
- Beams, J.W. (1932), 'A simple ultracentrifuge', *Physical Review*, Vol.39, p.858.
- Beams, J.W., A.J. Weed, and E.G. Pickels (1933) 'The ultracentrifuge', *Science*, Vol.78 (13 Oktober), pp.338-340.
- Beams, J.W., E.G. Pickels, and A.J. Weed (1934) 'Ultracentrifuge', *Journal of Chemical Physics*, Vol.2, p.143.
- Beams, J.W. (1935) 'The eye as an integrator of short light flashes', *Journal of the Optical Society of America*, Vol.25, p.48.

- Beams, J.W., and E.G. Pickels (1935) 'The Production of High Rotational Speeds', *Review of Scientific Instruments*, Vol.6, pp.299-308.
- Beams, J.W., and F.B. Haynes (1936a) 'An ultracentrifuge for gases and vapors', *Physical Review*, Vol.49, p.644.
- Beams, J.W., and F.B. Haynes (1936b) 'The separation of isotopes by centrifuging', *Physical Review*, Vol.50, pp.491-492.
- Beams, J.W. (1937a) 'A simple method of measuring rotational speeds', *Science*, Vol.85 (12 March), pp.273-274.
- Beams, J.W. (1937b) 'High Rotational Speeds', *Journal of Applied Physics*, Vol.8, pp.795-806.
- Beams, J.W., and F.W. Linke (1937a) 'An inverted Ultracentrifuge', *Physical Review*, Vol.51, p.689.
- Beams, J.W., and F.W. Linke (1937b) 'An inverted Air-Driven Ultracentrifuge', *Review of Scientific Instruments*, Vol.8, pp.160-161.
- Beams, J.W., F.W. Linke, and C. Skarstrom (1937) 'A tubular vacuum type centrifuge', *Science*, Vol.86 (24 September), pp.293-294.
- Beams, J.W., and A.V. Masket (1937) 'Concentration of chlorine isotopes by centrifuging', *Physical Review*, Vol.51, p.384.
- Beams, J.W., and L.B. Snoddy (1937a) 'The electrically driven ultra centrifuge', *Science*, Vol.85 (12 February), pp.185-186.
- Beams, J.W., and L.B. Snoddy (1937b) 'The separation of mixtures by centrifuging', *Journal of Chemical Physics*, Vol.5, pp.993-994.
- Beams, J.W. (1938a) 'High Speed Centrifuging', *Reviews of Modern Physics*, Vol.10, pp.245-263.
- Beams, J.W. (1938b) 'A Tubular Vacuum-Type Centrifuge', *Review of Scientific Instruments*, Vol.9, pp.413-416.
- Beams, J.W., F.W. Linke, and P. Sommer (1938) 'A Vacuum Type Air-Driven Centrifuge for Biophysical Research', *Review of Scientific Instruments*, Vol.9, pp.248-252.
- Beams, J.W. (1939a) 'The separation of gases by centrifuging', *Physical Review*, Vol.55, pp.591-592.
- Beams, J.W. (1939b) 'A High Resolving Power Ultracentrifuge', *Science*, Vol.89, pp.543-544.
- Beams, J.W., and S.A. Black (1939) 'Electrically-Driven Magnetically-Supported Vacuum-Type Ultracentrifuge', *Review of Scientific Instruments*, Vol.10, pp.59-63.
- Beams, J.W., and C. Skarstrom (1939) 'The Concentration of Isotopes by the Evaporative Centrifuge Method', *Physical Review*, Vol.56, pp.266-272.
- Beams, J.W. (1940) 'The Ultracentrifuge', in: G.A. Baitsell (ed.), *Science in Progress*, 2nd series, New Haven: Yale University Press, pp.232-264.
- Beams, J.W. (1941) 'High-Speed Centrifuging', *Reports on Progress in Physics*, Vol.8, pp.31-49.
- Beams, J.W. (1942) 'The Production and Maintenance of High Centrifugal Fields for Use in Biology and Medicine', *Annals of the New York Academy of Sciences*, Vol.XLIII, Art.5, pp.177-193.
- Beams, J.W., and J.L. Young, III (1946) 'The production of high centrifugal fields', *Physical Review*, Vol.69, p.537.
- Beams, J.W., J.L. Young, and III, J.W. Moore (1946) 'The Production of high Centrifugal Fields', *Journal of Applied Physics*, Vol.17, pp.886-890.
- Beams, J.W. (1947a) 'The Radial Density Variation of Gases and Vapors in a Centrifugal Field', *Physical Review*, Vol.72, pp.433-434.
- Beams, J.W. (1947b) 'High centrifugal Fields', *Journal of the Washington Academy of Sciences*, Vol.37(7), pp.221-241.
- Beams, J.W., F.W. Linke, and P. Sommer (1947) 'Speed Control for the Air-Driven Centrifuge', *Review of Scientific Instruments*, Vol.18, pp.57-60.
- Beams, J.W., and J.L. Young, III (1947) 'Centrifugal Fields', *Physical Review*, Vol.71, p.131.
- Beams, J.W. (1950) 'Magnetic Suspension for Small Rotors', *Review of Scientific Instruments*, Vol.21, pp.182-184.
- Beams, J.W., A.C. Hagg and E.V. Murphree (1951) *Developments in the centrifuge separation Projects*, Washington, D.C.: Atomic Energy Commission.
- Beams, J.W., J.D. Ross, and J.F. Dillon (1951) 'Magnetically Suspended Vacuum-Type Ultracentrifuge', *Review of Scientific Instruments*, Vol.22, pp.77-80.
- Beams, J.W., and H.M. Dixon, III (1953) 'An Ultracentrifuge Double Cell', *Review of Scientific Instruments*, Vol.24, pp.228-229.
- Beams, J.W. (1954) 'Production and use of high centrifugal fields', *Science*, Vol.120 (22 Oktober), pp.619-625.
- Beams, J.W., H.M. Dixon, III, A. Robeson, and N. Snidow (1955) 'The magnetically suspended equilibrium ultracentrifuge', *Journal of Physical Chemistry*, Vol.59, pp.915-922.

- Beams, J.W. (1957) 'The magnetically supported equilibrium ultracentrifuge', *Proceedings of the American Philosophical Society*, Vol.101, pp.63-69.
- Beams, J.W. (1961) 'Ultrahigh-Speed Rotation', *Scientific American*, Vol.204(4), pp.135-147.
- Beams, J.W., R.P. Boyle, and P.E. Hexner (1961) 'Magnetically Suspended Equilibrium Ultracentrifuge', *Review of Scientific Instruments*, Vol.32, pp.645-650.
- Beams, J.W. (1963) 'Double Magnetic Suspension', *Review of Scientific Instruments*, Vol.34, pp.1071-1074.
- Beams, J.W. (1965) 'Multiple Magnetic Suspension System', *Review of Scientific Instruments*, Vol.36, p.95.
- Beams, J.W. (1966) 'Speed control of magnetically suspended ultracentrifuge', *Review of Scientific Instruments*, Vol.37, pp.667-669.
- Beams, J.W. and Hodgins, M.G. (1971) 'Magnetic densimeter-viscometer', *Review of Scientific Instruments*, Vol.42, pp.1455-1457.
- Beams, J.W. (1975) *Early History of the Gas Centrifuge work in the USA*, Charlottesville (Va): University of Virginia.
- Beams, J.W., and D.W. Kupke (1977) 'Simultaneous Measurement of Viscosity and Density in Solutions Undergoing Change', *Proceedings of the National Academy of Sciences of the USA*, Vol.74, pp.4430-4433.
- Bernal, J.D., and Crowfoot, D. (1933), 'X-ray photography of crystalline pepsin', *Nature*, Vol.133, pp.794-795.
- Bijker, W.E. (1987a) 'The Social Construction of Bakelite: Toward a Theory of Invention', in W.E. Bijker, T.P. Hughes and T.J. Pinch *The Social Construction of Technological Systems*, Cambridge, Ma: The MIT Press, pp.159-187.
- Bijker, W.E. (1987b) 'The Social Construction of Fluorescent Lighting - An effort to integrate the analyses of social shaping and social impact of technology', Paper presented at the International Workshop on the Integration of Social and Historical Studies of Technology, University of Twente, Enschede, the Netherlands, 3-5 September 1987.
- Bijker, W.E. (1987c) 'De Sociale Constructie van Netwerken en Technische Systemen; Nieuwe Perspectieven voor de Techniekgeschiedenis', *Jaarboek voor de Geschiedenis van Bedrijf en Techniek*, Utrecht: Stichting JbGBT, Deel 4, pp.7-24.
- Bijker, W.E., T.P. Hughes and T.J. Pinch (1987) *The Social Construction of Technological Systems*, Cambridge, Ma: The MIT Press.
- Biscoe, J., Hercik, and R.W.G. Wyckoff (1936) 'The size of antibodies', *Science*, Vol.83 (19 June), pp.602-603.
- Biscoe, J., E.G. Pickels, and R.W.G. Wyckoff (1936a) 'Light metal rotors for the molecular ultracentrifuge', *Review of Scientific Instruments*, Vol.7, pp.246-250.
- Biscoe, J., E.G. Pickels, and R.W.G. Wyckoff (1936b) 'An Air-Driven Ultracentrifuge for Molecular sedimentation', *Journal of Experimental Medicine*, Vol.64, pp.39-45.
- Björnsthåhl, Y. (1934) *The new Laboratory of Physical Chemistry at Uppsala University*, Lund: Hakan Ohlsson.
- Black, S.A., J.W. Beams, and L.B. Snoddy (1938) 'Electrically Driven Vacuum-Type Centrifuge', *Physical Review*, Vol.53, p.924.
- Bloor, D. (1976) 'Wittgenstein and Manheim on the Sociology of Mathematics', *Studies in the History and Philosophy of Science*, Vol.4, p.173-191.
- Bodewitz, H.J.H.W., H. Buurma and G.H. de Vries, 'Regulatory Science and the Social Management of Trust in Medicine', in W.E. Bijker, T.P. Hughes and T.J. Pinch *The Social Construction of Technological Systems*, Cambridge, Ma: The MIT Press, pp.243-259.
- Boestad, G., K.O. Pedersen, and T. Svedberg (1938) 'Design and Operation of the Oil-Turbine Ultracentrifuge', *Review of Scientific Instruments*, Vol.9, pp.346-353.
- Bowen, T.J., and A.J. Rowe (1970) *An Introduction to Ultracentrifugation*, London, New York: Wiley-Interscience.
- Brohult, S., and N. Gralén (1944) 'The Institute of Physical Chemistry at the University of Uppsala - Some Notes on its History and Activities', in A. Tiselius and K.O. Pedersen, *The Svedberg 1884-1944*, Uppsala: Almqvist & Wiksells Boktryckeri AB, pp.623-638.
- Brohult, S. (1987) 'Svedberg as a Scientist', in: B. Rånby (Ed.), *Physical Chemistry of Colloids and Macromolecules*, Oxford, London, Boston, Melbourne: Blackwell Scientific Publications, pp.9-13.
- Brown, F.L. (1967) *A Brief History of the Physics Department of the University of Virginia 1922-1961*, Charlottesville (Va): University of Virginia.

- Brynielsson, H. (1963) 'The founding and first years of LKB-Produkter AB', *Science Tools*, Vol.10(1), pp.2-3.
- Bäcklin, E. (1927) 'Eine Neuauflösung des registrierenden Mikrophotometers von Siegbahn', *Zeitschrift für Instrumentenkunde*, Jhrg.XLVII, pp.373-380.
- Callon, M. (1980a) 'The State and Technical Innovation: A Case Study of the Electrical Vehicle in France', *Research Policy*, Vol.9, pp.358-376.
- Callon, M. (1980b) 'Struggles and Negotiations to Define what is Problematic and what is not: The Sociology of Translation' in: K. Knorr, R. Krohn and R. Whitley (eds.) *The Social Process of Scientific Investigation*, Dordrecht and Boston: Reidel, Vol.4, pp.197-219.
- Callon, M. (1986) 'Some Elements of a Sociology of Translation: Domestication of the Scallops and Fishermen of St.Brieuc Bay', in J. Law (ed.) *Power, Action and Belief: A New Sociology of Knowledge?*, London: Routledge and Kegan Paul, pp. 196-233.
- Callon, M. (1987) 'Society in the Making: The Study of Technology as a Tool for Sociological Analysis', in W.E. Bijker, T.P. Hughes and T.J. Pinch *The Social Construction of Technological Systems*, Cambridge, Ma: The MIT Press, pp.83-103.
- Callon, M., and J. Law (1987) 'The Life and Death of an Aircraft: A Network Analysis of Technical Change', Paper presented at the International Workshop on the Integration of Social and Historical Studies of Technology, University of Twente, Enschede, the Netherlands, 3-5 September 1987.
- Chiles, J.A. (1937) 'A Photographic Study of the Vacuum Spark Discharge', *Journal of Applied Physics*, Vol.8, pp.622-623.
- Chiles, J.A., and A.E. Severinghaus (1938) 'Hormone Studies with the Ultracentrifuge', *Journal of Experimental Medicine*, Vol.68, pp.1-16.
- Claesson, S., and K.O. Pedersen (1972) 'The Svedberg, 1884-1971', *Biographical Memoirs of Fellows of the Royal Society (London)*, Vol.18, pp.595-627.
- Claesson, S., and K.O. Pedersen (1976) 'The Svedberg', in: C.C. Gillispie (ed.), *Dictionary of Scientific Biography*, New York: Charles Scribner's Sons, pp.158-164.
- Clark, L.H. (1925) 'The Supercentrifuge', in: H.H. Holmes (ed.), *Colloid Symposium Monograph*, Vol.2, New York: The Chemical Catalog Company, Inc., pp.174-184.
- Cohn, E.J. (1925) 'The Physical Chemistry of the Proteins', *Physiological Reviews*, Vol.5, pp.349-437.
- Constant, E.W., II (1980) *The Origins of the Turbojet Revolution*, Baltimore: Johns Hopkins University Press.
- Corner, G.W. (1964) *A History of the Rockefeller Institute; 1901-1953: Origins and Growth*, New York: The Rockefeller Institute Press.
- Craigie, J., and F.O. Wishart (1934) 'The agglutinogens of a strain of vaccina elementary bodies', *British Journal of Experimental Pathology*, Vol.15, pp.390-398.
- Edsall, J.T. (1962) 'Proteins as Macromolecules: An Essay on the Development of the Macromolecule Concept and Some of Its Vicissitudes', *Archives of Biochemistry and Biophysics*, Suppl.1, pp.12-20.
- Einstein, A., (1905) 'Über die von der molekularkinetischen Theorie der Wärme geforderte Bewegung von in ruhenden Flüssigkeiten suspendierten Teilchen', *Annalen der Physik*, Bd.4(17), pp.549-560.
- Einstein, A., (1906) 'Zur Theorie der Brownschen Bewegung', *Annalen der Physik*, Bd.4(19), pp.371-381.
- Eirich, F.R., and E.K. Rideal (1940) 'Air driven Ultracentrifuge', *Nature*, Vol.146 (26 Oktober), pp.541-552.
- Elzen, B. (1985) 'De Ultracentrifuge: Op Zoek naar Patronen in Technologische ontwikkeling door een Vergelijking van twee Case-Studies' *Jaarboek voor de Geschiedenis van Bedrijf en Techniek*, Utrecht: Stichting JbGBT, Deel 2, pp.250-278.
- Elzen, B. (1986) 'Two Ultracentrifuges: A Comparative Study of the Social Construction of Artefacts', *Social Studies of Science*, Vol.16, pp.621-662.
- Eriksson-Quensel, I.B. and T. Svedberg (1936) 'Sedimentation and Electrophoresis of the Tobacco-Mosaic Virus Protein', *Journal of the American Chemical Society*, Vol.58, pp.1863-1867.
- Flory, P.J. (1953) *Principles of Polymer Chemistry*, Ithaca: Cornell University Press.
- Ford, T.F., G.A. Ramsdell, and L.W. Klipp (1955) 'An air-driven, air-floated capillary tube ultracentrifuge', *Journal of Physical Chemistry*, Vol.59, pp.922-929.
- Fruton, J.S. (1972) *Molecules and Life*, New York, London, Sydney, Toronto: Wiley-Interscience, a Division of John Wiley and sons.

- Fujimura, J. (1987) 'Constructing "Do-able" Problems in Cancer Research: Articulating Alignment', *Social Studies of Science*, Vol.17, pp.257-293.
- Fujita, H. (1975) *Foundations of Ultracentrifugal Analysis*, New York, London, Sydney, Toronto: Wiley-Interscience, a Division of John Wiley and sons.
- Gard, S. (1944) 'Några virusproblem i den moderna forskningen ljus', *Skandinavisk Veterinärtidskrift*, Vol.42.
- Garman, W.D. (1933) 'A study of the high-speed centrifuge', *Review of Scientific Instruments*, Vol.4, pp.450-453.
- Gilmer, T.E. (1937) 'The integrating Power of the eye for short flashes of light', *Journal of the Optical Society of America*, Vol.27, pp.386-388.
- Gordy, W. (1983) 'Jesse Wakefield Beams', in: *Biographical Memoirs*, Vol.54, Washington, DC: Nat. Academy of Sciences of the USA, pp.3-49.
- Graham, T. (1861) 'Liquid Diffusion applied to Analysis', *Philosophical Transactions of the Royal Society of London*, Vol.151, pp.183-224.
- Gray, W. (1951) 'The ultracentrifuge', *Scientific American*, Vol.184 (June), pp.42-51.
- Guyer, M.F., and P.E. Claus (1937) 'Growth of cancerous and of embryonic tissues stratified in the ultracentrifuge', *Proceedings of the Society for Experimental Biology and Medicine*, Vol.35, pp.468-473.
- Harvey, E.N., and A.L. Loomis (1930) 'A microscope centrifuge', *Science*, Vol.72 (11 July), pp.42-44.
- Harvey, E.N. (1932) 'The microscope-centrifuge and some of its applications', *Journal of the Franklin Institute*, Vol.214(1), pp.1-23.
- Harvey, E.N. (1933) 'A New Form of Centrifuge-Microscope for Simultaneous Observation of Control and Experimental Material', *Science*, Vol.77 (May 5), pp.430-431.
- Harvey, E.N. (1934) 'The air turbine for high speed centrifuging of biological material, together with some observations on centrifuged eggs', *Biological Bulletin*, Vol.66, pp.48-54.
- Henriot, E., and E. Huguenard (1925) 'Sur la réalisation de très grandes vitesses de rotation', *Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences*, T.180 (11 Mai), pp.1389-1392.
- Henriot, E., and E. Huguenard (1927) 'Les grandes vitesses angulaires obtenues par les rotors sans axe solide', *Le Journal de Physique et le Radium*, T.8(11), pp.433-443.
- Hess, E.L. (1970) 'Origins of Molecular Biology', *Science*, Vol.168 (8 May), pp.664-669.
- Holmes, F.T. (1937) 'Axial Magnetic Suspensions', *Review of Scientific Instruments*, Vol.8, pp.444-447.
- Holmes, F.T., and J.W. Beams (1937) 'Frictional Torque of an axial Magnetic Suspension', *Nature*, Vol.140 (3 July), pp.30-31.
- Hoxton, L.G., and J.W. Beams (1937) 'A steam driven ultracentrifuge', *Physical Review*, Vol.51, p.690.
- Hughes, T.P. (1983) *Networks of Power*, Baltimore, Md: The Johns Hopkins University Press.
- Hughes, T.P. (1986) 'The Seamless Web: Technology, Science, Etcetera, Etcetera', *Social Studies of Science*, Vol.16, pp.281-292.
- Hughes, T.P. (1987) 'The Evolution of Large Technological Systems', in W.E. Bijker, T.P. Hughes and T.J. Pinch *The Social Construction of Technological Systems*, Cambridge, Ma: The MIT Press, pp.51-82.
- Humphreys, R.F. (1939) 'Separation of Bromine Isotopes by Centrifugation', *Physical Review*, Vol.56, pp.684-691.
- Jaeger, F.M. (1938) 'De Analytische Ultra-Centrifuge en het Onderzoek der Filtreerbare Virus-Soorten', *Chemisch Weekblad*, Vol.35, pp.419-431.
- Janssen, L.W. (1941) 'Die Zentrifugierung und die Sedimentationskonstante des Maul- und Klauenseuche-Virusproteins', *Die Naturwissenschaften*, Jhrg.29, pp.102-103.
- Joly, J. and J.H.J. Poole (1920), 'An attempt to determine if common lead could be separated into isotopes by centrifuging in the liquid state', *Philosophical Magazine*, Vol.39, pp.372-375.
- Kay, L.W. (1986) 'W.M. Stanley's Crystallization of the Tobacco Mosaic Virus, 1930-1940', *ISIS*, Vol.77, pp.450-472.
- Kerker, M. (1986) 'The Svedberg and Molecular Reality: An Autobiographical Postscript', *ISIS*, Vol.77, pp.278-282.
- Kinell, P.-O. (1987) 'Svedberg and the synthetic Polymers', in: B. Rånby (Ed.), *Physical Chemistry of Colloids and Macromolecules*, Oxford, London, Boston, Melbourne: Blackwell Scientific Publications, pp.37-44.

- Kohler, R.E. (1976) 'The Management of Science: The Experience of Warren Weaver and the Rockefeller Foundation Programme in Molecular Biology', *Minerva*, Vol.14, pp.275-306.
- Krass, A.S., P. Boskma, B. Elzen and W.A. Smit (1983) *Uranium Enrichment and Nuclear Weapon Proliferation*, Stockholm International Peace Research Institute, London and New York: Taylor & Francis Ltd.
- Kraemer, E.O. (1938) 'Discussion', *Industrial and Engineering Chemistry, Analytical Edition*, Vol.10(3), p.128.
- Kupke, D.W. (1977) 'Obituary, Jesse W. Beams', *Trends in Biochemical Sciences*, Vol.2, p.284.
- Lamm, O. (1928) 'Zur Bestimmung von Konzentrationsgradienten mittels gekrümmter Lichtstrahlen', *Zeitschrift für Physikalische Chemie*, Bd.138, Abt. A, pp.313-331.
- Lamm, O. (1933) 'A new Method for Determining the Concentration Gradient in the Ultra-Centrifuge Cell', *Nature*, Vol.132 (25 November), pp.820-821.
- Latour, B. (1983) 'Give me a Laboratory and I will raise the World', in K.D. Knorr-Cetina and M.J. Mulkey (eds.) *Science Observed, Perspectives on the Social Study of Science*, London and Beverly Hills: Sage, pp.141-170.
- Latour, B. (1987) *Science in Action - How to follow scientists and engineers through society*, Milton Keynes: Open University Press.
- Laudan, R. (ed.) (1984) *The Nature of Technological Knowledge: Are Models of Scientific Change Relevant?*, Dordrecht and Boston: Reidel.
- Law, J. (1987) 'Technology and Heterogeneous Engineering: The Case of the Portuguese Expansion', in W.E. Bijker, T.P. Hughes and T.J. Pinch *The Social Construction of Technological Systems*, Cambridge, Ma: The MIT Press, pp.111-134.
- Lawrence, E.O., and J.W. Beams (1927) 'The instantaneity of the photo-electric effect', *Physical Review*, Vol.29, pp.903-904.
- Lawrence, E.O., and J.W. Beams (1928a) 'The Element of Time in the Photoelectric Effect', *Physical Review*, Vol.32, pp.478-485.
- Lawrence, E.O., and J.W. Beams (1928b) 'On the Time required for the Photo-electric Ejection of an Electron by Visible Light', *Physical Review*, Vol.31, p.709.
- Lawrence, E.O., J.W. Beams, and W.D. Garman (1928) 'An improved arrangement for obtaining high speeds of rotation', *Physical Review*, Vol.31, p.1112.
- Lepsius, R. (1964) 'The Svedberg', *Chemiker Zeitung*, Vol.88, pp.717-720.
- Leslie, S.W. (1983) *Boss Kettering - Wizard of General Motors*, New York: Columbia University Press.
- Lewis, M.S., and G.H. Weiss (eds.) (1976) *Fifty years of the ultracentrifuge*, Amsterdam: North-Holland Publishing Company.
- Longworth, L.G. (1950) 'National Academy of Sciences Conference on the Ultracentrifuge', *Proceedings of the National Academy of Sciences of the USA*, Vol.36, pp.502-510.
- Marston, W.L. (1936) 'Centrifugals', *Industrial and Engineering Chemistry, Industrial Edition*, Vol.28(11), editorial supplement, pp.55-58.
- Maskett, A.V. (1941) 'A quantity type rotor for the ultracentrifuge', *Review of Scientific Instruments*, Vol.12, pp.277-278.
- Mathews, J.H. (1966) 'Remarks at the Opening of the Fortieth National Colloid Symposium', *Journal of Colloid and Interface Science*, Vol.22, pp.409-411.
- McBain, J.W. (1909a) 'The Mechanism of the adsorption ('Sorption') of Hydrogen by Carbon', *Philosophical Magazine*, Vol.18, pp.916-935.
- McBain, J.W. (1909b) 'Die Mechanismus der Adsorption ('Sorption') von Wasserstoff durch Kohlenstoff', *Zeitschrift für Physikalische Chemie*, Bd.68, pp.471-497.
- McBain, J.W. (1926) 'A Survey of the main Principles of Colloid Science', in: H.B. Weiser (ed.), *Colloid Symposium Monograph*, New York: The Chemical Catalog Company, Inc.
- McBain, J.W., and A.M. Bakr (1926) 'A new Sorption Balance', *Journal of the American Chemical Society*, Vol.48, pp.690-695.
- McBain, J.W., and G.T. Bulton (1930) 'The Nature of the Sorption by Charcoal of Gases and Vapors under Great Pressure', *Journal of the American Chemical Society*, Vol.52, pp.2198-2222.
- McBain, J.W. (1931) *The Sorption of Gases and Vapors by Solids*, London: Routledge and Sons Ltd.
- McBain, J.W., and M.E. Laing-McBain (1933) 'Sedimentation equilibrium in the Ultracentrifuge-Types obtained with soap solutions', *Proceedings of the Royal Society of London*, Vol.A-139, pp.26-37.

- McBain, J.W., C.R. Dawson, and H.A. Barker (1934) 'The Diffusion of Colloids and Colloidal Electrolytes: Egg Albumin: Comparison with Ultracentrifuge', *Journal of the American Chemical Society*, Vol.56, pp.1021-1027.
- McBain, J.W. (1935) 'Some uses of the air-driven spinning top', *Nature*, Vol.135 (18 May), p.831.
- McBain, J.W., and C.M. O'Sullivan, S.J. (1935a) 'Development of an air-driven ultracentrifuge', *Journal of the American Chemical Society*, Vol.57, pp.780-781.
- McBain, J.W., and C.M. O'Sullivan, S.J. (1935b) 'The Development of the Air-Driven Spinning Top as Transparent Ultracentrifuge', *Journal of the American Chemical Society*, Vol.57, pp.2631-2641.
- McBain, J.W. (1936a) 'The Determination of Bound Water by means of the Ultracentrifuge', *Journal of the American Chemical Society*, Vol.58, pp.315-317.
- McBain, J.W. (1936b) 'Addendum to the Note of Williams and Watson', *Journal of the American Chemical Society*, Vol.58, p.2652.
- McBain, J.W., and R.F. Stuewer (1936) 'Anwendungen des einfachen luftgetriebenen Zentrifugen Kreisel auf Kolloid Chemische Probleme', *Kolloid Zeitschrift*, Bd.74, pp.10-16.
- McBain, J.W., and C. Alvarez-Tostado (1937) 'Sedimentation equilibrium in the simplest Air-driven Tops', *Nature*, Vol.139 (19 June), p.1066.
- McBain, J.W. (1938a) 'Opaque ultracentrifuges for direct analysis', *Journal of Physical Chemistry*, Vol.42, pp.1063-1070.
- McBain, J.W. (1938b) 'The Determination of Sedimentation Rate and Equilibrium in Centrifuges and Opaque Ultracentrifuges', *Science*, Vol.87 (28 January), pp.93-94.
- McBain, J.W., and F.A. Leyda (1938a) 'A Simple inexpensive Ultracentrifuge', *Nature*, Vol.141 (21 May), pp.913-914.
- McBain, J.W., and F.A. Leyda (1938b), 'Measurement of Sedimentation Velocity in simple Air-driven Tops as Ultracentrifuges', *Journal of the American Chemical Society*, Vol.60, pp.2998-3002.
- McBain, J.W. (1939) 'Opaque or analytical ultracentrifuges', *Chemical Reviews*, Vol.24, pp.289-302.
- McBain, J.W., and A.H. Lewis (1939a) 'Directly Air-Driven Transparent Ultracentrifuges', *Journal of Physical Chemistry*, Vol.43, pp.1197-1205.
- McBain, J.W., and A.H. Lewis (1939b) 'The Simplest Transparent Ultracentrifuge', *Science*, Vol.89, p.611.
- McBain, J.W. (1940) 'The Simplest Ultracentrifuge with Photographic Recording', *Transactions of the Faraday Society*, Vol.36, pp.381-384.
- McBain, J.W., and F.A. Leyda (1941) 'The Calculation of Particle Size and Molecular Weight from Current Centrifugal Methods', *Acta Physicochimica U.R.S.S.*, Vol.XIV, pp.421-432.
- McBain, J.W. (1950) *Colloid Science*, Boston: D.C. Heath and Company.
- McCosham, V.J., and J.W. Williams (1962) 'Reflections on an Ultracentrifuge', *Archives of Biochemistry and Biophysics*, Suppl.1, pp.119-124.
- McFarlane, A.S. (1935) 'An ultracentrifugal investigation of the serum proteins', *Biochemical Journal*, Vol.29, pp.407-429.
- McHattie, L.E. (1941a) 'The Production of High Rotational Speed', *Review of Scientific Instruments*, Vol.12, pp.429-435.
- McHattie, L.E. (1941b) 'High Rotational Speed with Small Rotors', *Physical Review*, Vol.59, p.468.
- McInnes, D.A. (1942) 'Introduction to the Conference on the Ultracentrifuge', *Annals of the New York Academy of Sciences*, Vol.XLIII, Art.5, pp.175-176.
- McIntosh, J., and F.R. Selbie (1937) 'The Measurement of the Size of Viruses by High-Speed Centrifuging', Vol.18, pp.162-174.
- McKenzie, D., and J. Wajcman (eds.) (1985) *The Social Shaping of Technology*, Milton Keynes: The Open University Press.
- McKenzie, D. (1987) 'Missile Accuracy: A Case Study in the Social Processes of Technological Change', in W.E. Bijker, T.P. Hughes and T.J. Pinch *The Social Construction of Technological Systems*, Cambridge, Ma: The MIT Press, pp.195-222.
- McShane, E.J. (1978) 'Biographical Memoirs: Jesse Wakefield Beams', in: *American Philosophical Society Yearbook*, , pp.45-50.
- Moore, D.H. (1943) 'Some improvements for the analytical ultracentrifuge', *Review of Scientific Instruments*, Vol.14, pp.295-297.
- Mulliken, R.S. (1922a) 'The separation of isotopes by thermal and pressure diffusion', *Journal of the American Chemical Society*, Vol.44, pp.1033-1051.
- Mulliken, R.S. (1922b) 'The separation of liquid mixtures by centrifuging', *Journal of the American Chemical Society*, Vol.44, pp.1729-1730.

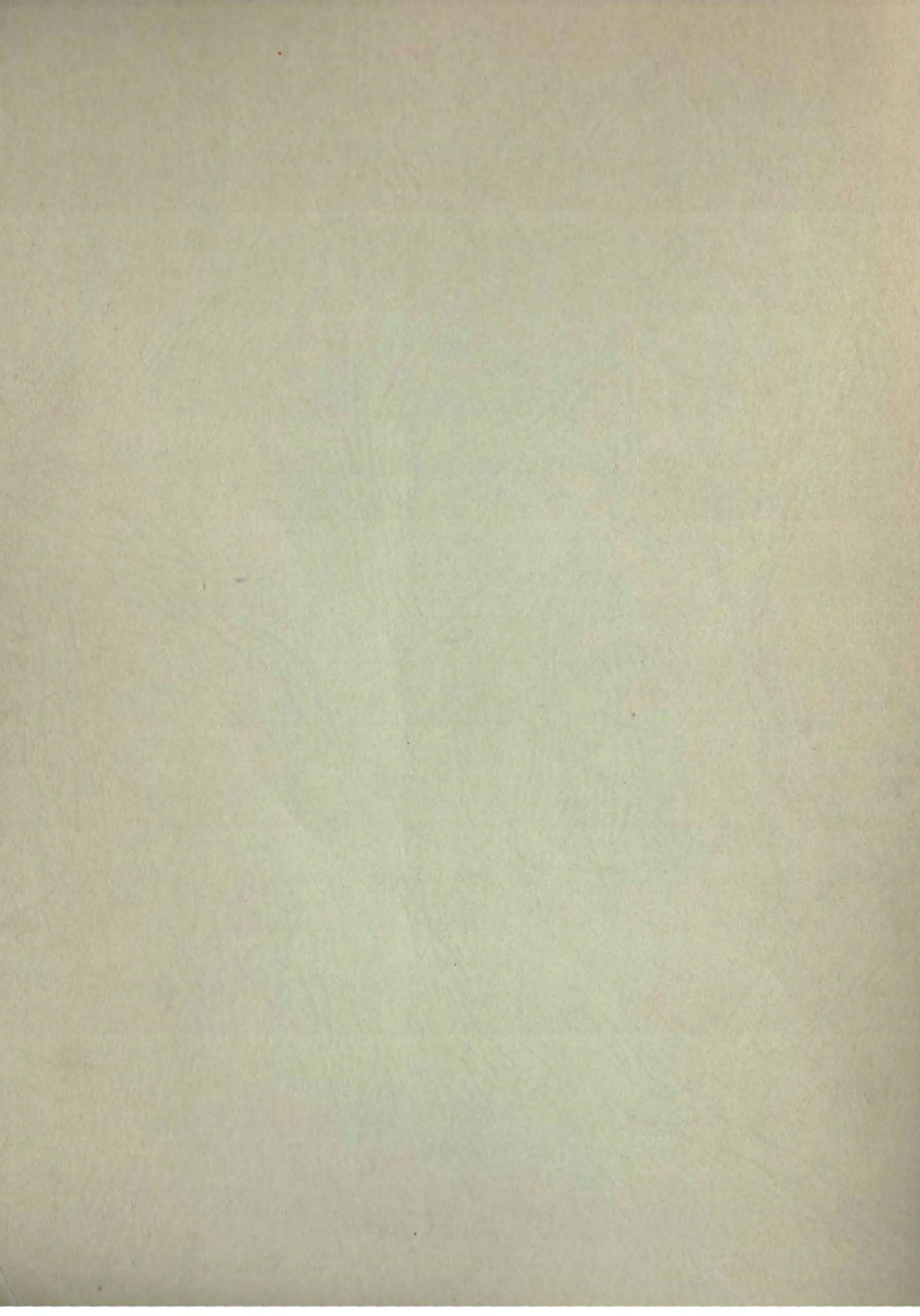
- Mutzenbecher, P. von (1931) 'Untersuchung der bei Serumelektrodialyse auftretenden Eiweissfraktionen mit der Ultrazentrifuge', *Biochemisches Zeitschrift*, Bd.235, pp.425-437.
- Mutzenbecher, P. von (1933a) 'Die Analyse des Serums mit der Ultrazentrifuge', *Biochemisches Zeitschrift*, Bd.266, pp.226-249.
- Mutzenbecher, P. von (1933b) 'Die Fraktionen des Serums', *Biochemisches Zeitschrift*, Bd.266, pp.250-258.
- Nichols, J.B. (1927) *Centrifugal Methods for Determining the Size and the Distribution of Size of Suspended Particles*, unpublished dissertation, Madison, WI.: University of Wisconsin.
- Nichols, J.B. (1928) 'The development of the ultracentrifuge and its field of research', in: H.B. Weiser (ed.), *Colloid Symposium Monograph*, New York: The Chemical Catalog Company, Inc., pp.287-308.
- Nichols, J.B. (1931) 'The application of the ultracentrifuge to some colloid-physical problems', *Physics*, Vol.1, pp.254-267.
- Nichols, J.B. (1932) 'The Ultracentrifuge and Its Field of Research', *Industrial and Engineering Chemistry, Analytical Edition*, Vol.4, pp.12-17.
- Nichols, J.B., E.O. Krammer, and E.D. Bailey (1932) 'The particle size and constitution of colloidal ferric oxide. I', *Journal of Physical Chemistry*, Vol.36, pp.326-329.
- Nichols, J.B. (1987) 'The First Svedberg Ultracentrifuges', in: B. Rånby (Ed.), *Physical Chemistry of Colloids and Macromolecules*, Oxford, London, Boston, Melbourne: Blackwell Scientific Publications, pp.45-48.
- Odén, S. (1931) 'Der kolloide Schwefel', *Nova Acta Regiae Societatis Scientiarum Upsaliensis*, Ser.IV, Vol.3, N.4, pp.1-193.
- Odén, S. (1915) 'On the size of the particles in deep-sea deposits', *Proceedings of the Royal Society of Edinburgh*, Vol.36, pp.219-236.
- Ogston, A.G. (1963) 'A Survey of the Uses of the Ultracentrifuge in Biological Research', in: J.W. Williams (ed.), *Ultracentrifugal Analysis*, New York, London: Academic Press, pp.263-272.
- Pedersen, K.O. (1935) 'Sedimentation Equilibrium Measurements with low Molecular Substances in the Ultra-Centrifuge', *Nature*, Vol.135 (23 February), pp.304-305.
- Pedersen, K.O. (1976) 'The development of Svedberg's ultracentrifuge', in: M.S. Lewis, G.H. Weiss (eds.), *Fifty Years of Ultracentrifuge*, Amsterdam: North-Holland Publishing Company, pp.3-18.
- Pedersen, K.O. (1983) 'The Svedberg and Arne Tiselius - The early development of modern protein chemistry at Uppsala', in: G. Semenza (ed.), *Selected Topics in the History of Biochemistry: Personal Recollections I*, Vol.35 in: M. Florkin and E.H. Comprehensive Biochemistry, Amsterdam, Oxford, New York: Elsevier Science Publishers, pp.233-281.
- Pedersen, K.O. (1987) 'Svedberg and the Proteins', in: B. Rånby (Ed.), *Physical Chemistry of Colloids and Macromolecules*, Oxford, London, Boston, Melbourne: Blackwell Scientific Publications, pp.23-27.
- Perrin, J.B. (1926) 'Discontinuous structure of matter', in: *Nobel Lectures Physics 1922-1940*, Amsterdam, London, New York: Elsevier Publishing Company, 1967, pp.138-164.
- Philpot, J.St.L. (1938) 'Direct Photography of Ultracentrifuge Sedimentation Curves', *Nature*, Vol.141, pp.283-284.
- Pickels, E.G., and J.W. Beams (1935) 'High rotational speeds in vacuo', *Science*, Vol.81 (5 April), pp.342-343.
- Pickels, E.G. (1935) *The Air-Driven Ultra-centrifuge*, unpublished dissertation, Charlottesville, Va.: University of Virginia.
- Pickels, E.G. (1936) 'Optical designs for observing objects in centrifugal fields of force', *Science*, Vol.83, pp.471-472.
- Pickels, E.G. (1938a) 'Practical Speed-Measuring Devices for High Speed Centrifuges', *Review of Scientific Instruments*, Vol.9, pp.354-358.
- Pickels, E.G. (1938b) 'A new Type of Air Bearing for Air-Driven High Speed Centrifuges', *Review of Scientific Instruments*, Vol.9, pp.358-364.
- Pickels, E.G. (1942a) 'An Improved Type of Electrically Driven High Speed Laboratory Centrifuge', *Review of Scientific Instruments*, Vol.13, pp.93-100.
- Pickels, E.G. (1942b) 'Stress Analysis and Design of High Speed Angle Centrifuges', *Review of Scientific Instruments*, Vol.13, pp.101-114.
- Pickels, E.G. (1942c) 'Ultracentrifuge Cell', *Review of Scientific Instruments*, Vol.13, pp.426-434.
- Pickels, E.G. (1942d) 'Practical aspects of the ultracentrifugal analysis of Proteins', *Chemical Reviews*, Vol.30, pp.341-355.

- Pickels, E.G. (1944) 'High-speed centrifugation', in: J. Alexander (ed.), *Colloid Chemistry*, Vol.V, Ch.19, New York: Chemical Catalog Co., pp.411-434.
- Pickels, E.G. (1949) 'Centrifuge for Speeds to 70,000 RPM', *Product Engineering*, (February).
- Pickels, E.G. (1950) 'Precision Speed Control', *Machine Design*, Vol.22(9), pp.102-107.
- Pickels, E.G., and P.F. Scofield (1950) 'Electronic Speed Control (assures safety at high speed)', *Electrical Manufacturing*, Vol.45, pp.66-69.
- Pinch, T., and W.E. Bijker (1984) 'The Social Construction of Facts and Artefacts: or How the Sociology of Science and the Sociology of Technology might Benefit Each Other', *Social Studies of Science*, Vol.14, pp.399-441.
- Pinch, T., and W.E. Bijker (1987) 'The Social Construction of Facts and Artifacts: Or How the Sociology of Science and the Sociology of Technology might Benefit Each Other', in W.E. Bijker, T.P. Hughes and T.J. Pinch *The Social Construction of Technological Systems*, Cambridge, Ma: The MIT Press, pp.17-50.
- Quensel, O., and T. Svedberg (1938) 'Studies of the brewing process by means of ultracentrifugal sedimentation, diffusion and electrophoresis measurements', *Meddr. Carlsberg Lab.*, Vol.22, pp.441-448.
- Rideal, E.K. (1953) 'James William McBain', *Obituary Notices of Fellows of the Royal Society*, Vol.8, pp.529-547.
- Rinde, H. (1928) *The Distribution of the Sizes of Particles in Gold Sols, according to the Nuclear Method*, Uppsala: Almqvist & Wiksells Boktryckari AB.
- Rosenfeld, M. (1942) 'Analytical cell for the ultracentrifuge', *Review of Scientific Instruments*, Vol.13, pp.154-157.
- Rothen, A. (1942) 'The Present Status of Molecular Weights of Proteins', *Annals of the New York Academy of Sciences*, Vol.XLIII, Art.5, pp.229-241.
- Rånby, B. (1987) 'Opening Address', in: B. Rånby (Ed.), *Physical Chemistry of Colloids and Macromolecules*, Oxford, London, Boston, Melbourne: Blackwell Scientific Publications, pp.3-4.
- Schachman, H.K. (1959) *Ultracentrifugation in Biochemistry*, New York: Academic Press.
- Schulz, F.N. (1903) *Die Grösse des Eiweissmoleküls*, Jena: Verlag von Gustav Fischer.
- Scudder Smith, C. (1941) 'High Rotational speeds in vacuum', *Review of Scientific Instruments*, Vol.12, pp.15-20.
- Sharples, L.P. (1939) 'Which centrifugal - and when?', *Industrial and Engineering Chemistry*, Vol.31, pp.1072-1075.
- Siedentopf, H., and R. Zsigmondy (1903) 'Über Sichtbarmachung und Grössenbestimmung ultramikroskopisches Teilchen, mit besonderer Anwendung auf Goldrubingläser', *Annalen der Physik*, Bd.10(1), pp.1-39.
- Signer, R., and H. Gross (1934a) 'Über das Verhalten von Polyesterolen in der Svedberg'schen Sedimentationsgeschwindigkeitszentrifuge', *Helvetica Chimica Acta*, Vol.17, pp.59-77.
- Signer, R., and H. Gross (1934b) 'Ultrazentrifugale Molekulargewichtsbestimmungen an synthetischen hochpolymeren Stoffen', *Helvetica Chimica Acta*, Vol.17, pp.335-351.
- Signer, R., and H. Gross (1934c) 'Ultrazentrifugale Polydispersitätsbestimmungen an hochpolymeren Stoffen', *Helvetica Chimica Acta*, Vol.17, pp.726-737.
- Skarstrom, C., H.E. Carr, and J.W. Beams (1939) 'Concentration of the chlorine isotopes by centrifuging', *Physical Review*, Vol.55, p.591.
- Skarstrom, C., and J.W. Beams (1940) 'The Electrically Driven Magnetically Supported Vacuum Type Ultracentrifuge', *Review of Scientific Instruments*, Vol.11, pp.398-403.
- Snoddy, L.B., E.J. Workman and J.W. Beams (1936) 'A Photographic Study of Lightning', *Physical Review*, Vol.49, p.860.
- Spinco (1960) *Analytical Ultracentrifuge*, Brochure SBE-3, Palo Alto, Ca.: Spinco Division of Beckman Instruments.
- Stanley, W.M., and R.W.G. Wyckoff (1937) 'The isolation of tobacco ring spot and other virus proteins by ultracentrifugation', *Science*, Vol.85 (12 February), pp.181-183.
- Stenius, P. (1987) 'Svedberg's early Studies in Colloid Chemistry', in: B. Rånby (Ed.), *Physical Chemistry of Colloids and Macromolecules*, Oxford, London, Boston, Melbourne: Blackwell Scientific Publications, pp.17-21.
- Sunderlöf, L.O., and K.O. Pedersen (1976) 'Physical Chemistry', in: *Acta Universitatis Upsaliensis-Uppsala University 500 years: 9 Chemistry*, Uppsala: University of Uppsala, pp.153-198.
- Staudinger, H. (1960) *Die hochmolekularen organischen Verbindungen - Kautschuk und Cellulose*, Berlin: Springer Verlag.

- Svedberg, T. (1905) 'Über die elektrischcedarstellung einiger neuen colloidalen Metalle', *Berichte der Deutschen Chemischen Gesellschaft*, Jhrg.38, pp.3616-3620.
- Svedberg, T. (1906a), 'Über die Eigenbewegung der Teilchen in kolloidalen Lösungen I, *Zeitschrift für Elektrochemie und angewandte Physikalische Chemie*, Bd.12, pp.853-860.
- Svedberg, T. (1906b), 'Über die Eigenbewegung der Teilchen in kolloidalen Lösungen II, *Zeitschrift für Elektrochemie und angewandte Physikalische Chemie*, Bd.12, pp.853-860.
- Svedberg, T. (1907) 'Studien zur Lehre von den Kolloiden Lösungen', *Nova Acta Regiae Societatis Scientiarum Upsaliensis*, Ser.IV, Vol.2, N.1, pp.1-160.
- Svedberg, T. (1909) *Die Methoden zur Herstellung kolloider Lösungen anorganischer Stoffe*, Dresden und Leipzig: Verlag von Theodor Steinkopf.
- Svedberg, T., and K. Estrup (1911) 'Über die Bestimmung der Häufigkeitsverteilung der Teilchengrößen in einem disperen System', *Kolloid Zeitschrift*, Bd.9, pp.259-261.
- Svedberg, T. (1912) *Die Existenz der Moleküle - Experimentelle Studien*, Leipzig: Akademische Verlagsgesellschaft.
- Svedberg, T. (1923) 'Colloid Chemistry Technique', in: J.H. Mathews (ed.), *Colloid Symposium Monograph*, Madison (Wi): Department of Chemistry, University of Wisconsin, pp.75-96.
- Svedberg, T., and Jette, E.R. (1923) 'The cataphoresis of proteins', *Journal of the American Chemical Society*, Vol.45, pp.954-957.
- Svedberg, T., and J.B. Nichols (1923) 'Determination of size and distribution of size of particle by centrifugal methods', *Journal of the American Chemical Society*, Vol.45, pp.2910-2917.
- Svedberg, T., and H. Rinde (1923) 'The determination of the distribution of size of particles in disperse systems', *Journal of the American Chemical Society*, Vol.45, pp.943-954.
- Svedberg, T. (1924) *Colloid Chemistry*, New York: The Chemical Catalog Company.
- Svedberg, T., and H. Rinde (1924) 'The Ultra centrifuge, a new instrument for the determination of size and distribution of size of particle in amicroscopic Colloids', *Journal of the American Chemical Society*, Vol.46, pp.2677-2693.
- Svedberg, T. (1925) 'Zentrifugierung, Diffusion und Sedimentationsgleichgewicht von Kolloiden und hochmolekularen Stoffen', *Kolloid Zeitschrift, Zsigmondy-Festschrift*, Bd.36, pp.53-64.
- Svedberg, T. (1926) 'Über die Bestimmung von Molekulargewichten durch Zentrifugierung', *Zeitschrift für Physikalische Chemie*, Bd.121, Abt. A, pp.65-77.
- Svedberg, T., and R. Fåhræus (1926) 'A new method for the determination of the molecular weight of the proteins', *Journal of the American Chemical Society*, Vol.48, pp.430-438.
- Svedberg, T., and J.B. Nichols (1926) 'The molecular weight of egg albumin. I. in electrolyte free condition', *Journal of the American Chemical Society*, Vol.48, pp.3081-3092.
- Svedberg, T. (1927a) 'Über die Bestimmung von Molekulargewichten durch Zentrifugierung. Zweite Mitteilung', *Zeitschrift für Physikalische Chemie*, Bd.127, pp.51-70.
- Svedberg, T. (1927b) 'The ultracentrifuge', in: *Nobel lectures chemistry 1922-1940*, Amsterdam, London, New York: Elsevier Publishing Company, 1966, pp.67-83.
- Svedberg, T., and A. Lysholm (1927) 'An ultracentrifuge of oil turbine type', in: *Nova Acta Regiae Societatis Scientiarum Uppsaliensis, Volumen extra ordinem editum*, Uppsala: Almqvist & Wiksells Boktryckeri AB, pp.3-24.
- Svedberg, T., and J.B. Nichols (1927) 'The application of the oil turbine type of ultracentrifuge to the study of the stability region of carbon monoxide-hemoglobin', *Journal of the American Chemical Society*, Vol.49, pp.2920-2934.
- Svedberg, T. (1928a) *Colloid Chemistry*, 2nd edn., New York: The Chemical Catalog Company.
- Svedberg, T. (1928b) 'The Molecular Weight of Hemocyanin', *Journal of the American Chemical Society*, Vol.50, pp.1399-1411.
- Svedberg, T., and Sjögren, B. (1928), 'The Molecular Weights of Serum Albumin and of Serum Globulin', *Journal of the American Chemical Society*, Vol.50, pp.3318-3332.
- Svedberg, T. (1929) 'Mass and size of Protein Molecules', *Nature*, Vol.123 (8 June), p.871.
- Svedberg, T., and F.F. Heyroth (1929) 'The influence of the hydrogen-ion activity upon the stability of the hemocyanin of helix pomatia', *Journal of the American Chemical Society*, Vol.51, pp.550-561.
- Svedberg, T., and B. Sjögren (1929) 'The molecular weight of Bence-Jones Protein', *Journal of the American Chemical Society*, Vol.51, pp.3594-3605.
- Svedberg, T. (1930a) 'Ultrazentrifugale Dispersitätsbestimmungen an Eiweisslösungen', *Kolloid Zeitschrift*, Bd.51, pp.10-24.
- Svedberg, T. (1930b) 'The Ph-stability regions of the proteins', *Transactions of the Faraday Society*, Vol.26, pp.740-744.

- Svedberg, T. (1931a) 'Molecular weights of the proteins in their native state', *Nature*, Vol.128 (12 December), pp.999-1000.
- Svedberg, T. (1931b) 'Les molecules dans un champ centrifuge intense', *Le Journal de Physique et le Radium*, T.7(2), pp.227-236.
- Svedberg, T., and I.B. Eriksson (1932) 'The molecular weights of phycocyan and of phycoerythrin. III', *Journal of the American Chemical Society*, Vol.54, pp.3998-4010.
- Svedberg, T. (1933) 'Sedimentation constants, molecular weights, and isoelectric points of the respiratory proteins', *Journal of Biological Chemistry*, Vol.103, pp.311-325.
- Svedberg, T. (1934a) 'Molecular weight analysis in Centrifugal fields', *Science*, Vol.79 (13 April), pp.327-332.
- Svedberg, T. (1934b) 'Sedimentationsmessungen mit der Ultrazentrifuge', *Die Naturwissenschaften*, Jhrg.22(15), pp.225-231.
- Svedberg, T. (1934c) 'Sedimentation of Molecules in Centrifugal Fields', *Chemical Reviews*, Vol.XIV, No.1, pp.1-15.
- Svedberg, T. (1934d) 'Die Molekulargewichtsanalyse im Zentrifugalfeld', *Kolloid Zeitschrift*, Bd.67, pp.2-16.
- Svedberg, T., G. Boestad and I.B. Eriksson-Quensel (1934) 'Possibility of Sedimentation Measurements in Intense centrifugal fields', *Nature*, Vol.133 (21 June), p.98.
- Svedberg, T. (1935) 'The ultracentrifuge and its applications', *Current Science*, Vol.4(5), pp.1-7.
- Svedberg, T. (1937) 'The Ultra-Centrifuge and the study of High-Molecular Compounds', *Nature*, Vol.139 (19 June), pp.1051-1062.
- Svedberg, T. (1938) 'The ultracentrifuge and its field of research', *Industrial and Engineering Chemistry, Analytical Edition*, Vol.10(3), pp.113-129.
- Svedberg, T., and Brohult, S. (1938) 'splitting of the haemocyanin molecule by ultra-violet light' *Nature*, Vol.142, p.830.
- Svedberg, T., and Gralén, N. (1938) 'Carbohydrates of well-defined molecular weight in plant juices', *Nature*, Vol.142, p.261.
- Svedberg, T., and Brohult, S. (1939) 'Splitting of protein molecules by ultraviolet light and α -rays' *Nature*, Vol.142, p.938.
- Svedberg, T. (1939) 'A discussion on the protein molecule', *Proceedings of the Royal Society of London*, Vol.170, Series A, pp.40-56.
- Svedberg, T. and Gralén, N. (1940), 'Soluble reserve-carbohydrates in the Lillifloreae', *Biochemical Journal*, Vol.34, pp.234-248.
- Svedberg, T., and K.O. Pedersen (1940a) *Die Ultrazentrifuge - Theorie, Konstruktion und Ergebnisse*, Dresden, Leipzig: Verlag von Theodor Steinkopff.
- Svedberg, T., and K.O. Pedersen (1940b) *The Ultracentrifuge*, Oxford: Clarendon Press. Reprinted by the Johnson Reprint Corporation, New York, 1959.
- Svedberg, T. (1947) 'The Cellulose Molecule. Physical-Chemical Studies', *Journal Phys. Colloid. Chem.*, Vol.51, pp.1-18.
- Söderbaum, H.G. (1926) 'Speech at Presentation Nobel Prize to R.A. Zsigmondy', in: *Nobel lectures chemistry 1922-1940*, Amsterdam, London, New York: Elsevier Publishing Company, 1966, pp.41-44.
- Söderbaum, H.G. (1927) 'Speech at Presentation Nobel Prize to T. Svedberg', in: *Nobel lectures chemistry 1922-1940*, Amsterdam, London, New York: Elsevier Publishing Company, 1966, pp.63-66.
- Taylor, H. (1956) 'James William McBain', *Journal of the Chemical Society*, pp.1918-1920.
- Tiselius, A. (1926) 'Über die Berechnung thermodynamischer Eigenschaften von kolloiden Lösungen aus Messungen mit der Ultrazentrifuge', *Zeitschrift für Physikalische Chemie*, Bd.124, pp.449-463.
- Tiselius, A. (1932) 'Über den Einfluss der Ladung auf die Sedimentationsgeschwindigkeit von Kolloiden, besonders in der Ultrazentrifuge', *Kolloid Zeitschrift*, Bd.59, pp.306-309.
- Tiselius, A., K.O. Pedersen and I. Eriksson-Quensel (1937) 'Observation of Ultracentrifugal Sedimentation by the Toepler Schlieren Method', *Nature*, Vol.139 (27 March), p.546.
- Tiselius, A., K.O. Pedersen, and T. Svedberg (1937) 'Analytical measurements of ultracentrifugal sedimentation', *Nature*, Vol.140 (13 November), pp.848-849.
- Tiselius, A., and S. Claesson (1967) 'The Svedberg and Fifty years of Physical Chemistry in Sweden', *Annual Review of Physical Chemistry*, Vol.18, pp.1-8.
- Urey, H.C. (1939) 'Separation of isotopes', *Reports on Progress in Physics*, Vol.6, pp.48-77.
- Vickery, H.B., and T.B. Osborne (1928) 'A review of the structure of proteins', *Physiological Reviews*, Vol.8, pp.393-445.
- Webb, J.H. (1936) 'The Photographic Intermittency Effect in the Region of Extremely Short Flash Periods', *Journal of the Optical Society of America*, Vol.26, pp.347-353.

- Weiser, H.B. (ed.) (1926) *Colloid Symposium Monograph*, New York: The Chemical Catalog Company, Inc.
- Williams, J.W., and C.C. Watson (1936) 'The spinning Top Ultracentrifuge and the Sedimentation of Small Molecules', *Journal of the American Chemical Society*, Vol.58, pp.2650-2651.
- Williams, J.W. (1942) 'Optical Problems of the Ultracentrifuge', *Annals of the New York Academy of Sciences*, Vol.XLIII, Art.5, pp.195-210.
- Williams, J.W. (1972) *Ultracentrifugation of Macromolecules*, New York and London: Academic Press.
- Williams, J.W. (1974) 'From colloid experiments to DNA', *Fractions*, No.2, pp.1-10.
- Williams, J.W. (1979) 'The development of the ultracentrifuge and its contributions', *Annals of the New York Academy of Sciences*, Vol.325, pp.77-92.
- Wyckoff, R.W.G. (1936) 'The ultracentrifugal concentration of pneumococcic antibodies', *Science*, Vol.84 (25 September), pp.291-293.
- Wyckoff, R.W.G., and R.B. Corey (1936) 'The ultracentrifugal crystallization of tobacco mosaic virus protein', *Science*, Vol.84 (4 December), p.513.
- Wyckoff, R.W.G. (1937a) 'Quantity ultracentrifugation with intense fields', *Science*, Vol.85 (16 April), pp.390-391.
- Wyckoff, R.W.G. (1937b) 'The ultracentrifugal purification and study of macromolecular proteins', *Science*, Vol.86 (30 July), pp.92-95.
- Wyckoff, R.W.G., J. Biscoe and W.M. Stanley (1937) 'An Ultracentrifugal Analysis of the Crystalline Virus Proteins Isolated from Plants Diseased with different Strains of Tobacco Mosaic Virus', *Journal of Biological Chemistry*, Vol.177, pp.57-71.
- Wyckoff, R.W.G., and J.B. Lagsdin (1937a) 'Improvements in the air-driven ultracentrifuge for molecular sedimentation', *Review of Scientific Instruments*, Vol.8, pp.74-77.
- Wyckoff, R.W.G., and J.B. Lagsdin (1937b) 'Quantity Heads for the Air-driven Ultracentrifuge', *Review of Scientific Instruments*, Vol.8, pp.427-429.
- Wyckoff, R.W.G. (1938) 'The Ultracentrifugal study of macromolecules', *Cold Spring Harbor Symposia on Quantative Biology*, Vol.6, pp.361-368.
- Zernike, F. (1941) 'De bouw der verschillende ultracentrifuges', *Nederlands Tijdschrift voor Natuurkunde*, Jrg.8, pp.222-229.



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