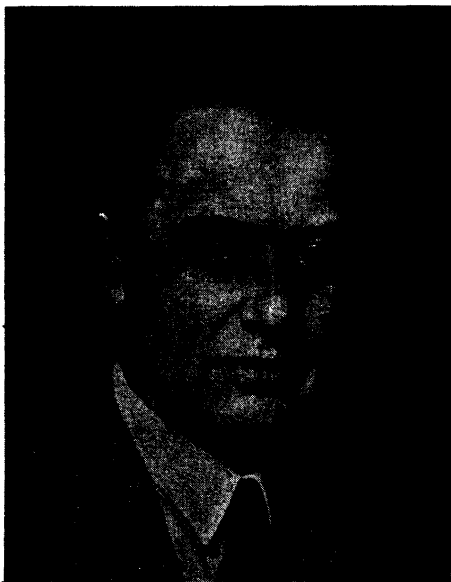


## Arne Tiselius



On November 4, 1948, it was announced that the Royal Swedish Academy of Science had awarded Professor Arne Tiselius, Upsala, the Nobel Prize for 1948 in chemistry for his work on electrophoresis and adsorption analysis and in particular for his discovery of the complex nature of the serum proteins.

Arne Wilhelm Kaurin Tiselius was born in Stockholm, on August 10, 1902 as son of the Swedish mathematician Dr. Hans Tiselius and his Norwegian wife Rosa Kaurin.

At school Tiselius had a very inspiring teacher in chemistry and biology who profoundly aroused his interest for chemistry. When the teacher discovered Tiselius' ability in chemistry, he gave him a private

key to the laboratory of the highschool, so that it was possible for Tiselius to carry out his own chemical studies when the lessons were over in the afternoon. In these years his intense love for science and especially chemistry was born. It soon became evident to him that he desired to go to Upsala to study under The Svedberg.

In 1921 he matriculated at the University of Upsala, where he took his first degree (fil. mag.) in chemistry, physics and mathematics in 1924. In 1925 he became research assistant in physical chemistry under The Svedberg and his scientific life started.

His first publication, in 1926, was together with Svedberg on a new method for determination of the mobility of proteins<sup>1</sup>. In this preliminary paper the light absorption method, already successfully used by Svedberg for following the rate of sedimentation in the ultracentrifuge, was introduced for the first time in the moving boundary method for studying the electrophoretic migration of proteins. In the next years Tiselius investigated very carefully the possible sources of errors in connection with the moving boundary method both from a theoretical and from an experimental point of view. He devoted special attention to all the effects that were found to cause »boundary anomalies» and he indicated how the method could be used in the study of the purity of proteins. Some experiments were also carried out on mixtures, but it was evident that if the method should be used for the analysis of protein mixtures the resolving power had to be improved considerably. He showed, however, that serum globulin prepared according to the classical methods

was definitely non-uniform in electrophoresis. His investigations were published as a thesis for the degree of doctor of Science at the University of Upsala in 1930<sup>2</sup> and gave him an assistant professorship in chemistry at this university.

By this time Tiselius had a family and had to think of the future. There was then in Upsala only one chair in general and inorganic chemistry, one in organic chemistry and a personal chair for The Svedberg in physical chemistry. At the other universities in Sweden the number of permanent positions in chemistry was not greater. Since the chair in general and inorganic chemistry was to become vacant in 1935, according to the rules, and as it could not be foreseen that other chairs in chemistry would become vacant in Sweden for quite a period he felt it his duty to try to get this chair.

After he had finished his work on the thesis it was quite natural for him to want to get some change in his studies. The electrophoresis problems were, therefore, put aside for several years, and he attacked new problems that gave him experience in other fields. The question of adsorption and diffusion in solid matter attracted him very much and he saw clearly that if progress was to be gained in this field one had to work with well defined and transparent crystals. Among the minerals belonging to the zeolite family he found valuable test material. As, however, it was difficult to find sufficient samples of selected material suitable for the experiments in the mineralogical collections in Sweden, he made a long trip to some of the most lonely islets among the isolated Faroe Islands in the Atlantic Ocean in the summer of 1932. He returned to Upsala with a beautiful collection of selected zeolite crystals.

When Tiselius started his work on the diffusion of water into a zeolite crystal, it was known that the optical properties changed when the dried crystal became rehydrated. Up to that date no quan-

titative study of the phenomenon had been made. Tiselius, however, saw the possibilities of this accidental observation, found the governing factors and developed a very elegant and accurate method for the quantitative measurement of the diffusion of water vapour and other gases into zeolite crystals. The work was extended by kinetic studies of the diffusion and adsorption processes occurring in the unhydrated crystal in the presence of various gases<sup>3</sup>. The later part of the work was carried out at the Frick Chemical Laboratory at Princeton in 1934—35, when Tiselius had a Rockefeller fellowship for studying under Hugh S. Taylor.

Shortly after his return from the States, the chair he had aimed at was given to Gunnar Hägg, a choice that Tiselius also considered the most correct. The committee investigating the candidates' qualifications, however, emphasised Tiselius' great experimental and theoretical qualifications and the high standard of his publications. There was no question that he was very well qualified for a chair in chemistry but there was only one vacant and he had to continue as assistant professor. One may question the wisdom of the Swedish system with the very few permanent university positions, where it is rather accidental whether the universities could keep the right people on their permanent staffs. If a young assistant professor does not get a chair in his subject before his seven year period has passed, the university has very few possibilities to keep him. Even in the case of Tiselius there was undoubtedly a risk that he could be forced to leave the university when his term as assistant professor was over.

Before Tiselius went to Princeton he admitted that if he was completely independent and free to do whatever he liked, he would concentrate on biochemistry, where he thought some of the most fascinating problems of modern science were still waiting for their solution. During

his stay in Princeton, he had much contact with the Rockefeller Institute situated nearby. He became good friend with John H. Northrop and M. L. Anson, and these scientists evidently further stimulated his interest in biochemical problems.

After his return to Upsala, he resumed his electrophoretical work this time with serum globulin which he earlier had found to be non-uniform in electrophoresis<sup>4</sup>. He soon found that if real progress should be made in solving the problem of the nature of the electrophoretical inhomogeneity of this protein, a complete reconstruction of the apparatus had to be made and a new experimental technique had to be introduced. From the work on his doctoral thesis he was familiar with all the factors that were important in electrophoretical experiments. On the basis of this knowledge a new apparatus for electrophoretical analyses was constructed in 1936<sup>5</sup>. In this instrument the movement of the boundaries could be followed optically and the U-tube could be divided into well defined sections after the conclusion of the experiments allowing samples to be taken out from different parts of the U-tube for chemical analysis and for tests of biological activity. While the U-tube up to that date had always a circular cross section, the new Tiselius apparatus was equipped with cells with long and narrow rectangular cross sections. This gives for a given cross section an increased optical sensitivity and a better removal of the heat generated by the electric current, thus minimizing the risk of heat-convection currents. This severe source of error is furthermore much reduced by carrying out the experiments at a temperature of 0° to 4° C, where the buffer solutions applied have their density maxima. The result is that the new Tiselius apparatus can be safely used with a potential gradient in the U-tube at least ten fold higher than in any of the earlier constructions. It also means, that a much higher resolving power for

protein mixtures is obtained. The first experiments with horse serum immediately demonstrated the advantages of the new instrument. The schlieren pattern showed five bands moving with different speed through the electrophoresis cell. The fastest band corresponded to the serum albumin boundary. The four other boundaries were tentatively by Tiselius called the  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -boundaries, respectively. He also showed that the  $\alpha$ -,  $\beta$ -, and  $\gamma$ -boundaries corresponded to three different groups of globulins, and that the antibodies usually were found in the  $\gamma$ -globulin or between the  $\beta$ - and  $\gamma$ -globulins. It was also discovered that the  $\delta$ -boundary was a salt boundary depending upon the protein concentration and the nature of the buffer salts. By suitable choice of the buffer salts and by using protein concentrations below 1 per cent the  $\delta$ -boundary could be practically eliminated.

In the following years the method was tested by Tiselius and by his coworkers in all possible ways and various minor changes were made. A considerable improvement in the observation of the boundary was made when the Philpot-Svensson method was introduced<sup>6</sup>.

In the meantime Svedberg had been active trying to get a permanent position for Tiselius at the University of Upsala. At the end of 1937 he succeeded in finding a generous patron who made an endowment of half a million Swedish crowns to the University of Upsala for a permanent chair in biochemistry. A few months later Tiselius was called to be the first Karin and Herbert Jacobsson professor of biochemistry in Upsala.

Shortly after the publication of the new Tiselius apparatus his electrophoresis technique was brought into use in laboratories outside Upsala. The introduction of the Philpot-Svensson and its American modification, the Longsworth schlieren scanning method improved the usefulness of the apparatus and hundreds of them are at

present in use all over the world. For the scientist working with biocolloids, especially proteins, Tiselius' method has been of immense importance. It has given the biochemist a tool by which he can visually determine whether a substance under investigation is electrophoretically pure or consists of several components. In a purification process it gives valuable information about the progress of the fractionation. It is now generally considered that one of the necessary criteria of purity for a protein is that it is homogeneous in electrophoresis over a wide pH-range. It is, however, by no means a sufficient criterion.

Tiselius has also used his apparatus for preparative purposes and he has shown how the separation between electrochemically closely related substances may be improved by superimposing a constant movement of the solution in the U-tube over the movement of the individual boundaries. This procedure was used by Tiselius *et al.* for the isolation of the  $\alpha$ -,  $\beta$ - and  $\gamma$ -globulins preceding their chemical analyses. It was hereby found that the chemical properties of the three fractions were different<sup>7</sup>. Tiselius suspected early that each of these three main globulin components might consist of several individual proteins that by chance had similar mobilities. This point of view has recently been verified particularly by the results from the large scale fractionation of blood plasma carried out in the United States during and after the last war.

The work of Tiselius and his coworkers on serum and serum proteins greatly stimulated new research on this important group of substances. The method is being used more and more in other kinds of biochemical investigations and the number of publications in which Tiselius' method has been used is sharply increasing from year to year. At present it is already in the hundreds. Short surveys on electrophoresis have been given by Tiselius<sup>8</sup>.

Tiselius himself had hoped that his new electrophoresis technique, besides the above mentioned applications, might also have been useful to him in the solution of a problem which interested him deeply, *viz.*, the question of the identification and the isolation of large fragments and polypeptides obtained by a mild break down of protein molecules. In this respect the method was, however, a disappointment. He therefore started to look for other methods that could possibly serve his purpose and he thought that he had found it in adsorption analysis.

In preparative organic and biological chemistry adsorption methods had been used to some extent. Willstätter and his school purified their enzymes by adsorption to colloidal aluminium hydroxide, separation of the adsorbed complex from the mother liquor and subsequent elution of the enzyme from the colloidal hydroxide. The chromatographic method originally developed by Tswett had been extensively used for the separation, fractionation and purification of a number of natural pigments. Tiselius saw the possibility of this method, investigated it thoroughly and developed the adsorption method to an exact quantitative method for analysis of mixtures of closely related substances such as for instance amino acids, carbohydrates and fatty acids<sup>9,10</sup>.

In the preliminary experiments Tiselius made use of the same optical arrangements as in electrophoresis. However, because the accuracy obtained was not quite adequate and because sometimes organic solvents were used, it was advisable to introduce other methods for following the experiments. In 1941 successive interferometric observation of the filtrate was introduced<sup>11</sup> and this has since been the standard method. A survey on adsorption analysis has been given by Tiselius<sup>12</sup> and a more detailed description of the various methods used may be found in Claesson's thesis<sup>13</sup>. Quite recently a very interesting

and promising new application of the adsorption method has been made by Claesson, who has shown how molecular weight frequency curves may be obtained from the adsorption analysis diagrams from high polymers<sup>14</sup>. With other high molecular weight substances, such as for instance the proteins, this kind of adsorption method has not been as successful, and since Tiselius himself has been especially interested in this group of substances, he has been looking for a modification of the technique which could make the method useful in this field, too. In the search for this, very encouraging results have been achieved by the introduction of «salting out adsorption»<sup>15</sup>. It is based on his observation that «proteins and other substances which are precipitated at high concentrations of neutral salts (salting out), often are adsorbed quite strongly already in salt solutions of lower concentration than is required for their precipitation, and that some adsorbents which in salt free solutions show no or only slight affinity for proteins, at moderately high salt concentrations become excellent adsorbents».

Tiselius is at present working on the development of this method along different lines and it seems as if it may offer a number of new possibilities in the fractionation of mixtures of proteins and high molecular peptides.

Beside his scientific activity Tiselius has also been engaged in very important committee work. In 1944 he became member of a governmental committee for proposing ways and means for promoting and intensifying pure scientific research in Sweden. He has been one of the most active members of that committee and his point of view has evidently played an important role in the editing of the report to the government. The majority of the proposals made by the committee were accepted by

the government and the parliament, and became effective on July 1, 1946. It has really meant a great improvement in the conditions for pure science in Sweden. A number of new positions for assistants and technicians were given to the universities, they received more money for their scientific institutes and last but not least a Research Council for Natural Science (Statens Naturvetenskapliga Forskningsråd) was created, which could spend 1 million Swedish crowns a year on pure research mainly at the university institutes. Tiselius was chosen as its first chairman and he is as such playing an important role in the organization of Swedish science.

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