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A Short Survey of the Scientific Work of Torsten Teorell

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Torsten Teorell was born in 1905 and already as a schoolboy TT, as we used to call him, was interested in chemistry. He had a small laboratory of his own in the basement at home where he collected minerals. His dream was to become a mining engineer. He even practised at a railway laboratory when he was 15.

His test in the Swedish language for the matriculation examination dealt with "the law of mass action", a subject that he later on used in a work on antigen-antibody interactions.

However, the 1920's were characterized by economic depression and becoming a mining engineer remained just a dream. Instead he enrolled as a medical student at the Karolinska Institute in Stockholm and was soon working as a young assistant in the department of medical biochemistry under Prof. Einar Hammarsten. He was entrusted with the teaching of physical chemistry to the medical students already when he was 21. This was the time when concepts like pH and Donnan equilibrium first appeared and when acid-base determinations were for the first time possible by the van Slyke apparatus. Teorell's father, who noticed his disposition for such matters gave him Höber's "Die physikalische Chemie der Zelle und Gewebe" as a Christmas present in 1926. This book became a Bible for the young man.

Hammarsten, who noticed Torsten's ability, set him to work on the topic of how thymonucleic acid and protein were redistributed when a cell was about to divide. (Thymonucleic acid is what we today know as DNA). This topic resulted in a few papers, and though it did not then attract his interest it brought him further in contact with the nucleus-containing red blood cells of the salamanders, to which he returned at a later stage.

Whether Teorell suffered from stress or overwork or something else I do not know, but for some reason he developed a gastric ulcer. And this aroused an interest in gastric acid. Hammarsten supported his interest as he himself was studying the intrinsic factor, important for pernicious anemia.

At the end of the 1920's a popular hypothesis about the formation of gastric acid was the notion that acid was formed by the hydrolysis of ammonium chloride. Teorell therefore developed an analytical method for the determination of ammonia in cat experiments, but found no evidence for that hypothesis.

In order to improve his experiments he started to work with isolated but perfused stomachs and for the perfusion he needed heart-lung preparations as used by Starling. He received a stipend to work at Starling's old department at University College in London. This was before the time of heparin so all blood had to be defibrinated before every experiment. Even if he did not succeed in getting the important results he hoped for, he learned physiological techniques thoroughly. However, a few of his discoveries are still important today: The energy demand was calculated to be 900 gcal per litre gastric juice of which 94 % could be accounted for by the accumulation of the hydrogen ions. He showed that the gastric mucosa has a negative respiratory quotient, i.e. for the formation of gastric juice the mucosal cells consume not only oxygen but also carbon dioxide. The consequences of the resulting negative Bohr-effect still remain to be studied.

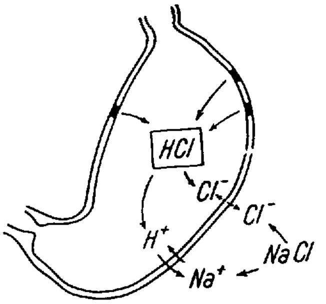


Fig. 1. The "Exchange diffusion" concept for the regulation of the gastric acidity presented in Teorell's dissertation (2)

Teorell's stay in London seems to have been of fundamental importance for his further scientific career, because there he met two of the contemporary scientific giants namely A.V. Hill and F.G. Donnan. Without doubt they influenced the main topic of his thesis entitled "Untersuchungen über die Magensaftsekretion" (2) and that was the so called "back diffusion theory" (Fig. 1). By instilling hydrochloric acid into unstimulated stomachs of cats he found that the hydrogen ions disappeared in a diffusion-like manner. This diffusion theory, as an explanation of the various acid concentrations in the stomach, gave Teorell a world-wide reputation.

On May 9th 1933 med.kand. Torsten Teorell defended his thesis. The faculty examiner was the professor of chemistry and pharmacy John Sjöqvist, who had himself 38 years earlier written a thesis about gastric secretion. His second examiner (according to the Swedish system) was Ulf von Euler, who quite recently had defended his own thesis and the third examiner was a friend, Torsten Åström.

The diffusion of hydrogen ions through the gastric mucosa could be mimicked by model experiments with artificial membranes and that was the start of an interest that occupied Teorell for the rest of his life.

In 1933 he not only defended his thesis. He also finished his medical studies, became assistant professor in medical chemistry and in addition a serving naval medical officer in the reserve. In this capacity he often had free hours in his cabin and this time he utilized for studies in mathematics. Second order differential equations became everyday fare for him and mathematical language came to characterize his continued scientific research. He became determined to acquire a broad and deeper knowledge in science and with a Rockefeller fellowship he managed to get to the Rockefeller institute in New York. There he worked at the department of General Physiology with the well-known professor Osterhout, at that time working with the "electric" alga Nitella. This model later became an often used model for Teorell as he found this alga in Uppsala quite near his home.

At the Rockefeller institute he was introduced into an extremely productive scientific environment, where besides Osterhout names such as Michaelis (Michaelis-Menten) and Wilbrandt may be mentioned.

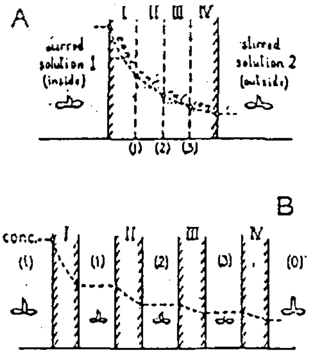


Fig. 2. The multimembrane technique for analyzing concentration profiles within a homogeneous membrane

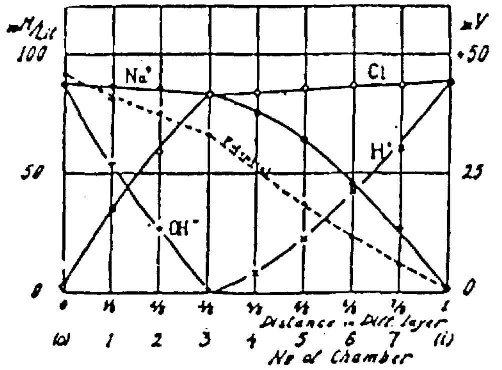


Fig. 3. Demonstration of non-straight-line concentration profiles in a membrane by the multimembrane technique

Teorell was interested in the concentration profiles within the membranes and invented an elegant way of studying them by creating the multimembrane technique (Fig 2). By putting several cellophane membranes in series and keeping the liquid interspaces between the membranes thoroughly stirred, he could consider this whole membrane battery as a model of a single membrane with the interspaces as locations within the membrane. - With this technique he found that the concentration profiles of ions in the membrane could deviate markedly from straight lines (Fig. 3). He further found that sometimes the transport of cations was larger than what could be expected from free diffusion and he postulated that the acceleration of cations could depend on "something" in the membrane itself. This "something" was later identified

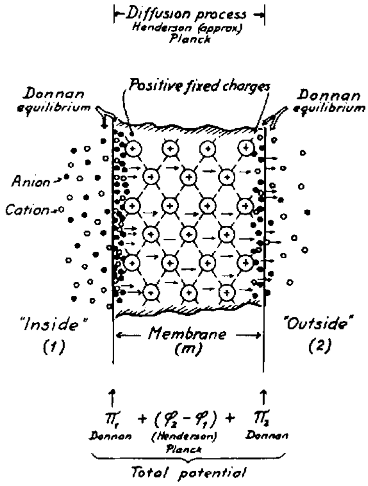


Fig. 4. Visualization of the effect of fixed charges in a membrane

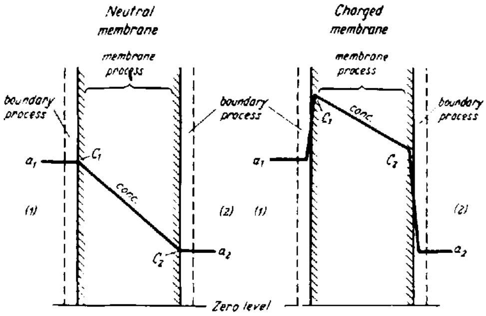


Fig. 5. A resulting concentration profile across a charged membrane of the type in fig. 4

as "fixed negative charges" (Fig. 4). At this time his work resulted in an important paper that he, with Osterhout's and Michaelis' blessing, published in the Proceedings of the Society for Experimental Biology and Medicine in 1935 (3) just before leaving New York. It consisted of only 3 pages and stated that the presence of immobile groups, e.g. carboxyl groups in a protein containing membrane created due to their indiffusibility a Donnan equilibrium at both sides of the membrane thus leading to a double Donnan potential. To this was added the Henderson-Planck diffusion potential within the membrane. The total membrane potential was thus the sum of three components (Fig. 5). This was something quite novel. The concentration profile within a charged membrane appeared to be quite different from the profile in a non-charged membrane.

Six months later Meyer and Sievers published almost identical ideas (1) and when the three of them met after the war they decided to call the new concept the "Teorell-Meyer-Sievers theory (TMS)". The theory mainly explained the electrical membrane potential but later Teorell expanded the theory to include also ion transport, electrical resistance, electrical rectification and other membrane characteristics. In 1951 he presented a complete theory at a meeting in Göttingen, which was later published in 1953 (7).

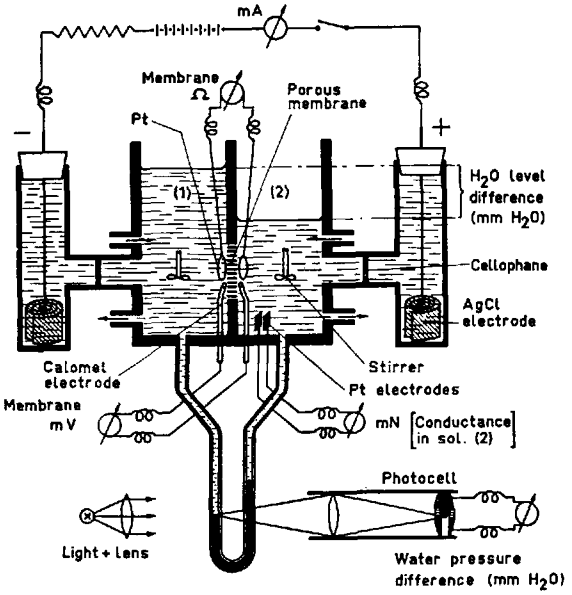


Fig. 6. A typical Teorell experimental set-up for simultaneous analyses of a multitude of variables

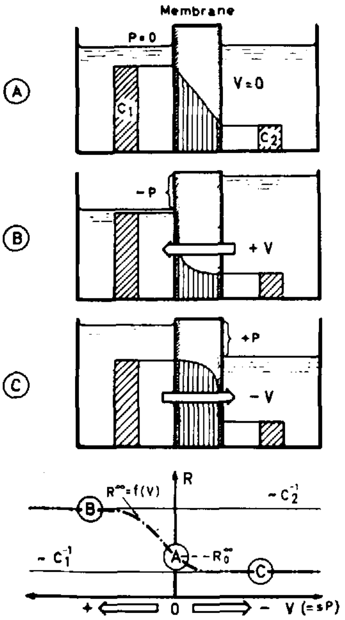


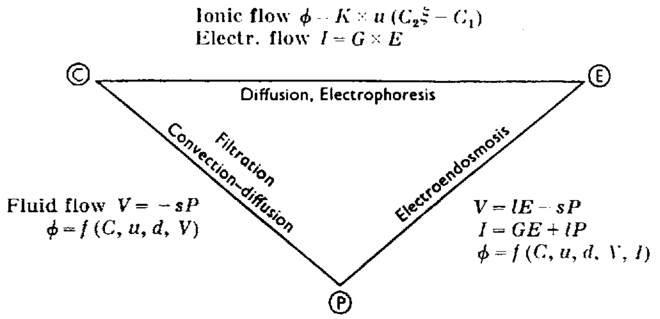
Fig. 7. A demonstration of the effect of hydraulic pressure across the membrane. The resulting bulk flow through the membrane will cause a change in the concentration profile and, as a consequence, a change in the electrical resistance

All calculations and theories were tested in elegant experiments with ingenious models, where all variables could be altered at will (Fig. 6).

For instance fig. 7 illustrates how water movement through a membrane due to hydrostatic pressure differences will affect the electrical conductance in the membrane.

Even if the fixed charge concept was an obvious spin-off from his stay in New York so was probably his discovery of the so called diffusion-effect. In a few words this describes a generalisation of the Donnan effect where the restrictions for ion movements also may depend on diffusion potentials.

Teorell from now on experimented with three simultaneous forces: the chemical potential; the electrical potential and the hydrostatic potential as illustrated in Fig. 8. He made many efforts to visualize the complicated interactions by building 3-dimensional models. In doing so it became obvious that sometimes negative conductances were present, i.e. unstable or metastable conditions, that proved to be of great importance for his later work.



C, concentration
E, electrical potential difference
P, hydrostatic pressure difference
u, mobility
G, conductance
I, current
d, membrane thickness
$\xi = e^{E/25}$

Fig 8. The three forces responsible for the property of a permeable membrane: the chemical, the electrical and the hydraulic potentials

THE MEMBRANE OSCILLATOR

So far my description has been based on his scientific progress, but now let us return to a chronological order.

After a short sojourn with the well-known immunologist Heidelberger, where he described the precipitin reaction with the use of the law of mass action, he obtained a position as associate professor in medical chemistry at Uppsala university in 1936. There he came into contact with Arne Tiselius and his electrophoresis techniques. It was during such experiments that he later discovered that red blood cell ghosts proved to be ideal osmometers enclosed by natural membrane material.

From 1939 and onwards, due to the war, Teorell became involved in various military medical problems, several of them together with the young Hans Ronge. In 1940 he was appointed professor in physiology at Uppsala university and when he returned to full research activities he once more addressed the gastric mucosa and made a number of important discoveries. Together with Richard Wersäll he mapped the electrical impedance of the mucosa (5) and in 1951 he made the important discovery that for each hydrogen ion secreted into the lumen a bicarbonate ion is transported to the blood side (6), a view that today is generally accepted.

After he published the comprehensive monograph about transport processes in membranes in 1953, he thought that at that time it was not possible to progress any further. But then - as he told me - one of those few golden moments of a scientist's life occurred one late evening in 1953. He was passing an electric current through a simple porous glass membrane and found as expected a water flow in one direction, but then suddenly the water started to flow backwards and a long series of oscillations of water movements and electrical potentials began. Thus was the

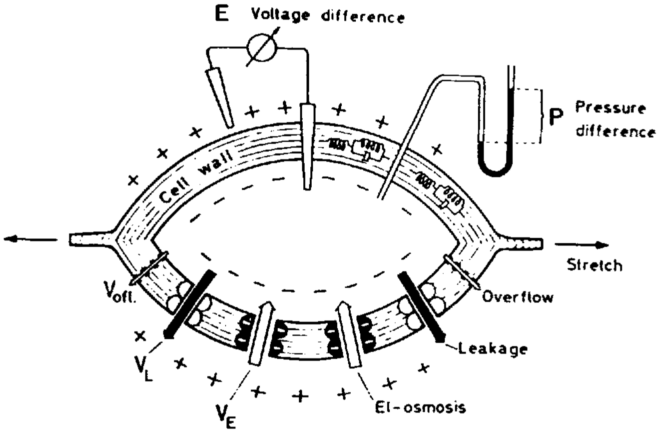


Fig. 9. The visualization of the "Mechano-Electrical Transduction"

"Membrane oscillator" discovered. This was the first time that it was shown that a pure electrolyte-membrane system could exhibit changes in potentials and resistances in the same way as was known for nerves. Hodgkin, Huxley, Code, Weidmann and others had concentrated on the development of the action potential but now also changes in conductance and volume could be explained. An important consequence was that now it was possible to explain how a mechanical stimulus could lead to an electrical impulse. This new discovery "the mechano-electrical transduction" could explain how reflexes originate (Fig. 9).

This new field resulted in an important number of publications and when during the 1950's and 1960's analogue computers appeared they became the totally dominant tool of Teorell's interest. He reproduced physiological reactions of all kinds and his activity was almost unbelievable. In 1970-1971 he collected his findings in an extensive article in the "Handbook of Sensory Physiology" (9), but his experimentation continued although he had deserted the analogue computer for the digital type.

He was encouraged in his work by several American and Swedish grants but he was disappointed as he did not seem to see any important impact of his work on physiology. He said: "Biophysics is too abstract and multifactorial to be used as long as more diffuse and unassailable hypotheses dominate the thinking". By now, however, Teorell was a renowned scientist, very well recognised abroad, much more than at home.

With an undertone of sadness he concluded that he had not got the credit for the progress of biophysical science, to which he had devoted his life. But instead his fame came in another way. A certain "youthful iniquity" gave him massive publicity. In 1937 he published two articles on the distribution of drugs in the body from a purely mathematical theoretical viewpoint (4). This was the start of pharmacokinetics, a subject that has since become an important topic in medicine and which is dealt with in another article in this symposium. At that time it was regarded mostly as a negative merit when he applied for the chair of physiology at Uppsala university. Today, however, he is in fact considered as "the father of pharmacokinetics".

In spite of his interest in many diversified fields of physiology and biophysics it is easy to find a common line in his research namely that of creating a physical picture of fundamental life processes. He had no definite long-term goal. Most important were the experiments themselves and solving problems.

Those of us who had the privilege of working with Torsten Teorell are grateful for being able to have known a great scientist, a great human being and a dear and beloved friend.

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