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physiology, biochemistry.

Weber was the son of Hermann Weber, a physician who, as *Geheimrat* and professor, was head of the medical department in several Berlin hospitals, and of Annemarie Becher Weber. After attending a private preparatory school, he entered the Mommsen Gymnasium in Berlin-Charlottenburg. In August 1914, immediately after the final graduation examination, he was called up for military service, which lasted until 1919. Weber was wounded in 1916, which gave him the opportunity to study medicine for a semester in Berlin (although artistic interests might have suggested training as a painter or sculptor). In 1919 he was able to resume his medical studies, first at Greifswald, then at Rostock and Heidelberg.

At Rostock, Weber studied with the physiologist Hans Winterstein, under whom he wrote a doctoral dissertation that brought him into contact with the physiology and biochemistry of the muscle, the area of his lifework. Winterstein gave Weber the task of experimentally investigating the role of lactic acid in the formation and relaxation of rigor mortis of the muscle. Winterstein had already studied this question. In the meantime the work of Otto Meyerhof at Kiel had drawn attention to the role of lactic acid in the energetics of the muscle.

At the end of 1921 Weber was awarded the M.D. degree. He approached Meyerhof, who was then *professor extraordinarius* at the Physiological Institute of Kiel University, and asked to be allowed to work in his laboratory. Weber spent half a year in Meyerhof's laboratory—a short time that had a lasting influence on him and his scientific approach. Through Meyerhof, Weber's interest was directed to "molecular energetics," and Weber took it upon himself to establish the physicochemical foundations for Meyerhof's energetics of the muscle.

In the autumn of 1922 Weber became an assistant to Winterstein at Rostock, a post Winterstein had promised him while he was still a student. That October he married Marga Oltmanns, a student of philosophy and history with artistic talent and interests; they had two daughters and a son. In 1924 he lost the assistantship because of financial constraints but received a Rockefeller Foundation grant that enabled him to finish his work to qualify as a lecturer.

At Rostock, Weber did work in the physical chemistry of muscle proteins because he regarded knowledge of muscle proteins as a precondition for understanding muscle contraction. In 1895 Otto von Fürth had studied the separation of muscle proteins into myogen and myosin. Weber took up these studies and developed methods for isolation of those substances. He examined their physicochemical characteristics, in particular the isoelectric point and the buffer action curve. From his investigation Weber concluded that myosin was a protein sui generis and probably represented the shortening substance of the muscle. At the same time he proved, on the basis of the isoelectric point, that neither the acid swelling theory of muscle contraction, for years an object of discussion, nor the deionization theory, suggested by Meyerhof, was supported by his data. In 1925 Weber qualified as *Privatdozent* in physiology at Rostock University.

That same year Weber went to Berlin, where he obtained a position as auxiliary assistant under Peter Rona in the chemistry department of the Pathological Institute. In the 1920's Berlin offered a wealth of inspiration for a young natural scientist, particularly through the institutes of the Kaiser Wilhelm Institute. Important to Weber was the contact with researchers using physical and physicochemical methods in the biological sciences. Besides Rona they included Leonor Michaelis, Otto Warburg, and Kurt Hans Meyer. Meyerhof also was working at the Kaiser Wilhelm Institute. Rona allowed Weber to work in his chosen field of muscle proteins, continuing his studies done at Rostock. About 1925 the research on proteins experienced a crisis. The chemical interpretation of the structure of proteins as macromolecules strictly in accordance with the laws of stoichiometry was confronted with the colloid chemistry interpretation of proteins as aggregates of smaller molecules with a bonding of small molecules or ions described as adsorption. Weber decided to investigate some basic questions of the physical chemistry of proteins and chose the muscle proteins as his subject.

With a theoretical study titled "Massenwirkungsgesetz und Kolloide" (1927). Weber embraced the "chemical" view of proteins. Working from the strict validity of the law of mass action in protein reactions, he derived equations for the dissociation of multivalent ampholytes that explained the known titration curves of proteins. In a 1929 study with David Nachmannsohn (later he spelled it Nachmansohn), who was also working with Rona, the hydration of protein ions was investigated. The work is theoretically related to Weber's studies of muscle physiology, since in 1912 Wolfgang Pauli had

amplified the acid swelling theory of muscle contraction with the hypothesis that the swelling is due to an intensified water bonding of the protein ions. Weber and Nachmannsohn furnished evidence that there is no connection between protein ionization and hydration.

In 1927 Weber became an assistant at the Physiological Institute of Münster University under Rudolf Rosemann. Here he was able to continue his studies on a larger scale. In order to explain the results of the Berlin study of the hydration of proteins, Weber had taken up the dipolar ion (*Zwitterionen*) theory of proteins. In 1923 Niels Bjerrum had comprehensively and theoretically substantiated the presence of dipolar ions in ampholytes. It was presumed that under certain conditions proteins could also be present as such dipolar ions. Weber proved experimentally, using various methods, that proteins are present as dipolar ions at their isoelectric point.

Weber's outstanding accomplishment while at Münster was the discovery and careful investigation of the oriented myosin thread (which today would be described as actomyosin thread). In 1928 Alexander von Muralt and John Tileston Edsall at the Harvard Medical School had developed a method for isolating myosin based on Weber's 1925 study (muscle physiologists still speak today of "Weber-Edsall myosin"). Weber obtained the myosin thread from such a myosin solution, about which he said:

It is indeed possible by a sort of stretch spinning method to produce from myosin solutions structures that behave mechanically, optically, and X-ray optically similarly to muscle fibrils. The method consists in injecting myosin solutions of very high purity from a capillary into distilled water in which they instantaneously solidify to a thread that can be flowingly stretched to about twice the original length. . . . These stretched myosin threads . . . represent . . . a sort of muscle model on which possibly also mechanical-thermal characteristics and perhaps some other forms of contractures can be investigated. . . . The research methods of the chemistry of fibers are applicable to the threads. ("Das Röntgendiagramm von gedehnten Myosinfäden," p. 269)

Weber investigated this thread model, using all available methods. With Gundo Boehm he was able to show that the fiber diagram obtained with short exposure to X rays is identical to that of the freshly stretched muscle. Weber also used mechanical and polarization optical methods. The birefringence of the muscle fiber had been known for a long time. The discovery of the flow birefringence in myosin solutions by von Muralt and Edsall in 1930 had shown the myosin to be composed of rod-shaped molecules and a probable source of the birefringence of the muscle. From his polarization optical and radiographic measurements Weber derived the first data on the probable size of the myosin molecule. He summarized the results for muscle proteins in the classic paper "Die Muskeleiweisskörper und der Feinbau des Skelettmuskels" (1934). Weber did experiments in which he added creatinin, for instance, to the myosin thread—without effect. He did not, however, use the newly discovered adenosine triphosphate (ATP), so he missed the key discovery made by Albert Szent-Györgyi in 1942.

In the meantime, Weber had been appointed extraordinary professor of physiology in 1931. At Münster, as at other German universities, after much hesitation efforts were being made to separate biochemistry (then called physiological chemistry in Germany) from physiology and to create separate chairs for them. In May 1933 an associate professorship of physiological chemistry was created that Weber, as unofficial extraordinary professor, occupied as a deputy. It was not until 1938 that he became a regular extraordinary professor of physiological chemistry, a delay that he attributed to the fact that the National Socialists considered him politically unreliable. An important recognition of Weber's studies of protein was an invitation from the Royal Society of London to a symposium titled "Discussion on the Protein Molecule" in November 1938.

In April 1939 Weber was offered the chair of physiology and physiological chemistry at Königsberg University. A few months later World War II broke out. Two outstanding studies emerged under the restricted working conditions during the war; in both of them Weber cooperated with recognized specialists. In 1941 Manfred von Ardenne in Berlin and Weber succeeded in representing for the first time thread-shaped structures from myosin solutions in photographs taken by means of the electron microscope. In 1942 Gerhard Schramm and Weber examined myosin solutions with the ultracentrifuge at the Kaiser Wilhelm Institute in Berlin-Dahlem. They found two monodisperse fractions, a discovery that shortly afterward was explained in the discovery of actomyosin.

At Königsberg, parallel to the investigations on muscle proteins, Weber had continued his work on the general physical chemistry of proteins. Outstanding was an experimental study with Ingeborg Lichtenstein of the various ionogenic groups of protein molecules. Previously information on this question came from calculations on the basis of amino acid analyses and was partly wrong. Weber summarized his studies in this field in "Eiweisskörper als Riesenionen" (1942).

In 1944 the *Oberkommando* of the army awarded Weber a research contract to study the use of animal serum albumin as a substitute for blood. This gave him the opportunity to leave Königsberg in January 1945, shortly before Soviet troops entered the city. (His family had already been evacuated to Western Germany.) In 1946 Weber was offered chairs of physiology at Berlin, Erlangen, Mainz, and Tübingen, He chose Tübingen, where, due mainly to the Kaiser Wilhelm Institute, evacuated from Berlin, an extraordinarily stimulating atmosphere was developing for the life sciences. In addition, the university had not been destroyed in the war, and therefore working conditions improved more quickly than at other universities.

While Weber was at Königsberg, research into muscle contraction had been directed into new channels by two important discoveries. At Moscow in 1939, Vladimir Aleksandrovich Engelhardt and M.N. Liubimova had observed the ATP-splitting effect of the Weber-Edsall myosin, and in 1942 Albert Szent-Györgyi at Szeged (Hungary) had determined that addition of ATP to myosin threads leads to shrinkage, which he interpreted as contraction. In spite of the war, Weber was able to visit

Szent Györgyi's laboratory and to obtain information about his discoveries, and thus started investigations while still at Königsberg. As soon as the institute directed by Weber at Tübingen was functioning, he and his colleagues began systematically to examine ATP's effects on the muscle proteins. Preparative methods were devised for the isolation of myosin and actomyosin, the latter having been recognized as a complex of myosin and actin by Brunó F. Straub at Szeged. The proteins were characterized extensively by measuring physical and physicochemical properties. Using a new extraction method, Weber's co-worker Wilhelm Hasselbach provided information on the quantity ratios of myosin and actin in the muscle.

One of Weber's basic ideas in the investigation of muscle contraction was the possibility of using suitable models to break down the complex physiological process into simple elements. The thread model discovered at Münster, which now turned out to be an oriented actomyosin thread model, offered one possibility, especially since it appeared to exhibit contraction on addition of ATP. A second model, the fiber model (more precisely, the singlefiber model), was developed by Weber's daughter Annemarie, who wrote her dissertation for the M.D. degree under her father in 1950 and became an assistant in his institute. In continuation of SzentGyörgyi's experiments, she produced glycerol-extracted individual fibers of such thinness that ATP could penetrate by diffusion into the interior of the fibers in adequate concentration.

In the following years the basic processes of the contraction cycle, the transformation of chemical energy from ATP hydrolysis to mechanical work, were individually investigated in these models and explained step by step, a considerable amount of this work being done in Weber's laboratory. First, the modulus of elasticity was measured with newly developed precision instruments. It was particularly important to block the ATP-hydrolyzing effect of actomyosin by poisoning—for instance, by SH-group blocking agents. This makes a double effect of ATP apparent: hydrolysis of ATP by actomyosin leads to contraction, and the binding of ATP on actomyosin when hydrolysis of ATP is blocked results in a plasticizing effect. The time analysis of the contraction cycle showed that ATP is the direct energy souce for contraction of the muscle and that this energy is liberated at the beginning of contraction. It was now also possible to settle the question of the cause of rigor mortis, which had been the subject of Weber's doctoral dissertation more than twenty years earlier: when all the hydrolyzable ATP is used up, the plasticizing effect is eliminated and the muscle becomes rigid.

However, the living muscle and the models differ in one important way. The living muscle exhibits a state of rest in which ATP is present but not hydrolyzed. On the other hand, in the models ATP, if its hydrolysis is not blocked, is always split and initiates the contraction. The models helped to clarify this situation. Weber's colleague Hasselbach discovered an inhibiting influence of large concentrations of calcium ions on the contratcion model, and it was possible to study this in the model. Shortly afterward it became apparent that there was a relationship to the relaxing factor, which B. B. Marsh and J. R. Bendall had discovered independently of each other. This factor is missing in Weber's muscle models. Weber recognized the importance of this discovery, and in the following years extensive investigations of this factor were carried out in his laboratory. Among other things they led to the discovery of the calcium pump by Hasselbach.

In spite of the great progress in the explanation of the mechanism of muscle contraction that numerous groups of workers had made in many countries, the actual molecular mechanism of the contraction was still unknown. Time and again researchers discussed the obvious idea that a folding and coiling of the thread molecules of the myosin causes the shortening, the energy needed for the relaxation. Weber also considered this. However, after investigations on the models had clearly shown that the contraction process governed by ATP hydrolysis is the energy-consuming part of the cycle, and not the relaxation, Weber dismissed the thermokinetic theories (1951).

The state of knowledge in 1954, indicated here only in quite broad outlines, was presented by Weber and Hildegard Portzehl in a brilliant summary titled "The Transference of the Muscle Energy in the Contraction Cycle" (1954). This again showed Weber's exceptional ability to analyze critically the important results of a field of research that was rapidly changing and to describe it in a synopsis.

In April 1954 Weber was appointed director of the Institute for Physiology of the Max Planck Institute for Medical Research at Heidelberg. This institute, which was founded in 1929 as the Kaiser Wilhelm Institute for Medical Research on the initiative of Ludolf von Krehl, and at which Otto Meyerhof was employed until his emigration in 1938, was headed by Weber until his retirement in 1966.

At Heidelberg it was possible for Weber to continue his previous work more extensively and with the aid of a greater number of co-workers, who included Wilhelm Hasselbach, Erich Heinz, Hartmut Hoffmann-Berling, Ingeborg Lichtenstein, Madoka Makinose, Hildegard Portzehl, Johann-Caspar Rüegg, Friedrich Tonner, Gerhard Ulbrecht, and Weber's daughter Annemarie. An ever-increasing number of study groups were formed, and under the guidance of experienced colleagues of Weber's they investigated the complex questions of muscle contraction. The experimental studies of this period were published to an increasing degree by Weber's colleagues without his coauthorship. Two particularly interesting areas of research will be mentioned briefly. While examining the relaxation factor, Hildegard Portzehl discovered that it is not an enzyme, as first assumed, but consists of ultramicroscopic particles. This cleared the way for a new field of study that connects the membrane activation of the muscle with the contraction process. (After Weber retired, his successor, Hasselbach, made this field a main area of research.) Hartmut Hoffmann-Berling added a further interesting contraction model to the thread model and the fiber model. He was able to prove the presence of ATP-dependent contractile substances in cells. On this basis the cell model was created (which cannot be discussed in any detail here).

At the beginning of the 1950's findings on the structure of myofibrils were obtained by the research groups of Hugh E. Huxley and Jean Hanson in London, as well as of A. F. Huxley in Cambridge, using microscopic and radiographic methods. These findings led in 1955 to postulation of the sliding filament theory of muscle contraction, which is generally accepted today. This theory, which came as a surprise to Weber (he had discussed the possibility of a dislocation of length-constant elements in 1942 but rejected this idea), was included by him in a lecture concerning a chemical theory of the whole process of contraction (1956). Weber thus once again provided an exceptional example of his ability to establish theories of complex processes.

At the International Congress of Biochemistry at Brussels in 1955, Weber lectured on the basic ideas of a new chemical contraction theory, which assumed a high-energy binding of a phosphate group of ATP to the contraction protein (phosphorylation). In 1956 he modified his theory and adapted it to the sliding filament mechanism. The importance of his descriptive theory lay in the assistance it offered for the understanding of the essential role of ATP and its relationship to the mechanical processes in muscle contraction, although the phosphorylation of the actomyosin assumed by Weber could not be confirmed.

At first Weber's scientific achievements found recognition abroad rather than in Germany. His physical-chemistry-oriented research was at first strange to many physiologists in Germany. He was elected a member of the Leopoldinische Akademie der Naturforscher in Halle (1955) and served as its vice president from 1963 to 1971. The Leopoldina honored him with its Carus Medal (1955) and its honorary presidentship (1971). It possesses a bronze bust of Weber created by his son, Jürgen, Weber was an honorary member of the Harvey Society (1953) and of the American Physiological Society (1959), and held honorary doctorates from Munich and Halle universities.

Weber's scientific importance lies in the fact that at an early date he directed modern muscle physiology along the path of molecular biological research. The outstanding contribution of his scientific approach through the analysis of suitable models was the explanation of the relationship between ATP hydrolysis and mechanical muscle contraction.

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