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## ALBRECHT KOSSEL, A BIOGRAPHICAL SKETCH**

"The number of Bausteine which may take part in the formation of the proteins is about as large as the number of letters in the alphabet. When we consider that through the combination of letters an infinitely large number of thoughts can be expressed, we can understand how vast a number of properties of the organism may be recorded in the small space which is occupied by the protein molecule."[45]

Modern knowledge of protein chemistry rests firmly on a number of fundamental discoveries extending back to the time of Beccarius and Scheele. Although it has been two hundred and twenty years since Beccarius isolated gluten from wheat, factual knowledge of proteins has accumulated with great rapidity only during the last century. It may be noted that the impetus was not only the increasing general interest in science, but in part a recognition of the need for a new division of scientific learning, biochemistry. This daughter-science of chemistry and physiology has gained its recognized place through the efforts of many, among whom Hoppe-Seyler and Albrecht Kossel were pioneers.

Kossel was convinced of the necessity of relating chemical constitution to biological function. His particular field was the study of the nucleus of the cell, and he contributed much to advance early knowledge of the nucleic acids and two classes of proteins, the protamines and the histones. They formed his main scientific interests, and in order to characterize them he was led to a quantitative study of their composition and especially to the chemistry of the basic amino acids which are their principal constituents.

Kossel's† life and work were harmonious and his personality well fitted for scientific research. He was born on September 16, 1853 in the city of Rostock in Mecklenburg, the son of Clare and Albrecht Kossel. His father was a merchant, bank-director, and Prussian Consul in this Baltic seaport.[11, 15] The family was a large one of nine children: seven sisters and a brother, Hermann,‡ who was eleven years younger than Albrecht. The

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† His full name was Albrecht Karl Ludwig Martin Leonhard Kossel.

‡ Hermann Kossel received the degree of M.D. in 1888. He worked with Robert Koch from 1891 to 1904 and thus most of his researches were concerned with bacterial disease. He did outstanding work on diphtheria, malaria, and tuberculosis. In 1910, he went to Heidelberg as Professor of Hygiene. He died on April 30, 1925.[18, 87]

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Kossel family was sufficiently prosperous so that the young man's education was in no way handicapped.

Rostock, one of the most important commercial cities on the Baltic, had been thriving and influential from the time of the Hanseatic League and as a result of this leadership had secured a peculiar and liberal municipal constitution so that it existed more or less as a separate state until 1880. It may have been that the independent atmosphere of Rostock was an important factor in Kossel's frequently expressed dislike of the more typical Prussian spirit.

An old city, Rostock contains many picturesque Gothic buildings of which the most famous is the Rathaus lying in the center of the old town. Outstanding also are its five churches whose construction dates from the thirteenth and fourteenth centuries. One of these, St. Peter's, has a lofty tower which serves as a landmark to ships at sea. These towers were dear to Kossel, for in his later years he would often speak of them, and in the autumn of the year he longed to go North, for then the sunlight on the countryside shone as in Rostock.[16]

He attended the Gymnasium at Rostock and as a youth showed a keen interest in chemistry and botany.[15] His interest in botany led him to spend his first year as a medical student (in 1872 when he was nineteen years of age) at the University of Strasburg. These years at the university meant a separation from his family and an introduction to a new environment different from his northern German home; they also provided the opportunity to study with outstanding scientific men who had left other universities to come to head the faculty at the new university, which had just become German at the close of the Franco-Prussian War.

Here he followed his interest in botany by attending the lectures of Heinrich Anton de Bary, a physician and botanist, who was noted for investigations in cryptogamic botany. The formal courses offered by Bary included "Outlines of Botany," "The Propagation of Plants," and work in the botanical laboratory. His other teachers of this period included Waldeyer, who offered lectures in general anatomy and microscopy, Kundt, whose courses included experimental physics and electricity, and Bayer, the organic chemist, who taught "Organic Chemistry by Experimental Illustration" and offered practical work in the chemistry laboratory. Perhaps most important among his teachers was Hoppe-Seyler, who at Strasburg headed the first and for a long period the only department of biochemistry in Germany. Kossel undoubtedly attended both courses offered by Hoppe-Seyler—physiological and pathological chemistry, and a practical medical chemistry course.[6]

For some reason Kossel finished his studies at the University of Rostock, a much older institution than Strasburg. The University, like the city, must have been a singularly independent institution at the time of its founding in 1419 as it was conceived as a university without a faculty of theology, typically the center of medieval university life. Such a bold act soon had repercussions, for six years after the founding of the school a papal ban caused it to move to Griefswald. The faculty did not return to Rostock until eighteen years later.

The school had recently expanded its quarters when Kossel entered, and many of the buildings were only a few years old. Here Kossel completed his studies and in 1877 passed his state examinations in medicine. Such a change from one university to another was not an uncommon feature in the education of German students. The determination of the adequacy of the preparation of a student of medicine depended not on the number or sequence of courses taken but on the ability of the candidate to pass the state examinations. Nevertheless, most German students spent ample time on course work. Kossel, for example, studied five years before he felt prepared to take the examination. Instead of entering a clinic or preparing himself otherwise for clinical medicine, Kossel returned to Strasburg as an assistant in Hoppe-Seyler's laboratory; thus began his career as an investigator.

Probably his grasp of the importance of the quantitative aspect of biochemistry was derived from Hoppe-Seyler, who was an excellent inorganic chemist as well as biochemist and had made several contributions to quantitative inorganic chemistry.[70] Hoppe-Seyler was interested in the chemical components of tissues and was engaged in investigations on hemoglobin, which he had named, using techniques familiar to him as a chemist and also examining the absorption spectrum of hemoglobin and its derivatives. He realized that hemoglobin acted merely as an oxygen carrier and carried oxygen in the molecular form and concluded that the oxidation of nutrients occurred in the tissues rather than in the blood.

Kossel's first investigations dealt with diffusion and dialysis of salts and peptones,[27, 28] and appeared in volumes two and three of the *Zeitschrift für physiologische Chemie,* launched by Hoppe-Seyler—in June 1877—the year when Kossel came to work for him. Kossel became editor of the Zeitschrift after Hoppe-Seyler's death in 1895 and held the post until his own death in 1927, a period of thirty-two years.

In 1878, Kossel started the investigations of nuclear materials which were to remain his life-long interest. Hoppe-Seyler's concern with the constituents of the red blood cell had led him and one of his students to investi-

gate a phosphorus component which they isolated and named lecithin. In 1869, Hoppe-Seyler, as editor of *Hoppe-Seyler's Medizinisch-chemische Untersuchungen,* received a paper from Friedrich Miescher which announced the separation of a nuclear substance from the pus cell, to which Miescher gave the name "nuclein."[78] His work was not the result of chance but of a conscious effort to find a chemical explanation of the differences in the morphology and physiology peculiar to nuclear material.

The properties of the new substance seemed unusual as it had more strongly acidic properties than proteins were known to possess. It was soluble in dilute alkali and insoluble in dilute acids, water, and organic solvents, thus resembling mucin, although it was not mucin. It contained no sulfur, but considerable amounts of phosphorus were present. At the time, the only known phosphorus-containing organic components of tissues were lecithin and proteins.

These claims seemed incredible to Hoppe-Seyler, who did not publish the paper at once nor return it to its author, but repeated Miescher's work with the aid of two students, Plosz and Lübavin. When satisfied in 1871 of the correctness of Miescher's claims, Hoppe-Seyler published the papers of Miescher, the original paper on "nuclein" from pus cells and a second on "nuclein" of egg yolk.[74, 75] Other papers in this issue were by Hoppe-Seyler and his students on the isolation of "nuclein" from yeast and red cells.[24, 64, 78]

In Basel, Miescher turned to the isolation of the new material from the sperm of salmon and discovered that the nuclear material of the ripe sperm consisted of a salt whose basic constituent was a protein which he named protamine.

It was this heritage from Miescher, who was anxious to explain the nature of the nucleus, and from Hoppe-Seyler, who was interested in the phosphorus of the red cell, that influenced all of Kossel's future work. His first paper, on the nucleins of yeast, appeared in 1878, in volume three of *Zeitschrift für physiologische Chemie,* and a second paper followed a year later; these dealt with the preparation and analysis of nuclein and the isolation of the bases hypoxanthine and xanthine from its hydrolytic products.[29, 30] Since Piccard had isolated these purines from the nuclein of fish sperm,[77a] Kossel's papers were confirmatory.

Kossel made his first prediction concerning the nature of proteins in 1881. Salomon and Chittenden had been able to isolate the xanthine bases from blood fibrin and albumin, and the idea was growing that these compounds occur in all proteins.[8, 80] Kossel did not agree; he held that the xanthine bases were components of nucleins but not of the simple proteins. Unfortunately, he had no proof to support his statement.[81] During this year

Kossel, aged 28, became a privat-dozent, receiving fees from the students to whom he offered two courses: "Concerning sepsis and antisepsis" and "Clinical-chemical research methods."[6, 25]

In 1881, he published his first book, *Untersuchungen über die Nukleine und ihre Spaltungsprodukte.*[26] It was evident to Kossel that nutritional tissues such as the liver or spleen have a larger nucleic acid content than have locomotive organs such as muscle, and therefore this nuclear material was not a reserve substance but was formed during the regeneration of tissue.

In 1883, Kossel left Strasburg for a more responsible post at the University of Berlin under E. DuBois-Reymond, succeeding Baumann as Director of the Chemistry Division of the Physiological Institute. His teaching status was not changed, but he taught physiological chemistry, both by lectures and by work in the laboratory, in place of hygiene.[6]

He continued research on the nucleus and in 1884 published a paper on a protein isolated from the red blood corpuscles of birds which was in salt-like combination with nucleic acid. It appeared to be different from Miescher's protamine and Kossel named it histone.[32]

Kossel discovered adenine, which he first isolated from pancreas, in 1885. He also isolated it from yeast nuclein, described its chemical transformation into hypoxanthine, and the formation of its simple salts.[33, 34, 36] In the following year, he demonstrated that nuclein from egg yolk yielded no xanthine bases on hydrolysis and proposed the name "paranuclein" for the material.[35]

In 1886, Kossel married Luise Holtzman, the daughter of Adolf Holtzman, who had been Professor of German Literature and of Sanskrit at the University of Heidelberg and one of the outstanding philologists of his day.[2, 60] Luise Holtzman was an intelligent and charming woman and an excellent hostess. She had a wide knowledge of languages and was well read. The Kossels were very devoted to one another throughout life. Kossel enjoyed music and literature but they were allotted only a limited space in his life which was so filled with science and home that he had little energy left for pursuit of the arts.[15] A party at the Kossel household was an extremely pleasant affair. Kossel, generally shy and retiring, drew on his past experiences and was an excellent storyteller when settled in the pleasant and familiar atmosphere of his home.

The Kossels had three children of whom two lived to adult life, a daughter dying when very young. Their son Walther,* was born in 1888, and their daughter Gertrude in 1889.[12]

* Walther Kossel is Professor of Physics at the University of Tubingen.[13] He is known for his theory of the physical nature of chemical valence and researches on x-ray and gamma-ray spectra.[13, 76]

In 1887, Kossel became Professor Extraordinarius in physiology. During this period he was busy with his new duties and with the publication of two books entitled, *Die Gewebe des menschlichen Körpers und ihre mikroskopische Untersuchung* (published jointly with Behrens and Schiefferdecker), and *Leitfaden für medizinisch-chemische Kurse.*[66] In the laboratory, he isolated theophylline from tea leaves and determined its structure and its relation to caffeine.[37, 38]

In 1888, Altmann announced his preparation of protein-free nucleic acid, and Kossel had the opportunity to study Altmann's product.[1] The results of his work were presented to the Physiological Society of Berlin on January 30, 1891.[39] Kossel announced the isolation of phosphoric acid, a considerable quantity of guanine and adenine, and a substance with the properties of a carbohydrate, from the products of hydrolysis of the nucleic acid. Two years later Kossel and his student Neumann isolated thymine and cytosine from "paranuclein," characterized thymine, and published a new method for the preparation of nucleic acids.[57, 58]

In January 1895, Kossel was called to Marburg to be Professor of Hygiene, but owing to the death of Kulz, he was appointed to the vacant seat as Professor of Physiology and Director of the Physiological Institute in April of that year.[21]

Marburg, in 1895, was a lovely town of 10,000 inhabitants. The University was the first to be founded as a Protestant institution in Germany; it was small, having only a few hundred students, but the faculty of medicine was distinguished and included Professors Korchelt in zoology, Hans Meyer in pharmacology, Schmidt in pharmaceutical chemistry, and Behring as Professor of Hygiene.[72]

Professor Kulz, Kossel's predecessor, noted for his work on sugar metabolism, had been a great friend of the Kultus Minister of Prussia, who built for him one of the finest laboratories of physiology in Germany. The laboratory was a stone building which contained a residence for the professor, with one or two rooms for the assistants, a library, an amphitheater, a laboratory with adjacent rooms for special techniques such as combustions, a professor's laboratory, and in the basement an animal room and a machine shop. The laboratory had desks for thirty to forty students and was used for both graduate and medical students. Kossel had seven graduate students at this time; T. H. Milroy from England, A. P. Mathews from the United States, Manilla Ide, Kutscher, who was later to be on Kossel's staff, Pierre Nolf from Belgium, Heine, and Noll.

Kossel offered courses in experimental physiology, general physiology, and the physiology and chemistry of urine secretion.[6] He had to teach the medical students elementary chemistry, as they were not given this instruc-

tion in the Gymnasium. Mathews reports that his lectures were clear and interesting.

At this time Kossel had the services of a personally trained assistant or diener, Petri, whom he had brought with him from Berlin. He, a native of northern Germany and an excellent technician, was responsible for arranging Kossel's demonstrations and carried out all his combustion analyses. Petri also looked after the students' supplies and even instructed the students in special techniques.

Kossel is reported not to have carried out an operation on an animal at this time.[72] But it is certain that he never lost his interest in carrying on his own chemical work. He is quoted by many of his colleagues as saying, "When I have discovered a new material, I will crystallize it myself."[16, 18] Like most chemists he had a special fondness for crystalline products and derivatives.

In August of 1895, Hoppe-Seyler died, and Kossel and E. Baumann, both students of Hoppe-Seyler, took over the editorship of *Zeitschrift für physiologische Chemie.* The first volume under their editorship (volume 21) contains an obituary written jointly by the two men, and the title of the journal was changed to *Hoppe-Seyler's Zeitschrift für physiologische Chemie.*[48] When Baumann died in 1897, Kossel carried on the editorship alone, which involved reading and criticising all of the papers submitted.

In 1896, Kossel isolated sturine and recognized its similarity to salmine.[40] This marks his entrance into the field of the proteins and nucleic acids of sperm, a work Kossel had taken up on Miescher's death. Kossel suggested that the term protamine should be used not only for the basic protein from salmon sperm, but as the name of a class of proteins. The isolation of the products of hydrolysis of protamines had led him to discover histidine as a mercury salt in 1895.[40, 55] Hedin independently isolated histidine as a silver salt in the same year. Kossel was so impressed with this work that he recommended Hedin highly for the vacant chair in physiological chemistry at the Jenner Institute in London.[10]

Probably the most important work produced during this period was the silver-baryta method for the determination of the basic amino acids, published in 1900 by Kutscher and Kossel.[56] The use of phosphotungstic acid, mercuric chloride, and silver nitrate had revealed to Kossel the possibility of a quantitative method to determine the basic amino acids. The method they developed was time-consuming and required a fair amount of material, but it was capable of producing accurate results if carefully handled. For many years it was the best method available for the analysis of basic amino acids.

Kossel's main interest now turned to the structure of proteins and in particular to that of the protamines. For years he sought an empirical formula for the protamines based on their amino acid content, thinking that they contained only basic amino acids without mono-amino acids, much as starch and glycogen are condensation products of glucose. This limited knowledge of the amino acid content of protamines led Mathews to ask Kossel (1895-1897) why he did not try to synthesize proteins from amino acids.[72] Kossel answered that he had considered the idea but had turned it over to Emil Fischer, who was better equipped to do that work and knew far more than he about organic synthesis. This does not indicate whether Kossel had considered seriously the mode of linkage between the amino acids which constitute a protein. If he had, he was not bold enough to state it publicly.

In a lecture to the German Chemical Society in 1901, Kossel discussed the position of protein chemistry and pointed out that the decomposition products represented many proteins, but that this did not mean that proteins were similar, for wide differences were found in the proportions of their various amino acids.[41] Kossel had shown that arginine is the main constituent of the protamines and that a large fraction of them consisted of basic amino acids, but he was never entirely satisfied with his methods and had considered the separation of amino acids through their esters. Dakin writes, "One of the bitter disappointments of his life was his failure to discover the ester method of separating amino acids. He supplied a student with adequate material but was assured that the higher amino acids did not form esters—a mistake he never forgave."[10]

He also continued work with students on the nucleic acids and in 1901, one of them, Ascoli, reported the discovery of uracil.[7] Evidently Kossel saw his graduate students often during this period, stopping by every afternoon to talk to them. Mathews found him a simple, friendly, modest, and kindly person. He describes Kossel as a fine-looking man about five feet ten inches tall, but who was often referred to as a tall man.

Mathews reports that he saw Kossel fussed but once.[72] DuBois-Reymond had died and the Berlin faculty was looking for a successor. The two people of choice were Kossel and Engelmann. The Kultus Minister, reported to be a stiff and arrogant Prussian, was coming to inspect Kossel and his laboratory. "We research men, the four or five of us, were stood at attention at our desks. Such a running around by Petri, Gerlach, the janitor, the assistants, and professor before he, the Minister, arrived you never did see!" Kossel did not receive the appointment, and Mathews remarks further, "Afterwards when Kossel went to Heidelberg, I asked him why he went there rather than stay at Marburg. He said he wanted to get out of

Prussia—he didn't like their domineering ways." Kossel told the following story himself: Kossel and his wife once took a trip to the Isle to Skye and were sitting on a bench enjoying the view. Kossel remarked, "Gott sei dank hier sind kein Berliner." Within a few minutes two Berliners sat down beside them.[10]

Whether or not this was the reason for his move, Kossel accepted in 1901 the chair of physiology and the directorship of the Physiological Institute at Heidelberg University that had become vacant on Kühne's death. This appointment was an honor because Heidelberg at the time had become the center of physiology in Germany. All of his students at Marburg travelled to Heidelberg with him,[22] so that when he reached there, he had a small group of graduate students which increased until in 1905, according to Mathews, there were thirty students from many lands. His lectures on physiology and physiological chemistry were attended on his arrival by one hundred students, and if the lectures became more popular as his fame increased, it is probable that the amphitheater (which seated only one hundred and fifty people) was always full.[77] He continued for a time to see his students rather frequently, but soon his visits were reduced to one or two weekly.[26] These students came from England, the United States, Russia, and Japan; in the early years at Heidelberg they were entertained informally at the Kossel home on the second floor of the Institute, but in later years these occasions became more formal.[77]

Kossel's lectures were always well prepared and up to date with the literature[9] and he used lantern slides and charts extensively.[77] He was not by nature a gifted speaker, and it speaks well for his preparative work that his students thought the lectures clear and interesting. To quote S. Edlbacher,[15] who worked with Kossel for fourteen years, "He spoke publicly with evident strain. It appeared to be a touch of modesty, against which he struggled until the last years of his life. He, therefore, spoke unwillingly at congresses and discussions." This shyness and reticence with strangers made him sometimes appear formal and stiff. He had a pleasant sense of humor and when telling stories his eyes twinkled with merriment and appreciation of the climax.[79] He spoke particularly well about the years he assisted Hoppe-Seyler, a period of his career which he remembered with great affection.[16]

His reserve seemed to detach him from everyday worries and troubles, and he solved his problems with an outward calm. Edlbacher, one of his students, comments, "In the fourteen years of almost daily contact, I never saw him (Kossel) annoyed. His equanimity invited the greatest respect."[15]

During this period Kossel sought to elucidate the structure of proteins by the following steps: (a) determination of the composition of the frag-

ments of hydrolysis, (b) the quantitative determination of their proportions, and (c) the mode of combination and arrangement of these fragments.[46]

He was not deluded into thinking that this would be simple; he stated the complexity of the task to Edlbacher thus: "I think of the protein molecule as one which can always answer to a chemical attack with some one of its characteristic groups. Much as grapes hang on a vine, so the protein molecule possesses a large number of characteristic groups; the guanidino group, the imidazole group, the indole nucleus, and so forth; perhaps necessarily in a given special combination, but they lie there in a manner which is accessible to attack."

Kossel considered the complex chemical constituents of the cell to be formed from simpler compounds which he termed Bausteine. These primary units were present in all living cells and from them were built by the processes of metabolism the secondary building stones which vary from organism to organism. These ideas were placed on a sounder basis when at Kossel's motivation Tamura carried out an analysis of bacterial cells and found that these small beings contained all the normal protoplasmic Bausteine.[83–86]

His view of the constituents of the cell was by no means that of it being a static system. He and his students showed that as the sperm matures, the proteins increase their content of basic amino acids. He spoke of this process as a step-by-step degradation of a more complex protein, containing a whole array of amino acids, to a simpler structure such as the protamines which contained relatively few amino acids. With F. Weiss he demonstrated that the muscle lost by the salmon contained sufficient arginine to account for the large accumulation in the maturing sperm and suggested that the other amino acids from the degraded muscle served as energy sources.[88] With Schenck, he investigated the testicle at varying stages of maturation and showed the increase in the content of basic proteins.[89]

Kossel tried to find some unit which might repeat itself in the protamines, by the silver-baryta method and Fisher's ester-distillation method. He and Dakin found the following proportions of amino acids in salmine:

| | | |
|---|---|---|
| Arginine nitrogen | | 89.2 per cent |
| Serine | " | 3.25 " |
| Valine | " | 1.65 " |
| Proline | " | 4.3 " |
| Loss | " | 1.6 " |

The molecular proportions would then correspond to ten molecules of arginine, two of serine, two of proline, and one of valine.[51]

Kossel suggested the following method for subdividing the protamines. If arginine is denoted by *a,* histidine by an *h,* lysine by an *l,* and monoamino acids by an *m,* and the relative amounts of these individuals by a number, a monoprotamine would contain only arginine as its basic component and could be represented by *am, $a_2m$,* or *$a_3m$* depending on the relative proportions of the arginine to the monoamino acid, or if it contained more monoamino acids than basic amino acids, as cyclopterine, by *$am_2$*. There would be two diprotamines: (a) those containing arginine and histidine and (b) those containing arginine and lysine. A triprotamine would contain arginine, histidine, and lysine; for example, sturine, which is represented as $(ahl)_2m$.[47]

Arginine was always of particular interest to Kossel. Hence it is not surprising that he and Dakin should discover arginase in liver;[50] the discovery was, however, somewhat accidental. Dakin had worked previously with Hedin on kidney autolysates but even with his help had been unable to find arginine. Kossel supplied Dakin with arginine carbonate and suggested that liver might be a better source than kidney. They were amazed to find that the blanks lost arginine rapidly, in five minutes or less, at this date an incredible speed. They showed that the arginine was converted enzymatically to ornithine and urea. Kossel also found a second intermediary product of arginine, agmatin, produced from arginine by decarboxylation.[42, 48]

One other enzyme, nucleinase, was studied by Kossel and his student de la Blanchardière in 1913.[14] They observed that certain tissue extracts caused a decrease in the viscosity of the nucleic acid solution before any chemical decomposition occurred.

Researches with Kennaway, Hiryama, and F. Weiss showed that arginine is bound in proteins by the $\alpha$ amino and carboxyl groups and that the guanidino group is free.[28, 54, 68] The same result was shown in studies on the imidazole group of histidine and the $\epsilon$ amino group of lysine.[49, 52]

Then Kossel turned to the isolation of peptides from his protamines. He studied the optical rotations of proteins and found evidence that treatment with alkali caused racemization while the amino acid was bound in the protein.[60–62]

He was interested as early as 1901 in crystalline derivatives of the basic amino acids, and asked Dakin to select compounds which he thought might yield such derivatives.[10] It was a fitting close to his life's work that he and E. Gross should have discovered (from a large number of aromatic compounds supplied by the Badischen Anilinfabrik) that dinitro-naphtholsulfonic acid, which Kossel named flavianic acid, formed an insoluble salt with arginine.[58]

To his credit, many of Kossel's students continued to work on problems in which he was interested. Levene, a student at Marburg, was a leader in the field of the nucleic acids and Dakin in amino acids and proteins. Steudel and W. Jones added to our knowledge of the nucleic acids. Folin not only advanced an important theory of protein metabolism but introduced methods of assay for tyrosine and tryptophan which enabled one to work with extremely small quantities of material. Many of Kossel's students such as Mathews, Hart, Henderson, and Cameron became outstanding investigators and as well able teachers. Kossel did not appear to be motivated in his work by the desire for personal acclaim but rather by curiosity and the satisfaction gained from the discovery of scientific truths. He was invariably modest about his own contributions and could not understand the base motives occasionally revealed by other scientific workers.[15] It has been said of him that he did not set his name on a publication unless he had contributed to the work[16]; a number of his students published papers from his laboratory on which his name does not appear. In the latter part of his life he was considered without doubt the leading German biochemist both by his own countrymen and by those abroad. The list of his honors extends from 1904, when he received an honorary Doctorate of Science from the University of Cambridge, up to the time of his death.*

From 1907 to his death he held the title of Geheimrat which placed him on the board of ruling members of the University of Heidelberg and assured him his position there for the remainder of his life. In the year 1908 to 1909, Kossel directed the business affairs of the University as Prorector.[15] On August 12, 1907 he opened the Seventh International Physiological Congress in Heidelberg, the first meeting of this group held on German soil, and, as host, gave the opening address welcoming the members.[19] This was a period of festivity for visitors but was devoted also to the more serious interchange of ideas; entertainments were most pleasant and included a trip in gaily decorated boats down the Rhine from Mannheim in the evening. On approaching Heidelberg, the castle was emblazed in a flood of light from fireworks. At the close of the meeting, it was unanimously voted that each member of the congress would send a photograph to Kossel as a souvenir.

In 1910, he received the highest honor given to scientific men, the Nobel Prize in Medicine, for his work on the nucleus of the cell. The prizes were

* Kossel received honorary degrees from the University of Greifswald (1906), from the University of Dublin (1908), from the University of Geneva (1909), and from the University of St. Andrews in Scotland (1912). He was made a member of scientific societies all over the world, including those in Stockholm, Upsala, Turin, Washington, Copenhagen, Gottingen, Leningrad, and Heidelberg.[9, 12, 21, 82]

presented by the King of Sweden on December 10, 1910, and amounted to £8000 each.[8] Kossel delivered on December 13 his statutory address, *Uber die chemische Beschaffenkeit des Zellkerns.*[44] The presentation of this award was followed by festivities at Heidelberg. The Student's Corps of the University honored him with a *Fackelzug,* or torch procession, and Kossel gave a party which was attended by his students, a number of the professors, and other academic guests.[26]

Probably Kossel was the honored guest at many German chemical and biochemical meetings, and he must have had to rely more on the help of his associates for the conduct of the routine academic duties. In particular, Petri was given more responsibility. He was devoted to Kossel, but like many persons of his status who have been given supervisory responsibilities, he began to consider that it was he who was actually in charge. Often Petri glorified his own wishes with the false statement that the Geheimrat wished it so, and his arrogance at times made life miserable for the students.[26, 72]

In the autumn of 1911, Kossel was invited to give the Herter Lecture at Johns Hopkins. He chose as his title, "The Proteins."[46] This was the only time Kossel came to the United States. It was a welcome opportunity for him to visit his many American friends and relatives, as well as those in this country with similar scientific interests. In preparation for the trip, he employed a woman student, Ruth Skelton, to tutor his daughter and himself in English conversation.[81] He knew the language slightly, for he could converse in English with his students when necessary. As part of the course of instruction, Miss Skelton read the *Pickwick Papers* to him. Kossel enjoyed them immensely and laughed heartily at the low-comedy characters like Sam Weller.[26] That Kossel enjoyed Dickens is not surprising, for his favorite German writer, and one whom he quoted fluently,[15] was Fritz Reuter, a man not unlike Dickens in many respects. Reuter wrote in Platt-deutsch about the people of Mecklenberg; he was an excellent humorist and a homely philosopher to the core. His characterizations rather than his plots made his stories, poems, and dramas real and full of a warmth particularly dear to his countrymen.

Kossel's wife, whose English was much better than his, found a book in this language on proteins and amino acids as source material for him.[26] His conversational English was evidently satisfactory; he stayed with the Dakins before the Herter lecture and several times used them as guinea pigs to test his skill. A guest, L. F. Barker, said that no German he had heard spoke English so well.[10] Dakin translated both his Herter and Harvey lectures into English for him. The Harvey Lecture was delivered in German on October 14, 1911, and was entitled "The Chemical Composition of the Cell."[45]

Kossel was an excellent guest and a very accommodating person. When Dakin apologized for the ugliness of the Third Avenue Elevated in New York, Kossel replied, ". . . But it gives shade!"[10]

He visited and gave lectures at several other universities, including the University of Chicago. A. P. Mathews, his friend and former student, was the head of the Department of Biochemistry at Chicago at the time, and the Kossels spent a pleasant week there.[72]

Kossel's wife had a number of relatives in this country who were very prominent citizens. These cousins were all members of the Hilgard family. Eugene Waldemar Hilgard was one of the leading geologists of this country in the latter part of the nineteenth century. In 1911, he was a professor emeritus of agricultural chemistry at the University of California in Berkeley, and the director of the agricultural experiment station in that state.[67, 69] Mrs. Kossel took back to Germany a rocking chair which he gave her, and it became the seat of honor in their home.[77]

Another cousin, Henry Villard (whose name had been changed to Villard from Hilgard), was a journalist, newspaper owner, and a financier of railroads and the Edison General Electric Company. His wife, Fanny Garrison Villard, was the only daughter of William Lloyd Garrison.[68]

The following years were sad ones for Kossel. His greatest loss occurred in 1913, when his wife died of acute pancreatitis. The impending war added to his sorrows. He was apparently not greatly interested in politics and seldom talked about them, although he is thought to have supported the more liberal Social Democrats. He never felt the necessity of maintaining "Germany's place in the sun."[10] His wife, who was undoubtedly more nationalistic, could embarrass him by mentioning this subject to guests at the dinner table. Kossel did not sign the Pronunciamento of German professors at the start of the war.[71] Perhaps the best description of his feelings during this period is that of his student, Edlbacher.[15]

> Kossel's life ran quietly. Difficult crises did not appear in his inner or outer nature . . . the World War with its consequences weighed on his soul, but his character was much too balanced not to overcome such blows of fate. The author knew him personally in 1913, when a great melancholy emanated from Kossel, as he still felt the loss of his wife . . . but a deep humor had helped him to surmount these years.
>
> The war had weighed heavily on his mind. Being aware of Germany's intellectual isolation, he realized, more than others, the plight of the fatherland. Certainly he, who had lived in harmony with the whole scientific world, must have felt strongly the breach of such a union. . . . Kossel felt very strongly from the start that the aggravating submarine warfare would bring America into the war.
>
> His strong love of truth suffered under all the confused mass of slander and lies which filled the world at that time. He was summoned, for example, each year to high

places to excuse official acts, by pronouncing that the allotted food provisions were sufficient. He refused this demand and others; still he was asked each time for a testimony, but would never declare untruths as truths.

Kossel still felt humble about Germany's rôle in the war in 1923, when he was honored as Germany's leading representative to the Eleventh Physiological Congress in Edinburgh.[20] Here he was given an honorary degree by the University, and when he appeared on the program of the Congress, he was greeted by applause lasting several minutes.[65] He was the guest of the president of the Congress, Sir Edward Sharpey-Schafer, who at this time was the sole surviving member of the original group that had founded the British Physiological Society and had acted to form the International Congresses. It is not surprising that Kossel was greatly pleased when Richet, a leading French physiologist, greeted him. Kossel realized that he might well have been passed by and said to Mathews, "You saw that he greeted me first!" It is reported that Kossel on his return to Germany again expressed his gratitude at the acclaim and recognition he had been granted by the members of the Congress.[65]

That year, 1923, marked Kossel's seventieth birthday, and in commemoration of the event, volume 130 (1923) of the Zeitschrift contained his picture near the titlepage, and the volume was dedicated to him.

In 1924, Kossel became professor emeritus, but he did not retire from active work. He continued to deliver his lectures in physiology and physiological chemistry.[6,17] He was fortunate in being able to carry on active research work at the Institute of Protein Research at Heidelberg which he had helped to found as the gift of the manufacturer, Fritz Behringer. Kossel had been the Director of the Institute, which was part of the laboratory of the Medical Clinic. On his retirement, he was asked by the Director of the Clinic, L. v. Krehl, to continue his research there.[15]

Probably the last scientific gathering Kossel attended was the Lister Centenary Celebration held in England in April of 1927.[5] He and the other delegates heard Sir E. Rutherford, President of the Royal Society, present the opening address to the King. In His Majesty's reply the hope was expressed that this gathering of scientific men would "strengthen the cooperation of all nations in the accumulation of scientific knowledge for the benefit of the human race." For Kossel this somewhat platitudinous message must have had a special meaning.

As the last years of Kossel's research were crowned with the discovery of flavianic acid, so his last months were spent in the labor of writing a monograph on the *Protamines and Histones,* which was published shortly after his death on July 5, 1927. Late in June he had an attack of angina pectoris which recurred on July 4, and he died quietly on the following day.

In the preface to his monograph he summarized the contributions made to that date by the researches on the chemistry of the nucleus. He felt that our knowledge "has so far been derived only from the descriptive side" and that the substances found in the nucleus were so far purely of chemical interest. However, the wide variety of chemical structures in the various species and genera of animals suggested that a more important morphological distinction might be found to result from these chemical differences. Kossel reiterated the hope that the protamines, as analogues of typical proteins, might be particularly favorable substances for the study of certain properties and structural relations of the proteins.

Thus Kossel in his seventy-fourth year was to the last still looking forward to new experiments which might solve some of the mysteries of the important rôle of the nucleus in the development of the cell and of the organism.

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