John Jacob Abel
1857-1938

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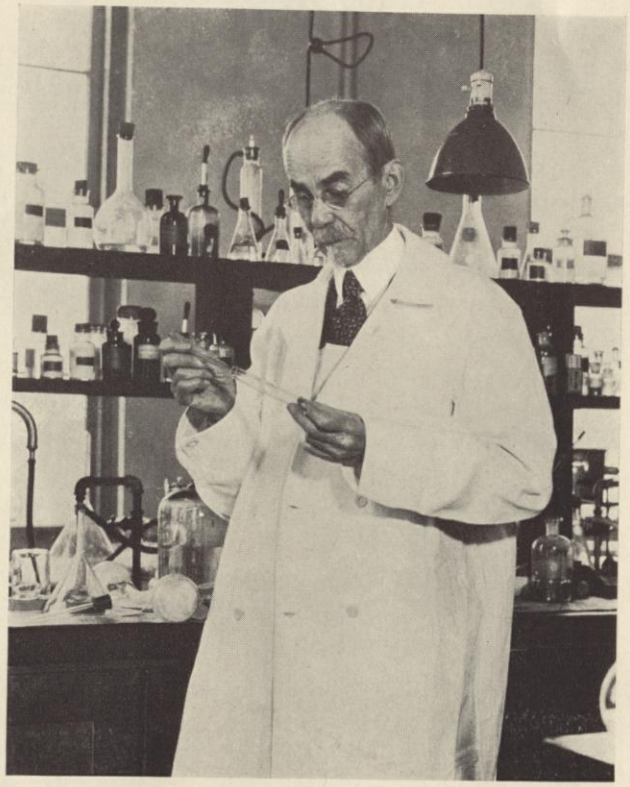
In the Johns Hopkins Hospital on the 26th of May, 1938, there came to an end, after a brief illness, the life of John Jacob Abel, one of the most distinguished representatives of medical science in the United States. Abel was one of the pioneers who helped build up American scientific medicine to the high place which it now occupies in the world. His great and wide influence extended over nearly half a century.

The life of this true scientist began on a farm near Cleveland, Ohio, where he was born on the 19th of May, 1857. Little is known about his parents save that his ancestors came from Germany. There is reason to believe that he owed his college education to his own initiative and this trait of his character he retained to an extraordinary degree throughout his long and fruitful life. At the age of 19 he began his college work at the University of Michigan. It was here that he took a course in physiological chemistry under Vaughan and physiology under Sewall. His college education was interrupted for three years during which time he was Principal of the high school and later Superintendent of Public Schools at La Porte, Indiana. He received his Ph.B. degree from the University of Michigan in 1883. After graduation he married Miss Mary Hinman, a teacher in his school at La Porte. This very kindly, intelligent and understanding woman was an ideal life companion for a man of Abel's temperament. She stood by his side through many tribulations and from the very beginning of their married life encouraged her husband in his intention to acquire a medical and a broad scientific education. In later years she related to the writer how they had spent their combined savings for this purpose. There can be no doubt but that Abel's happy family life was a potent factor in his scientific career.

The first academic year after graduation was spent in the Department of Biology of the Johns Hopkins University under Newall Martin, the able pupil of Michael Foster. Of Abel's work, Martin says "His diligence and conduct have been in all regards such as to merit approbation."



JOHN JACOB ABEL

At this time, in 1884, at the age of 27, he made the important decision to study medicine in Europe. Throughout his seven years of European study he showed a remarkable ability to select as his teachers many of the distinguished men of this period. From 1884 to 1886 he was in Leipzig, studying physiology under Ludwig and von Frey, histology under His, pharmacology under Boehm, pathology under Strümpell, and inorganic and organic

chemistry under Wislicenus. At the same time he completed his doctor's dissertation in Ludwig's laboratory. The winter semester of 1886–87 was spent in Strassburg under Kussmaul in internal medicine, under v. Recklinghausen in pathology and infectious diseases. The following summer semester he studied at Heidelberg with Erb in medicine and Czerny in surgery. During the summer vacation he attended clinics at Würzburg; 1887–88 brought Abel back to Strassburg where he took courses under Kussmaul, Naunyn, Hoppe-Seyler and Schmiedeberg. It was Schmiedeberg who aroused Abel's first interest in pharmacological research, particularly in its chemical aspects. In 1888 he received his M.D. degree from Strassburg. On October 30th of the same year he suffered the loss of his infant daughter, a severe blow. It is not unlikely that this loss determined him to leave Strassburg, where he had found so much inspiration and had made many friends, in order to pursue a year of postgraduate clinical work in Vienna with Nothnagel and others. But his yearning for laboratory research found Abel in 1889 to 1890 working in the laboratory of the outstanding biochemist v. Nencki in Berne, Switzerland. It was here that Abel obtained his first training in chemical research. In later years he often enthusiastically referred to this stimulating experience. There can be little doubt that at that time Abel had a clear vision of what a tremendous part chemistry was to play in the future of scientific medicine. Therefore, he resolutely determined to be prepared, irrespective of the expense involved which he could hardly afford. In Berne he completed a research on the "molecular weight of cholic acid, cholesterol and hydrobilirubin." Using Raoult's method he called attention to the limitations of this method for the purpose in view. Another paper dealt with the chemical composition of the melanins from hair and melanotic tumors, showing that these pigments did not contain iron in significant amounts. In Berne he formed a life long friendship with Cushny, who at that time was working in the laboratory of the Physiologist Kronecker.

After this year with v. Nencki, it was Abel's intention to return home where he expected "to carry on medical practice

and to do some research work, if possible, in internal medicine in connection with one of our American medical schools." This decision was partly due to the advice given in a letter by H. C. Wood, who, though recognizing Abel's "extraordinary training," told him he must first be known in America as a lecturer and independent investigator in order to have a chance to get a professorship of from $1,500 to $3,000 a year. However, the outlook for a clinical career would be more "promising." Having used up all his funds Abel decided reluctantly to enter clinical work. Then in the late summer while still in Berne, Abel received a cable from Vaughan which was the turning point in his life. On Schmiedeberg's recommendation Vaughan offered him the Chair of Materia Medica and Therapeutics in the University of Michigan, with the understanding that he was to establish a modern department of pharmacology; materia medica and therapeutics being retained in name only. Here was the chance Abel had looked for to enter a career in experimental research and with v. Nencki's advice he accepted the offer to return to his Alma Mater. But before returning home he induced Vaughan to let him have a last fling at biochemical research with the able biochemist Drechsel in Ludwig's laboratory. Drechsel at that time was doing important work on the chemistry of proteins and on protein metabolism. Drechsel and Abel thus began a joint research on the occurrence of carbamic acid in alkaline horse urine. This association led to a close friendship which lasted until Drechsel's death in 1897.

On his homeward journey Abel stopped at Berlin to obtain first-hand information on Koch's tuberculin treatment, which had attracted international attention. This was the subject of his first lecture at Michigan in January, 1891. In a letter to C. W. Edmunds he writes: "Here at Ann Arbor I was given the opportunity of starting the first professorship of pharmacology in the United States, whose holder should devote himself entirely to giving students the best possible instruction by means of lectures, demonstrations and quizzes, in the manner in which my European teachers (Schmiedeberg and Boehm) had long carried on their work. All my energy that was not given to

this kind of instruction to students was devoted to research work and to arousing the enthusiasm of others for it. . . .There was no laboratory of any kind at my disposal. There was not a scrap of apparatus, not even a test tube, a flask or a beaker." But soon he had organized his small laboratory and with a senior student, Muirhead, he immediately gave demonstrations on animals and carried out a research on the occurrence of carbamic acid in human and dog urine following the administration of large amounts of lime water.

In Michigan Abel began his work which later led him to isolate ethyl-sulfide from the normal urine of dogs. He also discovered the long lasting anaesthetic action of chloretone, valuable for certain experiments on animals, but too depressing for clinical use. An unpublished record refers to "A method for detecting and registering minute movements."

While Abel was active in Michigan the Johns Hopkins University under President Gilman began the organization of its medical school. Welch, Osler, Halsted, and Kelly had already been appointed, and equally outstanding men were needed to fill the chairs of the preclinical subjects. In January of 1893 Abel received a letter from Osler inquiring whether he would be a candidate for the chair of Pharmacology. He replied that he was strongly attracted by the prospective intellectual contacts with Osler, Martin, Welch and Remsen. His main concern, however, was the provision for adequate laboratory facilities. His appointment to the Professorship of Pharmacology went into effect for the academic year starting in the autumn of 1893 and with it Abel reluctantly also assumed the responsibility of giving the course in physiological chemistry. Before assuming his duties he obtained a few months of leave to complete some research with Drechsel and to consult his old teachers in Europe.

In his 45 years' connection with Johns Hopkins Abel added much luster to this world famous medical school and he exerted a profound influence on the development of pharmacology and physiological chemistry in the United States.

For the first few years Abel completed some researches which he had begun before coming to Johns Hopkins:—the work on

chloretone, ethyl sulfide, and the chemistry of the pigment of the negro's skin and hair. Of these contributions the one on the "labile" sulfur fraction of dogs' urine, and which resulted in the clean-cut isolation of ethyl sulfide, is the most significant. The experience gained in this work proved very useful many years later in his work on insulin. One cannot escape the conclusion that Abel's early researches on the isolation of carbamic acid, pigments and ethyl sulfide led him to the conviction of the fundamental importance of work on the chemical isolation of hormones. In a letter dated January 5, 1898, in replying to an inquiry by a representative of Armour and Company, he states: "First about the thyroids. I send you two samples of extracts which I made in 1895, before Baumann's work came out. I was just about to remove the proteids by peptonizing with boiling (5–10%) acids when the news of his discovery came to hand. . . . The samples I send you are made by the glycerine method. I need not give you the details of this method, because I think it not adapted to commercial purposes. . . .We stopped our work when the Baumann discovery was published." It is quite likely that Abel's work on the thyroid was the result of his sojourn in Berne, where at that time the distinguished Swiss Surgeon Kocher was well known throughout Europe for his work on endemic goiter. In all events Abel's interest in the chemical isolation of hormones dates back to 1895. Soon thereafter Abel became interested in the chemistry of the active principle of the adrenal medulla. Oliver and Schafer in 1894 had discovered the remarkable blood pressure raising action of adrenal extracts. With extraordinary vigor Abel threw himself into this work for nearly ten years. Many hot summer vacations were spent in his laboratory doing elementary analyses of his products. The first paper, published with Crawford in 1897, reported the isolation of a benzoyl derivative of the active principle. The idea of using benzoylation for the purpose of isolation of the active compound was probably based on Brunner's observation that alcoholic adrenal extracts gave the reactions for pyrocatechin. This suggested benzoylation as a means of separating the principle, on the assumption that the active substance con-

tained phenolic groups. Abel's association with v. Nencki, the discoverer of the so-called Salol principle, had familiarized the former with the use of benzoylation. The further progress of these studies is best given in Abel's own words in his Willard Gibbs lecture (Science, 1927). "On decomposing this benzoyl derivative with hot dilute sulphuric acid in an autoclave we obtained the active principle in the form of a sulfate which possessed the characteristic physiological activities of suprarenal extracts and reacted, furthermore, with a series of chemical reagents in a manner that is quite specific for such extracts and limited to them. The principle as obtained by saponification of the benzoyl derivative was thrown out of its solution by means of ammonia in the amorphous state and was shown to be a weak base. A picrate, a bisulphate and other salts of it were prepared, all of which were shown to possess a high degree of physiological activity. An acetyl derivative, a phenylcarbamic ester and other derivatives were also prepared and certain degradation products of the base were isolated and studied. . . .The elementary composition of the base was established by analysis of several derivatives, including the sulphate, and was stated to be represented by the formula $C_{17}H_{15}NO_4$. After I had completed the above described investigation and while I was still endeavoring to improve my processes, I was visited one day by the Japanese chemist, J. Takamini, who examined with great interest the various compounds and salts of epinephrine that were placed before him. He inquired particularly whether I did not think it possible that my salts of epinephrine could be prepared by a simpler process than mine, more especially without the troublesome and in this case wasteful process of benzoylating extracts of an animal tissue. He remarked in this connection that he loved to plant a seed and see it grow in the technical field. I told Takamini that I was quite of his opinion that the process could no doubt be improved and simplified. At this very time, also, v. Fürth had just prepared an amorphous, highly active, indigo-colored compound of the active principle, which he named suprarenin, but no analytical data were given and no empirical formula for his principle was established. Takamini prepared

suprarenal extracts more concentrated than mine and without first attempting to separate the hormone from its numerous concomitants by benzoylating or otherwise, simply added ammonia—the reagent that I had so long employed—to his concentrated extracts, whereupon he immediately obtained the native base in the form of burr-like clusters of minute prisms in place of my amorphous base. I have often been asked why I had not myself attempted to solve the problem in this very simple fashion. The truth is that I had tried to do so but always found that the dilute extracts tested simply turned pink in a short time on the addition of ammonia without depositing the base, either crystalline or amorphous. Inasmuch as even very dilute solutions of the salts obtained by me on saponifying the benzoyl derivatives always gave a precipitate with ammonia, I fell back on the hypothesis that other constituents of the impure extracts prevented its precipitation by ammonia from my dilute native extracts—an erroneous assumption. Takamini's success was due to the employment of ammonia on very highly concentrated, though impure, extracts. The fact that my amorphous base could be precipitated from even highly dilute solutions was, as I soon found, due to the fact that one benzoyl radical had not been removed during the saponification. Takamini adopted the empirical formula $C_{10}H_{15}NO_3$ as the 'probable empirical formula' of his substance, which was immediately patented in this country and manufactured, greatly to the advantage of medicine. I was soon able to demonstrate that my epinephrine—$C_{17}H_{15}NO_4$—had retained a single benzoyl radical, C_6H_5CO, that had resisted saponification and could only be removed from the base by drastic treatment with strong acids and heat, a treatment which at the same time obliterated every trace of the characteristic physiological action of the hormone (1901). I suspect that the retained radical was attached to the imide nitrogen of the side chain of the molecule—an unusual circumstance in any event. Subtracting the molecular weight of the retained radical from my original formula, $C_{17}H_{15}NO_4$, which formula is very close indeed to that assigned by Takamini to his crystalline base, and Aldrich, who had been my assistant

and who, coincidently with Takamini and quite independently of him, also discovered that the base is obtainable in crystalline form when ammonia is added in sufficient quantity to a highly concentrated superarenal extract, wrote, without knowing at the time that I had already discovered the concealed radical: 'It is interesting to note in this connection that if we subtract a benzoyl residue from Abel's formula of epinephrine—$C_{17}H_{15}NO_4$—we obtain a formula $C_{10}H_{10}NO_3$ which is not far removed from that of adrenalin.' I venture to say in extenuation of the blunders of a pioneer in this field that the results obtained by me and my close approximation to its true elementary composition of the hormone were not due to chance, but could have been obtained only from the study and analysis of a series of fairly pure chemical individuals. Every one of these derivatives had, however, as already stated, retained a single benzoyl radical. The efforts of years on my part in this once mysterious field of suprarenal medullary biochemistry, marred by blunders as they were, eventuated, then, in the isolation of the hormone, not in the form of the free base but in that of its monobenzoyl derivative. Aldrich finally established the true empirical formula, $C_9H_{13}NO_3$, the correctness of which was afterwards conclusively verified by others abroad."

Thus Abel described in restrospect, and quite objectively, the story of the first chemical isolation of a hormone. It was his work which laid the foundation for the final triumph, but above all Abel will be remembered as the pioneer who clearly recognized the importance of the chemical isolation of hormones as the first step of their synthesis, rational pharmacological study and therapeutic administration. His simple description of his long labor fails to convey even remotely the struggle and strife of his epinephrine period. Only his associates of that time know the tremendous efforts which Abel made to reach his aim.

An incident occurred during the epinephrine period which revealed one of Abel's characteristics, that of being a stoic. On the evening of December 11, 1900, Dr. Auer relates, he heard an explosion in Dr. Abel's laboratory and rushing there with Dr. Abel's helper found Abel at the sink sluicing water over his

face. Dr. Abel turned towards Auer and stated quite calmly: "My eye is gone, boys. I know it's gone." In spite of the loss of one eye, which was a considerable handicap in his scientific endeavors, Abel pursued his work from then on without ever referring to this accident.

Another human trait was Abel's refusal to patent any medicinal preparations for his financial benefit. It would have been an easy matter for him to take out patents on his active epinephrine preparations, but throughout his life, he maintained that the results of his scientific work should be the property of humanity.

During the epinephrine period (1895–1905) Abel not only carried on his researches and teaching, but he devoted a great deal of his energy to the foundation of scientific journals and societies. In the fall of 1895 he suggested to President Gilman of Johns Hopkins University the need for an American journal covering the field of experimental medicine, since at that time most of the American papers dealing with experimental pathology, pharmacology and biochemistry were sent to foreign journals. Gilman asked Abel to draw up a set of resolutions setting forth the need for such a journal and to present them to the medical faculty. The plan was speedily put into effect and Dr. Welch was induced to become editor in chief, with the following associate editors: Physiology—Bowditch, Chittenden and Howell; Pharmacology—Abel, Cushny and H. C. Wood; Pathology—Adami, Councilman, and Prudden; Medicine—Fitz, Osler, and Pepper. The *Journal of Experimental Medicine* appeared in January 1896 and ever since has played an important rôle in the promotion of medical research.

The success of the *Journal of Experimental Medicine* and the rapid growth of biochemical research in the United States encouraged Abel to initiate steps for the foundation of the *Journal of Biological Chemistry*. In the spring of 1903 he enlisted the interest of his friend C. A. Herter, professor of Pharmacology at Columbia University. At first it was doubtful whether a sufficient number of papers of high grade would be available and the question of financing such a journal presented another

problem. Herter promised this financial support. After numerous meetings and a large correspondence between Abel and Herter the first number of the Journal appeared in 1905, with Abel and Herter as joint editors and A. N. Richards as associate editor. These three men were responsible for the immediate and rapidly growing success of the Journal. In 1909 Abel withdrew as editor, having in the meantime become interested in another venture in the journalistic field.

After 1905 Abel passed through a short period of reorientation of his research work. About that time Jaques Loeb was engaged in systematic studies of the physiological action of ions. One of these studies dealt with the swelling of frog muscle caused by HCl and organic acids and appeared to indicate that organic acid was less effective than HCl. Abel carried out similar experiments, which suggested an apparent correlation between the degree of swelling and the diffusion constant of the acids, provided the intact muscle was immersed in isotonic saline containing acid of the same normality. If on the other hand the muscle was perfused with acid containing saline, the swelling was about the same with HCl and acetic acid.

A brief account of this work was presented in 1907 at the first meeting of the American Society of Biological Chemists. This new Society owed its foundation primarily to Abel. It was he who took the initiative to call a meeting of biological chemists in New York on December 26, 1906. A few of the biochemists had expressed their reluctance to the organization of a new society, fearing that it might weaken the American Physiological Society and American Chemical Society by the withdrawal of some of their respective members, who were biochemists. However, these objections were removed by the well considered and enthusiastic remarks made by Abel at the New York meeting. Among other things Abel said: "Scattered and divided forces cannot develop that coordination of effort that is desirable when many workers have one great interest in common. In such a case, organization is beneficial. It encourages research, it furnishes the mechanism of competent criticism and helpful discussion; and lastly, the very fact that

we felt impelled to organize will make it evident to faculties of science and medicine and to scientific and medical societies that a great and growing department of research demands its fitting place in the general scheme of higher education." Prophetic words spoken by a man of extraordinary broadmindedness. Consistent with this viewpoint, Abel from his earliest days as Professor of Pharmacology at Johns Hopkins advocated independent chairs of biological chemistry. In 1908 he turned over biological chemistry to Walter Jones, who was made head of this new department.

By this time pharmacology had made sufficient progress in this country for Abel to assume the leadership in the foundation of the JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS and in the organization of the American Society for Pharmacology and Experimental Therapeutics. These projects were discussed at length with his associates over the luncheon table. Abel induced the Williams & Wilkins Company to publish the JOURNAL, which was incorporated in the name of Abel, Hunt and Voegtlin. The first number appeared in June, 1909, with Abel as editor. In the editorial announcement Abel expressed the opinion that, "Every physician who has the best interests of his profession at heart feels that he must become familiar with the methods and principles and above all, with the actual objective results which are placed at his disposal by the sciences here represented." He quoted Paul Ehrlich's evaluation of these subjects: "There can be no doubt that the great fields of knowledge, pharmacology, toxicology and therapeutics, in their theoretical and practical aspects form the most important branches of medicine." During the 30 years of its existence the JOURNAL has been the medium for the publication of numerous important investigations and since 1934 has become the official organ of the American Society for Pharmacology and Experimental Therapeutics in association with the British Pharmacological Society.

The American Society for Pharmacology and Experimental Therapeutics was organized in 1908 with Abel as its first president.

The amazing talent for organization which Abel possessed in such a high degree and which is rarely found in a man who is primarily interested in research, has been of tremendous benefit to experimental medicine.

In 1908 Abel, having passed the half century mark of his life, was as youthful in spirit and enterprise as any of his youngest assistants and pupils. He had overcome the disappointment incident to his epinephrine studies. From this time until his death—30 years later—Abel devoted practically his whole energy to research. There followed in rapid succession year after year publications of his work, mostly in collaboration with pupils, demonstrating his broad interests. The work of these 30 years, even better than his earlier work, evidenced the profound influence of his scientific training on his research work. All those who had the good fortune to work in Abel's laboratory, either as his collaborators or as independent workers, will testify to the great stimulus they received from his example, his intense interest in his problems, his courage in attacking difficult questions, and his optimism in the final outcome. His simple, and in many respects primitively equipped, laboratory became the mecca of scientists from all over the world, an unusual opportunity for his staff to meet some of the most distinguished scientific leaders. In these days of expensively equipped laboratories it is refreshing to recall that Abel's laboratory produced results with relatively meager physical means, compensated for by ingenuity.

In 1907 and 1908 Abel and Ford published their work on the poisons of *Amanita Phalloides*. Ford had previously demonstrated the presence in this mushroom of a hemolysin and a nonhemolytic toxin. Abel and Ford by chemical fractionation obtained the impure hemolysin, which they believed to be a glucoside containing a pentose. This principle is destroyed by heat and acid and, therefore, was not considered as playing a part in the poisoning in humans consuming cooked mushrooms.

The hemolysin, on analysis, contained C, H, N and S, and failed to give the tests for proteins. The *Amanita* toxin was found to cause widespread fatty degeneration, and gave the

biuret and Millon tests. Antiserums were obtained by the use of both fractions.

In 1909 Abel and Rowntree published their paper on the pharmacological action of phthalein derivatives. With the double object in mind of studying (1) the influence of substitution in various parts of the molecule upon pharmacological action and (2) the discovery of a purgative suitable for subcutaneous injection, a thorough study was made of the absorption and elimination of a series of compounds. While no practical purgative resulted from this work, Abel and Rowntree discovered that phenolsulfonphthalein was rapidly and completely excreted by the normal kidney without causing any evident renal damage. This pharmacological property was used by Rowntree and Geraghty (1910) as a starting point for their studies which culminated in the sulfonphthalein test for kidney function. Abel had observed that tetrachlor phenolphthalein, after parenteral administration, was eliminated by the liver and excreted with the feces. He therefore performed some preliminary work indicating that the estimation of this dye in the feces could be utilized for determining liver function. Some years later, a pupil of Abel's, Rosenthal, elaborated this test by determining the rate of disappearance of the dye from the blood.

During this same period Abel became temporarily interested in chemotherapy, at a time when Ehrlich had just announced his epoch-making discoveries of the organic arsenicals. Tartar emetic had been known for some years to have some therapeutic value in certain trypanosome infections. Abel prepared the triamide of antimony trithioglycollate. This and a few related compounds were studied by Abel and Rowntree on experimental trypanosome infections in several animal species, and were found to be very effective. The antimony thioglycollates now have found a use in the treatment of granuloma inguinale and especially in Bilharzia infection so prevalent in Near Eastern countries.

While these chemotherapeutic studies were in progress Barbour and Abel were engaged in a study of the action of acid fuchsin on frogs. In his previous work on the penetration of acids into

frog muscle Abel had made use of acid fuchsin as an acid indicator and had observed that acid fuchsin produced a late strychnine-like tetanus. Barbour and Abel found that extreme fatigue by muscular exercise greatly hastened the appearance of the tetanus. They also made the interesting observation that partial ablation of the anterior cerebral lobes, either before or after the injection of acid fuchsin, shortened the latent period of the convulsions. This was explained on the assumption that destruction of the anterior lobes eliminates inhibitory influences passing from them in the intact frog to subcortical coordinating centers. Shortly after publication of this work Meltzer announced his theory of a hitherto unrecognized mechanism for the distribution of soluble substances in the animal body in the complete absence of the circulation. The theory was based on experiments with cardiectomized frogs. Acid fuchsin, strychnine and morphine injected into the truncal lymph sac of such frogs were found to be highly toxic, a fact which was believed to be due in part to the absence of hypothetical neutralizing or detoxifying substances normally liberated from the tissues and carried by the blood stream. The drugs were supposed to reach the nerve centers in cardiectomized frogs by diffusion, osmosis, capillarity, surface tension or even chemotaxis within the tissue spaces, and independently of the action of the lymph hearts. In a keen analysis of this problem Abel and Turner furnished convincing proof that the production of tetanus by acid fuchsin in cardiectomized frogs is dependent on the functioning of the lymph hearts, and that destruction of these means of distribution of lymph also prevents the convulsions in cardiectomized frogs. Abel also recognized that diffusion is too slow a process to explain the relatively rapid appearance of the tetanus. To quote the final opinion Abel and Turner concluded that "it is of course admitted that diffusion goes on in the tissue spaces of all organs, but these spaces cannot serve as routes for the *rapid* transmission of solutions. They are only effective when the distance to be traversed is very minute or when the time is sufficiently long. This last factor is of great importance and herein lies the greatest improbability of Meltzer's peripheral mechanism, for, being

energized by molecular forces only (surface energy and diffusion), it cannot compass the astonishing feat of transmitting a drug in a few minutes over a long distance and through intervening cell barriers to the tissues of the central nervous system." This view is supported by the later fundamental work of A. V. Hill and of Krogh on diffusion in animal tissues. The temporary controversy between Abel and Meltzer, however, in no way affected the long friendship between these two men.

The studies on acid fuchsin led Abel to investigate the pharmacological principles secreted by the parotid gland of the tropical toad, *Bufo Agua*. In the former work it was desirable to secure larger animals than the ordinary laboratory frogs in order to inject acid fuchsin directly into the anterior lymph hearts. While using *Bufo Agua* for this purpose Abel states: "our interest was aroused by the milky secretion which exudes from its parotid glands when the animal is greatly irritated. Scraping off some of the secretion with a knife, we were struck by the bluish-green discoloration which appeared on the blade soon after it had been used. This observation led us to test some of the diluted secretion with ferric chloride. The reagent was found to develop the characteristic green color of the pyrocatechin reaction. As this reaction is given by the active principle of the suprarenal glands, further tests were at once undertaken with the object of identifying the substance in the toad's secretion which reacts with ferric chloride as described. It was not a difficult task to demonstrate that we were here dealing with a substance which is identical with, or closely allied to, the suprarenal principle. Further work on the secretion of the glands demonstrated the presence of a second body which, in respect to its pharmacological action, is to be classed with substances belonging to the digitalis group of poisons." Abel and Macht published their extensive work on this subject in 1912. Epinephrine was isolated in pure crystalline form and was identified with the substance obtained from the adrenal medulla. It occurs in the crude venom up to nearly 7 per cent or in much higher concentration than in the adrenal. The poison glands give the characteristic chromaphil reactions. The discovery of epinephrine in this toad testifies

for Abel's acute power of observation. The second crystalline principle separated was called Bufagin. It is dextrorotatory, melting point 217–218°C. and was given the formula $C_{18}H_{24}O_4$. An exhaustive pharmacological study of Bufagin revealed its similarity with the members of the digitalis series. However, the hope that Bufagin might possess therapeutic value did not materialize. The drug was further investigated by two former pupils of Abel, Chen and Jensen.

In 1913 Abel became interested in a method for the removal of diffusible substances from the circulating blood of living animals by dialysis. Before starting the work he discussed his ideas and plans with his staff at the luncheon table. These informal daily meetings, which lasted throughout Abel's long career at Hopkins, will be remembered by his associates as extremely stimulating experiences. The underlying idea of the new method, which was to become known as "vividiffusion," was to provide means for the removal of substances detrimental to the animal body and to relieve the kidneys of this function in a variety of toxic conditions. The method, furthermore, was to serve the purpose of isolating and identifying the multiplicity of diffusible substances of the blood. Having enlisted the interest and collaboration of Rowntree and Turner work was soon under way. The task was to pass the blood of an animal which had been made incoagulable by hirudin from a cannula in an artery through a series of celloidin tubes surrounded by saline solution back into the venous system. Many technical difficulties had to be overcome, but in November, 1913, the first successful experiment was performed. In the following year the demonstration of the new method in London and at the Physiological Congress in Groningen aroused great interest. It could be shown that the elimination of salicylic acid by this "artificial kidney" compared favorably with the elimination of this drug by the natural kidney. While this method has not found a clinical application for the treatment of intoxications, Abel and his coworkers succeeded in isolating a number of blood constituents from the dialysate. Thus ethyl-sulfide was obtained from dog blood, as also urea and evidence of the presence of sugar, diastase,

lactic and B-oxybutyric acids. Of even greater interest was the identification in the dialysate of amino acids—alanine and valine, and the indication of the presence of histidine and creatinine. This actual isolation of amino acids was the first incontestable evidence of their occurrence in normal blood, a fact of fundamental importance in the study of protein metabolism. Shortly thereafter Abderhalden published his work on the isolation of amino acids from deproteinized normal blood.

While engaged in the work on vividiffusion, Abel, Rowntree and Turner carried out some experiments in "Plasmaphaeresis." Here again as in the work on vividiffusion the underlying idea was to devise a more scientific method for venesection. Experiments on dogs showed that large quantities of blood can be withdrawn repeatedly without apparent injury, if the corpuscles, separated by centrifugation from the plasma, are suspended in Locke solution and reinjected. This indicated that a large part of the reinjected corpuscles escape destruction. The paper dealing with this work (1914) contains this prophetic sentence: "In view of the fact that mammalian corpuscles retain their stability for three or four days when kept on ice a supply of human corpuscles might possibly be kept in this manner in operating rooms for rapid injection in emergencies that would otherwise prove fatal." In this instance as in many others Abel clearly perceived the possibilities of the practical application of his work, but he was above all interested in establishing new fundamental principles and facts, realizing that this new knowledge would sooner or later lead to results of practical value. Abel also recognized the value of plasmaphaeresis for the study of the regeneration of plasma proteins and he announced that work along this line was in progress. However, he did not publish such data and it remained for Whipple and his coworkers to employ plasmaphaeresis in their fundamental studies on protein production and exchange in the body.

The demonstration in the vividiffusion studies of the presence of amino acids in the circulating blood evidently aroused Abel's interest in other aspects of protein metabolism. He had observed a small amount of biuret-yielding substance in the dialysate.

Being familiar with the pharmacological action of cleavage products of proteins (peptones, Vaughan's fractions) and the controversy concerning the presence of proteoses in the blood and tissues, Abel in collaboration with Pincoffs and Rouiller (1917) engaged in an extensive investigation on the presence of albumoses in the tissues and in the blood, with particular reference to their occurrence in the gastro-intestinal mucosa. The paper on this subject again shows his keen desire to isolate physiologically active substances, not necessarily hormones, from the animal body. By an elaborate series of fractionations evidence was furnished of the presence of albumoses in the mucosa of the stomach and small intestine, the thyroid, gravid uterus, blood corpuscles and dialysates of portal, hepatic and systemic blood. The albumoses obtained from the gastro-intestinal mucosa were considered as evidence against the theory that the absorption of proteins is limited only to amino acids. Abel recognized the technical difficulties of eliminating sources of error which might lead to the formation of proteoses in the process of fractionation. At present it can be said that this fundamental problem is far from solved. New methods will have to be devised. The basic idea of Abel's work, however, may well have some justification, since evidence is accumulating of the interconversion of blood and tissue proteins (Whipple and associates), processes which may well pass through the proteose stage.

In 1924 Abel and Geiling supplemented the above work by a chemical and pharmacological study of Witte's peptone. This complex mixture of chemicals was separated into a fraction which was soluble in strong alcohol and a fraction difficultly soluble in this solvent. The former fraction gave the same type of depressor response in dogs as histamine, and was considered as a precursor of histamine. The alcohol insoluble (albumose) fraction was only feebly toxic and injected intravenously into unanesthetized dogs caused, in addition to the usual shock-like symptoms, a very marked reddening of the skin and mucous membranes, due to capillary dilatation. It is quite probable that further work on the action of proteoses and histamine-

like compounds will lead to interesting results as regards their physiological and pathological significance.

The work on the presence of albumoses in tissues led to an extensive investigation of the active principles of the posterior pituitary gland. In 1917 Abel and Pincoffs suggested that the oxytocic principle of the pituitary is not a hormone or substance specific to this organ, but is a rather widely distributed substance, which may have its origin in various tissues, in the gastric or intestinal mucosa, or which may be absorbed as such from among the products of digestion.

In 1919 Abel and Kubota published their results on the presence of histamine in the pituitary, striated muscle, liver, gastric and intestinal mucosa. Barger and Dale (1911) had previously isolated histamine from the intestine of the ox and Dale and Laidlaw had made the first important investigation of the pharmacological action of histamine. The similarity of the action of histamine and pituitary extract on the blood pressure and isolated uterus seemed to justify attempts to isolate histamine from the above mentioned tissues. In fact Abel and Kubota succeeded in obtaining from one pound of commercial dried whole pituitary a few milligrams of crystalline picrate, which had the same physical and pharmacological properties as histamine picrate. Evidence was furthermore obtained of the presence of histamine in other tissues, and in tryptic and acid digests of proteins. The conclusion was therefore reached that histamine is the plain muscle stimulating and depressor constituent of the posterior lobe of the pituitary gland, but that it is not specific to this tissue.

In 1920 Abel and Nagayama, on the basis of further work, abandoned this view. They failed to obtain significant amounts of histamine from perfectly fresh pituitary with avoidance of long contact with acid during the fractionation. They also found that brief acid hydrolysis destroys the pressor action of pituitary extracts, whereas histamine is not affected by this treatment. Tryptic digestion (Dale, Dudley) also destroys the pressor action. The depressor action of acid-treated pituitary extract is attributed to a "histamine-like" substance giving the

Pauli reaction and to histamine. The observation that different agents similarly alter the pressor and oxytocic action is regarded as evidence in favor of a unitary principle. Abel and Nagayama also report the preparation of a new pressor fraction many times more powerful on the uterus than histamine.

With his characteristic perserverance Abel continued these studies. In 1922 in collaboration with Rouiller he published significant new data. In the older work the pituitary was treated with $HgCl_2$. The precipitate thus produced was discarded and the filtrate was worked up for the separation of histamine. Now it was found that practically all of the pressor-oxytocic activity remained in the mercury precipitate. Decomposition of the latter with H_2S, followed by a few simple manipulations, yielded a fraction 20 to 30 times more active on the guinea pig uterus than an equal weight of histamine phosphate, and exhibiting a powerful pressor action, and an antidiuretic action in the rabbit. The interesting observation is reported, that whereas the first few intravenous injections always give a striking pressor response, subsequent injections cause a fall in blood pressure (inversion effect). This was later on explained by Geiling as being due to cardiac depression.

In 1923 Abel, Rouiller and Geiling reported further results on the fractionation of pituitary extracts. The decomposed mercury precipitate was put through several stages of purification by phosphotungstic acid, precipitation with tannic acid, conversion into a tartrate, treatment with picrolonic acid and again tartaric acid. The final products varied in oxytocic value from 600 to 1250 times histamine acid phosphate. Further evidence was submitted in favor of the view that the oxytocic, pressor, respiratory and diuretic actions are all due to the same hormone. Some of the tartrates with a fairly high oxytocic titer were shown to be powerful antidiuretic agents in several cases of diabetes insipidus.

Several years later (1928) Kamm reported the almost complete separation of the oxytocic from the pressor fraction of the pituitary. More recently (1938) du Vigneaud and his coworkers applied electrophoresis to the study of the posterior pituitary

hormones, using both freshly prepared juice and fractions obtained by methods similar to those of Kamm. Since the pressor principle traveled at a faster rate than the oxytocic principle these observations would seem to support the multiple principle theory. The final answer to this question must wait until chemically pure principles are obtained, but the present evidence is definitely in favor of the presence of at least two hormones. Abel's contributions to this difficult field will always remain an important milestone, since his partial success and enthusiasm encouraged others to carry on where he had left off.

While Abel was engaged in his studies on the pituitary hormones insulin was discovered (1921). Recognizing the apparently insurmountable difficulties with the pituitary principles, Abel with his characteristic courage and intellectual flexibility set himself the task of the chemical isolation of insulin. He began his work in collaboration with Geiling in the autumn of 1924. By this time quite a number of able biochemists had become interested in this problem. The first paper by Abel and Geiling (1925) described the partial purification of commercial insulin by a series of simple precipitations with the use of pyridine, phenol, acetic acid and NaCl, which increased the physiological activity from about 12 to 40 rabbit units per milligram. Organic sulfur and cystine had been reported previously as components of impure insulin by other workers. It was furthermore known that insulin was inactivated by short treatment with hot alkali. It will be remembered that Abel in one of his first scientific papers dealt with a labile sulfur compound of urine. On this basis Abel and Geiling established a correlation between the labile sulfur content and the physiological activity of their insulin fractions. They suggested that this unstable sulfur is an integral part of the insulin molecule. The following year (1926) Abel succeeded in obtaining crystalline insulin. This ammouncement was received by some chemists with scepticism as final proof of the isolation of the pure hormone. The criticism was made that the highly potent hormone may be adsorbed to a crystalline impurity. For a time the inaccuracies of the bio-assay method lead to contradictory results. But all these criticisms were

fully met by Abel, Geiling, Rouiller, Bell and Wintersteiner (1927). Abel's great achievement of the chemical isolation of insulin has not only furnished a constant standard for bio-assay and a simple procedure for the commercial purification, but what is of far greater importance it has made possible the study of the composition, structure and mode of action of the hormone. Insulin has revolutionized our conceptions of the chemistry of hormones. It is the first (and probably will not be the last) hormone which must be considered as a protein, having a molecular weight of about 35,000 (Svedberg).

In this last paper of Abel's on insulin the crystallization is discussed in great detail and it is explained why pyridine and brucine acetate are so essential in separating the insulin ampholyte from other ampholytic contaminations in the crude product during the isoelectric precipitation and crystallization. Furthermore, it was shown that repeated recrystallization under different conditions failed to modify the physiological activity of the crystalline material. Elementary analysis for C, H, O, N and S are given. The crystals gave the ordinary reactions for protein, were levorotatory and dimorphous. The final conclusion is reached that the crystals represent the pure hormone.

During the next few years further important contributions to the chemistry of insulin were published from Abel's laboratory by Geiling, Jensen, du Vigneaud, Eddy and Wintersteiner. It would lead too far to describe this work; suffice it to say that a number of amino acids were isolated from acid hydrolysates of crystalline insulin, and that the inactivation by heat and SH compounds was studied.

At the age of 75, in 1932, Abel retired from the chair of pharmacology, but not from research, which had been of such vital interest to him for so many years. As Director of Endocrinological Research he launched an investigation, which, as Sir Henry Dale points out in his fine obituary notice for the Royal Society, surprised his many friends and admirers. Abel's life long friend H. H. Mayer had put forward 40 years earlier his theory that tetanus toxin is absorbed by motor nerve terminals and carried by way of the peripheral nerves to the motor nerve centers in

the spinal cord and medulla, where the toxin causes the motor cells to send out abnormal stimuli resulting in muscular rigidity or increased reflex-excitability. In 1934 Abel published his critical analysis of the literature on this subject and pointed out that previous experiments were faulty due to disregard of leakage of toxin and antitoxin from the injected peripheral nerves and failure to establish a reliable lethal dose. The hypothesis was advanced that the action of the toxin is due in part to intoxication of the motor horn cells and in part to an action upon striated muscle. In subsequent papers in collaboration with Evans, Hampil, Lee, Jonas and Chalian, evidence was produced indicating the following: (1) the toxin is distributed throughout the body, (2) toxin which is not fixed upon the tissues can be demonstrated by bio-assay, (3) highly sensitive animals (horse, sheep) are able to fix only a limited amount, the excess circulating in the blood and lymph, (4) in the dog fixation begins soon, the amount fixed depending on the number of lethal doses, (5) fixed toxin cannot be recovered by perfusion, but before the appearance of symptoms the animal can still be saved by antitoxin, (6) the antitoxin easily reaches the poisoned centers, (7) the antitoxin has no curative value in monkeys, but is a very efficient prophylactic. The last paper deals with the various arguments which had been put forward in support of the nerve carriage theory and each is refuted on the basis of Abel's own work. Attention is called to the fact that with proper precautions, avoiding the leakage of antitoxin injected into nerve, no nerve blocking could be demonstrated. Furthermore, Doerr's dynamic activation theory is refuted. It is concluded that all the symptoms of tetanus can be explained on the assumption of a dual action of the toxin and its distribution by the vascular and lymphatic systems.

It is premature to evaluate the wealth of experimental data secured by this keen pharmacological analysis which Abel pursued to the last day of his life, even discussing with Chalian on his deathbed plans for further work. What an indomitable and valiant spirit!

Scope of Pharmacology. Abel's research work is characterized

by an extraordinary catholicity of interests, which was partly due to the broad scientific training he had received under the most distinguished teachers of his time. He, therefore, had not much patience with those who looked upon pharmacology as a narrowly defined applied science and often quoted Hoppe-Seyler's reply to Pflüger: "Every classification in the natural sciences is more or less artificial." Abel's conception of pharmacology as a scientific discipline is best expressed by a few quotations from a letter which he wrote in 1924 to Dr. Abraham Flexner, "The Chair of Materia Medica and Therapeutics (the term formerly applied to the present chairs of pharmacology) is one of the very oldest in medicine. The study of drugs and poisons was naturally one of the earliest concerns of mankind and there is little outlook that we shall soon give up such studies. The day of therapeutic nihilism has passed. Every year brings us new therapeutic weapons against infections, endocrine disturbances, occupational and industrial disease, and innumerable diseased conditions, such as rickets and a host of pathological states that cannot be here enumerated. Whether the agents that are to be used in all these pathological and functional states are formed in the plant kingdom (alkaloids, as quinine, etc.) or produced in the animal body (thyroxin, insulin, pituitary, epinephrine), or derived from the mineral kingdom (mercury, antimony, arsenic, etc.) or are synthetically produced in our laboratories in imitation of Nature's alchemy—all of these substances are *drugs* and constitute a great part of the proper field of study of the pharmacologist. I am fully aware that they also constitute a field of study for the physiologist, the pathologist and other medical scientists. The scope of this domain is so large that there is ample opportunity for all the above-named individuals to work without ousting the pharmacologist or subordinating him to some other field . . . I care little for labels and names—you can extend the use of physiology to clinical medicine; you can call pathology abnormal physiology; you can call pharmacology applied physiology; and make otherwise use of this term. All of this, however, does not alter the fact that the increasing and steadily growing content of pharmacological

science which is applying physics and chemistry in the most advanced and minute way to the problems of cell action, and which is almost daily making new additions to our armamentarium of drugs, cannot be subordinated to physiology which has its own problems which may or may not interlock with pharmacology. . . . The science has its own problems quite aside from achievements that are of immediate assistance to the physician, which are of a fundamental character and allied to physiology, but in reality belong to the vast realm of experimental biology and medicine. To these problems the pharmacologist brings his own viewpoints and methods, just as the biochemist or physiologist may do. . . . I have always maintained that the more varying types we have in the way of pharmacologists, physiologists, pathologists, and anatomists the better. Let one pharmacologist be more of a chemist, another more of a physiologist, another more of a clinician. The main thing, I think, is—taking ability for granted, as this is the main requisite—that all of these men should be more than mere pharmacolosists, or physiologists, or whatnot, but that their interests should be broad, that they could be classed as students, or investigators in the broad field of experimental medicine and biology. . . . I hope that pharmacology will keep on accumulating along with its practical discoveries an increasingly great amount of such apparently for the moment useless knowledge." Thus speaks a liberal man, whose influence was instrumental in securing for biochemistry separate departments in American universities.

In his earlier years Abel was looked upon by many as more or less of a visionary, but as the years passed his eminent qualities were generally recognized. No less a man than his former colleague, Osler, in a letter[1] in connection with the reorganization of the Oxford medical school, paid Abel the following tribute:—"The four lines of progress for our school are Pharmacology, Hygiene, the History of Medicine and a clinico-pathological laboratory in connection with the Infirmary. Of these, the first is a pressing need. Everywhere, I am sorry to say, except in this country, the science of Pharmacology is making rapid

[1] From Cushing's *Life of Sir William Osler*.

strides and the subject is universally recognized as of the first importance in university work. Moreover, it is one of the hopeful progressive departments of medicine, with great possibilities for public service. I can testify in the strongest possible way to the work of Professor Abel and his department with the Johns Hopkins Medical School. There are no classes more popular and the researches that have been carried on have been very valuable."

In later years Abel's distinguished contributions to medical science were recognized throughout the world. He attracted to his laboratory many collaborators from this country and from abroad. He was awarded the Willard Gibbs, Conné and Kober medals and the medal of the Society of Apothecaries, London. Honorary degrees were bestowed upon him by the Universities of Michigan, Pittsburgh, Harvard, Yale, Lwow (Poland), Cambridge and Aberdeen. He was an honorary fellow or member of the following societies: New York Academy of Medicine, Association of American Physicians, Chemist's Club, Institute of Medicine of Chicago, Philadelphia College of Pharmacy, American Institute of Chemists, Royal Society of Edinburgh, Kaiserliche Deutsche Akademie der Naturforscher, Physiological Society of Great Britain, British Pharmacological Society, Society for Biology of Buenos Aires, Chinese Physiological Society, Société de chimie biologiques, Wiener Biologische Gesellschaft. He was a member of the National Academy of Sciences and in 1932 served as President of the American Association for the Advancement of Science. On the last day of his life he received notification of his election to a foreign membership of the Royal Society.

Abel's lectures given in connection with the awards of honorary medals testify to his broad and scholarly knowledge and his interest in the history of medicine. Going to New England for his summer holidays he would pack into his trunk all kinds of books on science and the history of medicine.

Abel could not be called a great teacher of students, but he impressed them with his sincerity and broad knowledge. He had no hesitation in turning over much of the teaching to his staff,

who greatly profited from this experience. Abel believed in the value of laboratory teaching and the experimental course in pharmacology was always very popular with the students.

Abel by his example, more than anything else, exerted a powerful influence on his numerous assistants and pupils and passed on to them the finest of scientific traditions. His kindly interest in younger man, his dynamic enthusiasm for research, his intimate discussions over the lunch table, his hospitability at his home, endeared him to those who had the privilege of working in the "Professor's" laboratory. On occasions he did not mind rather heated arguments with his assistants. At other times they had to drop their work in order to accept his challenge at bowling. These human traits and his magnetic personality account in no small measure for his influence on younger men. Many of these now hold important positions. Returning on visits to his laboratory he gave them always a cordial welcome and demonstrating his latest discoveries often asked for their opinions. On his eightieth birthday his former assistants, pupils and a few friends gathered for dinner in the Welch Medical Library. His physique had become frail, but his mind was as alert as ever. He carried with undaunted courage heavy responsibilities and worries, known only to a few of his friends, but the "Professor" gave all evidence of immensely enjoying the party.

On January 20, 1938 he lost his devoted wife, a blow which he met with his usual courage. A few months later, on May 26, he lost his fight against coronary thrombosis, being interested to the last in his research. Thus ended a very rich life, lived with a purpose for the lasting benefit of humanity.

CARL VOEGTLIN.

The writer is greatly indebted to many of Dr. Abel's colleagues, friends and pupils for valuable information. He is particularly grateful to Dr. Paul D. Lamson, Dr. E. K. Marshall, Jr., Dr. William H. Howell, Dr. Abraham Flexner and Dr. Abel's two sons, without whose help this brief biography could not have been written.

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