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WILLIAM HENRY HOWELL

1860—1945

A Biographical Memoir by

JOSEPH ERLANGER

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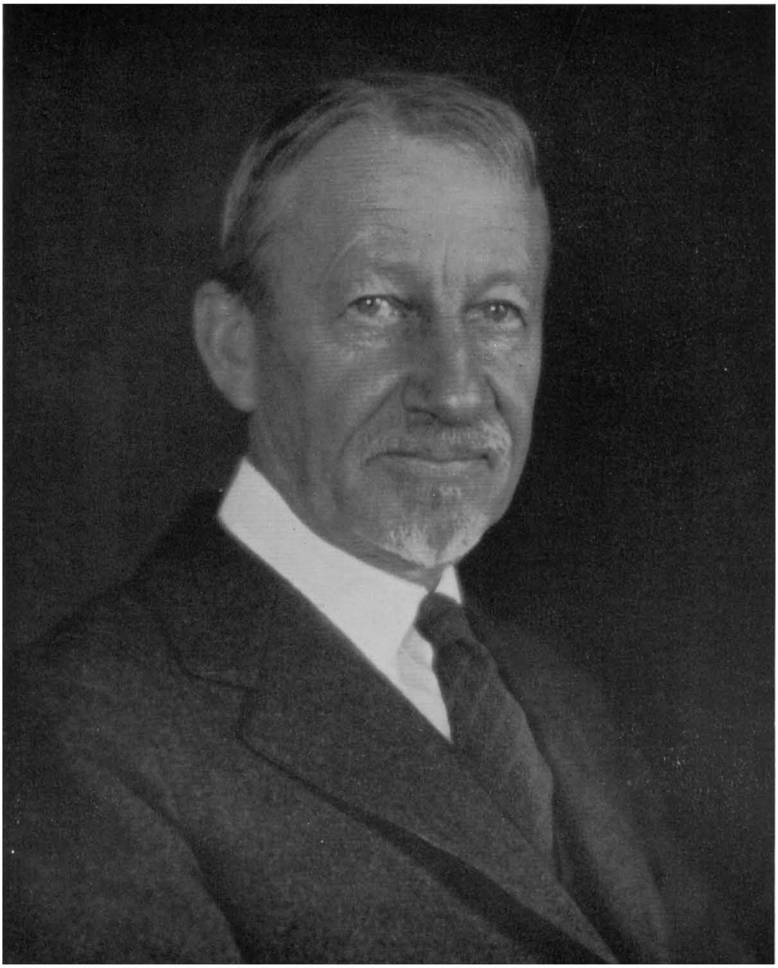

W. H. Howell

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The death of William H. Howell at Baltimore on February 6th, 1945, marked the passing of the galaxy of clinical and scientific talent entrusted with the organization of the departments of the Medical School of Johns Hopkins University prior to the opening of its doors to students of medicine in 1893, and of those of the charter members of the American Physiological Society who devoted their lives to academic careers in physiology. With his death America lost a leading figure in physiological science.

William Henry Howell, born in Baltimore, Maryland, February 20, 1860, was the son of George Henry and Virginia Magruder Howell. He was the fourth child of a family of four sons and one daughter. Both parents were natives of Maryland, coming of families that had lived since 1651 in the southern counties (Charles and Prince Georges) of the State. His father, after his marriage, moved to Baltimore where he engaged in commercial pursuits.

Education

The whole of Howell's formal education was acquired in Baltimore—in the public grade and high schools and in Johns

[1] The principal sources of material for this biography have been:

A. A brief autobiographic sketch filed with the National Academy of Sciences.

B. Some typed notes of what may have been an address delivered by Howell, probably about 1927.

C. A letter from Howell to the National Academy in response to a request to enumerate his "discoveries."

D. Howell's response on the occasion of "The Celebration of the Sixtieth Anniversary of Dr. William H. Howell's Graduation" (Johns Hopk. Hosp. Bull., 68: 291, 1941).

E. Some notes dealing with personal matters supplied by Janet Howell Clark.

F. History of the American Physiological Society, Baltimore, 1938.

G. Some notes on the organization of the School of Hygiene supplied by Dr. Clark.

The sources of passages quoted from the above are indicated in the text by corresponding letters.

Hopkins University. It was during his student days at the City College, as the high school then was designated, that his interest in science was kindled. At the age of fifteen he was appointed assistant to the professor of physics and chemistry there. In this capacity his duties were, as Howell playfully states it, "to prepare the class demonstrations in physics and chemistry and also to do some polishing of the handle of the big front door" (D). With the encouragement of his science teacher, the lad did some experimenting on his own initiative. Howell mentions particularly repeating Wöhler's classical (1828) experiment of converting ammonium cyanate into urea, the first demonstration of a test-tube conversion of an inorganic into an organic compound. This experience awakened in Howell an interest in medicine. While still in his senior year he left high school, applied for admission to Johns Hopkins University, and, after a personal interview with President Gilman, was accepted. There he pursued the chemical-biological course, designed by the University primarily as a preparation for a career in medicine.

Little is known regarding his activities as an undergraduate student. He must have been athletically inclined as a statement imputed to Henry Thomas describes him as an outstanding football player, especially skillful in tackling. There are indications that, as an undergraduate, Howell was not averse to participating in student pranks. During his college days Darwinian evolution was a subject of bitter controversy and many students became enthusiastic and obstreperous evolutionists. Howell relates (B) how they bought and surreptitiously installed in the university library a plaster cast of Darwin, how President Gilman remonstrated with them and how, at the latter's suggestion, busts of other naturalists were placed in the library, thus lessening the influence of Darwin's presence.

Upon graduation with the degree of bachelor of arts, Howell, in 1881, was awarded a graduate scholarship and consequently matriculated in the graduate school as a candidate for the degree of Doctor of Philosophy. That he had not abandoned his original intention of studying medicine is indicated by the fact that during his candidacy for the Ph.D. degree he took courses in anatomy and clinical medicine at the Medical School of the University of Maryland.

Howell's student days at Hopkins, from 1878 to 1884, coincided with the flowering of that institution into the foremost graduate school in America. Among those who were students during Howell's undergraduate and graduate years and ultimately became Doctors of Philosophy were Henry Crew, H. H. Donaldson, E. H. Hall, W. A. Noyes, H. F. Reid, Josiah Royce and E. B. Wilson, all of whom became members of the National Academy of Sciences. Many others achieved distinction in non-scientific walks of life, e.g., Maurice Bloomfield, G. W. Bright, John Dewey, K. Mitsukuri, Albert Shaw, A. W. Small, Woodrow Wilson, etc. Association with such as these must have had an influence in shaping Howell's character and interests, but as to this there is available no specific information. The faculty of that period also was unique. Howell mentions particularly his acquaintance with Gilman. Of him he writes (D) that as a graduate student, a fellow, and finally as a member of the faculty his contacts with him became increasingly more frequent and intimate. Mention is made also of W. Keith Brooks, professor of zoology, and Ira Remsen, professor of chemistry, but particularly of H. Newell Martin, head of the department of biology in which Howell majored. Of Martin he says, "He was my teacher and mentor in physiology. I owe him much; I had a very great affection for him" (F).

The degree of Doctor of Philosophy was awarded Howell in 1884. His dissertation deals with "The Origin of Fibrin Formed in the Coagulation of the Blood" (7). When Howell began this investigation two views were held with regard to the formation of fibrin. Schmidt believed that it is formed by a fermentation process, the substrate being furnished by fibrinogen and paraglobulin, whereas Hammarsten maintained that only fibrinogen and ferment are needed for the formation of a clot. Howell points out that Hammarsten's observations were not conclusive because his solutions of fibrinogen, made from mammalian blood, were not entirely free of globulin. By using blood of the terrapin, Howell was able to secure fibrinogen entirely free of globulin and found that clotting still occurred with the purified reagents, a result that has withstood the test of time. This study was the first of a number of papers on blood clotting, the problem which later became the major interest of Howell's life, and the subject with which his name will be associated through the years.

It was during Howell's student days that Martin described his important experiments upon the isolated mammalian heart, then a new procedure in physiology. Howell assisted Martin in the performance of some of these experiments, and in addition published five papers bearing his own name. All are significant, but one of them (4), published in the Philosophical Transactions of the Royal Society, merits special mention. In this research it was found that the output values per beat of the excised, perfused heart of the dog are 1/855 and (with a slow pulse) 1/700 of the body weight. These are values that agree well with those (1/800 and 1/700) obtained in 1924 [2] with improved methods and with the heart in situ.

As a Member of Martin's Department

Upon graduation in 1884 Howell was made chief assistant in Martin's department with the title of assistant professor of biology, and given charge of the laboratory course in animal physiology. In 1888 his title became associate professor in physiology. The courses he taught covered a wide range of subjects—animal morphology, vertebrate histology, mammalian anatomy and animal physiology. There is little additional information available concerning this period of his life. Henry Crew, whose residence at Hopkins overlapped Howell's, writes that "although physiology is quite outside my line, I was early inspired by Howell's style when he now and then read a paper —or discussed another's paper—before the Johns Hopkins University Science Club in the early eighties. . . . That 'unhurried' style and that 'directness and simplicity' of language—delighted me as a young man." Crew speaks also of Howell's imperturbable calm and his absolute sincerity and adds that

[2] E. K. Marshall, Amer. J. Physiol., 79:459, 1924.

his clear and ready English, combined with his ability as a listener, made him a master of the art of conversation. John Slade Ely, who collaborated with Howell during the first year of the latter's fellowship and who later became a professor of medicine in Yale, wrote that "he had found in Baltimore a man (Howell) who knew all of physiology and yet was fond of reading Shakespeare" (D).

Three papers were published during the four-year period (from 1885 to 1889) of Howell's connection with Martin's department as a staff member. Reference can be made to but one of them, one that led Howell to conclude that coagulation of the blood of limulus is due to a coalescence of corpuscles which then takes on the properties of fibrin (8), a view that has been confirmed by others.[3] One wonders whether the seeming relative inactivity of this period might not have been the result of increasing departmental responsibilities due, perhaps in part, to Martin's failing health. Yet Howell says that the experience of those years stands out in his memory as the golden period of his life (B).

Nearly all students of this period who became professional physiologists worked, often for years, in foreign laboratories, but Howell's only opportunity to gain foreign experience came during a summer's trip abroad at about this time. He elected to go to Munich to see Voit's laboratory, as the great new addition to physiology at that time was Voit's work in nutrition. "The laboratory," Howell wrote many years later (B), "exemplified the Gemütlichkeit which was traditional in Bavaria. At the meeting of the Gesellshaft the members sat around tables drinking Münchener beer while listening to papers and discussions and after the meeting the younger group adjourned to a nearby Keller where the discussion was continued with the help of a plentiful supply of Rhine wine." Howell mentions also a visit to Kühne's laboratory at Heidelberg (B). Apparently he did no investigative work at either place. The laboratories he visited, however, were devoted largely to aspects of chemical physiology. The choice possibly is indicative of

[3] L. Loeb, Biochem. Zeitschr., 24:95, 1910.

Howell's interest in that phase of physiology, an interest that is exemplified by the immense amount of time he later devoted to the identification of chemical reactants in the process of blood coagulation.

Ann Arbor and Harvard Periods

In 1889 Howell was called to Ann Arbor to succeed Henry Sewall who was giving up the chair in physiology because of ill health. Howell's initial title was lecturer in physiology and histology, but at the close of the first year he was advanced to the professorship in these subjects. An interesting note on Howell's experiences at Ann Arbor appears in an unpublished article by J. S. Lombard, dealing with the history of the department of physiology at Ann Arbor.[4] "It was not easy," Lombard writes, "to lecture to a mixed class of women and men, composed of students from the medical, homeopathic, dental, and liberal arts departments, some of whom, at least, had the reputation of being unruly. Howell concealed beneath a quiet, mild manner great strength of character, which came to the fore when certain students tried to take advantage of him. Howell decided that either they or he would leave the University. The students left, and he had no further trouble with his classes." Lombard is the authority for the statement that in 1891 a laboratory course in physiology became a requirement for all students at Ann Arbor, the first laboratory course in physiology to be required in any medical school of the country.

Howell's stay at Ann Arbor was brief, for in 1892, he accepted appointment as associate professor of physiology under H. P. Bowditch at the Harvard Medical School, where he remained for but one year. Before the termination of that year, Mr. Gilman, the president of Johns Hopkins University, called on Howell in Boston, told him of the plans for a new medical school in Baltimore and offered him the chair in physiology. Howell accepted at once without discussion, for, as he puts it, "I had . . . a deep affection for the University that had done so much for me, everything, in fact, so far as my career was concerned" (D). It is of interest to note here

[4] Supplied through the kindness of F. G. Novy.

that of those who first headed the four preclinical departments of Hopkins, Howell alone was without extensive experience as a worker in foreign laboratories.

Five papers were published during the Ann Arbor-Harvard period. In keeping with Howell's dual title at Ann Arbor these studies dealt as much with structure as with function. Three of the papers deserve special mention. In one (12) there is a description of particles in red blood corpuscles that take nuclear stains, which today (59 years later) are generally known as Howell-Jolly bodies. The other two papers (14 and 15) (published in three parts in collaboration with Huber) dealt with nerve degeneration and regeneration; this work was awarded the Weir Mitchell prize. The papers describe for the first time a number of regeneration processes, such, for example, as the general downward advance of medullation. They also describe, *quite independently* of v. Büngner,[5] the changes in the Schwann cells that result in the formation of what are now generally known as the "bands of v. Büngner."

Here it is necessary to digress in order to refer to Howell's reply to a letter from the Committee on Biographical Memoirs of the National Academy of Sciences. "I find it difficult," he wrote, "to comply with the request of your committee. My work, like that of most scientific men, has consisted largely in contributions to problems of current interest that have been useful, I believe, in throwing light upon the solutions reached but which considered alone can not be reckoned as discoveries. I may, however, cite three cases in which concrete facts of importance were discovered." The first of the discoveries mentioned belongs to this period. It was believed prior to Howell's work that serum albumen was required for the nourishment of the heart. Thus German investigators had found that peptone solutions, which do not support the heartbeat, will do so after they have been in contact with the mucous membrane of the stomach or intestine; and these investigators consequently had assumed that the peptone had been changed to serum albumen. Howell showed (16) that what happened

[5] Beitr. path. Anat., 10: 321, 1891.

in such cases was that inorganic salts had been added to the solution by diffusion and that it was those salts which maintained the beat of the heart, not proteins.

Howell at Johns Hopkins: the Medical School

During the Hopkins period, which extended through the rest of Howell's life, some 55 papers were published. It will be possible to refer specifically to only a few of the more significant of these. Such a paper was the very first of this series (18). Howell found that a nerve can be so treated that it will fail to conduct impulses before its demarcation potential has completely disappeared. He found that such agents cause failure of conduction before complete depolarization is attained.[6]

Howell's interest in the physiology of sleep led to the investigation of the effect of arterial pressure on the flow of blood through the brain. It was believed at the time that an increase in arterial pressure beyond the normal limits reduces the blood flow through the brain. Howell showed by a faultless technique (21) that the blood flow changes linearly with the arterial pressure even through extreme ranges. In another paper (24) observations were made on vasomotor responses of intracranial structures to electrical and to chemical stimuli. It was found that the dura mater is very sensitive to mechanical stimuli—indeed, that to gentle mechanical stimulation the dura seems more irritable than other sensory membranes of the body. Yet, apparently, it was not until 1938[7] that surgeons generally came to realize that there is a nerve distribution to the dura apart from that to its blood vessels.

Howell's interest in salt action (many of his students were assigned problems in this field) suggested to him the possibility that cardiac stoppage resulting from vagus stimulation might be due to the liberation of diffusible potassium in the heart. Guided by this hypothesis, he demonstrated that potassium actually is liberated during vagus stimulation, and in amounts sufficient to stop the heart (29, 32, 33). Later, Loewi found that acetylcholine is liberated during vagus stimulation, that atropine

[6] G. H. Bishop, Amer. J. Physiol., 97: 504, 1931.
[7] Proc. Assn. Res. Nerv. and Ment. Dis., 23: 196, 1938.

stops the action of acetylcholine but not that of potassium and consequently he concluded that acetylcholine is the inhibitor. However, it has been shown more recently by Lenhartz that acetylcholine liberates potassium, but not in the presence of atropine. It seems, therefore, that potassium actually is the chemical mediator of the action of the vagus on the heart, though this view is not generally accepted. Howell was the first investigator to suggest that the two lobes of the pituitary gland are functionally different. In a paper (20) read by invitation before the first Congress of American Physicians and Surgeons he described experiments showing that the circulatory effects of extracts of the pituitary gland are due entirely to substances derived from the posterior lobe. Ever since that time a distinction has been made between the functions of the lobes. This is the second of the three discoveries mentioned in Howell's letter to the Academy.

After 1909 Howell's efforts as an investigator were devoted almost exclusively to the study of problems in the field of blood physiology and pathology. Of 38 scientific papers published during this period all but 4 dealt with those subjects. Of these subjects it has been said as recently as 1944 that the briefest meditation of the strictly theoretic aspects of the clotting problem leaves one with the appalling feeling that tampering with the coagulability of blood, that protective mechanism of life, par excellence, is a hazardous business. Another worker in this field has said that the subject of blood coagulation now (1945) is in a state of anarchy: "the confused terminology, the multiplicity of hypotheses, the feeling of discomfort would all seem to point to that"; and the same author goes on to say that the clotting problem is difficult "because it is a border-line problem, involving some of the most refractory and least explored substances and reactions."

Howell was fully aware of these difficulties. He realized that the process of clotting involves chemical and physico-chemical reactions among substances whose nature and properties are known only imperfectly, and that a complete explanation of the details of the reactions must await a better comprehension of the chemistry and physical chemistry of the blood. Yet Howell devoted an immense amount of time to efforts to isolate and purify the blood reactants. If he had had available the information which can be and to some extent has been revealed since by the newer methods of analysis, such as electrophoresis, chromatography and supercentrifugation, his progress undoubtedly would have been faster and more certain and fewer revisions of hypotheses would have been necessary. Even so, his contributions have won for him the designation as the great American pioneer of blood coagulation. The frontispiece of the monograph by the Swedish biochemist, Jorpes, dealing with one of the phases of coagulation, is a portrait of Howell, whom he characterizes as "an *eminent representative of the series of* successful scientists who have advanced America's physiology and medicine to a leading position."

It is quite impossible, within the limits of this sketch, to give an adequate setting for Howell's contributions to this subject.[8] Briefly and categorically, when, in 1909, Howell resumed active interest in this problem, some four or five factors were known to be concerned with the clotting process. To Alexander Schmidt of Dorpat belongs the credit of having contributed to our knowledge of most of them. In papers published between 1861 and 1895 he showed that (1) a soluble blood protein, fibrinogen, is converted into the insoluble fibrin of the clot through the action of (2) thrombin (which he regarded as an enzyme); that the thrombin, however, is not present as such in normal blood but is formed in shed blood from a precursor, (3) prothrombin, through the action of (4) a "zymoplastic substance" secreted, Schmidt thought, by the white cells of the blood. In 1890 Hammarsten and Arthus and Pagés showed independently that (5) calcium plays a role in the conversion of prothrombin into thrombin. It was then found by Spiro and Fuld and by Morawitz, both in 1904, that zymoplastic substance, now generally known as thromboplastin, is derived from disintegrating blood platelets, indeed, from any damaged tissue cells, as in a wound.

[8] For an excellent summary of the problem of coagulation see Howell's Pasteur Lecture (58).

To this scheme Howell's investigation resulted in the addition of a *sixth factor*. His earliest (1884) work in this field had led him to the correct conclusion that (to use current terms) the normal plasma of terrapin does not contain thromboplastin—the plasma of the carefully drawn blood does not clot unless that factor is added. However, as a result of his 1912 studies he found that mammalian plasma differs from that of other vertebrates in that, as others had maintained before him, it contains within itself an available source of thromboplastin derived, most probably, from constantly disintegrating blood platelets, structures that are not found in the blood of lower vertebrates. Further work at that early date had led him to conclude, as had others before him, that intravascular mammalian blood does not clot, though it contains all of the necessary factors, because of the presence of an "antithrombin." Moreover, he convinced himself that such an "antithrombin" accounts for the incoagulability of drawn blood that results when a solution of peptone is injected into the blood stream of a surviving mammal.

Some three or four years after he had expressed these ideas he assigned to McLean, a second year medical student, the problem of obtaining from heart and liver certain "phosphatides" which were believed to *induce* clotting. In the process a product was isolated, presumed to be a phosphatide, which, instead of inducing clotting, actually *retarded* it. From this point Howell continued the investigation of this anticoagulant, which he named heparin because it was derived in large amounts from the liver. He soon found that it is not a phosphatide, since the purified product proved to be phosphorus-free, that it contains uronic acid, and indications were obtained that sulphur also enters into its composition. Subsequent investigations by others have confirmed all of this and have indicated that heparin is not a chemical individual, but may be a series of different polysulphonic acid esters of mucoitin. Howell succeeded in purifying heparin to the point where 1 milligram prevented the coagulation of 100 milliliters of blood for 24 hours at 0°C. Having demonstrated its presence in normal blood, he early designated it as a "physiological" anticoagulant. Justification for thus regarding it has been supplied through the findings by others that heparin is normally present in certain cells, now called heparincytes, in the walls of blood capillaries whence it can readily gain access to the blood. The incoagulability of the blood in peptone and anaphylactic shocks has been shown to be due to an increase in the amount of heparin formed by the liver. Heparin now is on the market, and is extensively employed to render blood incoagulable in physiological experiments and in the treatment of clinical conditions in which intravascular clotting of the blood is threatened or in process. To quote Jorpes, "Today . . . heparin is as specific in thrombosis as insulin is in diabetes."

Howell worked assiduously and long at efforts to isolate and determine the chemical nature of some of the other then known factors in the coagulation process, but reference can be made to but one other of these attempts. What now is known as thromboplastin had early (Wooldridge, 1886) been regarded as a combination of a protein with the phosphatide, lecithin. Howell's analyses (40) led him to conclude that the phosphatide constituent of thromboplastin is cephalin, not lecithin, and that the thromboplastic activity of the compound is due to the cephalin. His evidence consisted in part in showing that lecithin from several sources has no favoring effect on coagulation whereas he, and subsequently other investigators, found that pure cephalin possesses what was regarded as a high degree of thromboplastic activity. This finding Howell mentions as the third of his discoveries. "I was able to show," he says, "that cephalin is the so-called 'thromboplastic' substance in tissue cells." And he goes on to say that "while this . . . result is not accepted by all workers I am confident that it will prove to be correct."

But before considering Howell's further work with thromboplastin it will be necessary to refer to his protracted studies in hemophilia. His observations on this malady were made possible mainly through the rare opportunity that presented itself of three hemophilic brothers who served as his principal subjects. One of the brothers, Jesse Yaffe, became Howell's faithful laboratory technician—the primary and willing subject of his experiments, which included the testing of a number of so-called remedies mentioned in the literature, all of which proved to be worthless.

The studies on the blood in hemophilia were begun in 1914. In the first paper (43) it was concluded, but with great caution, that "in hemophilic blood *there seems to be* (italics ours) a relative excess of antithrombin owing mainly to an actual diminution in the amount of prothrombin." However, in 1926, after the discovery of heparin, it was found (59) that there is no excess of that anticoagulant in hemophilic blood and that prothrombin is present in normal amounts and possesses normal activity. The blood platelets, however, were found to be more than normally stable, and consequently Howell adopted the view that had previously been suggested by Minot (who at one time had worked in Howell's laboratory) and also by Fanio, that the prolonged clotting time might be the result of a slowing of the liberation of their thromboplastin, a view that still is held in some quarters.

It was in this connection that Howell again became interested in the nature of thromboplastin. He felt that if an homogenous, protein-free thromboplastin could be prepared it might prove to be of value in the control of the hemorrhages of hemophilia. In 1939 he believed he had succeeded in obtaining such a product from lung tissue (70). Lung, it should be added, was the source employed for the reason, among others, that Howell, in 1937, had found that the lung is the organ, par excellence, in which platelets arise (68). But in 1941 (71) he wrote . . . "I have been successful in obtaining from human lung a purified, active preparation . . . but I am not sure at present that it is free of contamination with inactive protein and lipoid constituents." In the meanwhile, Chargaff and Cohn (1940), as a result of analyses by electrophoresis, by supercentrifugation, and by other methods also, concluded that thromboplastin derived from the lung of cattle is a complex molecule made up of proteins and several lipides of which 26% is lecithin and 25% cephalin. This compound, they state, has no thromboplastic activity whatever, after removal of its phosphatides, though the protein-phosphatide compound is

1000 times more active than the total phosphatide fraction. In 1941, Howell says of this work that from the method used in its preparation one may feel uncertain whether this final product is a definite compound.

An account of Howell's last efforts in this quest was published posthumously in 1945. "It was possible", it is stated in that paper, "to remove the protein leaving a residue with marked" and stable "thromboplastic activity, the chemical nature of which has not been determined". The thromboplastic action of the crude material alone had been tested,—the human thromboplastin on a case of aplastic anemia with uncontrollable hemorrhages, "without unfavorable reactions", the pig thromboplastin on a strain of hemophilic pigs with results that "were interesting and suggestive". The question as to whether cephalin is the normal thromboplastic agent, therefore, must still be regarded as unsettled.

Howell, as did most other workers in the field, attempted from time to time to formulate his views on coagulation in the form of "theories". Since, however, reactants in the coagulation process still are being disclosed it is obvious that such statements should rather have been regarded as working hypotheses.

While Howell was engaged in the investigation last mentioned above he was having light heart attacks. On Thursday, February 1, 1945, he had a severer one than usual, and was ordered by his physician to remain at home for a week. In disregard of these instructions, he went to his laboratory on Monday, the 5th. Early Tuesday morning he had a very severe attack and died within a half hour, 14 days before his 85th birthday.

Spirit of Investigation

To the foregoing outline of some of the more significant of Howell's contributions to science should be added a word relative to his views regarding the spirit of investigation and the deportment of investigators. Quotations that reveal his attitude are the following: (1) In Martin's laboratory "the spirit of research was in the atmosphere. There was no pressure of any kind to produce results and there was no expectation that anyone was going to make a great discovery or even an important discovery. The sole animating motive was that we had the privilege of adding something new to the state of physiological knowledge . . ." (F). (2) "In medical research at present" (about 1927) "there is a keen, almost cruel, competition to secure results that will attract attention. It has its good side no doubt in stimulating productivity but it does tend to distort values and set up standards that give to scientific research something of the low motives of commercial warfare" (B). And (3) "Investigators by nature," Howell wrote in 1915, "are men who cannot refrain from following out their ideas. They are driven constantly to such work by interest or by irritation; either stimulus is sufficient. I fancy that among our greatest investigators it is the irritative impulse that predominates." If Howell's persistent attack on the elusive problem of blood coagulation was due to such a drive his mien in the laboratory gave no evidence of it during the six years of the writer's connection with it. At the departmental lunch table, for instance (this was in Howell's private laboratory), he spoke interestingly and freely about the progress of his current experiments. At no time was there a display of more than a quiet enthusiasm, though he was always ready to defend his findings. The same factual, calm discussions are to be found in review articles he wrote on controversial subjects to which he or his students had made contributions. From among these may be mentioned such articles as the Cause of the Heart Beat, the Chemical Regulation of the Processes of the Body by Means of Activators, Kinases and Hormones, Theories of Blood Coagulation, etc. Yet one wonders whether beneath Howell's outward calm there was not concealed this same drive. Howell was not a trained chemist. But when his years were running out he is said to have remarked, "I'd get along faster if I got an expert organic chemist to work with me, but it is more fun to do it myself." As a matter of fact, Howell was chemist enough to determine almost completely the composition of heparin, to recognize cephalin as a thromboplastic agent, and to devise a quantitative test for prothrombin, which, with slight modifications, is a commonly used clinical text today. He could easily have secured the collaboration of a trained chemist and so have speeded his quest. But the drive was there to do it himself.

Textbooks

The first cooperative effort by physiologists of the new world to write a book on physiology for the use of medical students was "An American Textbook of Physiology," published by the W. B. Saunders Company. Howell was the chosen editor of this work. It went through two editions, the first in one volume in 1896, the second in two volumes in 1900. Then, in 1905, Howell wrote his "Textbook of Physiology for Medical Students and Physicians." The preface to the first edition states that the art of presentation makes a textbook successful or unsuccessful and that the guiding principles are simplicity and lucidity in the presentation of facts and theories. This work, issued by the house that published the American textbook, was in its 14th edition at the time of Howell's death, and more than 140,000 copies had been sold. Moreover, after Howell's death the same publishers continued to issue, under other, now joint, authorship, a "Howell's Textbook of Physiology." No better evidence could be given of Howell's ability as a writer of textbooks! It may truly be said that his textbook was the main source of the written lore of physiology for American medical students through a period of 30 to 40 years.

Lectures, etc.

During the Hopkins period Howell delivered a number of formal addresses, many of which have appeared in print. The occasions for these were varied,—natal celebrations of institutions, such, for example, as the 75th anniversary of the founding of the University of Michigan, the 100th of the Yale Medical School, the dedication of the new buildings of the Washington University Medical School, etc. Especially noteworthy are his address on the Problems of Physiology of the Present Time, delivered at the unique, worldwide gathering of talent in connection with the Congress of Arts and Sciences under the auspices of the Louisiana Purchase Exposition, and the presidential address of welcome to the XIIIth International Physiological Congress in Boston. His discussions on these occasions dealt commonly with the historical development of physiology or the role of physiology in relation to science in general and to medical education in particular. Usually his addresses were delivered without notes and always were characterized by a happy choice of sound ideas, logically developed in simple terms. His delivery was unostentatious, his enunciation clear, his voice somewhat high pitched with a quality that was slightly musical.

In addition Howell responded frequently to requests to speak or to write in connection with less formal occasions, some of which were gala, such as presentations of portraits (e.g., Newell Martin's, Florence Sabin's, etc.) and anniversaries (e.g., "William H. Welch at Eighty"), and some memorial, such as obituary notices (e.g., Gilman's, Newell Martin's, Mall's, Abel's, Meltzer's, Finney's). For examples of Howell's superb handling of such topics one should turn to page 80 of "Welch at Eighty" [9] and to the obituary of J. M. T. Finney.[10]

Howell's classroom lectures to the medical students were of the same high quality. They were characterized, moreover, by an entire lack of dogmatism or ostentation; and this was accomplished without concealing his keen interest in the subjects under discussion. Together with his neatly executed experimental demonstrations at the lecture table, his lectures were by common consent an outstanding feature of the four years' course of instruction.

As an Executive

From 1899 until 1911 Howell served as dean of the Medical School in succession to William H. Welch, the first dean. It was during this period that Howell wrote his textbook. Despite these two extra demands on his time he continued as usual to carry the greater part of the formal teaching of the department and to carry on as an investigator. Outwardly he

[9] New York, 1930.
[10] Bull. N. Y. Acad. Med., 18: 552, 1912.

seemed as unperturbed as ever, but during this period he suffered for a time with gastric symptoms. The School prospered during his stewardship as dean. The size of classes on admission, which had been fluctuating around 50, increased to its present limit of 75, and the first additions to the facilities for medical teaching and investigation above those initially obtaining became available. These included the physiological laboratory and a laboratory for surgical research, both on the grounds of the Medical School, and, on the grounds of the Hospital, the Phipps Psychiatric Clinic and the Harriet Lane Home for Invalid Children, additions which made possible the establishment in the School of corresponding teaching and research departments. According to Simon Flexner it was during Howell's deanship that the Advisory Board of the Medical School began the discussions that culminated in the inauguration at Hopkins of so-called full-time clinical teachers and departments.

School of Hygiene and Retirement

Howell must have played an important role in the organization of the School of Hygiene at Johns Hopkins. William H. Welch was the initial director. In 1917 Howell was made assistant director and the following year he resigned his post as professor of physiology in the Medical School in order to accept appointment as professor of physiology in the School of Hygiene. Eight years later he succeeded Welch as the director. It is stated, in a report filed by Howell, that in organizing the School it was intended to restore physiology to the place it had occupied at the time (about 1840) of Pettenkofer in the prebacteriological days, as one of the fundamental subjects upon which scientific instruction in hygiene must be based. The first year of Howell's connection with the School was devoted to planning and organization. Teaching and research were begun in 1918 in the old physics building in West Baltimore. Howell gave the course in personal hygiene, a subject that was entirely new to him. His research, however, with but a single excursion into the field of hygiene, continued to deal with factors in blood coagulation. At the beginning the number of students in the school was small. They came to Dr.

Howell's house for Sunday tea and he became very well acquainted with them. They were extremely interesting years (G). After four or five years the School moved to the large new building in the vicinity of the Medical School in East Baltimore. The lecture room of the department of physiology was elaborately equipped for the study of ventilation. Students attending the lectures were required to file daily reports of their sensations of comfort. The analysis of these data formed the basis of a paper entitled "Humidity and Comfort" (66). It led to the conclusion that when provision is made for the removal and movement of air, the dry bulb thermometer is the important standard to maintain.

Howell was created emeritus professor at the age of 71. Then, for one year he served as Chairman of the Medical Division of the National Research Council and for the succeeding year as Chairman of the Council. Thereafter, except for revisings of his textbook, he devoted himself exclusively to research. The University provided him with a laboratory and funds were made available to him at first by the Carnegie Corporation and later from the fluid research fund of the Medical School.

Family Life

The relations between the members of the Howell family were intimate and happy. They quite regularly spent the three summer months on Great Chebeague Island in Maine, where they owned an old farmhouse. There Dr. and Mrs. Howell with their children and, later on, their grandchildren, enjoyed ideal outings. Howell, who previously had taken his exercise mainly in the form of tennis and golf, now took up sailing as his chief summer pastime. When his children became old enough they served as the crew of his 30-foot sloop on cruises along the Maine coast. On these expeditions they, and later on, their children, too, learned from him much more than they learned from their winters in school. The affection and admiration his grandchildren felt for him is evidenced by the fact that each of the then four of them, when in turn required at school to compose an essay on "the person you admire most," chose to write on their grandfather. During his last summers in Maine Howell turned to lawn bowling as his pastime and acquired as great a proficiency at this game as he had throughout his life with all other sports. His age brought no apparent dimming of his mental ability, no decrease in his interest in life, no change in his personality. He never lost his wonderful sense of humor.

In 1887 Howell married Anne Janet Tucker of Baltimore. She predeceased him by some years after a long period of failing health. Their three children are living. Janet Howell Clark, Ph.D., is Dean of the College for Women of the University of Rochester; Roger Howell, Ph.D., is Dean and Professor of Constitutional Law in the University of Maryland and Charlotte Teresa is the wife of Dr. E. O. Hulburt of the Naval Research Laboratory. There are seven grandchildren and, at this writing, two great-grandchildren.

General

Howell was one of the best loved of American physiologists. A kindly disposition and unpretentiousness of manner endeared him to all who knew him well. He held firm but carefully weighed convictions which, however, were never obtruded on casual acquaintances. His strength of intellect, his wisdom, his moral fiber gave him the peace of mind and the sympathetic understanding of his fellow men that were so apparent to all who knew him. He will be remembered not only for his important contributions to physiology, as an inspiring teacher and as an able and considerate administrator, but equally for his fine personal attributes—a calm, simple philosophy of life combined with the strength of character that enabled him to live in the light of that philosophy.

The position he occupied in American physiology is best indicated by the recognition accorded him by his colleagues. He was one of the twenty-eight charter members of the American Physiological Society and read the first paper at the first meeting of that Society. He was its fourth president and was younger by many years than were his predecessors at the time of their incumbency. He was reelected to the office five times, and was a member of the Council of the Society for twenty-two years. He was named chairman of the initial editorial committee of the *American Journal of Physiology* when, in 1914, the American Physiological Society acquired ownership and editorial control of that publication. He was chosen by American physiologists to be the president of the only International Physiological Congress that has met in the Americas. He was editor of "An American Textbook of Physiology," the first cooperative effort of the kind by New World physiologists. He was elected a member of the American Philosophical Society in 1903 and of the National Academy of Sciences in 1905, while relatively young. This is a record no other American physiologist has approached. Yet in his response at a testimonial dinner where his colleagues and students had had the opportunity of expressing verbally their sentiments of love and devotion, Dr. Howell (then approaching his eighty-first birthday) said with characteristic modesty, "there are some visions of the morning that have not been realized, but this happens no doubt to everyone."

Honorary Degrees

M.D., University of Michigan, 1890.

Sc.D., Yale University, 1911.

LL.D., Trinity College (Conn.), 1901; University of Michigan, 1912; Washington University (St. Louis), 1915; University of Edinburgh, 1923.

Other Honors and Memberships in Scientific Societies and Organizations.

Honorary Member, Physiological Society (Great Britain); Honorary Fellow, New York Academy of Medicine; Honorary Member, The Harvey Society, New York; Member of the Executive Committee of Science Service, 1931-42, Chairman and Vice-president; Member National Research Council, Chairman, 1932-33; Prize, American Physiological Society; Member National Academy of Sciences; Member American Philosophical Society; Member American Physiological Society, President, 1905-09; Member Society for Experimental Biology and Medicine; Member Society of Naturalists, President, 1924; Member American Association for the Advancement of Science, Vice-president, Section K, 1908; President International Physiological Congress, 1929.

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