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REID HUNT

1870—1948

A Biographical Memoir by
E. K. MARSHALL, JR.

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Biographical Memoir

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BY E. K. MARSHALL, JR.

"When I drive up to the Medical School through the Fenway on winter mornings, I often pass Reid Hunt striding along in all kinds of weather, his head bent forward in a thoughtful attitude and his little satchel crammed with books swinging in his hand. I think with regret, at such times, of the unfortunate circumstances which, in modern teaching of large classes with rigid curricula, prevent that close personal association between teacher and student which, in many cases, might represent the best that an educational institution could offer.

"I think also, as I watch him, of Reid Hunt the young man, starting one moonlight night many years ago to march with this same erect stride across the desert of the Sudan behind an escort of military convicts to carry his sick friend Saunders (sic) to care and safety. I see him then with eyes through which I wish his students could see him when he stands before them in the pit of the lecture hall. They would think of him, then, not only as the eminent scholar, shy beyond all display of learning, but also as the human being to whom his science has been a great adventure for the exercise of that courage and devotion which carried him and his friend safely through Kitchener's Sudan in 1898 (sic)."

These paragraphs, from Zinsser's introductory chapter of the Year Book of the Harvard Medical School Class of 1937, suggest certain characteristics of Reid Hunt: his kindness, shyness and modesty, his scholarly attitude, his encyclopedic knowledge, and his capacity for interesting, intimate conversation. For the sake of accuracy, it should be noted that Hunt took his sick friend Sumner from Berber to the railroad station, one mile away; and that instead of marching, he rode a white Egyptian donkey.

Reid Hunt was born on April 20, 1870, in Martinsville, Ohio. He was the son of Milton L. and Sarah E. (Wright) Hunt. His father was a small-town banker, and both parents were interested in literature. There was one other child, an elder

brother. Circumstances were such that no work or chores were required of young Hunt at home. His interest in science and medicine was acquired early while studying chemistry with the village druggist. After graduation from the Martinsville High School at the age of 16, he attended Wilmington College and the University of Ohio (Athens) for a year each. He then came to Baltimore, entered Johns Hopkins University, and received his A.B. in 1891.

After receiving his baccalaureate degree, Hunt entered as a graduate student at Hopkins in pathology under Welch and in biology under Newell Martin for the first half of the academic year, 1891-92, but in February he sailed for Europe. Here, he registered as a medical student at the University of Bonn, and was much impressed with Binz, the Professor of Pharmacology. The next fall, we find the young scientist returned as a graduate student at Hopkins in physiology. He evidently started his work under Newell Martin and a year later continued it with his life long friend William H. Howell. He acted as Assistant in Histology and Physiology in 1892-93, and in Physiology in 1893-94. In June, 1894, he was appointed Fellow in Physiology and was reappointed in June, 1895. In 1896, Hunt received his Ph.D. in Physiology. While studying for the doctorate in physiology, Hunt, apparently unknown to the Hopkins authorities, had been attending classes at the College of Physicians and Surgeons in Baltimore. He received his M.D. degree from that institution simultaneously with his Ph.D. from Hopkins. In those days, it was quite possible to obtain both the Ph.D. and the M.D. degrees in five years. That was before the days of the Flexner report and the medical course was mostly lectures repeated from year to year. Hunt was excellently prepared, probably much better prepared than most medical students of his period.

Two years were now spent as Tutor in Physiology under Curtis at the College of Physicians and Surgeons of Columbia University. In the fall of 1898, Hunt came back to Johns Hopkins as Associate in Pharmacology. The summers of 1898 and 1899 were devoted to two expeditions to Egypt in an attempt to obtain specimens of the African lungfish and its developmental stages. Both expeditions were led by N. R. Harrington,

a graduate student at Columbia. The first was sent out by the Zoology Department of Columbia University and consisted of Harrington and Hunt. Military conditions prevented the ascent of the Nile. The second expedition was financed mainly by Charles H. Senff, a friend of Henry Fairfield Osborn, and consisted of Harrington, Hunt and F. B. Sumner. This expedition went into the Sudan as far as Atbara. Harrington died of fever, and both Hunt and Sumner were stricken. Although the second expedition collected a number of local species of fish and some preserved material for histological study, neither expedition succeeded in its main objective of obtaining the lungfish.

From the fall of 1898 until the fall of 1904, Hunt was in Baltimore at Johns Hopkins with John J. Abel. In 1901, he was made Associate Professor of Pharmacology. During this period in Baltimore, two trips were made to Paul Ehrlich's laboratory at Frankfort, the first in the summer and fall of 1902, and the second in 1903. Apparently, Hunt returned to Baltimore each year to carry out his teaching duties. In 1904, he was called to the Hygienic Laboratory, U. S. Public Health and Marine Hospital Service, as Chief of the Division of Pharmacology. In 1910, his title was changed to Professor of Pharmacology. In 1913, Hunt accepted a call to become Professor of Pharmacology at the Harvard Medical School, from which position he retired as Professor Emeritus in 1936. Reid Hunt died after a long illness on March 10, 1948.

In December 1908, Reid Hunt married Mary Lillie Taylor of Washington, D. C., who survives him. They had no children.

As far as one can judge, Ehrlich exerted the most influence upon Hunt's career. His two major fields of work—the physiology and pharmacology of the thyroid gland and the relation of chemical constitution of onium compounds to their pharmacological action—stem from investigations undertaken at Frankfort. Hunt never tired of talking of Ehrlich and his Frankfort laboratory. One gets the impression that the months with Ehrlich were among the happiest of his life. Hunt believed very strongly in Ehrlich's chemotherapy, and in a letter to the *Journal of the American Medical Association* in 1907

(before Ehrlich's Salvarsan) he stated clearly his belief that the future therapy of infections lay in chemotherapy and not in vaccines and sera. It may be of interest to note that only a short time before Ehrlich and Shiga made their epoch making observations on the curative effect of trypan red in trypanosomiasis in mice, Hunt had started with Ehrlich the study of the action of dyes in this experimental infection. One who worked with Hunt at Harvard on the effect of organic arsenic compounds on tumor-bearing mice writes, "We never did turn the corner but in the light of all that has transpired in the field of chemotherapy in recent years, I shall always feel that it was a rare privilege to have had a chance to come in contact with one of the pioneers in the field. He certainly had a real 'vision of things hoped for' and an enthusiastic conviction that certainly received ample substantiation a few years later in the tremendous strides which have been made in chemotherapy." One wonders why Hunt, with his great belief in the future of chemotherapy, with his knowledge of the literature and with his experiences in Ehrlich's laboratory, did not work actively in this field.

In the connotation generally attached to these terms, Hunt was neither a brilliant nor a successful teacher. His lectures were delivered in a quiet, unassuming manner, and no attempt was made to cover systematically the factual content of pharmacology. These lectures proved disconcerting to most medical students, especially since at the time, there was no satisfactory text in which the subject could be reviewed. However, to the more advanced students, his lectures were intensely interesting. There were many entertaining side lights and excursions into historical aspects of his subject. Frequently, the whole hour was spent on discussion of a single point, sometimes of controversial nature. In informal conversation, Hunt was at his best and could talk in a most entertaining and interesting vein of his many and varied experiences in European and other laboratories. Hunt did not enjoy teaching and probably realized that it was not his forte. A colleague of the old days at Hopkins writes that Hunt was well pleased when he got the job in Washington with no teaching but that when the

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Harvard offer came he was not quite certain he should accept it as it meant more teaching than he wanted.

Many who were associated with Hunt have told me that those who worked in his department had a high regard for their "Chief", and that an exceptional spirit of loyalty prevailed in his laboratory. This in spite of the fact that he offered no direction to students or staff members, leaving them entirely free to work out their own problems. Hunt was an individual worker and neither enlisted the assistance of his departmental staff nor discussed his own experiments with them. His experiments were performed with the help of a very capable "diener" whom he brought from Washington to Boston. In the Harvard period, only a small fraction of his time was given to actual experimentation. He unquestionably exerted a type of leadership in his department, although the reasons for this seem intangible. They probably relate to Hunt's personal charm, his intense interest in and application to his own research, and also to the fact that he was always ready with helpful advice when problems were brought to him. His quiet observations were given out of a surprisingly complete knowledge of the literature. His attractively hesitant way of putting forward his ideas made an exchange of views with him a pleasant and profitable experience. Hunt devoted many hours in the library to the reading of current literature, not only in his own field but also in the broad field of medicine. I am told that after a meeting of the Advisory Board of the Hygienic Laboratory in Washington, he would go to the library to read scientific journals before returning to Boston. One gains the impression that Hunt until the end of his scientific career was as much or more interested in acquiring knowledge as in advancing it. One of his colleagues at Harvard said to a student seeking information, "Let's go and see Hunt—The Encyclopedia". At one time on the campus at Harvard, it was said that "Hunt knew as much about chemistry as Folin, as much physiology as Cannon, and as much pharmacology as Reid Hunt." One regrets that on account of his shyness he did not in any great measure transmit his profound knowledge to those around him.

As far as I can find, Hunt had few interests outside his

laboratory and his home. He was very fond of travel and delighted in visiting and talking with people in laboratories in all parts of the world. He went as a delegate to many meetings in various parts of Europe. In 1923, he was Visiting Professor to the Medical School at Peking, China. An American pharmacologist who was stationed at Peking at this time writes: "He was cautious in his decisions, whether they had to do with choice of words or with policies, plans or interpretations of research work. He was better acquainted with the literature than anyone else I have ever met. While he was there we received a sample of a Burmese arrow poison, with a request for information about it, and he at once suggested that it might be Antiarin, of which I had never heard before or since. This was easily checked and was found to be correct. He had an amazing store of general and specific information which was usually very accurate though his extreme diffidence made it difficult for him to share this." In spite of his shyness and desire to keep out of the limelight, he enjoyed an acquaintance with the leaders of medical research in this and other countries, equalled by few of his contemporaries. He was known the world over, never as Hunt, but always as Reid Hunt, despite the fact that there was no one with that surname with whom he might be confused.

Hunt's first published paper was entitled "The Fall of Blood Pressure Resulting from Stimulation of Afferent Nerves". This was published in 1895, and was submitted to the Board of University Studies of Johns Hopkins University as a thesis for the degree of Doctor of Philosophy. In this paper one finds the scrupulous attention to detail and the wide knowledge of the literature which were so characteristic of the man in later life. This research was apparently undertaken at the suggestion of Howell.

However, this was not the first research undertaken by Hunt and brought to the stage of publication. His well known work on the relation of the inhibitory to the accelerator nerves of the heart was begun before Howell returned to Baltimore, and was probably undertaken on his own initiative. Howell stated in 1934: "My acquaintance with Hunt dates back to 1893. When

I returned to Hopkins to take the chair of physiology in the newly founded Medical School, I found him in the laboratory busy with his experiments, so well known in physiology, on the results of simultaneous stimulation of the vagus and accelerator nerves of the heart."

He was later led to study the cardiac nerves of lobster, opossum, and calf, as well as the usual laboratory animals (rabbit, cat, and dog). The important result of this work was to show the antagonism of the cardiac nerves; when vagus and accelerator are stimulated simultaneously the effect is determined by relative strength of stimuli and the effect is approximately additive. This early work on the vagus and sympathetic may have led to his later interest in the pharmacology of the autonomic nervous system.

Hunt's first pharmacological work was done as a special expert of the U. S. Department of Agriculture for the investigation of poisonous plants. He succeeded in finding that the poisoning ascribed to Death Camus (*Zygadenus venenosus*) was due to alkaloids with pharmacological properties similar to the veratrum alkaloids. A paper in 1902, on the toxicity of methyl alcohol made the danger of this substance known to the American physician shortly after it had been recognized in Germany. During the prohibition era, he examined one hundred consecutive samples of confiscated "bootleg liquor" and was able to show that "poison liquor" owed its poisoning property mainly to the ethyl alcohol content and not to methyl alcohol or other impurities.

Most of Hunt's later work stems from two investigations which he carried out in Ehrlich's laboratory at Frankfort. The first of these was a study of the toxicity of a number of nitriles and the antidotal action of certain sulphur compounds toward them. These nitriles are toxic due to the liberation of hydrocyanic acid. There was a variation in the toxicity of different nitriles depending on the rate at which hydrocyanic acid was liberated. Some of these nitriles on a molecular basis were more toxic than hydrocyanic acid. Hunt explained this fact on the theory that the distribution of the drugs was different from

hydrocyanic acid—they penetrated the nervous system before splitting off hydrocyanic acid.

The second research undertaken in the Frankfort laboratory was concerned with the toxicity of certain quinine derivatives. The problem was to determine if the vinyl group in quinine is essential for toxicity. Hunt showed that this group was without especial significance for toxicity. Of especial interest was the finding that saturation of the vinyl group with hydrochloric acid results in a compound with decreased toxicity for mammals and increased toxicity for infusoria. This suggested that derivatives of quinine may be found to be of value in protozoan diseases in which quinine is of little value.

Hunt's work on the relation of chemical constitution to pharmacological action of the choline derivatives was initiated with an observation made in 1899, although the later trend of these investigations was markedly influenced by his experience with Ehrlich. He found that extracts of the suprarenal glands, from which epinephrine had been removed, caused a fall of blood pressure in anesthetized animals, but a rise of blood pressure after the administration of atropine. He isolated choline, but found that it did not account for the full effect of the gland extract. He obtained evidence that a second body was present in the suprarenal extract which differed from choline in causing a fall of blood pressure after atropine. With chemical manipulation, the second body disappeared; at the same time, the amount of choline seemed to be increased. Later, Hunt pointed out that if choline played a part as an active physiological agent in body processes it was probably in the form of one of its more active derivatives.

These observations made at the turn of the century led Hunt, when he returned from his stay with Ehrlich and when he had moved to Washington, to study intensively derivatives and analogues of choline with the idea of relating chemical constitution to pharmacological action. His first publication with Taveau in 1906 described among other things the important discovery of the remarkable activity of acetylcholine in causing a fall of blood pressure. This preliminary paper in 1906 was followed in 1909 and 1911 by two long papers with Taveau. In

the first of these, the purpose behind the investigation of the effect of drugs on the autonomic system is given. After stressing the extraordinary physiological activity and relatively slight toxicity of acetylcholine as a basis for some of these compounds having therapeutic value, Hunt writes: "Before taking up the subject, however, it seemed desirable to determine the general laws governing the toxicity of such compounds, for when these are determined it may be possible to make compounds which, while preserving the desired physiological action, have a low degree of toxicity".

The second paper concerns the effect of a large number of choline derivatives and analogues on blood pressure.

A long series of papers now appeared extending to the end of Hunt's scientific career on the action of onium compounds on the autonomic nervous system. These were mainly with the chemist, Renshaw, who had worked in Hunt's laboratory for a few years after World War I and who was later Professor of Chemistry at New York University. All types of choline derivatives and analogues were prepared and studied—the arsenic, antimony, phosphorus, and sulfur analogues of the nitrogen compounds; ethers, thioethers, etc.

In regard to this work, Hunt wrote in 1915, "Choline which has a simple structure, is readily prepared synthetically; many modifications of it, and analogous compounds, can readily be made: these vary greatly in not only the degree but in the kind of their physiological action. In fact, few fields seem more inviting for a study of the relation between chemical constitution and physiological action with the possibility of discovering drugs having certain desirable properties (upon the pupils, intestines, heart, etc.)".

The fact that acetylation of choline increased its activity in lowering blood pressure "100,000 times" impressed Hunt greatly, and he was fond of calculating the number of cats whose blood pressure could be reduced by a single milligram of acetylcholine. That he had made a discovery of the greatest biological importance, he could scarcely have realized at the time.

His studies on the action of several hundred derivatives and analogues of choline at first in regard to toxicity and effect on

blood pressure and later in regard to "muscarine" action, stimulating "nicotine" action and paralyzing "nicotine" action allowed him to develop a concept of the relation between chemical structure and physiological action of these compounds on the autonomic nervous system. This enabled him to predict the properties of certain compounds as to stability, intensity and duration of action. Ehrlich's concepts were the guiding principle in this work.

Hunt assumed that the blood pressure lowering action of acetylcholine and similar compounds was due mainly to a negative inotropic cardiac action. In 1914, Dale showed that acetylcholine (and certain other choline esters) caused a decrease of blood pressure from peripheral vasodilatation, and in addition that after atropine a rise of pressure resulted from large doses due to a "nicotine" type of action. Hunt frankly admitted his errors in two excellent papers on vasodilator reactions published in 1918. In these papers he confirmed Dale's previous work, but found great difficulty in explaining the vasodilator action of acetylcholine which was abolished by atropine. From these studies he concluded "the above experiments, and those of the preceding paper, show that there is widely distributed in at least certain animals a vasodilator mechanism which has not hitherto been clearly recognized in physiology, pharmacology or pathology; the outstanding features of it are (1) its ability to respond, with great energy, to a limited group of compounds of the cholin type and to pilocarpine and perhaps a few others; (2) that this action is prevented by atropine; and (3) that it apparently is not connected with any of the known vasodilator nerves. It seems appropriate to speak of a 'mechanism,' for different blood vessels react unequally, i.e., something other than the contractile elements of muscular tissue is involved, and because the action is prevented by atropine; the latter reaction is usually interpreted as indicating the presence of a 'nerve-ending' or of a 'receptive substance,' i.e., some kind of a 'mechanism.'"

The second field of work in which Hunt carried out investigations for many years was that of the physiology and pharmacology of the thyroid gland. His interest in this field also

stems from his work with Ehrlich on the toxicity of and antidotes for nitriles. On the hypothesis that the toxicity of acetonitrile was due to a change to hydrocyanic acid partly by oxidation, he expected that the administration of thyroid gland by increasing basal metabolism should enhance the toxicity of the substance. In accord with his expectation, the lethal dose of acetonitrile for rats and guinea pigs decreased after several days administration of thyroid gland. On the other hand, mice reacted in the opposite way: they became very resistant to the poison. His first paper on this subject was published in 1905. For the next twenty years he employed this "acetonitrile reaction" in a series of extensive and painstaking studies of various problems in connection with the physiology and pharmacology of the thyroid gland. Some of the results of this work were: the detection of small amounts of thyroid substance, for which there were no satisfactory chemical methods; the correlation of physiological activity with the iodine content of the thyroid, upon which was based the pharmacopoeial standard for thyroid; the finding that iodides and certain kinds of diets markedly influence the function of the thyroid gland; and the observation that the physiological activity of thyroxin is less than that of dried thyroid gland when expressed in terms of iodine content. In addition to the above, very extensive studies on the influence of various diets on toxicity to various drugs, mainly acetonitrile, were made. Another interesting finding was that animals to which a "moderate" amount of ethyl alcohol had been administered for some time acquired an increased susceptibility to acetonitrile, the poison being more rapidly broken up in the body. This, as far as I know, is the only evidence available today of a physiological change from prolonged administration of small amounts of alcohol.

While in Ehrlich's laboratory during 1903, Hunt formed a close friendship with Christian A. Herter which was maintained until the latter's death in 1910. When Abel and Herter initiated the *Journal of Biological Chemistry* in 1905, one of their most valued consultants in that enterprise was Reid Hunt. Likewise, when the American Society for Pharmacology and Experimental Therapeutics and *The Journal of Pharmacology*

and Experimental Therapeutics were initiated by Abel, Hunt was closely associated with him in both ventures. He did a great deal of the work necessary for the gathering of the charter members of the Society and was its first secretary.

Dr. Hunt was elected to the National Academy of Sciences in 1919.

No account of Hunt's work can be considered complete without reference to his most important activities in connection with the U. S. Pharmacopoeia and with the Council on Pharmacy and Chemistry of the American Medical Association. He was a member of the 1910 U. S. P. Revision Committee. In 1920, he was elected president of the United States Pharmacopoeial Convention, serving for the next decade. He realized the importance of the Pharmacopoeia in promoting standards of high purity and reliability for important drugs, and, also, that the pharmacopoeias of the world must assume an international character to truly represent the needs of the medical profession. He was appointed a member of the Permanent Standards Commission of the League of Nations Health Committee.

Hunt became a member of the Council on Pharmacy and Chemistry in 1906, only one year after its formation. He served for thirty years, the last nine of these as Chairman. There seems little doubt of the great service which Hunt rendered to the medical profession by his activities in these organizations. Hunt's successor as a member of the Council, recently stated: "Only the members who worked with him on the Council have an adequate appreciation of the enormous amount of time and labor that Reid Hunt put into the Council activities. As someone said, he made a vocation of a hobby. Many of the difficult reports published by the Council were prepared personally by Dr. Hunt. It is the type of work that does not receive the public recognition that it deserves, but certainly, he did a fine service to American Medicine. Throughout his active career, he always maintained an interest and a fair attitude toward pharmaceutical houses, and weighed their merits. I have heard it said, repeatedly, that few people have ever given nearly as much service to the Council as Dr. Hunt."

At the turn of the century, there was a small group of men

who subjected themselves to a rigid and wide discipline in the fundamental sciences without losing their interest in medical problems. Reid Hunt was one of these. It was such men who carried a new spirit of fundamental research to American preclinical departments. Hunt gained a well deserved reputation as one of the pioneers in American pharmacology.

KEY TO ABBREVIATIONS USED IN BIBLIOGRAPHY

- Amer. Jour. Phar.=American Journal of Pharmacy
 Amer. Jour. Physiol.=American Journal of Physiology
 Arch. Internal Med.=Archives of Internal Medicine
 Arch. internat. pharm.=Archives internationales de pharmacodynamie
 Arch. internat. physiol.=Archives internationales de physiologie
 British Med. Jour.=British Medical Journal
 Bull. Mass. Coll. Phar.=Bulletin of the Massachusetts College of
 Pharmacy
 Centr. Physiol.=Centralblatt für Physiologie
 Ind. Eng. Chem.=Industrial and Engineering Chemistry
 Johns Hopkins Hosp. Bull.=Johns Hopkins Hospital Bulletin
 Jour. Amer. Med. Assn.=Journal of the American Medical Association
 Jour. Amer. Pharm. Assn.=Journal of the American Pharmaceutical
 Association
 Jour. Biol. Chem.=Journal of Biological Chemistry
 Jour. Exper. Med.=Journal of Experimental Medicine
 Jour. Pharm. Exper. Therap.=Journal of Pharmacology and Experi-
 mental Therapeutics
 Jour. Physiol.=Journal of Physiology
 New Eng. Jour. Med.=New England Journal of Medicine
 Quart. Jour. Inebriety=Quarterly Journal of Inebriety

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