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OF

WILLIAM GEORGE MacCALLUM
1874–1944

BY

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William George MacCallum was born in Dunnville, Ontario, Canada, on April 18, 1874. His family had lived many years in that region, for his grandfather, George MacCallum, a Scotchman, born in 1818, had come to Canada as a young man. He settled in the Province of Ontario, married, had five sons and lived to a very old age. The eldest of these sons, born in 1843, was named George A. MacCallum. He studied medicine, married Miss Florence Eakins of Sparta, Ontario, and began his professional work as a general practitioner in the village of Dunnville. He was doctor and surgeon, not only for the village but also for the surrounding country. Natural history seems to have been, at this time, his hobby though later in life zoology became a subject to which he devoted serious attention. Even during the busy days when his practice was most pressing, he found time to collect specimens of various sorts which he arranged in a small museum. There was also a shed that served as a laboratory where specimens could be examined.

It was in this atmosphere that William MacCallum, the second child of George and Florence MacCallum, lived as a boy. First the public school and then the High School of Dunnville furnished him an education which he must have acquired easily, for he was ready for college at 15. It is very likely, however, that he learned quite as much at home as he did at school; for he spent a great deal of time with his father, and was in the habit of driving all over the country with him when Dr. MacCallum visited his patients. He even lent a hand at an operation on occasions when help was needed, though in later years he wondered whether he was actually of much assistance. This pleasant companionship between the boy, William MacCallum, and his father formed the basis of a very close and devoted association that lasted until his father died.
The final three years of school were busy ones, for MacCallum was preparing for college and was deep in the study of English, the classics and mathematics. He entered the University of Toronto at 15 years of age. Greek had a fascination for him. He worked at it during his entire four years at college, but on the advice of his father he also took courses in zoology, chemistry, physics and geology. Partly due to his father’s influence, partly stirred by Prof. Ramsay Wright, the biologist at Toronto, he became interested in collecting insects and plants and paid some attention to the study of trematode parasites. MacCallum graduated from Toronto in 1894.

At this point he wished to continue Greek as a life work, but his father was convinced that there was no possible career for him except medicine, and with reluctance he acceded to this point of view and decided to enter a medical school. By some accident he had heard of the Johns Hopkins Medical School and learned that the first class of students had entered in 1893. He applied for admission, and as he had completed at the University of Toronto the equivalent of the first year’s work in medicine, he hoped to be allowed to join the students who had entered in 1893. There was some opposition to this proposal by members of the faculty, but he was finally granted permission to enter the second year and thus became a member of the first class of the Johns Hopkins Medical School. He graduated with the degree of M.D. in 1897.

After graduation he spent one year as an intern at the Johns Hopkins Hospital and then became assistant resident in pathology under Dr. William H. Welch. This appointment marked the start of a career in a medical science which absorbed his interest during the remainder of his life.

In 1900 MacCallum went to Germany and worked in the laboratory of Prof. Marchand in Leipzig. Shortly after his return to Baltimore in 1901 he was made resident pathologist, then Associate Professor of Pathology and finally was promoted in 1908 to the position of Professor of Pathological Physiology, a chair created especially for him. In 1909 he accepted a call to Columbia University and from 1909 to 1917 he held the positions
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of Professor of Pathology at Columbia University and Pathologist to the Presbyterian Hospital in New York.

The first fifteen years which MacCallum spent in Baltimore furnished him an opportunity to pursue his work under the most favorable circumstances. His research and teaching were carried on in the laboratories over which Dr. Welch presided, and as his position in this department became more and more important, his relations with Dr. Welch grew more and more intimate. There were opportunities, too, for almost daily contact with other men of superior attainments. Osler's interest in pathology was proverbial; Simon Flexner was in the department for a year or two after MacCallum entered it; Thayer was studying malaria, a subject to which MacCallum had already made an outstanding contribution, and an interest in the thyroid and parathyroid glands resulted later in a close association with Halsted, whom he admired extravagantly. Eugene Opie and Harvey Cushing were more nearly of his own age, and there were other contemporaries all working at problems in medicine and busy with teaching. It was a period when there were few distractions, and, as will appear later, one in which MacCallum did much of his best work.

The move to New York in 1909, however, brought many new responsibilities with it. Important developments in medical education were under way at this time in New York, for the College of Physicians and Surgeons of Columbia University and the Presbyterian Hospital were contemplating an affiliation which was expected to lead eventually to a close combination of the two institutions. MacCallum was appointed a member of a Committee of the Medical Faculty to formulate plans for this interesting development. Many hours, therefore, were spent in conferences and much thought was devoted to considering ways and means by which this new venture could be most successfully brought about. It was several years, however, before these early deliberations came to full maturity and MacCallum had left New York long before the great modern structures which house the "Medical Center" had been erected on Washington Heights.

There were other problems of a somewhat different nature
that demanded his attention. Among these was an effort to abolish the coroner system which was then in vogue in New York City. This system he regarded as highly inefficient and undesirable, and proposed to substitute for it a better arrangement. It was largely through his influence and against considerable opposition, that the coroners were replaced by medical examiners who were required to be doctors of medicine, as well as skilled pathologists, and who were selected from the civil service list by competitive examination. The reform was an important one and the system has been adopted by other cities.

It was during this same period of varied and intense activity that MacCallum was persuaded to write a text book of pathology. The work was original in conception for he planned it with the idea of discussing disease, as far as possible, upon the basis of etiology. There was no systematic description of all the abnormal conditions that may affect each organ, but an effort was made to consider the general principles of pathology as illustrated by a study of the commoner and more important diseases. The entire treatise "was constructed," as he pointed out in the preface, "upon the idea that all pathological disturbances are the result of some form of injury or of the immediate or more remote reactions of the body to injury." It was an admirable work and went through many editions; but unfortunately a great deal of his time was occupied in the years that followed the first publication of the book in 1916, by the many revisions that were required by the repeated demand for new editions.

In 1917 Dr. Welch relinquished the chair of pathology at the Johns Hopkins University to assume the directorship of the newly established School of Hygiene and Public Health. MacCallum was chosen his successor and returned to Baltimore in the capacity of Baxley Professor of Pathology in the Johns Hopkins University and Pathologist to the Johns Hopkins Hospital. This second period in Baltimore started as a busy one, for the country was then at war and MacCallum was called upon to act as pathologist on a commission which was appointed to study pneumonia in the Army cantonments. In 1920 the pathological laboratory was destroyed by fire. This necessitated the use of
temporary quarters and MacCallum was plunged into the intricate business of drawing plans for a new building. He became deeply interested in the task and contemplated the possibility of broadening the conventional scope of pathological research, as it had been pursued in most schools of medicine, by extending it to a study of diseases in animals, plants and even fishes. For this purpose a small green-house was constructed near the roof of the building and space for an aquarium was provided. An adequate chemical laboratory was also included in the plan. Ample arrangements were made for all forms of photography, upon which he laid great stress as a method of recording pathological material.

Teaching was one of his major interests and a profession in which he excelled. His methods of approach to the study of pathology were so broad and so varied that they attracted many advanced students to apply for work in his laboratories. An innovation upon which he laid much stress was the collection in separate rooms of pathological material illustrating the alterations occurring during the course of any one of several common diseases, so that small groups of students could concentrate their study upon one disease at a time. There was one room devoted to rheumatic fever, another to tuberculosis and so forth. These isolated collections replaced the conventional museum of pathology and were used constantly for the instruction of students.

Another exercise which proved very stimulating was the clinical pathological conference which he and Dr. Thayer conducted every Wednesday morning at twelve o'clock. Thayer's accurate diagnosis, based on his thoughtful clinical discussion of the cases, was followed by MacCallum's illuminating exposition of the pathological conditions that he had found at autopsy. The room was always crowded with students, members of the hospital staff and visitors who listened with rapt attention to the lively discussions that took place during this exercise.

Neither MacCallum's interest in teaching nor his investigations in science appeared to satisfy his restless mind completely, which seemed almost impatient in its requirements for knowledge, nor did they fulfill altogether his emotional needs which
sought continuously for new experiences. Greek never lost its fascination for him, though curiously enough in all his travels he never appears to have made a journey to Greece. He was an omnivorous reader and, since he was perfectly familiar with both French and German, his knowledge of literature was very extensive. He was fond of music and enjoyed especially hearing both German and French opera.

One pastime in which he frequently indulged was to explore the historical aspects of medicine. Dr. Osler had founded in 1890 the Johns Hopkins Historical Club, of which Dr. Welch was the first president and an enthusiastic supporter; and at its meetings many papers of considerable value were presented by members of the University and Hospital staffs. MacCallum was sometimes among the contributors and thus from the time that he was a student developed a taste for medical history. This led him to acquire from time to time some valuable copies of early medical works, among which was a first edition of Vesalius. He also gathered together a large collection of medical prints which he had framed with appropriate captions and hung upon the walls in the corridors of his laboratory.

Perhaps above all diversions, however, he delighted most in travel. There was almost no country on the face of the globe that he had not visited at one time or another. Europe was thoroughly familiar to him. He studied pathology and heard opera in Germany, learned to bind books during one summer's vacation in Paris, and performed autopsies during another summer in the Ospedale Maggiore in Milan. The West Indies, South America, South Africa, Australia, India, Siam, Japan and the South Sea Islands were all regions that came within the scope of his travels. In Jamaica he investigated an epidemic of alastrim, a mild form of smallpox, and later wrote a monograph on the subject. In Singapore and Rangoon he performed autopsies. In Calcutta he had a severe attack of dengue fever; in the Fiji Islands, Java, Singapore and Kuala Lumpur he studied leprosy; and in the course of his travels he made innumerable photographs in Bali, Borneo, Tahiti, at the Angkor Vat and of the Taj Mahal. The material which he collected
and the records which he made on these numerous trips formed a source of valuable information concerning the tropics as well as the diseases common to them, and these he used to excellent advantage in his lectures on pathology and in his seminars with students.

MacCallum never married. It may have been partly on this account that he seemed to many of those who knew him to lead, in some respects, a curiously isolated life. Not that he was a recluse, for he often sought society and had hosts of friends and acquaintances all over the world; but he was rather fastidious in his tastes; while his intellectual qualities, his acute perception and his sensitiveness appeared to require an immediate and sympathetic response, without which his interest seemed to fade away.

He showed, nevertheless, a generous feeling of responsibility and affection towards the members of his own family, and he was always loyal to his many friends, though he reserved a real devotion for a very few.

The role which MacCallum's father played in the son's life was undoubtedly an important one; for the help and inspiration which the youthful MacCallum must have received from his father was repaid in later years by the constant devotion of the son. He was ever thoughtful of his father's needs, and when the elder MacCallum retired from his active work in Canada and moved to New York to be with his son, William MacCallum equipped a room in his laboratory where his father could work to his heart's content, and where the old gentleman spent many happy years in studying the parasites of fish of which he found some new varieties.

While MacCallum was a student at Toronto University he came under the influence of Ramsay Wright, an Edinburgh man, who was a zoologist and the Professor of Biology. Wright's particular field of interest was comparative anatomy, and it has been said that MacCallum's attraction towards the biological sciences was first aroused through this association. It is, however, clear that the one person who probably had the most profound influence upon his life was Dr. Welch. The
admiration and devotion which MacCallum showed for Dr. Welch approached that which he had for his father. The attachment was formed early when MacCallum first entered upon his career in pathology and continued uninterruptedly until the time of Dr. Welch's death. It was natural that MacCallum should turn to Dr. Welch for advice concerning the problems upon which he was working in the laboratory, and it is probable that he rarely embarked upon an investigation without discussing at some time the situation with him. Certain it is that the respect for Dr. Welch's judgment, and reliance upon his counsel grew to such an extent that MacCallum rarely made any important decision on policy without seeking his advice. It would perhaps be impossible to overestimate the influence which the older man with his wisdom and knowledge and his balanced judgment exerted upon the younger man with his enthusiasm, his brilliance and his ingenuity that sometimes appeared almost erratic. It is not surprising, therefore, that while MacCallum worked in the congenial and inspiring atmosphere of Dr. Welch's laboratory his genius for original investigation flourished.

MacCallum's contributions to pathology and to the biological sciences were numerous, varied and often highly original, and as remarked above the most productive years were those which he spent in Baltimore before he went to New York. He published a great deal during this period, but there were three major contributions of such importance as to deserve special attention.

The first of these was, in fact, a notable discovery. It was made under somewhat unusual circumstances, while he was still a student at the medical school.

His summer vacations were spent at Dunnville with his family where there was, what he described as "a makeshift laboratory in the woodshed" of his father's house, in which Dr. George MacCallum and his sons examined specimens culled from the countryside. During the summer of 1896 William MacCallum was interested in the study of the malarial parasites of birds and spent much time examining the blood of crows infected
with the "Halteridium" parasite. According to his own account, he obtained blood from a crow one day when he was far from home, so that he was obliged to bicycle several miles before he could inspect this particular specimen under the microscope. On careful examination he saw very actively motile forms of the malarial parasite which he had never observed before. It was evident that the crow itself must be had for further study and consequently he went back and procured the bird so that he might watch the parasites in the blood for long periods of time, for it occurred to him that these peculiar bodies might have developed during the long ride on his bicycle. These further observations led to the discovery of the penetration of flagellated forms of the non-granular gametocyte (microgametocyte), or extracellular parasite, into the granular gametocyte (macrogamete), which was then transformed into the actively motile body that had originally excited his interest.

Though the flagella of the malarial parasite had been frequently seen and described before, these structures were supposed to represent nothing more than degenerated forms of the plasmodium. This view was especially supported by the Italian investigators. MacCallum was convinced, however, that he had observed a sexual conjugation of the parasite, and concluded that the granular extracellular form was the female, the non-granular form the male, and that the flagella corresponded to spermatozoa, which entered the female parasite with consequent fertilization. He noted that never more than one of the flagella was able to penetrate the female gametocyte. On his return to Baltimore he succeeded in showing that the same process took place in the aestivo autumnal parasite of human malaria. Somewhat later Ross discovered that the fertilized motile form of the malarial parasite penetrated the wall of the mosquito's stomach where it formed spores.

The second contribution was of a totally different character. MacCallum went to Germany in 1900 where he worked in Marchand's laboratory in Leipzig. There he embarked upon a study of the lymphatics in the skin of the pig embryo. These experiments were completed and published (1903) on his return
to Baltimore. The relation of the lymphatic system to the connective tissue spaces was, at that time, not clearly defined, and there was still a question as to whether the tissue spaces opened into the lymph channels either directly, by canaliculi, or through pores or stomata in the walls of the lymphatic vessels. MacCallum was able to demonstrate that the walls of the lymphatics, although extremely delicate and easily ruptured, are nevertheless possessed of a complete endothelial lining which shows no pores or open communications with the surrounding tissue. The structure of the walls of the lymphatics, therefore, is thus analogous to the lining of blood vessels. The well known ability of solid particles to pass into the lymphatics could be explained, MacCallum thought, by the process of phagocytosis. It seemed reasonable to suppose that leucocytes might penetrate the wall of the lymph channels as readily as the wall of blood vessels and in doing so could carry with them the solid particles which they had previously engulfed. Somewhat later in an investigation of the lymphatics of the diaphragm and of the peritoneum of the dog, he was able to show that this actually occurred; for when granular material was placed in the peritoneal cavity it was readily taken up by leucocytes and carried by these phagocytes first through the lining cells of the peritoneum, and then between the endothelial cells forming the walls of the lymphatics into the actual lumina of the lymphatic channels. The structure of the lymphatics in the diaphragm, however, was such, and the mechanical action of the diaphragm during respiration upon them so contrived that a few solid particles were forced or sucked into the lymphatic lacunae and lymph channels without the intervention of phagocytes.

MacCallum devoted a great deal of time, throughout his career, to a study of the glands of internal secretion. This interest developed very early, for even in 1903 he was investigating the structure of the thyroid and parathyroid glands. At that time his investigations were directed towards the supposed interrelation between the function of the thyroid gland and parathyroid bodies, about which there was some confusion and uncertainty. Experiments made a little later convinced him
that the function of the thyroid and parathyroids is entirely independent, a conclusion which was in accord with results obtained by some previous investigators. It became clear, therefore, that tetany which had long been known as an occasional sequel to operations upon the thyroid gland was due entirely to injury or removal of the parathyroid glands. Some previous reports had been published, by Vassale and others, which appeared to show that tetany, following the experimental removal of the parathyroid glands, might be modified or favorably affected by injections of emulsions of the parathyroid material, and MacCallum found that the intravenous injections of emulsions of the parathyroid glands of dogs and of beef would sometimes control the symptoms in experimental tetany of dogs, though this could only be accomplished with some difficulty. The probability had occurred to MacCallum that some metabolic disturbance followed the removal of the parathyroid glands, which could account for the acute symptoms of tetany, and that the disturbances might be reflected in an abnormality of the blood. Several physiologists, among whom was Jacques Loeb, had called attention to the fact that the loss of calcium from the body would result in muscular twitchings, or, as Sabbatani had shown, to an increased excitability of nerve cells. With the assistance of the chemist, Carl Voegtlin, therefore, MacCallum made studies upon the effect of the injection of salts of calcium, sodium, magnesium and potassium in experimental tetany. The results of these important experiments were published in 1905. The conclusions were that the injection of a solution of a calcium salt into the circulation of an animal in tetany checked all the symptoms and restored the animal to an apparently normal condition; whereas the intravenous injections of sodium and potassium salts had no such beneficial effect. The injections of magnesium salts were toxic in themselves. It was also found that there was a marked reduction in the calcium content of the tissues, especially of the blood and brain, during tetany and at the same time an increased output of calcium in the urine and faeces. These experiments, which have now become classical, went far to
elucidate several perplexing problems relating to the mechanism of tetany. They demonstrated that the parathyroid secretion in some way controls the calcium exchange in the body, and in the absence of the parathyroid glands, an impoverishment of the tissues with respect to calcium takes place with the consequent development of hyperexcitability of the nerve cells and tetany. Only the restoration of calcium to the tissues can prevent this. Further experiments upon the galvanic hyperexcitability of the nerves, which was found to be a characteristic feature of tetany, were reported to the German Pathological Society in 1912. By severing nerve trunks and through transfusion of the limbs of dogs it could be shown that the hyperexcitability was due to some change in the blood which followed removal of the parathyroid glands, and which was capable of affecting the nerve terminals.

It had long been known that an entirely different form of tetany, described as gastric tetany, occurs not infrequently in children and in adults who suffer from an obstruction at the pyloric outlet of the stomach. In this form of tetany the parathyroid glands are normal. MacCallum was naturally attracted to a study of this condition, and in 1909 started some observations on dogs in which the pylorus had been closed by an operative procedure. The experiments were continued in New York and a preliminary report of the results was made before the American Society for Experimental Pathology in 1917, but owing to the press of work during the war and his departure for Baltimore the final paper was not published until 1920. These studies demonstrated that when the pylorus was obstructed and the gastric juice with its hydrochloric acid was removed, there ensued a decrease in the chlorine of the blood plasma. Accompanying this loss of chlorine there was an increase in the alkali reserve of the blood which became extreme. The electrical excitability of the nerves was in general heightened and spontaneous twitching of the muscles appeared. In most of the dogs violent convulsions led to death. All of this could be prevented if chlorides were constantly furnished to the animal. These experiments led to the conclusion that the
mechanism responsible for gastric tetany was totally different from that following parathyroidectomy, for in gastric tetany the electrical excitability of the peripheral nerves was dependent upon an imbalance of the electrolytes of the blood, due to the constant and excessive loss of hydrochloric acid.

His interest in the thyroid gland led also to careful studies of the pathological changes in this organ removed from patients with exophthalmic goitre, and to observations on the mechanism of the remarkable exophthalmos that is such a striking and characteristic feature of Graves disease.

The physiology of the circulation in valvular disease of the heart attracted his attention at one time, and he devised methods to study the problem experimentally. Long hooks and ingeniously contrived knives were made with which he could cut or injure the valves of the heart in the anaesthetized dog without opening the heart itself. This was accomplished by passing the instruments through the carotid artery into the chambers of the heart. With this technique it was possible to produce most of the lesions of the heart valves that are commonly encountered under pathological conditions in man. Both insufficiency and stenosis of the mitral valve were successfully initiated, while regurgitation of the aortic valve was quite readily reproduced. The principal value of these experiments was that they furnished an opportunity to study the direct effect which these lesions had upon the mechanics of the circulation; but another use to which they were put with excellent effect was to teach medical students pathological physiology. The novelty of these experiments, the ingenuity with which they were carried out, and their application to the teaching of pathological physiology attracted considerable attention.

In 1917 and 1918 an opportunity came to study the pathology of epidemic pneumonia which was sweeping through the army camps in this country and causing great numbers of deaths. The situation was complicated first by the epidemic of measles and then by the pandemic of influenza. MacCallum's important and extensive studies were published in several papers and
finally collected in a monograph which stands as one of the most comprehensive studies upon the subject.

MacCallum was always devoted to the study of pathological anatomy and throughout his life published innumerable descriptions of unusual forms of disease or of peculiar lesions occurring in common diseases that had escaped the attention of others. As he grew older he tended to confine his attention to this form of investigation, and added considerable information, gained from a meticulous microscopical study of tissues, to the existing knowledge of the finer structure of many pathological lesions.

His eminence in this field was unquestioned. He was invited to give many important lectures, among which were the Harvey Lecture, the Beaumont Lecture, and the Harrington Lectures. In 1940 he was appointed by the Association of American Physicians to be Kober Lecturer.

He was an active member of many scientific societies in this country, an Honorary Fellow of the Royal Society of Medicine, corresponding member of Societas Regia Medicorum Budapestinesis, an Honorary Member of the Société d'Endocrinologie of Paris and an Honorary Member of the Pathological Society of Great Britain and Ireland. He was elected a member of the National Academy of Sciences in 1921.

In the winter of 1943 he suffered an illness which forced him to go to Florida for a rest. Shortly after his arrival he was stricken with a hemiplegia which steadily progressed until he was completely incapacitated. His death occurred on February 3, 1944.

MacCallum was undoubtedly one of the outstanding pathologists in this country and was, moreover, recognized internationally for his original investigations. His attainments might be attributed in large part to a peculiar combination of respect for tradition and search for the unknown.

On the one hand, he upheld vigorously the opinion that a knowledge of pathological anatomy was of fundamental importance for a proper understanding of clinical medicine. True to the conventional training of older pathologists, he never
relinquished his habit of acute observation of morbid states, and in consequence enriched the descriptive science by constantly adding new information.

On the other hand, he was forever stressing the vast unknown, pointing out the flaws in arguments and finding the weak links in a chain of evidence that led to unconvincing conclusions. In his experimental work he discarded all previously conceived ideas, and by using any methods that were available or that might be adapted to his purpose attacked the problem from a new and original point of view. Though MacCallum's important experimental investigations were not great in numbers they were original in conception, and so complete and accurate in their conclusion that some should remain as permanent contributions to medical science.
KEY TO ABBREVIATIONS USED IN BIBLIOGRAPHY

Am. Jour. Hygiene = American Journal of Hygiene
Am. Med. = American Medicine
Anat. Anz. = Anatomischer Anzeiger
Arch. Path. = Archives of Pathology
Int. Assoc. Med. Mus. = International Association of Medical Museums
Int. Clin. = International Clinics
J. H. H. Repts. = Johns Hopkins Hospital Reports
Jour. Mt. Sinai Hosp. = Journal of Mt. Sinai Hospital
Jour. Morph. = Journal of Morphology
Jour. Path. and Bact. = Journal of Pathology and Bacteriology
Med. = Medicine
Med. News = Medical News
Med. Rec. = Medical Record

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Physiol. Rev. = Physiological Reviews
Tr. South. Surg. Assoc. = Transactions, Southern Surgical Association

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