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PHILIP DURYEÉ MCMASTER
1891—1973

A Biographical Memoir by
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Biographical Memoir

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PHILIP DURYEÉ McMASTER

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BY WALTHER F. GOEBEL

MY FIRST ENCOUNTER with Philip McMaster was in the locker room of the squash court at the Rockefeller Institute more than fifty years ago. I had come to New York but a few weeks before as a research assistant in the laboratories of Dr. Oswald T. Avery. I was in search of exercise that day, and how well I remember the sound of the squash ball on the wooden walls of the court as I entered the locker room, and the shouting and cursing which issued from the tiny balcony above the court itself. Then, suddenly, Phil and his opponent emerged panting and laughing. He extended his hand to me and introduced himself. My first impression was of a man small in stature, witty, and cordial: something unique for me, for I had as yet made few friends in this new and overpowering metropolis. Friends we became, and we remained so from that day forth.

Philip McMaster was born at Chestnut Hill in Philadelphia on the fourteenth of September 1891. His father was John Bache McMaster, a distinguished historian who headed the Department of History at the University of Pennsylvania and a scholar still identified as the author of *History of the People of the United States*. His mother was Gertrude Stevenson of Morristown, New Jersey. There was always a constant flow of professors through the McMaster household, and because of this, Phil's academic background was assured. In this environment he was to remain throughout his long and productive life.

His early education in Philadelphia was obtained in private schools, and upon his graduation he entered Princeton University, from which he graduated in 1914. During his summers, as a boy, he accompanied his family to Kennebunkport, Maine, and to Cape Cod, where he developed his love of the outdoors and of the sea as well. These were hobbies which never left him. His early taste for biology undoubtedly arose when he accompanied his father and Professor Edward Conklin on frequent field trips to collect biological specimens. Conklin was professor of biology at the University of Pennsylvania and spent his summers at the Marine Biological Laboratory in Woods Hole. These forays were always made on bicycles, and the treasures which they collected were returned to the laboratory, where they were subjected to exhaustive scrutiny by the professor. Philip's summers in Maine were filled with water sports of every description. At the age of nine he was given his first sailboat, a craft some fifteen feet long, of which he soon became master.

After Philip graduated from Princeton in 1914 with the degree of bachelor of science, he entered the medical school of the University of Pennsylvania, where he was graduated the year World War I ended. Fortunately, McMaster was not devoted totally to scholarship during his college years, for as an undergraduate, not long after he entered Princeton, he was made coxswain of the freshmen crew—a happy choice, for he and water, both fresh and salt, remained inseparable during his entire life.

I am fortunate to have in my hand an account of his life and his scientific achievements ("Dr. Philip D. McMaster: His Work and Its Significance," unpublished), which he himself wrote for Dr. Herbert Gasser, the second director of the Rockefeller Institute. Phil was the younger of two sons, the elder of whom died of pernicious anemia at the age of twenty-five. But Phil was to live beyond the allotted biblical span to pursue his distinguished scientific career, all of it at our Institute. He him-

self says that during his boyhood there was but little evidence of a scholarly attitude on his part, despite the academic atmosphere in which he was raised. Personally, I doubt this.

Philip served as resident physician at the medical school hospital during the last year of his medical training at the University of Pennsylvania and again during the year following his graduation from medical school. He was commissioned as a first lieutenant in the U.S. Army shortly before the war was over.

At the termination of the war and in the autumn of 1919, he came to the Rockefeller Institute as a research associate in the laboratory of Dr. Francis Peyton Rous, where he embarked upon his first investigative work. In the ensuing pages I shall attempt a résumé of his more important contributions.

During his first three years at the Institute, McMaster collaborated intimately with Rous in their research. Among their achievements was the devising of methods for the intubation and sterile drainage of the gallbladders and bile ducts of a variety of animal species, a technique which permitted them to collect bile from the individual liver lobes of a number of different experimental animals and thus enabled them to compare them. These studies revealed that the normal gallbladder rapidly concentrates hepatic bile but that the diseased organ fails in this function. These observations were promptly utilized by clinical surgeons as a basis for diagnostic dye tests for the presence of gallstones and gallbladder disease. The basis for the test lay in the fact that in the normal organ the concentration of x-ray opaque dyes, when injected into the bloodstream, is excreted in the bile. This is not the case in the diseased gallbladder.

As a result of these studies it became important to learn whether the liver bile of animals lacking a gallbladder is excreted in a form more concentrated than that of those species possessing the organ. To test this, the pigment content of bile—an index of its concentration—was compared in two closely related species, namely, the mouse, which has a gallbladder, and

the rat, which does not. Thus, the bile of rats was found to be several times more concentrated than was the bile of mice when collected by semimicro methods from individual lobes of the animals' livers. Yet when the bile of the mouse was collected from the common duct after the secretion had been acted upon by the gallbladder, the pigment content was several times greater than that of the liver bile. These studies and others on bile secretion, which extended over a period of several years, led to the development of wholly new techniques and threw new light upon the effects of diet inanition, exercise, and liver derangement on bile secretion. Their studies yielded, furthermore, convincing evidence that bilirubin had no other source than hemoglobin.

McMaster's three years of association with Dr. Peyton Rous served well as a period of initiation for the work upon which he was next to embark with Dr. Robert Elman, namely, the pathology and physiology of urobilin. This was a problem much disputed at the time and was one of considerable importance to the understanding of the mechanism of the pigment changes in certain liver derangements, including pernicious anemia. The two men developed a procedure for collecting sterile bile, a technique which allowed them to collect the secretions either from the whole liver or from a part. Prior to this experiment, it had been thought that only the damaged liver formed urobilin, an assumption that arose as a result of finding some animals bearing infected bile fistulas. Yet, when it became possible to obtain bile which remained sterile by using their intubation technique, the complete loss of the secretion from the body resulted in the total disappearance of urobilin and urobilinogen from the bile, feces, and urine. This occurred when the animals were subjected to severe liver damage, biliary obstruction, or blood destruction. On the other hand, all of these led to severe urobilinuria, a condition in which bile was permitted to reach the intestines. Thus it became clear that urobilin could not be

formed by the damaged liver. In brief, these experiments settled once and for all the question of the origin of urobilinuria. Thus urobilin in the urine depended first on its absorption from the intestine, or the infected biliary tract, and next upon the failure of the liver cells to remove pigment. Their findings were subsequently confirmed by other investigators.

It was with Dr. Douglas Drury, whom I had met many years before on the first day with McMaster in the squash court locker room, that McMaster developed the technique for the partial or total removal of the liver of experimental animals. These two men were among the first to perform hepatectomies successfully enough that the animals survived sufficiently long to enable the investigators to study the effect of liver deprivation or insufficiency upon carbohydrate and fat metabolism. This work on hepatectomized rabbits revealed that the liver was the source of blood fibrinogen.

Shortly after the completion of this work, McMaster spent a sabbatical year at Harvard University, where he worked with Dr. Harry Murray in the field of psychology. Upon his return to the Rockefeller Institute he again joined Rous and his colleague Hudack in a study of the fluid interchange between the smallest blood vessels and tissues. They found that by injecting vari-colored dyes in the bloodstream of rabbits and mice, they could observe the pattern and spread of the dye's passage through the various vessel walls and changes in vascular permeability resulting from a variety of physiological and pathological conditions such as light, trauma, heat, or cold. These experiments, to be described subsequently, were, I think, some of his finest.

McMaster next turned to a study of the lymphatic system and the mechanisms of lymph flow, an investigation in which Dr. Hudack again collaborated. The two found that when bright blue vital dyes were injected into the skin of animals superficially, and more particularly into the ears of mice, they rendered the minute lymphatics visible. These experiments pro-

vided an entirely new concept of the activities of the lymphatic system.

To me, these numbered among McMaster's most interesting and rewarding experiments. How well I remember his enthusiasm for the work as it was being executed, perhaps some four decades ago, not only on experimental animals, but upon himself and other normal human subjects as well. These experiments proved that instead of being passive drainage canals, the lymphatics were very active in the process of fluid exchange. Their walls respond rapidly to various influences such as sunlight warmth or a stroke that does not break the skin. For the first time, too, these investigators were able to render the lymphatic capillaries visible in the skin of man. When a blue dye was injected into the skin of the legs or arms, it was taken up into torn lymphatics and rendered them visible. The color appeared later as blue streamers in the draining lymphatic trunks running up the limbs.

In collaboration with Dr. Robert Parsons there followed many experiments to determine the influence of the factors responsible for the movement of peripheral lymph. Both the pulsation of blood vessels as well as the mechanical effects of muscular contractions proved to be of importance. The two devised ingenious methods for measuring the pressures which existed within cutaneous lymphatic capillaries and in the interstitial tissues outside of them, both under normal conditions and in edematous states. They found that a gradient pressure exists between the two tissues and lymph in the capillaries sufficient to account for the flow of lymph in motionless skin. The structural conditions in the interstitial tissues of the skin revealed that fluids move along fibrillae and fibers and that open tissue spaces, filled with free fluid, such as seems to be present in sections of fixed dehydrated tissues, probably do not exist in living intradermal tissue. Instead, a gelatinous ground substance is apparently present between the formed elements.

They next turned their attention to the flow of lymph under pathological conditions. By injecting dyes into the cutaneous lymphatics of edematous humans, they found differences of flow in various forms of edema. Thus, in patients with cardiac insufficiency and severe edema of the legs, the cutaneous lymphatics were more dilated than in those suffering from nephrotic edema or in normal individuals. On the other hand, patients who suffered from nephrotic edema, yet who had good cardiac action, exhibited a flow of lymph more rapid than in normal humans. It should be added that in the first group of patients, those with cardiac insufficiency, it appeared that the lymphatic valves no longer functioned and the patients suffered from valvular incompetence of the lymphatic vessels, allowing stagnation of lymph in peripheral areas and even permitting retrograde flow when slight pressure on the skin was made with the finger moving toward the foot, a fact which was not true in normal individuals.

These experiments of McMaster and his younger colleagues had far-reaching consequences. Other investigators employed his techniques to study cancer patients in order to trace the lymph drainage from the diseased areas and render the lymph nodes blue, hence visible, in regions where metastases could occur through the lymph stream. McMaster's studies brought ample evidence that injury to the skin, however superficial, invariably involved the lymphatics and that local intradermal injections were, in reality, a general injection because of rapid lymphatic distribution. Every injury that breaks the continuity of the skin permits bacteria, viruses, and other foreign matter to enter the lymphatics, and because of this drainage it is not improbable that the regional lymph nodes play an important role in the defense of the body against invasion by an infectious agent.

There now followed important experiments, first with Dr. Stephen Hudack and later with Dr. John Kidd, in which it was conclusively demonstrated that lymph nodes, draining skin sites

injected either with bacteria or viruses, formed antibodies against these agents in very high concentrations. Confirmation of this important discovery was made in many other laboratories. These studies were extended to ascertain the type of cells within the lymph nodes themselves and within the spleen which might be responsible for antibody formation. The clear-cut proof which McMaster's experiments presented led to a resurgence of interest in the activities of lymphocytes.

With the entrance of our country into World War II, McMaster became completely involved in wartime activities, first with the director of the Rockefeller Institute—Dr. Herbert Gasser—and Dr. René Dubos, then later with Dr. George Hogeboom. This work was done under the auspices of the National Research Council and the Office of Scientific Research and Development and consisted of research itself as well as consultation with the army and navy in an effort to devise tests for war gases and prophylactic ointments against vesicants and treatment for vesicant burns. This work consumed nearly five years of McMaster's fruitful life, and knowing him as I did, and knowing his love of fundamental research, I am not wrong when I say that during this interval there were times when he was truly frustrated.

The war ended. Once again McMaster was free to return to his research and the important problems concerned with antibody formation. In this work he made use of azoproteins colored intensely blue to study their escape through the vessel walls and to use them as tracers in order to learn about their storage and localization during antibody formation. He observed that mice previously injected and then injected a second time some weeks later suffered intense anaphylactic shock. When anesthetized animals were placed in plasteline molds with their ears spread out on a white porcelain plaque, the vascular changes and the accompanying changes in blood flow could readily be observed in the unmolested tissue of the ear. An extraordinary local and

general constriction and dilation of both arterial and venous vessels occurred, yet the capillaries showed no apparent reaction. This technique using these intensely colored antigens proved extraordinarily sensitive and enabled him to follow their fate in the mammalian body. Thus, their injection into the bloodstream of mice revealed that the antigens were taken up both by cells of the reticuloendothelial systems throughout the body, especially the Kupffer cells of the liver, and by macrophages and reticular cells of the spleen and the lymph nodes. In this manner they revealed certain of the sites from which the first stimuli to antibody formation arose.

These early studies on the sites of antibody formation in mice were considerably extended by McMaster when he next employed a much more highly diffusible blue azoprotein complex. When the latter was injected into the animal the complex was eliminated from the body with speed, in approximately two hours, and it was impossible to see any residual granules in the cells. Nevertheless, minute amounts of blue material, whether complete antigen or not, persisted in certain tissues of the animals. In order to understand more fully the mechanism of antibody formation, McMaster had to determine whether or not this was intact antigen or whether it was the chromophoric group which split off from the carrier protein. Without entering into detail, let me say that by means of very sensitive passive anaphylaxis experiments McMaster showed that the antigenic material itself and not the chromophoric group of the antigen persisted in very small amounts in the tissues of the experimental animals. Despite these findings, it still remained possible that the persistence of the protein antigens in donor mice might exist because the animals formed antibodies very poorly; hence the antigen might indeed persist because of a lack of antibody to destroy it. The experiments were therefore repeated in rabbits, animals which are well known to be excellent antibody producers. In these experiments, McMaster employed bovine

gamma globulin as the antigen. The results were in essence the same.

By following the fate of the tracer antigen, McMaster and his co-workers next attempted to study the mechanism of antibody formation under various conditions. Since the first step in the formation of an antibody appears to be the capture of the antigen by phagocytic cells or even other cellular types, it seemed likely that something might be learned by observing the fate of the tracer antigen in mice which had been stimulated to form antibodies but prevented from doing so by large doses of cortisone. Although the drug reduced the size of the lymph nodes and spleen by some ninety percent, it was observed that the shriveled organs took up as much of the tracer as did organs of normal mice, thus demonstrating unequivocally that the inhibition of antibody formation did not result from the faulty uptake of antigen. Nor did it result from an impairment of the antigenicity of the antigen or from a more rapid destruction than that which occurs in animals given no cortisone. Mice injected with foreign protein were prevented from forming antibodies by the administration of cortisone for nearly two weeks, yet upon withdrawal of the drug, antibodies promptly appeared. Clearly, the antigen had remained in the organs of the mice in a form capable of engendering antibodies.

Cortisone did not inhibit antibody formation by interfering with the storage or distribution of the tracer antigen or by destroying it. The phagocytic cells, even under the influence of cortisone, continued to localize and store the tracer antigen. The undisturbed function of these cells suggests that they do not form antibodies, although they partake of the first step in antibody formation by capturing and holding the antigen. It is the cells of the lymphoid series, though greatly injured and reduced in number by cortisone, which appear to be the units which form the antibody.

At about this time there appeared accounts in the literature

that certain bacterial endotoxins enhanced antibody formation, stimulating McMaster and his capable assistant Dr. Robert Franzl to examine the cellular changes accompanying the presumed enhancement. These collaborative studies of Franzl and McMaster extended well over a decade, from 1956, when Franzl first came to the Rockefeller Institute, until and beyond McMaster's death. As Franzl has said in a communication to this writer, "our task was to clarify some of the early mechanisms involved in antibody formation *in vivo*, more specifically those pertaining to the cellular uptake and subsequent fate of antigens and their presumed role in the induction of immune processes."

Sheep red blood cells were used as the antigen because of the exquisite quantitative method available for measuring the hemolysin formed. Upon the introduction of *S. typhosa* endotoxin into mice, together with the antigen via the same route, the two did indeed note a greatly increased antibody formation. Yet, surprisingly, antibody formation failed to appear if the endotoxin was administered prior to the introduction of the antigen.

Since the endotoxin, administered alone or administered before the antigen was given, produced a marked depletion of the lymphoidal elements in the spleen and mesenteric nodes of the mice, it presented an excellent means of preserving the type of cells which appeared in the relatively empty lymphoidal tissue both during the enhancement as well as the suppression of antibody formation. Thus, when large amounts of antibody appeared, all of the known cellular changes usually accompanying or preceding this in normal animals were enhanced. The proliferation of extraordinarily large numbers of large pyroninophilic cells was considered to be responsible for the early formation of antibodies. Activated germinal centers appeared in much greater numbers than are usually seen in mice forming antibodies to simple injection of antigen without endotoxin. These changes were all absent in the mesenteric nodes and spleens of

control mice that formed no antibody. These findings and those reported in the experiments with cortisone make it seem probable that the suppression of antibody formation does not depend so much upon the fate of the antigen as upon the proliferation and development of lymphoidal elements in the injected mice.

In foregoing account, I have attempted to survey rather broadly the achievements of Dr. McMaster during his many active years at the Rockefeller Institute, now the Rockefeller University. To be sure, this attempt has been brief, and if the reader wishes to learn in greater detail McMaster's scientific objectives and goals, he must of course refer to the scores of scientific contributions which appeared in various journals over the decades and were in great demand by scientists throughout the world, a demand evidenced by massive requests for reprints. A perusal of this bibliography impresses one with the diverse spheres of interest which McMaster had and which expanded over his many fruitful scientific years. One need but read a few of the accounts to appreciate how meticulously and precisely he planned and pursued his work and to gain a broad insight into the mind of a truly splendid investigator.

McMaster held memberships in many scientific societies and in social clubs as well. The two he cherished most were the Century Club in New York City and the National Academy of Sciences (elected 1952). He is survived by his two children, Abigail P. (Mrs. Charles) Alling and Dr. Philip Bache McMaster, and by his charming widow, Elizabeth.

Now a different and equally pleasant task falls to my lot, to give you a picture of Dr. McMaster as a human being away from the laboratory, away from the animals and the microscope with which he worked, away from the stained sections over which he poured in reaching many of his important conclusions. This is not easy, for one usually sees his colleagues in a perfunctory manner; yet I knew him well.

First of all, Phil was forever a jovial person, witty and sharp in his judgment of people and of situations. On one occasion,

however, I recall when his judgment was not good. It was when he asked me and two of my colleagues to sail his yacht from Huntington, Long Island to Woods Hole. Only one of us, Tom Hughes, who was then associated with the Rockefeller Foundation, knew anything at all about sailing and navigation. But under Hughes' short and forceful tutoring we made it, by good navigation, luck, and some dead reckoning, for we were engulfed in a heavy fog the entire distance.

His widow, Elizabeth, whom I also know well, has permitted me to read several personal letters which she received over the past fifty years from her husband, and from these I have gotten certain impressions that I otherwise would not have had, despite the fact that we were friends of many years standing.

At home, he was a charming host. He frequently entertained guests with his violin or his accordion, both of which he played with equal facility. His dress was at times a bit bizarre, for I saw him frequently on his way to the Rockefeller Institute, particularly in a snowstorm, dressed in the garb of a Maine woodsman, unconventional, to say the least, in the city of New York. His relationship to his wife was one of deepest affection, as attested to by two very personal letters which Elizabeth permitted me to read. They were written during World War II, when he was stationed in Florida. These letters also served to express his opinion of the shortcomings of military red tape. I have at hand, too, several letters written to Mrs. McMaster, in which the writers refer to Dr. McMaster and his work. I wish to quote from two of these, for they are from men of distinction in their own right. Dr. Merrill Chase of our Institute, in a letter to Elizabeth, says, "I look back over the years to Phil's exciting work in tracing the lymphatics of the human skin and in animals too. He was a highly ingenious research worker and I learned much from him." Then again in a telegram of condolence, James and Margaret German say, "We send love to you and our deepest sympathy. We will miss Phil because he was one of those few who showed that it was good to be human and alive."

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