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WILLIAM DE BERNIERE MACNIDER

1881—1951

A Biographical Memoir by

A. N. RICHARDS

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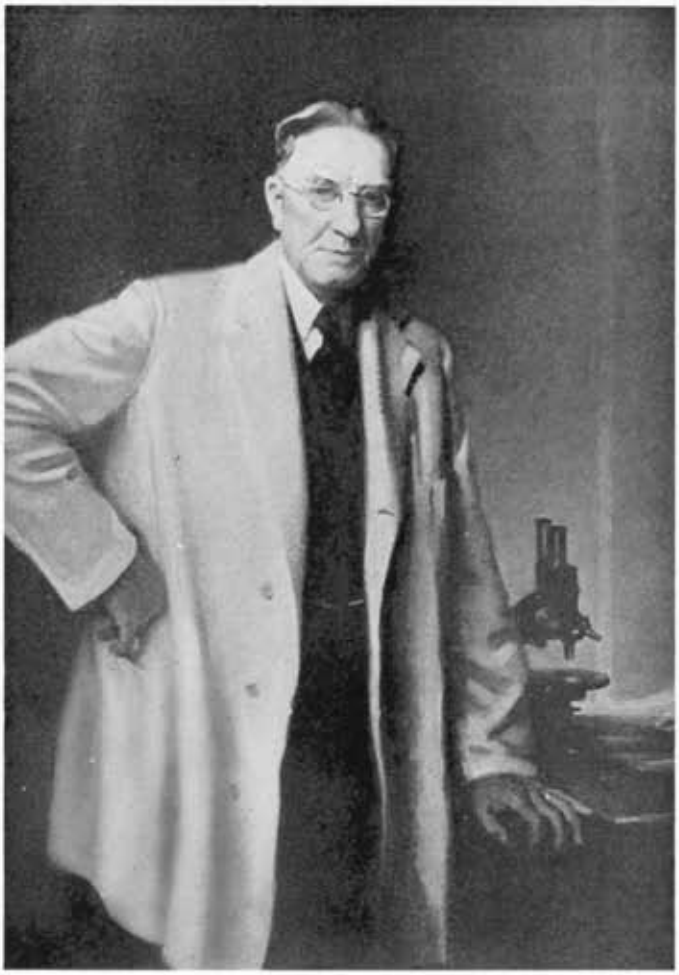

Wm deB. MacNider

WILLIAM deBERNIERE MacNIDER

June 25, 1881—May 31, 1951

BY A. N. RICHARDS

WILLIAM deBERNIERE MACNIDER, son of Virginius St. Clair MacNider, M. D., and Sophia Beatty (Mallett) MacNider, was born in Chapel Hill, North Carolina, on June 25, 1881, in a house on West Franklin Street, a few hundred yards from the University to which the work of his adult life was devoted. He died in near-by Watts Hospital of Durham on May 31, 1951, from an acute development of a chronic respiratory disorder from which he had suffered intermittently for many years.

His father's ancestry has been traced back to the MacNair clan who, prior to about 1600, dwelt on the Isle of Skye. They emigrated to Ayrshire and intermarried with Clan MacAdair, with the result that the name successively became MacNadair, MacNader, and finally MacNider. John MacNider, ancestor of Virginius, joined Neal MacNeal's colony and came to the Cross Creek Section of North Carolina, near Fayetteville, in 1749.

His mother, Sophia Mallett, daughter of Dr. William P. Mallett, was descended from the Huguenot family of Malet of Rochelle, France of which Daniel Malet, "the original Mallett," was Governor General. Four of the Mallett brothers fled from France to England and from thence, in 1780, came to America. Two of them were the founders of the city of New Rochelle, N. Y.; a third remained near Charleston, S. C., their port of entry; the fourth came to Wilmington, N. C., thence to Fayetteville, where he founded the North Caro-

lina branch of the family, of which William P. and his daughter, Sophia, were members.

Dr. William P. Mallett, born in Fayetteville, educated at Trinity College, Hartford, and the Medical College of South Carolina, practiced medicine in Chapel Hill from 1857 to 1889, the year of his death. His personal character and professional competence gave him a position of outstanding eminence as a citizen and as a general practitioner and consultant not only in Chapel Hill, but also in the surrounding county areas. In 1852 he performed one of the earliest Caesarean sections in this country; he served the University of North Carolina as physician to students and faculty and, although he died when his grandson, William, was only eight years old, his memory was one of the influences which directed the boy's mind toward the profession of medicine.

No evidence is available to indicate that as a boy, William showed a precocious bent toward science, but it is written that "he hunted in all the fields and woods, loved and cared for every wild flower; cultivated, enjoyed and shared every beautiful thing in the form of flower and shrub which can grow in Chapel Hill." That passion for natural beauty endured throughout his life. The chief formative influences of his early years were derived from the characters and devotion of his mother and her sister, "Aunt Eliza" Mallett, from his reverence for the tradition left by his grandfather Mallett, from associations with gifted members of the University faculty who were frequent guests in his mother's home, and from the experiences he enjoyed as a boy of thirteen or fourteen while accompanying his future teacher, Dr. Whitehead, on professional visits.

As an undergraduate in the College of the University, he got inspiration from the exceptionally able professor of biology, Henry V. P. Wilson, whom he served as student assistant during the school year 1899–1900. In MacNider's words, "Professor Wilson gave me rigorous instruction in zoology and under his guidance I saw for the first time the nephridium of the earthworm, perfect in its function and symmetrical beauty."

In 1899 MacNider enrolled as a student in the Medical School, then limited to two preclinical years in the laboratories at Chapel Hill. The Dean was the friend of his boyhood, Dr. Richard H. Whitehead, brought to Chapel Hill from the University of Virginia in 1890 to establish the North Carolina school, a man who attained great distinction not only from his success as an administrator, but also from his abilities as a scientist and physician. As professor of anatomy, he equipped a laboratory for research in histology and embryology; he also taught physiology and materia medica; he was physician to the University as well as to many families in the Chapel Hill area. His research interest in anatomy was broadened by summer work with Barker in Chicago and Mall in Baltimore. MacNider was appointed his assistant in anatomy from 1900 to 1902 and came to share his love of experimentation.

At the end of the academic year 1901–1902, MacNider had finished the work of three of the four years required for the M. D. degree and was contemplating a fourth and final year in another institution. It happened that in the spring of 1902 the decision was made by President F. P. Venable to bring to realization a plan inaugurated by Venable's predecessor, E. A. Alderman, which would add two years of clinical instruction to the existing preclinical years, and thus enable the University of North Carolina to award the degree of Doctor of Medicine. Hubert A. Royster, thirty-one years old, an able, ambitious, and courageous gynecological surgeon of Raleigh, N. C., was chosen to be dean, with the duties of designing the curriculum, choosing the clinical faculty, and managing the whole undertaking without expense to the mother University. Instruction was to be given in Raleigh. In addition to Royster, who took the chair of gynecology, the first major faculty consisted of four professors, all eminent practitioners in the Raleigh area, among them Royster's father, W. I. Royster, as Professor of Medicine. The doors of the clinical division opened in September, 1902. William deBerniere MacNider, the first applicant, was admitted to membership in the senior class; he was joined later by three others. Two applicants were ad-

mitted to the junior class, thus making a student body of six. MacNider received his M. D. degree in 1903, and for the two following years remained in Raleigh as Instructor in Medical Diagnosis. He lived at Dean Royster's home during those years and collaborated with him in the study of clinical problems in gynecology, from which two publications resulted, the titles of which head the Bibliography appended to this account. In 1910 the Raleigh project had to be abandoned, and the two-year course of the school was resumed.

In 1905 MacNider was recalled to Chapel Hill as Professor of Pharmacology. In those early years after graduation, he sought to amplify his training by spending summers in other medical centers. The first, in 1904, was in Baltimore in Osler's clinic at the Johns Hopkins Hospital. That experience left an indelible impression, memorialized in his essay, "The Way of a Teacher." Another summer was spent in Chicago, where he worked in physiology with S. A. Matthews and G. N. Stewart. Still another, 1908, was in Cleveland in the pharmacological laboratory of Torald Sollmann at the Western Reserve University Medical School.

The duties to which he was assigned upon his return from Raleigh to Chapel Hill were not restricted to pharmacology; he also taught or took part in the teaching of bacteriology, clinical diagnosis, and minor surgery; he shared in the responsibility for the medical care of students and faculty in the University Infirmary, a task which his grandfather, Mallett, and his teacher, Whitehead, had successively discharged years before him; he engaged in the practice of medicine in the community.

In 1918 he was one of the first five faculty members to receive the rank and title of Kenan Professor, bestowed as a recognition of "distinction in research, in teaching, or in service to the University." Among the others similarly honored were President Venable and MacNider's former teacher, Professor Wilson. In 1924 MacNider's title was changed to that of Kenan Research Professor; in 1937, while still retaining his professorship, he became Dean of the Medical

School and served in that capacity for three years. In 1950, he retired from active duty.

MacNider's work in Sollman's laboratory in Cleveland in 1908 constituted the beginning of his investigations of the structure and functions of the kidney, a subject which became a central research interest for the rest of his life. It is described in a preliminary publication in 1910 from the two laboratories, Western Reserve and North Carolina, followed by one in 1911 from the Chapel Hill laboratory. In it he aimed to study processes of regeneration in a necrotic area of the kidney, produced by ligation of a branch of the renal artery in dogs and cats. Most significant in relation to his future work was the finding that as blood vessels and connective tissue cells grew into the area new tubules were formed, the cells of which were flat and lacking in clearly defined boundaries.

At about the same time, influenced by the work of Schlayer in Germany and Pearce in the United States, in which were described the effects of a group of poisons on renal structure and function, he undertook to relate the effects of such poisons to urine formation and to the action of diuretics. Regarding the urine-forming mechanism of the kidney as made up of two systems, the blood vascular including the glomeruli, and the epithelial cells of the tubules, he hoped to find a poison which, by selective action, would disable one system, leaving the other intact and thus yield conditions for a conclusion as to which system is more largely responsible for urine formation and for effectiveness of diuretic drugs. As the previous workers had shown, cantharidin and arsenic exhibited predominantly vascular effects; chromates, mercury, and uranium acted predominantly upon the epithelium. MacNider found that urine continued to be formed and diuretics increased urine output, even when the vascular elements were the seat of congestion, provided only that the tubular epithelium was not seriously damaged; however, when the epithelium had become swollen, vacuolized, or necrotic, urine output decreased, even to the point of anuria, and diuretics failed to

act. These latter effects he attributed to obstruction of the tubules by the swollen epithelium or by debris of necrotic cells. His conclusion, emphasized then and in later work, was that the functional capacity of the nephritic kidney depends more upon the integrity of the epithelium than upon the responsiveness of the vascular mechanism.

In the acute experiments with diuretics uranium was the toxic agent used. The principal effect of a small dose was the production of cloudy swelling of the epithelium of the distal segment of the proximal convoluted tubule; larger doses caused fatty degeneration, vacuolization, and necrosis, extending to the ascending limb of Henle's loop, where stainable lipoid accumulated. Glucose, albumin, casts, and acetone bodies appeared in the urine. By judicious selection of dose and time interval, the character and severity of the toxic effect could, to some extent at least, be predetermined. From this time (1913) on, uranium was one of the chief tools with which MacNider's renal explorations were made.

Further study of diuretics in uranium nephritis not only confirmed the conclusion stated above, but added other leads. These were: (1) that the severity of the changes which uranium produces in renal structures and urine composition is greater in adult than in young animals, and (2) that chloroform, used as an anesthetic to permit measurement of blood pressure and kidney volume, intensifies the severity of the uranium effects, and that its effect, too, is more pronounced in old than in young dogs.

Like others who had studied experimental nephritis, MacNider was impressed by the frequency with which the kidneys of seemingly normal dogs showed evidence of chronic nephritis, naturally acquired through unknown causes. Their urine contained albumin and casts; the kidneys, examined histologically, revealed a primary chronic glomerulo-nephritis. Pathological alteration of the tubules was relatively insignificant. Some tubules were found to be lined with flattened, atypical cells, evidence, it was assumed, of previous degeneration and repair.

Experiments carried out on these "naturally nephropathic" dogs, showed: (1) that the damaging effect of uranium was more intense and wide-spread than in normal dogs; (2) that the tubular regeneration which followed the acute effects of uranium was characterized by the production of flat cells, structurally less specialized than the normal cells which they replaced; and (3) that the cells of the regenerated epithelium, when subjected to a second poisoning with uranium, were less susceptible to its destructive effects than are normal cells. In these experiments, too, age was found to be a factor; the older the animal the more severe was the damage effected by uranium.

Early in his experiments with uranium, MacNider was impressed with the occurrence of glucose, acetone, and diacetic acid in the urine of poisoned animals. There was a rough parallelism between the excretion of these substances and the severity of the poisoning. The conclusion that acid intoxication is a factor in the degree of damage produced by uranium was strengthened by finding that intravenous sodium carbonate lessened not only the excretion of acetone bodies but also the severity of epithelial damage; it restored the capacity of the kidney to respond to diuretics.

In more detailed experiments, the acid intoxication from uranium was further defined by measuring the decrease in blood pH, alkali reserve, and alveolar CO_2 tension. The excretion of injected phenolsulfonephthalein (PSP) was diminished; urea and creatinine were retained in the blood. All of these effects were more pronounced in old than in young dogs. The disturbance in acid-base equilibrium was taken to represent a "tissue acidosis," ascribable to a general inhibition of oxidative enzymes and consequent depression of internal cell respirations. It was assumed that such enzymes are more abundant in the tissues of young animals, and that this was a possible reason for their greater resistance to the action of uranium.

The foregoing statements indicate the direction of MacNider's chief efforts during the first decade of his investigative career. They disclosed and partially clarified problems which were to occupy a

large share of his future work and thought. He had focused upon uranium because of the selective and predictable characters of its action and because of the resemblance between the nephropathy produced by it and certain nephroses encountered in human pathology. His study of naturally acquired glomerulo-nephritis in dogs offered similar opportunities. The toxic actions of chloroform on the kidney presented problems of practical as well as scientific interest; so did the acidosis produced both by chloroform and uranium. Most important of all were the leads which he had opened on the factor of age in the severity of tissue poisonings and on the characters of tissue repair after injury.

In studies of the chronic effects of uranium, specifically directed at the factor of age, MacNider found that dogs less than one year old consistently survived the effects of dosages of uranium which were invariably fatal to dogs over six years of age. The old dogs excreted albumin, casts, and glucose in large amounts; urea and creatinine accumulated in the blood; PSP excretion diminished to zero; the alkali reserve of the blood was markedly reduced. Profound degeneration and necrosis of the tubular epithelium was found at autopsy.

Equivalent doses in the young dogs produced far less intense effects both upon blood and urine and upon renal structures. Swelling, edema, and necrotic changes were less severe, and as early as the tenth day extensive regenerative repair could be identified. The regenerated epithelial cells were flat and less specialized in structure than were the normal cells which they replaced. Urinary abnormalities, with the exception of decreased PSP excretion, disappeared. The acid-base equilibrium of the blood as indicated by the alkali reserve was restored to normal. After recovery the kidneys presented the picture of a permanent "chronic diffuse nephropathy."

In some of these experiments, the chronic effects of uranium were followed for as long as five years. Histological study of the kidneys of these animals revealed two different types of epithelial repair. In one type there was reconstruction of typically normal cuboidal cells,

brought about by processes of mitosis from cells which had not undergone extensive destruction. In the other type, structural repair took place by an ingrowth of the flat cells, above referred to, relatively nonspecialized and imperfectly differentiated.

Studies were made to learn how these two types of regenerated epithelium would react to a second attack by uranium. In those animals which had survived a first poisoning and whose kidneys on biopsy showed restoration of epithelium of the normal type, the second poisoning produced even more severely destructive effects than did the first. They succumbed with all the symptoms, functional and pathological, produced by a larger dose given to a normal animal.

On the other hand, animals which had survived a first poisoning with the development of a chronic nephritis and replacement of normal tubular epithelium by flat, atypical cells, survived a second dose even larger than the first, with no degenerative changes in those atypical cells. It was apparent that a resistance to the toxic action of uranium had been acquired as a result of the substitution of atypical "embryonic" cells for the more specialized, more susceptible cells which had been destroyed by the first poisoning.

Concurrently with MacNider's studies of the pathology of renal damage inflicted by uranium or chloroform came his recognition of disturbances of general metabolism as indicated by the associated acidosis. He found that reduction in the alkali reserve of the blood might occur before morphological changes in renal structure could be identified. His conclusions in this connection are summarized at the end of a series of papers in the *Journal of Metabolic Research* (1926) as follows:

First, "The nephrotoxic action of uranium nitrate is in large measure due to its ability to induce and maintain a disturbance in the acid-base equilibrium of the blood which is furnished to the kidney, and in which blood chemical environment this organ must attempt to functionate in a normal manner. There is no reason to

suppose that a similar statement does not apply to other organs equally important,"

Second, "In certain animals acutely nephropathic from uranium the use of sodium bicarbonate maintains the equilibrium of the blood. In such animals there is less evidence of renal injury and a more perfect maintenance of renal function," and

Third, "In other acutely nephropathic animals and in all animals with a naturally acquired glomerulo-nephropathy in which an acute injury has been superimposed on the chronic process, the use of sodium bicarbonate was unable to maintain this equilibrium. In such animals there was a marked disturbance in both the functional response of the kidney and in the degree to which the kidney was histologically preserved."

In these conclusions can be discerned the recognition of a general condition which he came to refer to as the "instability of the acid-base equilibrium of the blood"—a state in which, while measurement of the actual blood balance of acid-base may yield a normal figure for the alkali reserve, the total reserves of the body are inadequate to provide supplies of base necessary to compensate for excessive demands incident to excessive acid production or accumulation. The situations in which such instability is to be found were old age, advanced pregnancy, particularly in old animals, and chronic renal disease, either naturally acquired or resulting from an acute chemical or pathogenic insult from which partial recovery had occurred.

Although the chief focus of MacNider's investigative interest was the kidney, he was wholly aware that other physiological systems are involved in the complex of effects produced by the poisons which he studied. As early as 1919 he described the acute effects of uranium and mercury on the liver, and in 1932 he systematically undertook experiments on that organ, similar in design to those on the kidney. Uranium and chloroform were the agents used; excretion of phenoltetrachlorphthalein (TCP) served as a test of liver function; alkali reserve of blood indicated the state of the acid-base equilibrium;

morphological changes were followed by histological examinations of liver tissue, repeatedly taken at biopsies during the course of and again at the end of each of many experiments. The results were so like those obtained in studies of the kidney that they require only brief description.

A small dose of uranium (2 mg. per kilo) caused albuminous degeneration and edema of liver cells with little extensive necrosis. Excretion of TCP was delayed and alkali reserve reduced. Some four weeks later, cell structure had become normal, TCP excretion approached normal, and the alkali reserve was restored. When such a dog, after recovery, was given a second dose of uranium the effects were as severe as those which followed the initial dose.

When a larger initial dose of uranium was given (4 mg. per kilo) extensive necrosis of liver cells resulted, with greater decrease in alkali reserve and longer delay in TCP excretion. After four to six weeks the degenerated liver epithelium was found to have been replaced by flattened cells, less specialized in structure than the normal, which frequently formed syncytial cords of imperfectly differentiated cell substance.

Dogs which survived the larger dose, when again poisoned with uranium, resisted the second poisoning if the second dose of uranium was the same as the first. The atypical cells did not show injury; function as indicated by TCP was little affected. Tissue resistance had developed. However, if the second dose of uranium was sufficiently large, degenerative change in the atypical cells did occur. Their acquired resistance did not constitute an immunity.

Similar results yielding similar conclusions were obtained in experiments in which the second poisoning was produced by chloroform rather than uranium.

Finally, it was found that in some "senile" dogs, the "normal" liver epithelium was of the flat, syncytial type, and that these animals exhibited a resistance to uranium and chloroform similar to that exhibited by animals in which atypical epithelium had developed as a sequel to the acute injury.

In concluding a description of the above experiments MacNider remarks that in considering susceptibility or non-susceptibility to disease, especially those characterized by degenerative rather than inflammatory processes, the factor of changed morphology and changed power to resist must be recognized. Such shifts—metaplasias—in fixed cell types, as these experiments demonstrate, are examples of adaptation of animal tissues and organisms as a whole to an initially unfavorable physico-chemical environment; they may in part explain the survival of the fittest.

The foregoing account is limited to the major and what is believed to be the most important part of MacNider's investigative efforts. It is inadequate in that it fails to portray the passion for the discovery of new truth through experimentation which animated his life. "Research in any field is done primarily to find some new truth or part of a truth—regardless of immediate or practical application. . . . The finding of some small piece of truth is sufficient reward" (1920). "The desire to understand the unknown and the will to sacrifice to gain such information is the spiritual inwardness of University life" (1945).

It fails also to picture the enthusiasm which carried him through recurring discouragements in the course of his studies. Hundreds of experiments, requiring countless observations, analyses, and studies of tissue sections were conducted at the cost of unceasing labor and great personal expense; the camera lucida drawings and photomicrographs with which his papers are suberbly illustrated were secured largely at his own expense. At times he was desperate for funds needed to carry his dogs over a summer vacation. Once the Ella Sach Plotz Foundation came to his rescue; at other times he pledged his own property. Nights, Sundays, and vacation days were opportunities for research, as much as for relaxation and rest. Often a new observation would arouse excitement. In 1932, for example, a hastily written letter begins, "Did I tell you I had found a peach of a thing in the liver?" It goes on to describe the discovery of flattened, ribbon-

like cords of liver cells, highly resistant to chloroform, in a dog, normal except for advanced age, and continues with the surmise that "the entire question of resistance and immunity can not be explained on a humoral basis, antibody formation or on the activity of wandering cells."

MacNider realized that the morphological changes which he identified must be the visible manifestations of chemical and physical complexities which were beyond the powers of his microscope and his chemical skill; thus deterred from their more intimate analysis, in his later years he devoted some of his energy to the development of broader biological generalizations. These reflected the influence of wide, serious, nontechnical reading, and especially of the philosophical writings of two scientists whom he revered, L. J. Henderson and J. S. Haldane. This phase of his mind is shown in the titles of papers published during the last decade of his life such as "Adjustability of the Life Process to Injurious Agents" and "Age, Change and the Adapted Life." This account would be incomplete if these themes were not represented in it.

Concerning adaptation: "Fixity of any order, even fixity of purpose, tends to bind and render inelastic the structure or the individual in which such a property develops. It is a quality which is inimical to adaptation, and tissues or organisms without this quality of elasticity, of variability, have difficulty in meeting the exigencies of life which is made up of periods of adequate adaptation which may be of such a specialized nature as to produce the symptoms and later show the signs of disease.

"In thinking of the adjusted normal animal organism and the changes it can withstand one must conclude with a certain degree of assurance that the life span of such an individual was intended to be much longer than we now make it.

"Such natural factors of safety have not been appreciated by us as reserves. Through excess we have foolishly drawn upon them in their abundance for our normal way of life and depleted these fac-

tors of safety. Over-exercise, over-eating, over-worrying, more rarely over-drinking diminish these factors of endowed and natural safety, this abundant reserve tissue, and prepare us for the advent of tissues so different from the reserve that we designate them pathological. However, even tissues of this order may safeguard us against ourselves by furnishing us an excess of tissue which, although altered, not only functions and in part adjusts us, but at the same time endows us with a factor of resistance against further injury.

"Even in those states of tissue change which are designated disease there is evidence that we may become readjusted to them at certain modified levels of physiological effectiveness. There is an inherent urge on the part of cells, not for death, but for life. The changes of degeneration which many such units can withstand and their capacity of recuperation and repair, if given an opportunity, constitute, as a composite, one of the major manifestations of life.

"These changes in cell form as life adjusts and adapts itself to a variety of chemical experiences are impressive as they give to one a conception of the elasticity and adjustability of such changes, ever tending to adapt an organ in which they occur and the organism, the individual as a whole, to life at some level of effectiveness. The observations lead one away from a concept of the fixity, the static nature and inelasticity of life processes, even when expressed as chemical equations within cells, as a form of life. It would appear that change is the essence of life and that an organ or organism, with the greater degree of adaptability to changed conditions is in turn the more likely to survive.

"Finally and in summary, when we contemplate our varied factors for safety, for a continuation of life as an everchanging, shifting, yet balanced living entity, we may wonder at the brief duration of our life span. The duality of certain organs and the superabundance of reserve tissue in those not so paired, the ability of tissues automatically to throw into operation functional defense mechanisms, degenerative changes in tissues leading to processes of repair which

afford tissue resistance, all tend to hold us not only in life, but in a balanced and, in some measure, an effective life."

It will have been noted that even in the very early stages of MacNider's studies of the reactions of tissues to poisons he clearly recognized the influence of age on the intensity and quality of effect; as more and more evidence accumulated, he insisted with increasing emphasis upon the importance of the study of the aging process. It was natural, therefore, that he should have been one of those who, more than twenty years ago, advocated and worked for the development of gerontology and geriatrics as discrete divisions of human biology and medicine. His mature belief is indicated in the following quotation:

"Many are interested in embryonic life; the life of infancy and childhood; the changing life and puberty; but few are interested in the changing life of the middle aged as it advances into senility and finally to a senile and perhaps physiological death.

"Understanding the physical and chemical changes associated with the aging process is more important and more difficult than that of changes in infancy and childhood. In the latter the life urge is toward survival; in the former the tendency is the reverse.

"Infancy and youth, the aged, and the senile represent chemical equations in progressive adventure from life into death. The usual concept of age is that of a fixed, natural and irreversible process, chronologically determined by the species of animal, which within certain fairly constant limitations terminates in death. Age and the processes constituting it should be seen and appreciated as living, fluid, elastic states of give-and-take for the sake of adjustment as an organism passes through its life span with those changes indicative of aging being in some measure manifestatious of an attempt of such an organism, man, to effect a working adaptation to these years. Certain of these signs of aging represent failures in such an attempt. The important consideration for the student of aging is to ascertain the reasons for such failure and the cause for those states of premature aging and instability which unrelate the individual to

that environment in which he has to live and maintain functional adjustment.

"The aging process is not one which proceeds from a certain peak of perfection uninterruptedly downward. Its course is characterized by variations in cell susceptibility and transitory states of cell resistance which give an irregular curve of downward progress—points of depression, increased susceptibility; points of elevation, variable in duration at which resistance is increased. As aging progresses such transitory states of cell adaptation to it become less and less effective, finally manifesting their inability in terms of such depressed function or lack of function on the part of an organ system that the life of the organism as a whole comes to an end."

It is appropriate now to attempt to identify and estimate the influence which MacNider's work, ideals, and personality exerted upon the progress of medicine, upon the University in which he worked for more than half a century, and upon the individuals with whom he lived.

His part in the early stages of development of gerontology and geriatrics in this country—disciplines which now have their own national societies and journals—was an outcome of his long insistance on the part played by age in the reactions of tissues of laboratory animals to poisons and upon age alone as a factor in tissue change. In 1937 he was an active participant in a conference of some twenty scientists called to discuss material on aging which was to be assembled in a book planned by E. V. Cowdry and published in 1939 under the title *Problems of Ageing*. That conference was the first of a long series, sponsored and supported by the Josiah Macy Jr. Foundation, which gave strong impetus to the advancement of knowledge of that field. For six consecutive years, 1940 to 1946, MacNider was chairman of those conferences, and the group, under his chairmanship, has been credited with having played the leading role in the development of the field of aging in this country. When the Gerontological Society was founded, MacNider was its first presi-

dent. He was a member of the National Research Council's Committee on Aging and became consultant on aging to the National Institutes of Health.

Similarly specific examples of leadership in the broader, more general areas of medicine are less easy to define, but there are many impressive evidences available which prove the extent and value of his influence. In the south particularly, he came to be regarded as the regional personification of the relationship between experimental science and medical advance—witness his presidencies of the North Carolina State Medical Society (1925–26) and the Elisha Mitchell Scientific Society, his honorary degrees from the Medical College of Virginia (1933) and from Davidson College (1934), and the many invitations he received to address southern medical organizations. A member of the Association of American Physicians, in 1941 he received its highly prized Kober Medal. He received and accepted one of the annual invitations given by the Medical Staff of the Peter Bent Brigham Hospital to come to Boston and for a month to assume the duties of Physician-in-Chief in that hospital—an extraordinary tribute to be given to a laboratory man. Another distinction, similarly unusual, was the selection of Dr. MacNider to deliver the Convocation Address at the twenty-second annual session of the American College of Physicians in 1942. For many years he served as a member of the National Board of Medical Examiners; in 1927 he was chairman of the Section of Pharmacology and Therapeutics of the American Medical Association; for two years, 1932 to 1934, he was the elected president of the American Society of Pharmacology and Experimental Therapeutics, and in 1941–42 was president of the Society for Experimental Biology and Medicine. The New York Academy of Medicine gave him the Gibbs Prize for the year 1930–31, and he received the Research Medal of the Southern Medical Association in 1933. Dr. MacNider was elected to the National Academy of Sciences in 1938.

His work on the effects of anaesthetics on acid-base equilibrium can be regarded as having had an influence in hastening recognition

of the importance of protecting the electrolyte balance in relation to pre- and postoperative surgical care. He was a member of the research committee of the National Anaesthesia Research Society, and in 1934–35 was president of the International Research Society.

Neither an account of MacNider's laboratory investigations nor a listing of his services to medical organizations and of the honors bestowed on him represents, it is believed, the most important fruits of his character and activities—those which will be longest remembered and have the most lasting influence. These are more difficult to portray. They require familiarity with the spirit of the man, shown in devotion to his profession, to the University which he loved and served, to his students, to his neighbors, and to his friends, who were legion.

First of all, he was a physician, a true country doctor, whose readiness to care for the sick never lessened. It is as remarkable as it is unusual that one whose chief pursuits were in the laboratory and classroom should have so long continued to be on call for patients who wanted him. His earliest models were his grandfather, Mallett, and his teacher, Whitehead; later he was strongly influenced by the two Roysters, father and son, and, in a special degree, by Osler. Like them, he never regarded a patient as "a case," but always as a whole human being in need of all the help that another human being who happened to be a doctor could give.

He had little respect for a doctor who looked upon his profession as a means of personal enrichment, or for one who allowed social engagements or the financial status of a patient to influence his response to a need. One of his friends, disclaiming interest in what MacNider did in his laboratory, asked "How does he manage to get around to help so many folks who are sick or otherwise in trouble?"

He was a competent doctor. During the influenza epidemic of 1918, he was made responsible for the medical care of students and faculty in the infirmary. His associate, Dr. Coppridge, said he had

never seen Dr. MacNider's peer in the art of diagnosis or in the mastery of scientific therapeutics.

He did not spare himself. One twenty-four-hour day can be cited. Called one evening to a farm two miles from town he found a woman, pregnant with twins, in a state of eclampsia. Helped by the husband and a Negro midwife who gave chloroform, he did a forceps delivery of the first child, breech presentation; he encountered no difficulty with the second. Treatment for shock was inaugurated with heat, coffee, and morphine. Back to the University for an 8:00 A.M. lecture in pharmacology. That finished, back to his patient, who was responding well to treatment. The midwife was feeding the babies with warm milk and corn bread crumbs! Then in the afternoon, a lecture in pathology. A final visit to the patient, and the day was over.

In considering MacNider's service to the University as a whole, it is interesting to recall that his fifty-one years of faculty membership lasted for slightly more than one third of the active existence of the University up to the year of his death, that period covered the full terms of office of four presidents and the beginning year of a fifth. The University and the town of Chapel Hill were founded at the same time, 1795. The University had its most vigorous growth from a college to a university during the years 1900 to 1930, and the population of the town grew in those years from 1,100 to about 3,000, so that there is literal truth in the statement that MacNider grew up along with both the University and the community.

The following quotations from a tribute written by Chancellor Robert B. House shortly after MacNider's death are excellent expressions of what the writer of this memoir wishes this section to contain:

"Will MacNider was the most completely identified personality in body, mind and spirit with Chapel Hill and its environs and its people, and with the University of North Carolina of any man with whom we have been associated. . . . I found him attuned to every main value the University stood for and able to convey to students the spirit and feeling of what education was all about.

"He was almost a life-long member of the University Advisory Committee. . . . I know of nothing of any significance in any department or field of University effort which Dr. MacNider had not lovingly and thoughtfully considered and advised on with perfect frankness and sincerity.

"I think that such beauty as architecture has given to our campus, such protection of woods and natural beauty here as has been achieved by zoning, owe much to Bill MacNider. . . . He was almost all his life a member of the University Building Committee, instant and stalwart in support of appropriateness, dignity and beauty."

In 1946, his colleague Dr. Coppridge wrote:

"In 1936 the life of the Medical School was threatened because of certain actions taken by national standardizing bodies, directed against the two-year medical schools of this country. Dr. MacNider, in an able and energetic presentation of the case for the two-year schools, won for them the approval that was necessary for their continued existence. He argued sanely and eloquently that there is a place in any university for the teaching of basic medical sciences, and the weight of his arguments has held until this day."

One of the great material benefits which issued from Dr. MacNider's devotion to the University was a new laboratory building for the medical sciences, for it was largely through his efforts while Dean of the Medical School from 1937 to 1940 that the funds required for its construction were acquired. After his death, by action of the trustees, the building was named for him.

Because of the part which MacNider played for half a century in the growth of his University it seems fitting that this account of his relations with it should close with a sentence written by the Louisville newspaper editor, Mark F. Ethridge, in 1939:

"When the historian comes 50 years from now, to deal with the Southern Renaissance, he will have to say, as he can say in all truth, that its primary impulse came from, and its greatest influence was

the University of North Carolina. This little City of Chapel Hill has become indeed the Capital of the Southern Mind."

What is now to be written concerning MacNider's influence upon the students who made up his classes in the Medical School relates to the dominant element of his life work. Forty-four successive classes received instruction and inspiration from him. The core of his educational philosophy was put into words written in 1909: "The development of such a course [pharmacology] depends primarily upon the intensity of the desire on the part of the instructor to aid in turning out better medical men; and secondly it depends upon the appreciation of animal work when it is carefully and accurately done by the student."

That sentence shows that his aim was to help his students to become good doctors—not research scientists; but it gives no hint of the intimacy with which he entered into their lives and gained their friendship. Because the Chapel Hill school offered only a two-year course, it was necessary that his students, on leaving should gain admission to a four-year school elsewhere in order to achieve the M. D. degree. Wherever they went, the quality of their two-year training caused North Carolina students to be regarded as preferred candidates; they bore an impress clearly recognizable as that of MacNider's sincerity of character and love of truth. He told his students, "You must not be satisfied with the statements of others, but you must doubt, you must inquire and you must express your misgivings by tests." Again and again he sought to inspire them with humility and reverence in the face of the mysteries of living creatures. In their third and fourth year work in other schools, they found it hard to tolerate teachings which seemed to run counter to what they had learned from him. Their lasting trust in him and his friendship brought many of them back to him in later years for counsel in their difficulties.

When he retired from teaching in 1950, a former pupil, then in the armed forces overseas, wrote: "I feel sure that if you could know

the real place you have in the hearts of forty-four years of doctors you would seek no other reward and no other justification for having taught so long, for having been."

And the medical class of 1949 gave him a scroll, signed by each member:

"Throughout the lifetime of a student of medicine he attends many classes, listens to innumerable lectures, is instructed by countless individuals. Occasionally, indeed rarely, it falls his privilege to be associated with some truly outstanding personality, a person whose influence is woven into the pattern of the student's life.

"We, the class of Nineteen Hundred Forty-nine, desirous of recognizing such a man as this, do hereby present this certificate of appreciation to:

DR. WILLIAM deBERNIERE MACNIDER

"Though our association has been brief, he has given to us a glimpse of the knowledge which is never found on the printed page of a text-book or medical journal. He has taught us pride without snobbishness, and devotion to a concept without bigotry. With his own life, he has presented us with an ideal of Christian counsellor, loyal friend and truly good physician."

One of the students was responsible for the conception which led to the publication in 1953 of a book, *The Good Doctor,* in which selections from MacNider's writings are assembled, together with tributes from University officials; some of the quotations in this memoir have been taken from that book.

What remains to be written concerns personal relations with family, friends, and the community of which he was so intimate a part. After his marriage in 1918 to Sarah Jane Foard of Salisbury, N. C., the old home in which he was born was given up and he and his wife moved, with his mother and his aunt, to the house on East Franklin Street which they occupied during the rest of his life. It became a center of hospitality for his friends in Chapel Hill, a symbol

of southern welcome to his friends from the north. His wife was a never-failing support and ally; her reticent Presbyterian uprightness was a foil to the seeming insouciance with which he often masked his Episcopalian faith.

They had no money to waste. He tended to be extravagant in such things as books, orchestral and operatic records, travel to scientific meetings, and entertainment; she was the one who, knowing what those things meant to him and sharing his enjoyment of them, at the same time knew how to keep the family economy in balance.

It was in that home that his daughter, Sallie Foard, was born; she became his most intimate companion in everything which exercised his mind and heart.

MacNider was possessed of a deeply religious belief, which unobtrusively permeated all of his relationships. He loved the Episcopal Church of which he was a vestryman, and found solace in its service. On one Good Friday he is known to have dismissed his class and led them to the service there. He seemed to be on terms of informal intimacy with Jesus, often startling, as when, in a quandary, he would blurt out the question "What would He do in such a case?" In this he saw no inconsistency with good fellowship and conviviality.

It has already been said that he approached his own and his students' experiments with an attitude of reverence for the mysteries which they disclosed—to him they were "manifestations of the presence and the wisdom of God."

Reference has been made to his love of nature. The environs of Chapel Hill, especially when the dogwoods were in bloom, were a source of intoxicating joy; his garden, planted and cultivated by himself, was his delight. In the April before his death he wrote, "Just at the rear of our home is a triangular piece of land, 300 by 100 feet at the base. Hundreds of jonquils, the bulbs planted five years ago, are now in bloom, not bedded, but free and happy. On either side of the triangle a japonica hedge, also in full bloom." From that garden, every spring, he carried flowers to his near-by friends and sent them to those more distant. Regularly, too, he sent

his marigold seeds to the people he loved, not only in this country but abroad. His love of flowers was part of his faith.

MacNider's death in May, 1951, brought mourning not only to hosts of his friends in Chapel Hill, where he had become a landmark of integrity and helpfulness, but also to many others more remote. The comment then most frequently spoken and written was, "He had a genius for friendship." The secret of this was not only his warmth of heart, his love for and interest in people, but also in his unique willingness to give them expression. In his own words, "When I curb my heart I am unhappy."

"The whole earth is a sepulchre of famous men; and their story is not graven only on the stone over their native earth, but lives on, far away, without visible symbol, woven into the stuff of other mens' lives."

KEY TO ABBREVIATIONS

Am. J. Med. Sci.=American Journal of Medical Sciences
Am. J. Phys.=American Journal of Physiology
Am. J. Surg.=American Journal of Surgery
Ann. Int. Med.=Annals of Internal Medicine
Arch. Int. Med.=Archives of Internal Medicine
Boston Med. Surg. J.=Boston Medical and Surgical Journal
Bull. J. H. Hosp.=Bulletin of the Johns Hopkins Hospital
Charlotte Med. J.=Charlotte (N. C.) Medical Journal
J. A. Am. Med. Coll.=Journal of the Association of American Medical Colleges
J.A.M.A.=Journal of the American Medical Association
J. E. M. Sci. Soc.=Journal of the Elisha Mitchell Scientific Society
J. Exp. Med.=Journal of Experimental Medicine
J. Geront.=Journal of Gerontology
J. Med. Res.=Journal of Medical Research
J. Metab. Res.=Journal of Metabolic Research
J. Pharmacol.=Journal of Pharmacology and Experimental Therapeutics
J. S. C. Med. A.=Journal of the South Carolina Medical Asssociation
Ky. M. J.=Kentucky Medical Journal
N. C. Med. J.=North Carolina Medical Journal
N. Y. J. Med.=New York State Journal of Medicine
N. Y. Med. J.=New York Medical Journal
Penn. Med. J.=Pennsylvania Medical Journal
Physiol. Rev.=Physiological Reviews
Prensa Med. Mex.=La Prensa Medica Mexicana. Mexico, D.F.
Proc. Exp. Biol. Med.=Proceedings of the Society for Experimental Biology and Medicine
Sci. Monthly=Scientific Monthly
S. G. O.=Surgery, Gynecology and Obstetrics
South. Med. J.=Southern Medical Journal
South. Med. Surg.=Southern Medicine and Surgery
Trans. Assn. Am. Phys.=Transactions of the Association of American Physicians
Trans. Conf. Liver Injury=Conference on Liver Injury. Transactions.
Trans. Med. Soc. N. C.=Transactions of the Medical Society of the State of North Carolina

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