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BIOGRAPHICAL MEMOIR

OF

THEOBALD SMITH

1859-1934

BY

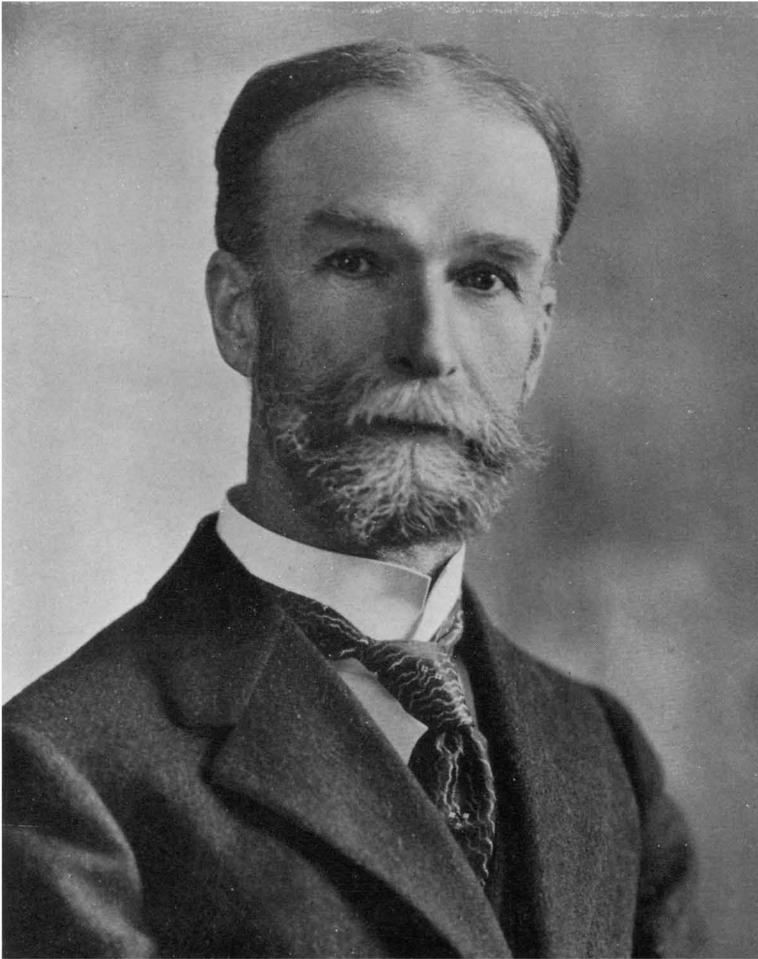
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*Theobald Smith*

## THEOBALD SMITH

1859-1934

BY HANS ZINSSER

One is constrained to write simply of Theobald Smith, for he was a simple person, simple in the sense in which one uses this word in connection with Pasteur and Claude Bernard, with Huxley and Haeckel; or in which one applies it to some American contemporaries of Smith himself who have carried the great tradition of the founders of modern biology into our own generation.

It is surely not an accident that one can point to so many examples of men, who during this period, achieved great scientific distinction and, at the same time, possessed qualities of character which extended beyond their scientific preoccupations into all their other relations. The writer of these notes has, of course, lived too long among scientists to claim that one can deduce general rectitude from distinguished scientific intelligence. But among the greatest, in whose ranks posterity will give Theobald Smith an unchallenged place—there are so many whose lives were characterized by qualities of unpretentious probity, by almost childlike guilelessness, and by an instinctive integrity of thought and action that one is tempted to attribute their achievements in discovery in part, at least, to these qualities. One saw them in Ehrlich and in Metchnikoff as one sees them in Bordet, Nicolle, C. J. Martin, and F. Gowland Hopkins. For it is true, surely, that without complete intellectual integrity of purpose no problem can be truly resolved. And, for them, such a manner of approach does not represent an act of mental discipline but is the instinctive expression of personality.

Theobald Smith was born in Albany, New York, on July 31st, 1859. His father was a German who came to this country shortly before 1850; and though we have no exact record, the time of immigration and the quality of the stock indicate that he was one of those of 1848 who saw in the new land, the

promise of freedom of thought and action which brought so many of that temper to America during those years. The family was native of the region near Limburg on the Lahn. The name was Schmidt, but almost immediately changed to Smith. The mother was Theresa Kexel, some of whose family are still living in Frankfurt am Main.

The new country was perhaps disappointing in material opportunities, for Philip Smith, the father, kept a small tailoring shop in Albany, but the quality of the man was apparently that of so many of his immigrant contemporaries with whom material circumstances were utterly unrelated to dignity, pride, and intellectual aspirations. The household seems to have been one in which there prevailed that atmosphere of affectionate contentment and intelligent simplicity which one associates with Germany before 1870, for which there is an untranslatable German word, "Biederkeit." There was music in the house—Theresa Kexel's people had been school teachers and musicians, and the boy, Theobald, had from his mother the taste and technical instruction which, later, gave him his most comforting relaxation in his hours at the piano. In a practical way his music was a great help, since it made it possible for him to earn a part of his livelihood while a student at Cornell by playing the organ for service in the chapel.

His early education was in the public schools of Albany which at that time must have been unusually good. The boy seems to have been a prodigious worker and it appears likely, also, to one familiar with the type represented by his parents, that he was vigorously encouraged to intellectual effort at home. The habits of work formed at this time persisted throughout his life. The writer once, some years ago, remarked to one of Doctor Smith's assistants that the professor must be an extraordinarily hard worker to cover so much ground. The answer was: "Well, Doctor Smith occasionally takes a Sunday afternoon off." His early inclinations seemed to favor mathematics, an interest which—like the piano—became one of the relaxations of his leisure moments. On graduation from the high school at eighteen, he won a State Scholarship to Cornell by competitive examination. Professor Gage, who was one of his

teachers at this time tells us that his career as a scholar was so brilliant, that in spite of the necessity of earning money to pay his way, he was encouraged to specialize in almost every subject in which he showed interest; in consequence he found it extremely difficult to decide which course to follow as a profession.

His first plan after graduation was to teach school. Medicine became second choice when he failed to get a job. One wonders what would have happened if some condescending high school principal had, at this time, offered him a thousand dollars a year to teach algebra. It is more than likely that an astronomer or physicist would now be writing this memoir. When he did finally choose to enter the Albany Medical School, some of the mathematicians at Cornell said that they "had a grudge against the biologists for spoiling a perfectly good mathematician."

He entered the Albany Medical School in 1881 and, during the course—two years in those days—spent one spring semester in the biological laboratory at Johns Hopkins. He was fortunate in his masters. At Cornell he had been associated with Gage and Wilder, at Hopkins he came under the influence of Newell Martin and Brooks. Laboratory life was still in the tradition of close contact between teacher and student, and the activities of teaching and research were still—as they always should be—so closely allied that intellectual relations struck root deeply. That it is convention and not material circumstances that has threatened to change this is exemplified by the continued influence of men like Edmund B. Wilson, Morton Wheeler and some others, now all too rare. At any rate, the men with whom Theobald Smith worked at this period of his career had a powerful influence in bringing out his latent talents and ripening his inclinations;—and they must have gathered much comfort from him. Realizing, when he graduated as a Doctor of Medicine in 1883, that the two years of study had not prepared him for the practice of medicine and having no taste for an apprenticeship in country practice, Smith returned to Cornell for graduate study. He was engaged in his early studies on histological technique when Dr. Daniel E. Salmon, chief of the Bureau of Animal Industry at Washington, con-

fronted with serious economic problems of disease in domestic animals, appealed to Doctor Gage for a young man adequately trained to help him with his difficult tasks. In 1884, at the age of 25, Smith went to Washington. He knew no bacteriology and little pathology. His training in the biology of the Darwin-Huxley tradition had been as good as this country could furnish at that time. But, for the specific work in which he was, almost immediately, to become eminent, he had had no teaching, no books and no journals. He undertook to teach himself and, as Doctor Flexner has said, the textbooks from which he learned his profession were the papers of Pasteur and of Koch. This was the meager training of one who—as Dr. Preston Keyes has justly said—will be increasingly regarded as “the most notable figure in American medicine of his period.” Meager it was from the modern point of view. One wonders, however, whether we could not draw a lesson from it in regard to the value of reading the great classics of experimental discovery, an exercise not often now practiced in our courses.

Theobald Smith's productive career began while he was still a medical student. Two papers on pathological technique, published in collaboration with his teacher and life-long friend, Professor Simon Henry Gage of Cornell, appeared in 1883 and 1884 respectively. His last important publication, his book on Parasitism and Disease, appeared in 1934, the year of his death. The span of his activity, therefore, covers almost the entire course of modern bacteriology—from shortly after its beginnings to the present day. Koch's work on anthrax was done in 1876 and 1877; and Pasteur's studies on the same subject, in which he had hesitated to embark because of his “utter ignorance of medicine,” fall into the same period. Methods of pure-culture isolation and of staining came between 1881 and 1885. The tubercle bacillus was discovered in 1882. Pasteur's first fundamental studies on immunization, culminating in the historic anthrax experiment at Pouilly-le-Fort, were carried out in 1882. In this the “Golden Age, the Romantic Age of discovery in medicine,” to use Dr. Welch's expression, Theobald Smith began his work. His contemporaries of those years, in the breaking of furrows through the rich soil of a new sci-

ence, were the men whom we of today regard as of another generation. And yet, of him, one of the pioneers—companion in early adventure of Duclaux, Chamberland, Roux, Metchnikoff, Pfeiffer, Loeffler, Ehrlich—we think of as no less our own contemporary, as young as the youngest of us into his 75th year, yielding nothing in elasticity of mind, in receptiveness to change and new conception to men twenty and more years his juniors. Of that great group only Bordet and Nicolle<sup>1</sup> are left, ten or more years younger than he but, with him, examples of that indestructible youthfulness of spirit that seems to be an attribute of the greatest only. A man grows old, at whatever age, when he loses his capacity to change his views with new information. Never throughout his long career did it occur to anyone of his professional colleagues, old or young, that Theobald Smith “was through,” that he had exhausted his originality or his capacity for discovery. Of few men can this be said into three score and ten.

The qualities of mind which made this extraordinarily prolonged productivity possible can, to some extent, be discerned from some of his own writings. In 1933 in a letter to Professor Krumbhaar, Dr. Smith elaborated upon remarks he had made at a dinner in his honor in Philadelphia. He was then 74 years old. Among other things, he said; “To those who have the urge to do research and who are prepared to give up most things in life eagerly pursued by the man in the street, discovery should come as an adventure rather than as the result of a logical process of thought. Sharp prolonged thinking is necessary that we may keep on the chosen road, but it does not necessarily lead to discovery. The investigator must be ready and on the spot when the light comes from whatever direction.” And again—“We must not be discouraged if the products of our labor are not read or even known to exist. The joy of research must be found in the doing since every other harvest is uncertain. . . .” In the same letter he, whose observations form strong bulwarks of a number of fruitful theories, has this to say:—“In general a fact is worth more than theories in the

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<sup>1</sup> Charles Nicolle died shortly after this memoir was written.

long run. The theory stimulates, but the fact remains and becomes fertile. The fertility of a discovery is perhaps the surest measure of its survival value." He combined, with the capacity for infinite pains in detail, a philosophical power of generalization. But he never generalized on any problem until the ascertainable facts bearing upon it had been marshalled in an orderly conception. He had the sane wisdom of carrying a problem as far as he saw prospects of solving it, then leaving it to lie fallow until new light made progress possible. "I have always taken up the problems that lay spread before me," he said. "My interest in a problem usually lagged when certain results could be closely formulated or practically applied. To continue to analyze still further every link of the established chain either failed to hold my interest or was made difficult or impossible from causes lying outside the problem."

It may be remarked, in passing, that in these quotations, as well as in much that Theobald Smith wrote and said there is an evidence of a sense of style and a sensitiveness in the choice of word and phrase which reveal the quality of his mind—perhaps in another sense—but no less than do his scientific achievements.

To give a detailed account of Theobald Smith's work is quite impossible in a short memoir. There is before us an incomplete list of his published investigations—some 240 titles—exclusive of addresses and government reports. We must limit ourselves to brief discussions of those major achievements which have given him his permanent place among the founders of our science.

In 1884, a young man of 25, one year out of the Albany Medical School, he became an assistant in the Bureau of Animal Industry at Washington. Unable, for lack of means, to spend a year or two—as he would have liked to, in Europe, under the eyes of the masters, Pasteur, Koch, and Virchow—he undertook to teach himself; and in the year of his first professional appointment introduced the methods of Koch to American laboratories. This was the beginning of his interest in tuberculosis, the brilliant culmination of which will be discussed below.

His early papers dating from 1885 to 1890—about 28 in number—treated of a variety of subjects, obviously suggested

by the necessity for the development of technique and by the problems of a practical nature referred to the Bureau in which he was serving. He studied and extended Koch's technique for the isolation and cultivation of tubercle bacilli and introduced improvements in the methods of isolating pure cultures. He, even then, recognized the variability of pathogenic organisms and called attention to the dangers of relying too rigidly upon the study of old laboratory cultures. Although at that time and long afterward there was no knowledge of bacterial dissociation as we now understand it, Theobald Smith throughout his investigative career, as we know from occasional remarks and from the advice he gave others, insisted on the study of fresh isolations for accurate information. Just what it was that changed he could not determine, but accumulated experience told him that adaptation to saprophytic habits modified organisms so that they no longer represented the exact biological agent parasitic in the animal body. This was perhaps an outgrowth of his attitude toward the study of infectious disease which to him was always a specific example of parasitism, to be studied along the broadest biological principles.

If one reads carefully his papers on bacterial variability, together with his observations on the adaptation of pathogenic bacteria to different species of animals, one gains the impression that except for the chemical definition of antigenic structure he had formulated and applied the essential principles of what we now call dissociation. The same trend of thought appears in his later views on the intermediate forms of tubercle bacilli ranging between the bovine and the human type.

It is more than likely that this early preoccupation with bacterial variability, which later extended to analogous observations in respect to serologic reactions, initiated the conceptions formulated in 1903, in his paper with Reagh. In this study it was shown that the flagella of motile bacteria may possess antigenic constituents other than and separable from those contained in the bacterial bodies, a discovery which, today, by the work of Felix and others, has become of great importance, both theoretical and practical.

Into this period also falls his interest in the bacteriology of

drinking water, as an outcome of which he devised and introduced the fermentation tube, a small thing in itself and merely an ingenious adaptation to bacteriological purposes of a piece of apparatus long in use for sugar analysis in biochemical laboratories. But the purposes for which Smith employed this simple device exerted an immediate and far-reaching influence on bacteriology since it furnished an easy method for the determination of gas production by bacteria, for preliminary gas analysis, for the study of reducing powers and for the cultivation of anaerobic organisms in fluid media.

Work with his fermentation tubes led him almost directly to the discovery of one of the most useful and, today, indispensable methods for bacterial differentiation. In 1889 he reported the fact that on glucose media the typhoid bacillus produced no gas, whereas the bacilli of the colon group caused copious gas formation. Later, in 1892, he discovered, with the same method, the differential value of lactose and saccharose in the classification of the bacteria of this group, establishing a simple procedure which is still basic to many of our most useful methods for differential isolation, for stool and water analysis and for the recognition of forms in the difficult field of systematic bacteriology. The extension of this method to the investigation of practically all other groups, engaged the attention of many bacteriologists all over the world for half a generation after the publication of this short paper.

Much of Doctor Smith's bacteriological skill was developed, during this period, by his studies of the diseases of swine. Among the many maladies by which these animals are afflicted there are two which were often confused—one, Swine plague (Schweine-seuche), the other, Hog cholera (Schweine-pest). Smith clearly established the separate existence of the two diseases in the United States (1891), confirmed the presence, in the former, of the bacillus suissepticus (one of the so-called pasteurella, a non-motile organism discovered by Kitt) and described, in the second disease, a motile bacillus of the paratyphoid B group now known as the Hog cholera bacillus. Smith was quite naturally led astray in these studies, since nothing whatever was known at that time about the ultra-microscopic agents, one of which is concerned in Hog cholera. He, however, was the

first to observe the frequent association of a particular organism with a given virus infection, a phenomenon not uncommon and not yet understood or accounted for.

His interest in the disease of swine was fortunate from another point of view. It led him into the study of methods of immunization and, with Salmon, he published two papers, one in 1886, the other in 1887, both carried out with the Hog cholera bacillus, which established the possibility of actively immunizing animals with the products of bacteria in liquid culture and with the dead bodies of organisms killed at 56° C. This was an observation of major importance which, extended by Pfeiffer and others, has given us most of our present methods of active immunization in man.

In surveying this early and, in point of volume per year, most productive period of Theobald Smith's activity, the fact which is most impressive is his almost uncanny instinct for a problem. His work was scattered over a considerable number of more or less disconnected subjects. He was feeling his way into his subject, picking up threads here and there as they appeared in the pattern of his daily work. Each one he unravelled in turn up to a point at which it led either to the establishment of a principle, the accomplishment of a useful result, or the devising of a tool which others could reliably employ. Then he dropped it and started in another direction. It may well be that he did a great many things, during these years, which ended in blind roads, but there is little evidence of this in his publications or in anything one can learn about him. Study of this period reveals practically no lost motion. Moreover, the papers themselves are written with a classic simplicity, the unadorned recording of exact observation presented with critical restraint of conclusion, in other words, with a scientific honesty of expression which was more characteristic of that period than of our own; for one finds the same thing in the publications of Pasteur, Koch, Behring and most of the early discoverers. There was, as yet, no haste or competitive spirit and public interest had not yet begun to throw its disturbing spotlight on the scientist.

Of the crowning achievement of this early period we have

yet to speak—the work which demonstrated once and for always his extraordinary qualities as an investigator, and which alone, if he had never done anything else, would have given him a prominent place in the history of our science. These were his studies on Texas Cattle Fever (Tick Fever, Southern Cattle Fever, etc.). There has been some confusion in regard to the exact part which Smith had in them and it may be well, therefore, to discuss them at some length.

In doing so, we take much of our information from the article on Smith as a Parasitologist, recently (1935) published by M. C. Hall. When Smith, in association with Kilborne, first approached the problem experimentally (1889), there was already some information about this disease and interest in it was stimulated by its great economic importance.

There had been, for a long time, an impression among cattle ranchers, vague but persistent, that ticks were in some manner related to the infection. In 1885, the geographical distribution of the disease had been approximately established by Salmon and its northern limits defined. In 1889, Curtice, the entomologist of the Bureau of Animal Industry (4th and 5th Annual Reports, Bureau Animal Industry, p. 436) spoke of an experiment carried out in the Chicago Stockyards, in which five cows were placed into a pen in which Texas cows had been held, with the result that four of them died of the cattle fever. This experiment had been suggested by the "oft repeated experiment of allowing native cattle to live on the trail of Texas cattle." A similar experiment was reported in the same year by Kilborne but, in this attempt, northern cattle were mixed, in one pen, with southern cattle rendered free of ticks—while in another pen the ticks were left on the infected animals. The result was no infection in the former, death of the animals in the latter. Again, in the same year, Smith, undoubtedly working in close association with his colleagues, described (Medical News, Philadelphia) the little bodies in the red cells of infected cattle which he later (1891) recognized as protozoa and eventually named *Piroplasma Bigeminum*. In announcing this discovery, Smith with the fairness and generosity of character to which "priority" squabbles were abhorrent suggests that these

bodies were probably identical with those seen by Stiles in 1869, but probably unlike those of Babes (1888) because the latter claimed to have succeeded in cultivating the organism he had observed. In the longer report of 1891 Smith, with Kilborne, reported on a more extensive and thorough series of transmission experiments in which four animals were infected by the direct application of ticks. Further, they had placed southern cattle in pens with northern stock—in some cases after the removal of ticks, while in other enclosures the ticks were left on the infected animals. Also, native cattle were kept in fields in which infected ticks had been scattered on the ground. The report which is one of the classics of medical literature, established beyond question the role of the tick as the carrier of the disease. And not the least of the achievements of these experiments was the observation that the infection could pass, in ticks from mother to offspring, a new and extraordinary phenomenon of parasitism which has found its analogy in tick infection with the *Rickettsia* of Spotted Fever. It is certainly not a disparagement of Smith's greatness to correct the erroneous impression created in some popular accounts which belittle the merits of his associates, by stating that these fundamental discoveries were in fact collaborations between a group of well-trained and intelligent men, rather than entirely the work of Smith alone. In doing so it is quite certain that we are stating the case in the manner in which he would have wanted it told. Moreover, from what we know of him and his experimental acumen, it seems more than likely that his was the leading spirit in this collaboration by which, for the first time, the complete cycle of transmission of disease by insects was established. It is true, of course, that as early as 1877, Manson had discovered that embryo filaria, taken up from the blood of infected men by mosquitoes, developed in the insects into the final larval stages. But Manson's studies did not show how the filaria again reached man. Though the reinfection of man by the bite of the infected mosquito was indeed suggested in 1883 by an anonymous reviewer of Manson's work (see Manson-Barr, *Life of Sir Patrick Manson*, p. 58), the actual fact was not established until 1899 by Thomas Bancroft, some time after Ross' demonstration of the

mosquito origin of human malarial infection. The investigations of Smith and his collaborators were, therefore, the first to establish the complete cycle of transmission by arthropod vectors—a discovery which represents one of those fundamental steps forward that alter the entire course of a science, and which has practical consequences of inestimable and permanent importance. We have presented this particular work with a certain degree of emphasis upon the parts played by others than Smith and upon the significance of earlier discoveries which undoubtedly helped to shape Smith's thoughts and experiments. This we have done, not only in the interests of accuracy, but with the feeling that it would be an irreverent disservice to write about this great man's accomplishments in a manner which would have deeply displeased him and which would represent a disregard of other worthy achievements entirely foreign to his own nature.

The problem of Texas Cattle Fever had hardly been solved when Smith's attention was absorbed by another economically important disease of animals, the "black head" of turkeys. This condition was killing a large number of the birds, especially in Rhode Island, and Smith began his work at the Experiment Station in Kingston, Rhode Island. After determining, by a large number of autopsies, that he was dealing with an infectious disease, Smith convinced himself that the cause of the condition was an amoeboid protozoan which accumulated in lesions localized largely in the mucosa and the submucosa of the large intestine. In his first paper on black-head (1895) he described the disease and the parasite to which he gave the name, "*amoeba meleagridis*" (later reclassified *Histomonas meleagridis* by Tyzzer). Maurice Hall says of this paper that "This work alone would have ensured Smith a permanent and high place" in connection with the disease. It, however, left the study of transmission incomplete. And with characteristic persistence Smith went back to the problem many years later. In 1917 (with Graybill) he found that the simple feeding of feces from infected birds would not produce the disease in susceptible turkeys; it was necessary to feed, at the same time, embryo forms of a nematode (*Heterakis gallinae*). Graybill and Smith, at this time, considered the *Heterakis papillosa* as a

preliminary agent which served to lower the resistance of the turkeys to invasion by the protozoan. Their observation of the constant association of the worm with the disease, however, had consequences of far greater biological significance in that it enabled Tyzzer and Fabyan, in 1922, to demonstrate the actual carrying of the protozoan in the infected embryos of the nematode—an observation unique in biology representing an entirely new cycle of parasitism.

In 1895, Smith accepted the invitation of Doctor Walcott of the Department of Public Health of Massachusetts and of President Eliot of Harvard to come to Boston. He took over the directorship of the State Antitoxin Laboratory, and, in 1896 became, at the same time, professor of Comparative Pathology at Harvard. During the Boston period (1895 to 1915) Smith again permitted himself to roam widely, for he published, among other things, on the control of water supplies, on sewage disposal, on typhoid transmission by milk, on the cultivation of anaerobes, on the reducing action and indol formation by bacteria, on the adaptation of bacteria to different species of animals, on the distribution of mosquitoes in New England, and on a host of other subjects which would have exhausted the energy and made the reputation of a lesser man, but which, to him, were the minor by-products of a vitality and enthusiasm that seemed to have no saturation point. His major activities of this period were his studies on diphtheria and those on tuberculosis.

His duties at the Massachusetts State Laboratory included, among other things, supervision of the production of smallpox vaccine and of diphtheria and tetanus antitoxins. Again, in the logical development of his interest in a new subject, his first attention was to matters of technical accuracy and standardization. It is characteristic of all his work that no problem was ever directly approached until methods had been carefully adjusted and accurate technical procedures devised. The percentage of inevitable experimental error, was thus always interpolated in any deductions he permitted himself to make. Thus, his first papers on diphtheria treated of conditions of cultivation and of the constituents which favored the production of

strong toxins. Later he made similar studies on tetanus. Next he occupied himself with problems of toxin-antitoxin standardization, and only then turned to questions of actual immunization. Here as throughout all of his work, one discerns that tranquility of progress that masters desire for haste and the meticulous assembling of detached observations which gradually accumulate, as in a condenser, into the tension of an ultimate major discovery. For the student of bacteriology there is a wealth of valuable information in the papers that lead up to his important contributions. For the investigator there is a lesson in the manner in which he approached each new undertaking with a scrupulous survey of the ground, taking nothing for granted and testing all the struts of earlier claims before he entrusted them with the weight of a new experiment. In a brief review of his achievements, it is possible to deal only with the final phases.

Two things came out of his diphtheria studies which have made medical history. One of these is the recognition, in distinct contradiction of Ehrlich's "Zell-reiz" theory, that the best way to speed up the early production of antitoxin in horses is to treat them, at first, with neutral mixtures of toxin and antitoxin. In his summary of this subject (in 1909) he introduced a new principle into the science of immunology which has had far-reaching consequences. In a paper (with Brown) published in 1910, he showed that immunity can be produced in animals by the injection of completely neutralized mixtures of toxin and antitoxin and that when, in such mixtures, there is a slight excess of toxin, enough to produce a local lesion, the subsequent immunization is enhanced far above that obtained by the injection of toxin alone. A by-product of this work was the observation of passive immunity in offspring born to actively immunized female guinea pigs. One of the last sentences in the paper of 1910 (in which he permitted himself to speculate on the probable mechanism of the observed results), is so characteristic of his manner of thinking that it seems worth quoting. "Hypotheses bring largely scaffolding for furnishing footholds in the building up of facts. We place no special value on the one here presented excepting insofar as it helps stimu-

late further investigation etc.” In this case Smith’s observations became not only the basis for more effective antitoxin production in horses but undoubtedly suggested to Behring the active immunization of man with toxin-antitoxin mixtures, a method later perfected by Park to the enormous benefit of American children and only now being superseded by the “anatoxin” methods of Ramon, Glenny and others. It is also quite certain that these observations called attention to the possible reversibility of antigen-antibody reactions, a conception which has so profoundly modified physico-chemical views of these phenomena.

In the course of his diphtheria studies Theobald Smith had noticed that guinea pigs which had been used for toxin-antitoxin standardization and had survived such mixtures without apparent injury, would show signs of respiratory distress and, on occasion, would die when subsequently injected with horse serum. One wonders just why such experiments were done. Undoubtedly they were controls in the course of his other work. We will never know what was in his mind when he reinjected these test animals with horse serum, for, he, himself, though the occurrence is now known as the “Theobald Smith phenomenon” never wrote a word about it. Nevertheless, he noted it and considered it—as he did every unexplained occurrence which appeared with regularity—as sufficiently important to follow up. He told Ehrlich about it in 1904. Ehrlich named it the “Theobald Smith effect” and set Otto to work on its analysis. Richets’ observation of 1902 on actinocongestin had been but vaguely understood. The “Arthus” phenomenon, in rabbits, though of an importance equal to that of the guinea pig observation, was not systematically studied by investigators until much later. In the hands of Otto and of Rosenau and Anderson the “Theobald Smith phenomenon” became the cornerstone of our modern knowledge of hypersensitiveness, the foundation of that extraordinary chapter of investigation which has had so profound an effect upon all our conceptions of immunity and which opened new paths in clinical medicine. It is the only instance we can recall of any man’s permanent and justly appraised distinction in connection with a phase of scientific development about which he himself never published a word.

Smith's publications on tuberculosis began with the papers of 1884 in which he introduced Koch's methods to American laboratories—(methods which he had learned and successfully applied entirely on his own initiative). In 1886 he developed a modification for the isolation of tubercle bacilli but, diverted by other problems, he did not resume the serious study of tuberculosis until 1893. At this time Koch himself seems to have had no doubt about the complete identity of the tubercle bacilli which infected man and those which caused the disease in cattle. This view was generally accepted and freely stated by the German school, in spite of the fact that Villemin (we take our citation from the scholarly article on Smith by William Bulloch) in his "Études sur la Tuberculose" (1868) had said: "Nous ferons remarquer qu'aucun de nos lapins (!) inoculés avec du tubercule humain, ne nous a présenté une tuberculisation aussi rapidement et complètement généralisée que celle que nous avons obtenue avec l'inoculation du tubercule de vache." In the years 1894-1895 Smith isolated and studied a bovine culture and one from a racoon-like animal (*Nasua narica*) probably infected from a tuberculous man. He was struck by the great difference in virulence for cattle between these strains and noted differences in morphology and cultural behavior. In 1896, these studies were more systematically resumed in the new laboratories at the Harvard Medical School and, by 1897, he had isolated a sufficient number of pure cultures of both the human and the bovine type to take advantage of the cooperation of the Massachusetts Cattle Commission for experiments on animals on a satisfactory scale. His first publication on differences between the two types appeared in 1896. By 1898 he had definitely formulated his conception of these differences in a manner so soundly founded upon precise observation that no further doubt was possible. He differentiated his strains not only by the variations in virulence of those of bovine origin for cattle, rabbits, and guinea pigs, but described differences of morphology and of growth on glycerine media. In 1905, he added the so-called "Smith acid curve" on glycerine broth. These observations, rapidly confirmed by Vagedes, Dinwiddie, Ravenel and eventually by Koch himself, apart from

their important biological value, introduced new conceptions in regard to the transmission of tuberculosis by milk, and influenced practical methods of control. It is of incidental interest that Smith, himself, even at this time, realized that the differentiation he had discovered was not an absolute one in all cases. He says, for instance (1902), "We may now maintain without fear of contradiction that the bovine bacillus presents certain traits which serve to distinguish it *from the great majority* of bacilli isolated from the human subject. These traits or characters are not the exclusive property of the bovine bacillus as contrasted with those from human sources. I am merely emphasizing the constancy of such characters and not their peculiarity." He called attention to the variability of individual strains of human origin and steadfastly refused to follow speculatively beyond the boundaries set by precise experimental information, rejecting, in turn, the extreme view of Koch, that bovine bacilli do not pass to the human subject and the subsequently formulated opposite extreme of Behring, that most human infections are acquired in childhood from infected milk. He regarded all such speculation as premature, advocated continued efforts to isolate and classify tubercle bacilli from larger numbers of human cases of all clinical types, saying in this connection, at a time when his greatest contemporaries were taking sides: "Whatever deductions and inferences we make from time to time, must ultimately derive their authority from actually observed fact. The larger the number of cultures isolated and studied according to a uniform scheme, the more reliable our inferences and conclusions." On a material necessarily limited, since this type of work takes time, he concluded that bovine infection of man occurs but does not represent the most frequent manner of human infection—a point of view which all subsequent work has confirmed. There have been no important modifications in the conception of this summary since he wrote it in 1902.

Considering the obvious possibility that the differences between the two major types might be consequences of an adaptation of parasite to special host, a matter which always interested him beyond all other subjects, he carried out experiments, lasting

more than two years, on serial animal passages of both human and bovine strains, obtaining inconclusive results and saying so. It was his habit, when he reached a blind end through which he could see no rational experimental escape, to drop the subject and for a time to turn to something else. The problems which he left unsolved in regard to bovine and human tuberculosis stand, at the present day, just about where he left them.

In 1901, the newly founded Rockefeller Institute for Medical Research was ready to appoint a director. Theobald Smith was the natural candidate and Doctor Welch urged him to accept the responsibility. Smith, though tempted, knew that this was not the work for him at this time. He "anticipated much good from this new institution" but he was suspicious of organized research and said (a remark from a letter quoted by Professor Simon H. Gage) ". . . you and I know that research cannot be forced very much. There is always the danger of too much foliage and too little fruit." Individualist by inheritance, inclined by character and training to scientific still-hunting on his own, seeking cooperation only when it was indispensable for a specific objective, he knew that he was not the man at that time to undertake the organization of such an institution. Although the subsequent history of the Institute has shown that his apprehensions were unjustified and fruit has appeared plentifully among the foliage, he was probably wise and a better judge of himself than others in refusing when he did. He took administrative responsibilities too seriously, worried and was made unhappy by them. He was, surely, however, a tower of strength to the director subsequently appointed, and was far more useful as a member of the board of scientific directors and, after the death of Doctor Welch, as president of this board. Later, in 1914, he did accept the directorship of the branch of the Rockefeller Institute established at Princeton, for the investigation of the diseases of animals. Harvard did not like to let him go and the writer has often wondered why Doctor Smith who had refused in 1901, was willing to undertake such a responsibility in 1914. A remark made by Doctor Flexner at the farewell dinner in Boston and quoted by Doctor Gage throws some light on this question. Doctor Flexner, speaking of the discussions which

had led up to the formation of the new laboratory, said: "It was Doctor Smith's vision of such an independent department, itself conceived on broad lines, that made it attractive first to his colleagues in the directorate and then to the founder who was to give it his financial support. This support, you may be interested to know, came promptly as soon as it was known that Doctor Smith would undertake the direction of the new work himself." In the jargon of our day, Doctor Smith was "on the spot." He had, by this time learned, moreover, that an Institute need not necessarily be an organization for regimented volley firing, but that, as in universities, well-selected workers could be left to themselves. Opportunities for work could be rendered as convenient as possible and cooperation made available when required without being organized like a battalion in the field. He had begun to realize, as many of the rest of us did, that institutes of research could be like university laboratories without the teaching obligations, and to foresee what is now happening, that university laboratories to be effective must approach somewhat the organization of the research institute. At any rate, he undertook the new work without the slightest intention or fear of relaxing his own experimental efforts. Whether he was a good "director" or not no one will ever know from the expressed opinions of others. If he had his faults they were so smothered by the distinction of his mind and the affection aroused by the simple sincerity of his character that they carry no weight. We pose the question only because he seemed to us the extreme antithesis of what is known as an "administrator." Yet, even though his administration may have lacked some of the characteristics most approved of by those who believe in such things, the fact remains that when he relinquished his directorship in his 70th year (1929) his institute was doing distinguished work and he had gathered about him a group of younger associates, some of whom are doing brilliant work and many of whom caught fire on the sparks from his anvil. Whether another with his characteristics could have done the same thing is doubtful. To work with or near Theobald Smith was an inducement that was worth more than large salaries; and there is no one among the younger bacteriologists in this

country who, if he possesses common sense enough to be a good bacteriologist, does not wish he had been, at one time or another, a pupil of this great and lovable man.

The manner in which Theobald Smith approached his new work is above all revealed by the fact that his own contributions continued in uninterrupted series. We have on our list between 1915—the year in which, at the age of 56, he assumed the new directorship—and 1934, the year of his death, sixty-five papers, eight addresses, and a book of almost 200 pages on Parasitism. Some of these papers are continuations of his tuberculosis and diphtheria studies and, in others, he continued his work on “black head” in turkeys, of which we have spoken in another place. A few deal with parasitism in its broader biological significance, leading up to a final summary in his book. One paper (with Brown) brought a considerable degree of orderliness to the confused streptococcus problem. The major part of his work during his latter years, however, concerned itself with infections of animals in which he had the opportunity to follow his favorite line of thought, that of the factors which determined adaptation changes in closely related bacterial species. In this field he occupied himself with spontaneous paratyphoid infections in rodents and with the *Brucella*. As early as 1912 he had become interested in infectious abortion of cattle, had—“accidentally” as he called it—observed and described the lesions produced in guinea pigs by the bacillus of Bang and “was reminded” of similar observations made in a guinea pig infected with centrifugalized milk seventeen years previously, thus calling attention to milk as a vector of the infection. It is important as a side-light on his methods of work to quote a footnote from his 1912 article. “Since that time (the time of his first observation of the milk infection, 1894) I constantly looked for repetition of these lesions but never found them. Now, after seventeen years, I may consider them explained. At that time I suspected accidental contamination of the milk.” That sort of thing goes far toward letting us understand the secret of his extraordinary productiveness. In further studies of the organisms of this group he described the first appearance of the porcine variety of the disease in the eastern United States,

devised the partial CO<sub>2</sub> atmosphere method of cultivating the organisms, observed the location of the bacilli in the bovine foetal membranes, defined the relationship of the bovine and porcine types to those isolated from man and suggested the direct contamination of man from swine. Incidentally he described another possible cause of bovine abortion—a spirillum which he named *Vibrio Fetus*.

Overlapping his abortus studies were his investigations of another bovine disease, "scours" a diarrhoeal condition which accounted for a high "infant mortality" among calves. On this subject alone he published some ten papers. As usual, he familiarized himself with the clinical characteristics and the pathology of the disease. He then discovered the association of the malady with failure of maternal feeding during the first week of life. This suggested colostrum and led to a field experiment in which ten calves receiving colostrum survived and eight out of twelve, deprived of colostrum, died. One was killed when nearly dead. In cultures from these animals he obtained bacillus coli. He found that early death was due to a flooding of the bloodstream and organs with the colon bacillus and that, in the few that survived, lameness and arthritis were due to persistence of the infection in the joints. Suspecting that the action of the colostrum might be attributable to its immunological properties he successfully substituted cow serum for colostrum. Following this, he determined that the blood of new-born calves contained no antibodies though their dams might have blood titers as high as 1 to 2,000. Antibodies in cattle, therefore, do not pass from mother to offspring through the placenta. On the other hand, when fed by mouth in the form of cow's serum antibody feedings rapidly appeared in the circulation of the calves. Colostrum thus could be regarded as a "most efficient transporting agent of antibodies" from mother cow to calf. The problem of "scours" prevention had been transformed from the almost hopeless efforts of isolation and the protection of food to a relatively simple immunological one for which there were several solutions—the easiest one that of leaving the calf with the cow during the early weeks after birth.

The account of Doctor Smith's work which we have given represents little more than an outline of those major accomplishments on which his permanent place among great discoverers in biology will rest. It has been necessary to neglect a great number of papers and notes which represent marginal observations and transitional studies carried on at times when intervals between the larger undertakings gave him leisure to follow incidental ideas. Among these, for him, minor preoccupations, there is enough material and thought to have made the reputation and to have satisfied the ambitions of most men of lesser intellectual vitality. Many of these investigations deal with matters of technique. Others were observations on diseases of animals—usually interesting him as illustrations of the extraordinary flexibility of parasitic adaptation. These papers deal with rabbit septicaemia and coccidiosis, with the spirillosis of hogs, with bacterial infections of poultry, the coccidiosis of sparrows, the sporadic pneumonia of cattle; with actinomycosis and the mycosis of the bovine foetal membranes; with intestinal sporozoa, with the encephalocytozoa of rabbits and with milk-borne streptococcus diseases. A study of a non-toxic diphtheria bacilli (1914) anticipated our present information on the dissociation phenomena of these organisms.

In the field of the general biology of microorganisms he published on the relationship between parasitic and saprophytic bacteria; on the origin and source of pathogenic forms; on temporary and permanent modifications of physiological characters in mixed cultures; on the adaptation of parasites to different species of animals; on parasitism as a factor in disease, and on the passing of infections from one generation to another.

Correlating his bacteriologic studies with problems of public health he developed a reliable technique for bacteriological water analysis, described the "presumptive test" for colon bacilli, and contributed papers on channels of food infection, sewage disposal on farms, sources and prophylaxis of malaria in temperate climates, anopheles distribution in New England, the horsefly as a disseminator of disease, and the prevention of tuberculosis. Taking an active part in the educational and administrative problems of his period he outlined the reorganization of the Harvard

Veterinary School and formulated plans for the organization of public health laboratories. He defined the place of research in university medical schools and his paper on scholarship in medicine was, at the time of its publication, a wholesome differentiation between trade and profession. He pleaded, one of the first to do so, for a closer relationship between medicine and public health and pointed out the economic aspects of the study of comparative pathology.

We begin by marveling at the long duration of his active career. We end by wondering how, in a short (to him, surely, a very short) fifty-one years, he could have accomplished the enormous volume of work that stands to his credit. We study his amazing productiveness and are still more astonished by the fact that, great as it is, it contains almost no errors. In all but a very few of his papers, the facts observed remain today as they stood when he recorded them and the deductions based on them are sound in that he never permitted himself to stray speculatively beyond his lines of communication with facts. Moreover, when he did allow himself to speculate—as in his studies on bacterial variation, flagellar agglutination, bovine and human tuberculosis and in his many papers on parasitism, he anticipated, in principle, a number of things that later discoveries established in fact; proof that he possessed, to a high degree, that quality of scientific imagination which Whitehead has defined as “speculative reason” and which is probably the determining attribute which differentiates men who are truly great from those who are merely able.

It is usually futile but always interesting to explore the intellectual pattern which made possible great accomplishments. We have already spoken of the quality of simple integrity which was as much a part of Theobald Smith as his physical build. This, coupled as it was in Pasteur, Claude Bernard and others of his kind, with extraordinary intelligence, infinite patience and technical accuracy, goes far to account for his success. There were other contributing factors, however, which were peculiar to him. His investigations were never academic in the sense that they took off from theoretical preconceptions. As he said himself, he took his problems as they were spread out before him by

questions that were crying to be solved. There is perhaps a lesson in the fact that until the last stage of his career he was never a pure research worker but held positions in which the currents of his activities were to some extent directed by specific duties which had to be performed and from which his problems took origin. In his approach there was deliberate preliminary study of conditions and of technical methods. His choice of methods was always the simplest, determined by the shortest path to his objective. It is, incidentally, strange that, although an accomplished mathematician (Professor Wheeler has told us that he did problems of calculus for amusement in the same way that he played the piano) there is no instance in all his work in which he employed mathematical methods. This is probably due to the fact that he adapted his procedures with the greatest economy to the purposes he was pursuing and he recognized that the particular materials he worked with were not ready for mathematical treatment. He possessed an extraordinary sense for the essential and was not easily diverted by side-issues. He wasted no time in trying to break through when he came to the end of methods for further precise observation but dropped problems in which he could see no immediate logical paths of approach, postponing them until new methods or ideas turned up. But he kept them in mind with an extraordinary memory for detail and rarely failed to resume work once begun when obstacles had been cleared away by new discovery or when chance revealed new methods of attack.

In occasional discussions with him, we learned to our profit—as undoubtedly many others did—that, in approaching a new problem of infection, however detailed the immediate objective of his experiments, he never failed to bear in mind the disease itself as a complete entity. There has been a tendency, with the increased availability of precise methods of the fundamental sciences, for bacteriological investigation to segregate isolated fractions of a problem for analysis with frequent neglect of the correlation of results with the problem as a whole. This is inevitable under circumstances, progressively more common, where the biologist cannot be trained in the more difficult methods of chemistry and physics and the chemist or physicist does

not possess the medical or epidemiological knowledge necessary for the assembly of the isolated facts into a coordinated conception. Theobald Smith exemplified what, to us, appears an important principle, that the biologist who approaches a problem of infectious disease cannot afford to confine his attention to the bacteriological and immunological details which are the immediate objectives of his observations but must familiarize himself with the clinical, pathological and epidemiological conditions as well—a task which is entirely feasible for the well-trained bacteriologist though he may be entirely incompetent to control those methods of chemistry and physics the results of which he must interpolate by intelligent cooperation with the chemist. This is more or less what Theobald Smith did in his work; and a few paragraphs from the introduction to his treatise on parasitology appear to us to define the relation of the experimental method in biological study to other approaches more clearly than this has been done since the publication of Claude Bernard's book.

“The great development of experimental science in the study of the phenomena of life has thrown somewhat into the shadow the older comparative method. The latter looks at things in nature, describes and compares them, and deduces from such comparisons certain underlying concepts. The experimental method takes the same phenomenon and tries to check or limit all but one of the activities entering into it so that this one activity can be observed, recorded, measured, and weighed. *Obviously the phenomenon has not been entirely elucidated by this process. Even after we review all conceivable manifestations of the natural phenomenon in this way, there still remains the problem of formulating the properties of the whole on the basis of the interacting activities of its parts.* And so it happens that if we apprehend or appropriate an idea that is based on definite experimental proof we are apt to let it overshadow other perhaps more inclusive ideas which have not yet been demonstrated or which from the nature of the case cannot be subjected to rigid demonstration. Both methods have their special advantages and disadvantages. The whole must be supplemented by some means for looking beneath the surface and

observing the mechanism that controls its activities. *The experimental method must not let too many machines get between it and the whole and must find some way of putting the fragment surgically removed for experimental purposes back into the whole.* The comparative method is frequently in position to restrain the generalizations deduced from experimental procedures and to keep the experimenter from steering away from the goal, which is an understanding of the totality.

“The subject to be presented deals with living things and the observational, comparative method shares equally with the experimental, analytic method the burden of trying to pry into the behavior of two organisms in conflict. Living things, we are learning day by day, have unlimited capacity for variation and adaptation. They are primarily individualistic and in our experiments can be kept unchanged only by strictest adherence to uniform conditions, not only of environment, but of descent. Watching the evolution of our individual fields of work we can plainly see past errors in the acceptance of uniformity where there has been none to speak of.

“In the study of disease due to microbic and higher parasites we can see quite distinctly two lines of development, the theoretical trying to dig beneath the observations towards more fundamental concepts embodied in physics and chemistry, and the medical or practical striving towards the surface to bring research into use.”

Theobald Smith's preeminent contribution to the progress of bacteriology in general is obvious from the summary of his work. The influence which he exerted on the development of our science in our own country was greater than that of any other individual. Never, except for a short period, a teacher in the organization of formal courses, he, nevertheless, by his writings, through the men he trained in his laboratories and by the unvarying kindness with which he gave advice and encouragement became, in a sense, the most important teacher we possessed. He showed interest in any problem intelligently presented to him and his advice was never given in a patronizing manner, always as from one scholar to another, however young and inexperienced the applicant provided he was clear-headed and

honest and the problem one that deserved attention. He had, moreover, the quality of looking at experimental results with utterly unprejudiced eyes, examining them in complete detachment from preconceptions. He never tried to fit a set of phenomena into a theoretical pattern until he had finished with it as a thing in itself, a habit by which, in appraising the work of younger men, he often corrected premature interpretations and helped to avoid error. Even when dealing with subjects in which fundamental conceptions had been fairly well established his point of view possessed a quality of originality which stimulated thought. In 1911, when the present writer was working for a few months in a Berlin laboratory, Smith was exchange professor at that university. His lectures on immunity, delivered in excellent German, were probably unlike any other lectures ever given on this subject. They were secondarily immunity, primarily Theobald Smith—scaffoldings of accepted views became the themes for the discussion of observations drawn from his immense experimental experience. They were lectures quite disappointing to those who wanted a review of conventional trends, intensely interesting to those who had begun to develop critical insight and investigative curiosity.

Of Theobald Smith the man, of his friendships and his more intimate personal relations, Professor Simon H. Gage has warmly written. And even if a memoir of this kind were the proper place for the recording of such things, there are few who could do justice to these aspects of his life since, though kindly and possessed of a natural friendliness, there was about him an unobtrusive pride, a reserve tinged with austerity which did not invite easy intimacy.

But even without such intimacy, as one studies his life and tries to formulate a conception of the man in his wide influence, one develops an affection for him something like that which one feels after reading the lives of Pasteur or of Huxley. To the younger bacteriologists whose lives overlapped his own, Theobald Smith was a hero to be emulated and whose approval was a mark of distinction. He illustrated to them the dignity of austere devotion to scholarship and the modesty of wisdom. But always they stood a little in awe of him. He, with Welch,

were the two greatest individual influences that helped to hold the younger men working in the medical laboratories steadfast in the faith of the worthiness of honest effort. But Welch was loved instinctively for the warmth of his heart and for the urbane benevolence with which he encouraged younger men and commended them often beyond their deserts. Of Theobald Smith they thought as the dispassionate critical mind by which they were impersonally, though justly, appraised.

In following his career and studying his work a warmer current flows into one's thoughts of him. One feels that he was lonely in the restraints by which reason disciplined him. One wishes one had been more intimately his pupil. And in realizing the great debt our science owes to him, one begins with admiration and ends with affection.

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#### ADDENDA

1886-1891

Material provided for the following reports of the Chief of the Bureau of Animal Industry of the U. S. Department of Agriculture:

- 2nd Annual Report for the year 1885, 1886, pp. 184-246.
- 3rd Annual Report for the year 1886, 1887, pp. 20-100.
- 4th/5th Annual Report for the year 1887/8, 1889, pp. 49-166.
- 6th/7th Annual Report for the year 1889/90, 1891, pp. 28-62.

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