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THEOBALD SMITH

By EARL BALDWIN McKINLEY, M.D.

DEAN AND PROFESSOR OF BACTERIOLOGY, SCHOOL OF MEDICINE, THE GEORGE WASHINGTON UNIVERSITY

SCHOLAR, sanitarian, pathologist, parasitologist, bacteriologist, immunologist, teacher, administrator, philosopher—regarded by many as America's greatest medical scientist—who could lay claim to more? In one lifetime he accomplished in several fields what most of us would be happy to accomplish in part in one branch of science. Theobald Smith was a colossal figure—no other phrase can adequately describe him. The reading of his more than two hundred and fifty titles in English and German, which we have done in recent months, readily demonstrates his greatness. However, to many he has always been great but at the same time a simple, modest, loyal and lovable friend. It was a privilege to know him intimately. Each hour spent with him was an enriching experience, and his death has left a void which can not be filled. As one of his friends, I have been requested to prepare this appreciation of Theobald Smith and do so with trepidation, realizing fully my inadequacy to do justice to such a large subject. I shall try to keep my deep affection for the man in the background and to present a picture of Smith, the scientist, as the world knew him and as history will record him for all time to come.

Theobald Smith was born at Albany, New York, on July 31, 1859. He died in New York City on December 10, 1934. Two weeks before his death he wrote as follows: "I came down here (Hospital of the Rockefeller Institute) for three days to be drawn and quartered for the discovery of why I am down and out. Have done nothing for three or four weeks. . . . My case is a combination of minor things including a cold or influenza, but I shall wait for light from the people here." Later, a few days before his death, he wrote, "It was with great regret and much disappointment that I made up my mind not to attend the coming

meeting of those interested in tropical medicine. . . . I am sure the meeting will be a great success and that I am the loser." These two of his last letters illustrate the simplicity, the humor and the loyalty of the man in speaking of himself and of the groups with whom he was associated. Since his death no less than ten appreciations of Theobald Smith have appeared. The first by Stockard[1] appeared shortly after his death. Stockard said, among other things, "He was in the highest sense a naturalist. . . . Theobald Smith was one of Nature's high priests. He believed with Pasteur that science, in obeying the law of humanity, will always labor to enlarge the frontiers of life; and with Goethe, that the first and last thing required of genius is the love of truth. He built temples to Nature and communed in them by whispering questions to her. And Nature answered back to this favored son—and he understood." A second appreciation appeared in March, 1935, by Conklin[2] and his committee of Sigma Xi, which closes with the following significant sentence: "The Princeton Chapter of Sigma Xi places on record its sorrow in the loss by death of its most distinguished member and its confidence that his influence and work are immortal." During the same month Wolbach[3] wrote, "The results of his labors can not be appraised now because practical application of science lags. Every problem he attacked was so carefully worked out and reported that probably much information of significance not indicated by the titles of his papers still awaits consideration. . . . Devoted to his work, his personal life was one of asceticism and intellectual detachment and integrity worthy of the best ideals of the Stoic philosophers." The following month, April, 1935, there was a minute on Theobald Smith read at the meeting of the Board of Scientific Directors of the Rockefeller Institute for Medical Research. Written by Flexner[4] it closed with the statement, "It can be said of Doctor Smith, as of few men, that the good he did will live after him as long as knowledge grows and science endures." Perhaps one of the finest tributes paid to the memory of Theobald Smith was written by Bulloch[5] and published in May, 1935. That Smith belonged to the world and not merely to America is illustrated in this appreciation of him from abroad. Of particular significance is the statement, "It is certain that America in days to come will look on him with that veneration with which France cherishes the name of Pasteur and Germany that of Robert Koch."

During the past summer there appeared an article on Smith by Gage,[6] with whom he published his first scientific contribution in 1883. This paper, as an appreciation by an intimate friend, is particularly illuminating concerning Smith, the man. In July, 1935, there appeared an address by Craig,[7] who succeeded Smith as the president of the American Academy of Tropical Medicine, the founding of which was one of Smith's last absorbing interests. The American Academy of Tropical Medicine had made Theobald Smith its first president, but he did not live to give the first presidential address. Craig's scholarly tribute to Smith in connection with his work on the insect transmission of disease will long be remembered by Smith's colleagues, who loved and revered him. During the same month a short tribute appeared in the *Journal of Bacteriology* by Brown.[8] In August, 1935, Hall[9] published an appreciation of Smith as a parasitologist, and the final tribute which has come to our attention appeared in October, 1935, in the *Journal of Heredity* by the same author, Hall.[10] It is possible that other reviews of the life and work of Theobald Smith may have escaped our notice, but these which have been recorded give lasting evidence of the high place this great man occupied in the realm of science and in the hearts of his friends and colleagues.

It is doubtful if few who have not reviewed the work of Theobald Smith in some detail appreciate the extent and magnitude of his researches. Even to those who felt they knew the man and his work intimately, such a study has been most informative. As a result of this study an outline has been prepared which is presented below for the interest of students, colleagues, friends and admirers of this scholar and scientist. In so far as we have been able to determine from the literature, this outline presents a brief picture of the scope of his work, although a complete appraisal of his contributions and their significance is difficult at this time. Without doubt many years will elapse before the full significance of his discoveries is entirely appreciated or even recognized.

Outline of the Work of Theobald Smith[11]
(1883 to 1934)

I. Tuberculosis (1884–1933):
   1. Bacteriology (sputum, milk, morphology, cultures, reactions, variation, pathogenicity,

[1] Charles Stockard, SCIENCE, 80: 579–580, December 21, 1934.
[2] E. G. Conklin, and Committee, *Sigma Xi Quarterly*, 23: 50–52, March, 1935.
[3] S. Burt Wolbach, *Harvard Medical Alumni Bull.*, 9: 35–38, March, 1935.
[4] Simon Flexner, Minute read at the meeting of the Board of Scientific Directors of The Rockefeller Institute for Medical Research on April 20, 1935.
[5] William Bulloch, *Jour. Path. and Bact.*, 40: 621–635, May, 1935.
[6] Simon Henry Gage, *The American Scholar*, summer, 1935.
[7] Charles F. Craig, *Am. Jour. Trop. Med.*, 15: 407–414, July, 1935.
[8] J. Howard Brown, *Jour. Bact.*, 30: 1–3, July, 1935.
[9] Maurice C. Hall, *Jour. Parasit.*, 21: 231–243, August, 1935.
[10] Maurice C. Hall, *Jour. Heredity*, 26: 419–422, October, 1935.

thermal death point, human and bovine types, biology)
2. Prevention
3. Clinical studies in cattle
4. Pathology
5. Relation between human and bovine tuberculosis
6. Channels of infection and therapy
7. Immunity (natural and acquired, anatomical and histological expression)
8. Vaccination
9. Science and practice

II. Swine Plague and Hog Cholera (1885–1897):
1. *B. luteus suis*
2. Bacterium of swine plague, variability, etc.
3. Bacillus of hog cholera
4. Studies on immunity in swine plague and hog cholera (use of live attenuated and killed cultures)
5. Variability of infectious diseases
6. Collateral causes contributing to fatalities among swine
7. Epidemiology
8. Prevention

III. Sanitation (1886–1927):
1. Bacteriology of water (water analysis and filtration)
2. Relation of drinking water to some infectious diseases
3. Disinfection of dwellings
4. Purification of water
5. Channels of infection (water, milk)
6. Studies on *B. coli* group
7. Historical survey of water-borne diseases
8. Sewage disposal
9. Foreign body injury in gastro-intestinal tract of cattle
10. The housefly as disseminator of infectious diseases
11. Meat inspection and relation to disease
12. Studies on paratyphoid bacilli
13. Epidemiology of paratyphoid infection

IV. Texas Cattle Fever (1886–1899):
1. Etiology
2. Transmission
3. Pathology
4. Prevention

V. Immunology (1886–1934):
1. Vaccination (killed cultures, etc.)
2. Diphtheria (toxin, antitoxin, studies of mixtures, atoxic strains, variation, destruction, conditions influencing titer, etc.)
3. Tetanus (toxin, antitoxin, etc.)
4. Agglutination (group antigens, somatic and flagella antigens, mutations in *B. coli*, capsular antigens, action of agar, etc.)
5. Studies on colostrum (serum substitutes, agglutinins, agglutinin absorption, proteinuria, immunizing characteristics, nephritis in relation to intake, immunological significance)
6. Hay fever (etiology, etc.)
7. Parasitism and disease

VI. General Bacteriology and Pathology (1883–1929):
1. Technique (media, apparatus, etc.)
2. Isolation and cultivation of microorganisms
3. Glanders
4. Fermentation
5. Anaerobiasis
6. Indol production
7. Typhoid
8. Fractional sterilization
9. Diarrhea in calves
10. Variation and mutation of microorganisms
11. Morbid anatomy (cirrhosis of the liver, copper poisoning, etc.)
12. Morphology, life history, saprophytes, biology, pleomorphism
13. Broncho-pneumonia in calves, bovine pneumonia (*B. abortus* in fetus)
14. Brucellosis (relation to Malta fever, immunity, vaccination, etc.)
15. Vibrio fetus (relation to cattle abortion, etc.)
16. B. *actinoides* (relation to pneumonia in calves)
17. Rabbit septicemia, fowl typhoid, streptococci in milk
18. Swine erysipelas (experimental scurvy incidental)
19. Fungus infections (actinomycosis, infection fetal membranes)
20. Studies on the red blood corpuscle

VII. Parasitology (1889–1927):
1. Coccidia in the mouse, rabbit, sparrow, calves
2. Sporozoon in intestinal villi of cattle
3. Parasites infecting liver of domestic animals
4. Sarcosporidiosis in the mouse (*Sarcocystis muris*)
5. Amebiasis in domestic pig
6. Encephalitozoon in kidney of rabbit
7. Elimination of parasites in lambs by feeding cow's milk and segregation at birth
8. Malaria (study of hypotheses of transmission)
9. Mosquitoes in Boston
10. Blackhead of turkeys

VIII. Philosophy (1900–1934):
1. Science (comparative pathology, epidemiology, public health laboratories, causes and antecedents of disease, transmission of disease, insects, parasitism and disease, public health progress and race progress, decline of infectious diseases in relation to modern medi-

[11] The above outline does not attempt to imply all the title contents in Smith's bibliography but rather to indicate his general interests.

cine, research and public health, biography, respiratory diseases, etc.)
2. Medical education (research, scholarship, etc.)
3. Economics (medical economics and relation to society, importance of animal pathology to agriculture, biologic and economic aspects of comparative pathology, etc.)

It requires but a most cursory glance at the outline presented above to appreciate the wide range of interests which Smith had in science. His papers are gems of detailed accuracy and thoroughness, of simple, clear, logical thinking and of a characteristic directness in method of attack and solution of the particular problem at hand. He was indeed "one of Nature's high priests." From 1883, when he published his first paper on "Serial Microscopic Sections" with Professor Simon Henry Gage, now professor emeritus of histology and embryology, Cornell University, until his death fifty-one years later, Smith was actively engaged in research. During the summer of 1934 his last large work appeared in the form of a volume entitled "Parasitism and Disease," which was published by the Princeton University Press. In the intervening half century he was amazingly productive. Aside from the significance of his contributions, several of which have made medical history, his influence on the development of medical science and upon his contemporaries and students is incalculable. Indeed, one wonders if this should not be listed as one of his great achievements ranking only with his outstanding fundamental scientific contributions.

We have indicated in the outline the inclusive years over which certain subjects occupied Smith's interest and attention. It is noteworthy that the subjects of tuberculosis and of the general field of immunology remained permanently absorbing throughout his scientific life. His first independent work was published in 1884 on the "Diagnostic and Prognostic Value of the Bacillus of Tuberculosis in the Sputum of Pulmonary Diseases," and a few weeks shortly before his death he discussed with us at his laboratory in Princeton some new studies on tuberculosis in which he was then engaged. The emphasis of his first work in this field was directed toward a study of the etiological agent, *M. tuberculosis*. In his first paper he concluded, "If, therefore, there is as yet little evidence to support the prognostic value of the bacillus of tuberculosis, we may cling with greater faith to its value in diagnosis." In his second paper, which appeared later in 1884, he discussed critically the procedures then employed in demonstrating the organism, and in speaking of Koch's method, he stated, "A thorough understanding and accurate application of this method ought to precede any attempt at modification."

Then followed a period of years when Smith's attention turned to the study of other diseases as a result of his connection with the Department of Agriculture. Swine plague, hog cholera and Southern (Texas) cattle fever were making inroads among our live stock and these problems had to be met. However, this intensive work with his colleagues in the Department of Agriculture did not prevent important delvings into sanitation, immunology, general bacteriology and pathology, and parasitology. In fact, several valuable studies were made in these fields, some as by-products of the main work at hand, others as a result of independent forays into problems which had fired his fertile imagination. His work on swine plague, hog cholera and Texas cattle fever will be described later and also some of his contributions in the other fields mentioned. Meanwhile, in 1893, he again published on the subject of tuberculosis, and for forty years contributions to our knowledge of this subject emanated from his laboratory. Smith early recognized the importance of the study of tuberculosis in cattle and its possible relation to the human disease. In 1893, he mentioned the possible dangers to health in consuming meat and milk from tuberculous cattle and urged the enforcement of rigid inspection of dairy herds, since he was able to isolate *M. tuberculosis* from the udders of animals which showed no visible signs of infection. He urged also, as preventive measures, the removal of infected animals and general sanitary procedures, such as disinfection of stables, housing of animals as little as possible and boiling of milk given to younger cattle. In 1894, he described the pathology of tuberculosis in cattle and the mechanism of spread of the infection from the primary focus. At this time, with regard to the question of heredity of the disease in cattle, he stated, "There is every reason to believe that most of the tuberculosis in cattle is *not* transmitted at or before birth, but is contracted later on in life by contagion."

Smith's work in the field of tuberculosis continued. In 1894, he was engaged with Kilborne and Schroeder in the study of the tuberculin reaction in cattle. In 1896, he reported comparative studies of tuberculosis organisms obtained from the bear and the bull, and again he stresses the necessity for the medical profession to probe more thoroughly the subject of possible milk infection. In 1897, he began to make critical comparative studies of human and bovine strains of tuberculosis germs. In culture he found that human strains grew more vigorously than bovine strains; that growth of human strains was whitish and of varying thickness while bovine strains had discrete colonies or ground-glass appearance; that the size of human strains varied while the size of bovine strains remained quite constant; that the bovine strains were less affected by modification in media. Rabbits were

found to be susceptible to bovine strains but not susceptible to human strains. Pathogenicity of both types was also tested in guinea-pigs, mice, pigeons and cattle, and detailed pathology presented. In 1898 and 1899, we find him interested in the comparative virulence of strains of tubercle bacilli which he concluded depended greatly upon their source. During the latter year, he studied the thermal death point of tubercle bacilli in milk and other fluids. The general trend of all this work was leading up to the discovery of a certain method of differentiating between human and bovine strains. In 1902, he discussed again the possible relation between bovine and human tuberculosis. He concluded that there was no evidence that bovine tubercle bacilli infect human beings indiscriminately, but that evidence did exist that bovine strains have been isolated from human beings. It must be remembered that for some time Smith had been aware of the phenomenon of variation among microbes. At the first meeting of the Society of American Bacteriologists in 1899, he had presented a paper on microbic variation with particular reference to the organisms of rabbit septicemia and of swine pest, though mention was also made of *C. diphtheriae, M. tuberculosis, B. pyocyaneus* and *V. cholerae*. It remained for other bacteriologists to begin the intensive cultivation of this field some twenty-five years later. Between 1903 and 1905, Smith found a solution to the problem of differentiating between human and bovine strains of tuberculosis. During this time three important papers appeared dealing with the subject. He found that the reaction produced by the organisms in glycerin bouillon separated mammalian strains into two groups, one corresponding to human types and one to bovine types. This study of the reaction curve of tubercle bacilli and of the differentiation of the two types was of great fundamental importance to future investigations on tuberculosis and must be set down as a major contribution to twentieth century medicine. In subsequent years publications appeared on various phases of the tuberculosis problem. The following subjects were included: The nature and significance of the capsular substance, which Smith believed to be an overproduced outer membrane. Further emphasis on the significance of bovine strains in relation to the human disease, particularly as it affects children. A review of the etiology, pathology and immunity (1908). The efficacy of vaccination of calves with human strains of tubercle bacilli (1908–1911). Additional observations of the reaction curve of strains in glycerin bouillon and interpretation in which Smith disagreed that the second part of the curve is due to autolysis and insisted that it is caused as a part of the life processes of the organism. In further study of the biology of the tubercle bacillus, he showed that the human type, after two to four weeks of growth, produces much more acid in 5 per cent. glycerin bouillon than the bovine type (1913). In 1915, Smith reported that intravenous injection of bovine tubercle bacilli in calves, following preliminary injection of human strains and attenuated bovine strains, caused an increased resistance manifested by a shifting of the lesions from the parenchyma of the lungs (alveolar walls) to the bronchioles serving the lobules. The disease was chronic and the vessels were not invaded. The cellular reaction was the same in the udders as in the lungs. In this paper he stated that endothelial and giant cell reaction is greatest in animals having a low resistance. Lesions in the apical lobes in man are best explained by less active aeration and less active lymph current. Rib pressure may contribute toward fixation of the bacilli. He also stated that the evidence points to man as having a high resistance to the disease. Then followed his Mellon Lecture at Pittsburgh (1916), which was devoted to the subject of natural and acquired resistance to tuberculosis. In regard to the rôle of cellular and humoral factors in immunity in this disease, he remarked that the weight of opinion favors the cellular elements. In 1924, we find him discussing the tuberculosis problem before an audience in Edinburgh. In 1926, Smith addressed the National Tuberculosis Association in Washington, D. C., as its president, pointing out that the tubercle is not a highly specific structure, since monocytes are also characteristic of some other infections, such as typhoid and paratyphoid. He stated at this time, "The gathering of one type of cell is not in itself indicative of any formidable defense reaction. . . . It is quantitative, and only to a certain degree qualitative, conditions to be measured in the study of the focal reaction to tubercle bacilli." He concluded that parasitism is a universal phenomenon, of which tuberculosis is one type, that we have inherited parasitism from our geological ancestors and wish to rise above it, that the cost is high but, quoting Biggs, "Health is purchasable." Smith aptly adds, "We can not raise ourselves to a level of health and stay there without continual effort. We are in fact perpetually mortgaged to health." During the same year, in his address before the fifth conference of the International Union Against Tuberculosis, he said, "The curve of attainment, which arises so precipitously at the beginning of a great epoch, like that with its origin in the discovery of the tubercle bacillus, soon changes its slope toward a dead level, when we must work simply to hold what has been accomplished by those who preceded us. Or, to put it in another way, we are now working in the heat of the day; the freshness of the morning is gone." It was fitting that Smith should close his specific treat-

ment of this great problem of tuberculosis in his scholarly William Sidney Thayer and Susan Read Thayer Lectures in 1933, since he was to be lost to science and to the world a year later. In speaking of the affinity of certain bacteria and cell types for each other, he made this statement, "The outcome of such affinity may be death to the host or suppression of the parasite, with various intermediate stages." He noted also that the epithelioid type of cell reaction is associated with tuberculosis, bovine paratuberculosis, glanders, leprosy, and induced brucella and streptococcus disease in guinea-pigs, and that it is assumed that the reticulo-endothelial system is the source of these cells. Giant cells tend to appear in the secondary manifestations and they indicate increased resistance. These cell foci permit the organisms to live, multiply and leave the host, and do not, as commonly supposed, destroy the organisms. The focus favors both host and parasite. Difference in histological structure of lesions may imply different races of microbes and variation of *M. tuberculosis* should be further studied.

We have discussed Smith's work on tuberculosis first because it was the first disease to engage his attention and the one with which his entire career was identified except for the short interval in the eighties and the early nineties when he was working on swine plague, hog cholera and cattle fever. Let us return to this period and review briefly his work on these diseases.

Smith's interest and work on swine plague and hog cholera extended from 1885 to 1897. His work on Texas cattle fever was accomplished from 1886 to 1899. It will be recalled that Smith, who was largely self-trained in the field of bacteriology, after receiving his degree of M.D. from the Albany Medical College in 1883, was offered an appointment as assistant in the Bureau of Animal Industry in the U. S. Department of Agriculture at Washington. The bureau was just being organized under the direction of Daniel Elmer Salmon, a graduate of Cornell University in veterinary science, who, a few years before, had been commissioned by the Department of Agriculture to study swine diseases and cattle epizootics of the southern states. Salmon was chief of the new bureau from 1883 until 1905. Smith joined his staff at the age of 24 and soon was made director of the pathological laboratory. A short time later he became connected with the teaching staff of the School of Medicine of the university now known as The George Washington University, and held from 1886 to 1895 what we believe to be the first chair of bacteriology in a medical school in America. In 1896, he left Washington to accept the chair of comparative pathology created for him at Harvard University. Here he remained until 1915, when he became director of the newly established Department of Plant and Animal Pathology in the Rockefeller Institute for Medical Research at Princeton, New Jersey. Upon his retirement in 1929, he was made emeritus director.

We have seen that his first interest at the new Bureau of Animal Industry in Washington was the subject of tuberculosis. However, Salmon was interested in the swine diseases and cattle epizootics, and soon he and Smith, who was nine years his junior, were busily engaged with these problems. Salmon believed that there were two diseases of swine in the United States differing from swine erysipelas. One of these was designated swine plague and the other hog cholera. In 1885, he published a paper with Smith on the discovery of a chromogenic bacillus (*B. luteus suis*) isolated from three separate cases of swine plague, but this organism appeared to have no pathogenic properties. The swine fevers were in a terrible mêlange and the work of Salmon and Smith accomplished little in unraveling their mysteries. However, important by-products of their work did emanate from these studies. In regard to swine plague and hog cholera it must be realized that, during the years from 1885 to 1897, when Salmon and Smith, and Smith independently, were carrying on their work, there was as yet little knowledge of the virus diseases of lower animals and man. The virus of the mosaic disease of the tobacco plant had been demonstrated as early as 1892, but it was not until 1898 that the virus of foot-and-mouth disease was discovered. As has been true in the virus field since then, investigators have always been prone to look for visible, cultivable organisms. Nearly every virus disease now known possesses a characteristic history wherein one or more such organisms have been described as playing the etiologic rôle. The same was true for hog cholera when Smith was working on it. Klein, in 1884, had described a motile bacillus which was believed to cause the disease. In 1889, Smith was willing to state that hog cholera is a bacterial disease, that a similar disease known as swine plague may exist as a complication in outbreaks of the former, and that this disease has also a bacterial incitant. Several reports were made on the morphological and cultural characteristics of these organisms, among which was the comprehensive survey of the hog cholera group of bacteria published in 1894. During this year an announcement was made that liquid cultures of the bacillus of hog cholera could be sterilized by heat and, when injected into pigeons, would protect against fatal doses of the living organism. Although Smith did not succeed in solving the hog cholera problem, this fundamental discovery of the use of killed vaccines to produce immunity opened up other large and important fields such as typhoid fever and plague.

With these studies on swine plague and hog cholera

in progress, Smith was assigned to study the problem of Texas cattle fever. His publications on the etiology, transmission and control of this disease date from 1889 until 1893, although he wrote again (1899) on the subject in connection with new views regarding the transmission of malaria. This paper followed the work of Ross on malaria, which was published from 1895 to 1898. Texas cattle fever had been present in the southern states for years, and its prevalence was one of the reasons for Salmon's having been called to the Department of Agriculture for its special investigation. All that was known of the disease seemed to have been based upon the observations of cattlemen. Cattle transported from the South brought the disease to northern cattle. Northern cattle placed in pens occupied, or formerly occupied, by southern cattle would develop the affection after a certain lapse of time, usually thirty days or more. The disease appeared to have a seasonal variation, being severe in the warm periods and absent in the cold months. There did not seem to be any direct transmission from southern to northern cattle. Cattlemen thought that the condition was in some way linked up with the presence of cattle ticks. Smith and Kilborne tackled the problem, and Smith felt certain from his preliminary studies that the disease was not bacterial in origin. In fact, in 1886, Smith had observed peculiar, intraglobular bodies in the blood of infected animals but had not realized their significance. However, he published a preliminary paper (1889) on the microorganism of the disease, describing the ovoid and pear-shaped bodies in the blood stream of infected animals. He also made the observation that Stiles, in 1867, had probably seen the parasite too, judging from his description of punched-out disks in the blood elements. This report contains clinical and pathological studies of the disease. The bacteriological studies on the blood are reported as negative. In the Annual Report of the Bureau of Animal Industry for 1889–90, Smith reviewed these observations and reported for the first time his work with Kilborne on the relation of ticks to the transmission of cattle fever. It is important, in view of certain criticisms which have been made in the past, to emphasize that in this first report Smith gave due credit to Kilborne for his part in the work. He said in part, "During the summer of 1889, Dr. F. L. Kilborne conceived the happy idea of testing this popular theory of the relation of ticks to the disease." He continued by describing how ticks were removed from southern cattle when they were introduced into one enclosure, but left on southern cattle in another enclosure. Then healthy animals were placed in each pen. In the first no fever developed—in the second all the healthy cattle developed the disease and died. This experiment was repeated in September with the same results. It was concluded that Texas cattle fever is not a bacterial disease, that it is probably caused by a protozoan, that southern cattle without ticks can not infect northern cattle, that ticks alone scattered in pastures can produce the disease in healthy animals and, finally, that the period of incubation is explained by the life history of the tick. Smith stated, "Meanwhile the evidence accumulated thus far seems to favor very strongly the dictum: No ticks, no Texas fever." From 1889 to 1893, several papers appeared in which the parasite was described in detail, its probable life history suggested, and a name, *Pyrosoma bigeminum,* given. The anemia produced by the infection and the question of immunity were also studied. Smith concluded that the disease was more fatal to adults than to young cattle, and that two mild attacks, or a severe one, would probably prevent a subsequent fatal attack in every case. The parasite may persist in the blood for nearly a year after recovery, and inoculation of healthy animals in the fall or winter with blood from such cases may produce nonfatal attacks leading to immunity. The tick, *Boöphilus bovis* (*Margaropus annulatus*) was also studied.

Without doubt this discovery of the rôle of the cattle tick in transmitting a disease represents the first conclusive experimental proof that insects may act as intermediary hosts or carriers. In 1878, Manson is said, by Manson-Bahr, to have ". . . made the important observation that the mosquito subserved the parasite as intermediary host . . ." in the disease, filariasis. However, as Bulloch points out, this demonstration "was not quite conclusive, although often claimed to be, and Bruce's great work on trypanosomes and *Glossina* was not done till 1894–1895." In his investigation on cattle fever we have early evidence of the genius of Smith, not only in his method of attack, but also in the thoroughness with which he carried his problem to its final solution. At thirty years of age he had already demonstrated to an unusual degree his integrity and capacity as a scientist of the first rank.

We may now pass on to review briefly some of Smith's other accomplishments in the fields of sanitation, bacteriology, immunology, pathology, parasitology and philosophy. Few have considered Smith in the rôle of sanitarian, but his publications in this field date from 1886 to 1927, and include a rather wide range of interests. He was first intrigued by a bacteriological analysis of the water of the Potomac River during his early years in Washington. The subject of water-borne diseases and the relation of drinking water to public health continued to interest Smith, as did the questions of sewage, disinfection of dwellings and other channels of infection, such as milk and food supplies. Publications on those subjects undoubtedly

contributed to the steady improvements in efficiency which have been made in our health organizations during the past four decades. His investigation of *B. coli communis* and related forms falls naturally into this group, and his early observations on fermentation and quantitative gas studies, on reduction, indol formation, microbic variation and agglutination reactions laid the foundation for much work which was to be developed to a high degree many years later.

The phenomena in the field of immunology interested Smith throughout his scientific life. With Salmon, in 1886, he first published on the production of immunity with the use of the chemical products of bacterial growth. It was thought that the chemical products, or ptomains, in culture liquid were responsible for induced or artificial immunity. In 1887, these authors reported in more detail their use of killed bacterial cultures in the production of immunity. They used their so-called "bacillus of hog cholera" to immunize pigeons which were susceptible only to large doses of the living organism. Pigeons thus immunized were immune to subsequent injections with large doses of the living organism, although controls died. Similar experiments with rabbits and swine failed. Salmon and Smith believed that pigeons, which were less susceptible to the living germs, became immune because they needed less assistance from without than the other test animals. This work established a very important fundamental which later proved of great value in typhoid fever, and also in plague and cholera to a lesser extent. Smith was concerned as well with the preparation of smallpox vaccine and early suggested plans for safeguarding its purity and efficacy, such as government inspection of commercial vaccine plants. He wrote several papers on the use of vaccines and was never misled that in these agents we had attained a panacea for prevention or treatment. In 1910, he wrote, "No vaccine should be administered simply because it produces an occasional drop in temperature and symptomatic improvement. Only the final outcome of the disease process should serve as a guide for subsequent cases." A few years later (1913), in speaking on the same general subject of the uses of vaccines, Smith said that all parasites tend to increase the resistance of the host in which they live and multiply and that in any disease it is worthwhile to try to raise this resistance. However, he stated that in general vaccines applied during disease will rarely, if ever, be life-saving, although they may contribute to recovery. Smith was always concerned with the underlying problems of immunity. In his Pasteur Lecture in 1921, an insight into Smith's philosophical appreciation is given. In beginning this paper on the theories of susceptibility and resistance, he quotes from Walt Whitman's "The Song of the Open Road":

" 'It is provided in the essence of things that from any fruition of success, no matter what, shall come forth something to make a greater struggle necessary.' " In the same paper he said, "The function of great men seems to be not only to bring revolutionary ideas and concepts into the world before they are due, but vigorously to maintain and defend them in a hostile environment. Many great ideas are launched but not developed and defended. The systems in vogue are either indifferent or hostile to them and the individual unable to meet indifference or hostility, hence they are lost for the time being. Pasteur not only brought forth ideas revolutionary to biologists, chemists and physicians of his age, but he developed and perfected them and advanced them into practical life in the face of great opposition."

In a short treatise it is impossible to review all the contributions of Smith in the field of immunology. The outline already presented will give some indication of the extent of his interests. However, his work on diphtheria and colostrum should have special mention, and some of his other contributions may be cited in passing. His studies on diphtheria toxin, antitoxin and mixtures of the two covered a period of twenty years while he was a member of the Massachusetts State Board of Health and in charge of antitoxin production. In the first paper dealing with this subject (1895) on "The antitoxic and microbicide powers of the blood serum after immunization," he offered the conclusion, "In all departments of scientific research designed to promote man's welfare, the conviction has entered the minds of men that the forces of Nature herself must be sought out and subjugated in order that we may overcome the difficulties which beset the race at every onward step. Even the tillers of the soil no longer look for miracles but laboriously try to placate Nature by obeying the rules of a scientific agriculture. . . . But practical medicine is still somewhat behind. A long queue of empiricism is still dangling from an otherwise distinguished crown." Smith had become interested in the destruction of diphtheria toxin in culture, and as early as 1896 suggested the best conditions under which toxin might be produced, taking into consideration such factors as sugar and peptone in the media and the oxygen supply. He also carried out extensive investigations on comparative studies of various strains of diphtheria bacilli. Several papers were presented on diphtheria antitoxin, its nature and mode of action, and its standardization. Then followed studies on the transmission of immunity from immune female guinea-pigs to their offspring, particularly when the mothers were immunized with toxin-antitoxin mixture. Smith published, with Brown (1910), concerning the immunizing effect of mixtures of diphtheria toxin and antitoxin. They

offered the hypothesis that free toxin when injected into horses produces immunity with, of course, antibodies. When more toxin is injected, some is combined with circulating antitoxin and the mixture contributes to further immunity up to a definite limit. If no free antitoxin were present, toxin would tend to be held locally in an immunized animal injected locally. It was in 1904, while Smith was engaged in his studies of diphtheria, that he mentioned to Ehrlich an observation which was later shown to be serum anaphylaxis in guinea-pigs. This came to be known as the "Theobald Smith phenomenon."

In 1922, Smith took up the study of colostrum and showed that calves fed soon after birth, intravenously or subcutaneously, with cow serum in place of colostrum developed normally, while those receiving serum added to milk did not fare so well. Further work demonstrated that, because of its antibody content, colostrum is very significant in preventing diseases in young calves. Following complete elimination of colostrum from the diet and its replacement with fresh cow's milk, only a small percentage of calves survived. He stated, ". . . that any deviation from the highly specialized and highly adapted processes of nature, like the ingestion of colostrum, can not be modified or tampered with unless some adequate counter measure thoroughly studied beforehand is applied to readjust the disturbed equilibrium." In connection with these studies Smith called attention to a focal interstitial nephritis in the calf following interference with the normal intake of colostrum. This condition was associated with, or preceded by, invasion of a special, virulent type of *B. coli,* resulting in what he called a "spotted kidney." In 1930, he summed up his work on the immunological significance of colostrum in three papers, and in the final paper of this series called attention to certain intranuclear inclusions in the straight and convoluted tubules of the kidneys.

In passing we may mention briefly Smith's studies on the phenomena of agglutination, which included observations dealing with somatic, flagellar and capsular substances. He discussed mutations and their immunological significance. One of his last papers dealing with the agglutinating action of agar on bacteria showed that certain organisms agglutinate in the water of condensation of agar tubes, although not in bouillon, salt solution or plain water. In addition there is also his paper on the etiology of hay fever, published in 1913. Many of his ideas concerning fundamentals are recalled in his volume, "Parasitism and Disease," appearing in 1934, shortly before his death.

Smith's interests in general bacteriology and pathology covered a very wide range of topics. His first scientific paper, with Gage in 1883, dealt with the technique of cutting serial microscopic sections, and his second paper with this author described a section flattener to overcome curling of the dry sections. During the next few years, he was concerned with bacteriological culture technique and published on this subject with Salmon, and also independently. In the early nineties, he was interested in fermentation, gas production and the growth of anaerobes. In 1897, he studied indol production by bacteria and the action of typhoid bacilli on milk with reference to carbohydrates. During this year he also published on discontinuous sterilization. In 1905, there appeared, with Brown, further observations on fermentation and anaerobes. Smith's work on bacterial variation began very early and, in 1899, he read a significant paper before the Society of American Bacteriologists on this subject. This interest continued, and even in 1932, we find him discussing Koch's views on the stability of bacterial species before the historical section of the College of Physicians in Philadelphia. His interest in morbid anatomy throughout the years is illustrated by several papers. In 1893, he published his first paper on an organism isolated from a mare after abortion. Many years later he came back to this subject in connection with abortion in cattle and *B. abortus* Bang (1911). He prepared a demonstration of microscopic preparations of this disease while in Germany in 1912, and from 1918 to 1929 contributed much material on the subject. Besides studying the localization of *B. abortus* in the bovine fetal membranes and the cultural characteristics of the organism, he delved into the questions of immunity against the infection. In 1926, for instance, with R. B. Little, he showed that the partial protection afforded by four injections of a heated culture of *B. abortus* of normal virulence during the first pregnancy is in part lost in the second, and demonstrated the superiority of a single injection of living cultures of relatively low virulence in both pregnancies. In 1929, he described a strain of *B. abortus* isolated from an outbreak of infectious abortion in swine in the eastern United States. In the course of his studies on infectious abortion, Smith also described a spirillum which he believed to be associated with that type of infectious abortion in cattle in which *B. abortus* could not be demonstrated. Mention may also be made of his work on *B. actinoides* and bovine pneumonia and of his studies on rabbit septicemia and fowl typhoid. Special emphasis should be given to his work on swine erysipelas in the late nineties, chiefly because a by-product of this study was undoubtedly the first experimental production of scurvy. His investigations in the field of mycology were limited to studies of lumpy jaw and of a fungus infection of the fetal membranes in cattle. His blood studies included work on the pathological effects of periodic

losses of blood and the resistance of red corpuscles to differing osmotic tensions.

In the general field of parasitology, we come to some of Smith's most important work. Although studies on blackhead were the most outstanding, brief reference should also be made to his work on coccidia in mice, rabbits, calves and sparrows; to a sporozoon infection of the intestinal tract of cattle; to parasitic infections of the liver in domestic animals, including cattle, horses and swine; to the production of sarcosporidiosis in the mouse; to intestinal amebiasis in the pig; and to *Encephalitozoon cuniculi* as a kidney parasite in the rabbit. In 1899, 1900 and 1903, Smith also wrote on the subject of malaria with particular reference to mosquito transmission and sources, favoring conditions, and prophylaxis of the disease.

Smith's interest in blackhead of turkeys began in 1895, when he published his first paper on a protozoan disease affecting these birds. He reported several investigations on this disease during the next twenty-five years. Briefly, he discovered a parasite which he named *Amoeba meleagridis* as the cause of the disease, although later it appeared that the organism is not an amoeba but a flagellate, now known as *Histomonas meleagridis*. However, this parasite appears as an "amoeba" when it invades the liver where it produces abscesses. In 1920, he published a series of papers with H. W. Graybill which dealt with the epidemiology of the disease. It was demonstrated that a round worm, *Heterakis papillosa,* plays an important rôle in the dissemination of the disease. Later Tyzzer and his group demonstrated that the flagellate is transmitted in the eggs of the *Heterakis*. Smith and Graybill had shown that blackhead may be transmitted experimentally by feeding embryonated eggs of the roundworm to healthy incubator-raised turkeys and brooder chickens. Though Smith never solved this problem completely, he laid the groundwork for its solution, and his research on this disease is characteristic of his great genius as an investigator.

When one considers the busy productive life of Smith, which must have consumed so much of his energy, one is surprised at the number of formal addresses which he presented in various parts of this country and abroad. His willingness to prepare these and his courtesy in visiting various localities give us an insight into his generous nature and his deep enthusiasm for the work in which he was engaged. He appeared literally before dozens of organizations over a period of several decades, and it is in some of these addresses that we best see Smith, the philosopher. His subjects included various phases of scientific problems, public health, medical education, and even medical economics.

Smith was always interested in comparative pathology. During the three or four years before his death he was constantly emphasizing the importance of this subject in connection with problems of the American Leprosy Foundation, the medical board of which he was a member, and in connection with our recent study on the geography of disease in which he felt animal diseases should also be included. It was his hope that at some future time such a survey might be made. In 1900, he addressed the Philadelphia Pathological Society on the relation of comparative pathology to biology and medicine and, among other things, stated, "The progress of medicine, like that of other departments of human inquiry, consists of retreats as well as advances." He defined comparative pathology as ". . . the study of the phenomenon of disease for its own sake, abstracted from any immediate association with a particular subject, such as man, on the one hand, and a particular object, such as a cure, on the other. It is a biologic study of disease, or, in other words, an attempt to explain its origin, incidence, and place as a phenomenon of life and its relation to other phenomena." Later in this same address he said, "Parasitism, from a general point of view, is a weapon used by Nature to eliminate those that fail to reach a certain standard."

In 1905, Smith addressed the section on hygiene of the American Social Hygiene Association on the general subject of research into the causes and antecedents of disease and its importance to society. Several comments in this address are of very great interest. With regard to research in medicine, he said, "Many think that, if only enough money can be applied to research, medicine may come to control natural laws and save us from the consequences of transgression. All that research can do, however, is to analyze more profoundly and teach us more thoroughly the natural laws which govern disease and the necessity for submitting to them." Speaking of the period just passed, Smith said, "But the disappearance of the popular conceptions of cure, as reflected in pages on pages of advertised nostrums and miles of bill-boards, does not supplant the physician. His skill will no longer depend upon the mysterious formulae he may carry in his pockets, but upon that keen, delicate touch with Nature and the adjustment of hundreds of details which will put forces acting on him from within as well as from without. He will be more needed than ever with the growing complexity of our environment and his skill and breadth of knowledge must be proportionately greater." His prophecy was indeed borne out during the following quarter of a century. He continued, "The gradual analysis of the causation of disease by modern medical science is the foundation of that other branch of medicine which, instead of dealing with the individual directly, deals with him

collectively through Society or the State. As causation is indissolubly linked to the idea of prevention, so State medicine is essentially preventive in scope." And, "The antithesis then is between individual and social medicine, between conceptions of cure and prevention, between superstition and science." Later on he states that what may appear to be an antithesis is really not so, for all forces are in reality working for the same solution in the end. Besides being costly in terms of money, curative medicine is also costly in human energy since it requires much human energy to care for the sick. He stated that preventive medicine is in the last analysis much cheaper and that "Individual medicine depends really upon a surplus of energy in the world. When in the distant future that shall have been exhausted, only public medicine will survive." This address was written thirty years ago. Twenty-five years later, America began to seriously study the problem of the cost of medical care, concerning which a report has only recently been published. In this same address one also finds these interesting comments: "Parasitism is not an unknown phenomenon in the social and political life of mankind, but here we observe the curious fact that the parasites belong to the same species as those who support them. Among the lower forms of life, and especially in the causation of disease, the parasite stands at a much lower level than the host. We may, of course, say that the political parasite lives upon the 'organization' rather than upon the individuals composing it, but to the tax-payer this distinction would not be very convincing. . . . The political parasite is but one of a great variety of species. We have others, such as the tariff parasite, the rebate parasite, the franchise parasite, and so on. . . . I believe that much mutual assistance could be obtained by an occasional interchange of ideas and theories between the student of social and the student of biological pathology." And finally, "This preventive medicine is really the medicine of the social organism, the people's medicine, as contrasted with the treatment of the individual which often requires resources beyond our reach, because momentum of disease to be resisted has become so great when it has once manifested itself in the individual."

Also, in 1905, when speaking before the Harvard Medical Alumni Association of New York City, Smith stated, "The University School must have teachers who are investigators." This axiom is fundamental in all good institutions of medicine at the present time, thirty years later. During the next few years, several publications appeared by Smith on various subjects, such as the relation of animal disease to human disease, animal diseases transmissible to man, insects as carriers of disease, influence of infectious diseases upon a preexisting parasitism, parasitism and disease, etc. In 1915, he addressed the students at Harvard Medical School on scholarship in medicine, as follows: "The scholar's rewards will always be small. The distinguished men who have gone before have not been in the habit of thinking of themselves, and this habit should not be encouraged. In the ideal future state of society when we will be doing our tasks instinctively, when we will say with Luther, 'I can do nought else, God help me,' we shall not be thinking much of ourselves . . . great discoveries are due to the eruption of genius into a closely related field, and the transfer of the precious knowledge there found to his own domain. It is not so very long ago when medicine paid but little attention and less respect to the unusually rich field of animal life as a source of information. Today, every department of medicine fills its available working spaces with animals which are the subject of profound study. The results have revolutionized human medicine within a generation."

In subsequent years, important addresses dealt with such subjects as the significance of laboratory research in medical education, the importance of animal pathology to agriculture, etc. In 1921, in speaking on parasitism as a factor in disease before the Association of American Physicians, Smith said, "Observation and experiment, alternating, cooperating, and reacting on each other, are the only sure guides to a rational interpretation of disease. . . . Perhaps one of the most promising movements to bring into correlation with parasitism the other necessary conditions of disease is the study of epidemiology not from a statistical but from a biological viewpoint." In 1924, Smith addressed the Royal (Dick) Veterinary College at Edinburgh on the biological and economic aspects of comparative pathology. In 1927, he gave the Samuel D. Gross Lecture in Philadelphia and stated, "To sum up, we have seen that, while the natural defenses set up through evolutionary and selective processes are not very efficient, they undoubtedly tend to save life in its earliest stages. Our observations, furthermore, intimate that when natural processes are interfered with much may transpire in the earliest days which acts either precipitously to destroy life or else to produce open disease later on in the earliest months. To what extent the events transpiring in the early days of human life are responsible for the high mortality of the first year is a problem for human medicine to solve."

During the next few years, he wrote and spoke on such subjects as public health progress and race progress, the decline of infectious diseases in its relation to modern medicine, the influence of research on public health and medicine, the life and work of Noguchi, the general problem of respiratory diseases, etc. In 1934, he made these comments concerning his scientific phi-

losophy in a letter which was circulated widely among students of bacteriology: "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 a 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. . . . The joy of research must be found in doing since every other harvest is uncertain and even the prizes do not always go to the discoveries to which we would assign them. . . . In the three different environments in which I have spent my active life I have always taken up the problems that lay spread out before me in the new environment, chiefly because of the easy accessibility of material without which research can not go on; for in the early years material and resources were exceedingly scant and this meagerness determined the direction and scope of all research. My interest in a problem usually lagged when certain results could be clearly formulated or practically applied. To continue and analyze still further every link of the established chain either failed to hold my interest or was made difficult or impossible for causes lying outside the problem. As I look back it is precisely these links that have provided innumerable problems to others. Each link has grown into a chain and the end of successive chain making is not in sight."

Theobald Smith lived one of the most useful lives of modern times. His contributions to mankind are comparable with those of any citizen rendering conspicuous service of world moment during the past century. He received honors in abundance from foreign countries and from numerous universities. His friends and colleagues will always regret that certain institutions and international organizations failed to honor themselves by awarding him their recognition. However, in the minds and hearts of scientific men he occupies a place of far greater importance than would be indicated by any further tangible reward which might have come to him. Time will add increasing luster to this great name. Theobald Smith is lost to the world, but his achievement will remain one of the most significant chapters in the history of medicine.

SCIENTIFIC EVENTS

PHOTOGRAPHS TAKEN FROM THE STRATOSPHERE

PHOTOGRAPHS taken from the stratosphere, showing the earth's actual curvature on the horizon more clearly than ever before, and revealing how the world looks from the greatest height at which pictures ever have been made, have been developed from films exposed during the stratosphere flight of the National Geographic Society–Army Air Corps balloon on November 11.

The photographs were taken by Captain Albert W. Stevens, commander of the expedition, while the stratosphere balloon was at its "ceiling" of 72,395 feet, a new world altitude record, over Parmelee, South Dakota.

The picture showing the lateral curvature of the earth includes a stretch of the horizon 220 miles in length. This represents more than three degrees of a circle—nearly 1/100th of the total circumference of the earth. The curve of the horizon is easily noticeable when the picture is projected on a screen. When the edge of a ruler is laid along the horizon line the curvature is even more plainly visible.

In taking this picture the Fairchild camera used by Captain Stevens "saw" a distance of approximately 300 miles, far beyond the range of the human eye. The horizon showing in the photograph is estimated to have been at that distance from the camera. The photograph was taken by infra-red light which is capable of piercing distant haze. All the other colors of sunlight are shut out of the camera by a red filter in making this kind of long-distance photograph.

The picture shows a vast stretch of western South Dakota, covering roughly 33,000 square miles, equivalent to the area of the state of Maine. The Black Hills, from which the flight started and which have an area of about 6,000 square miles, appear as a large dark area at one side of the picture 160 miles in the background. Mountain peaks, rivers, and in the foreground towns and farms, are visible.

The horizon line in the photograph is represented by a stratum of haze estimated to lie about 10,000 feet above the earth. This stratum of haze, however, conforms closely to the sea-level surface of the earth and its curvature reflects accurately the curvature of the earth itself.

The only other photograph showing the lateral curvature of the earth along the horizon also was made by Captain Stevens while flying over the Andes in South America in 1930, from a height of 21,000 feet. The new photograph, however, shows a stretch of horizon three times as long as the earlier picture and so reveals the curvature much more plainly.

Both still and motion pictures taken directly downward from the stratosphere balloon while it was at its ceiling of 72,395 feet, the highest-altitude pictures of the earth ever taken, also were made by Captain Stevens. They show the earth as a huge plain marked