SCIENCE

Vol. 86 — Friday, October 22, 1937 — No. 2234

SCIENCE: A Weekly Journal devoted to the Advancement of Science, edited by J. McKeen Cattell and published every Friday by

THE SCIENCE PRESS

New York City: Grand Central Terminal
Lancaster, Pa. Garrison, N. Y.
Annual Subscription, $6.00 Single Copies, 15 Cts.

SCIENCE is the official organ of the American Association for the Advancement of Science. Information regarding membership in the Association may be secured from the office of the permanent secretary, in the Smithsonian Institution Building, Washington, D. C.

THE CONTRIBUTIONS OF CHARLES DENISON AND HENRY SEWALL TO MEDICINE[1]

By Dr. FLORENCE R. SABIN
THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NEW YORK, N. Y.

It gives me the greatest pleasure that you have invited me to come home, as it were, to have a share in this ceremony to commemorate two great men and the distinguished services they have rendered to the development of medicine in this community. To those of you who are students in this medical school, the significance of the evening lies in the future, for the dedication of the Charles Denison Memorial Library and the starting of the Henry Sewall Lectureship in Medicine are gifts that mean continuing opportunities for your education. But to those of us who are of an older generation the occasion is crowded with memories.

We who knew Dr. Denison, and indeed you who never saw him, save in the revealing portrait which hangs in the library, recognize him as a physician, as the type that all through the ages has been attracted to medicine. In his portrait one can see his extraordinary kindliness as well as the fact that his most outstanding characteristic was his objectivity. By temperament interested in people, he was the kind of man that the Germans have called a *Menschenfreund*. Beloved of his patients, he carried them through their illnesses. He was trained for medicine in an earlier day, 1867–1869, when observation of the patient was the main method for the diagnosis of disease, yet he was quick to accept the advances of his time. He was inventive and repeatedly published articles on new tools of precision for his work—a new stethoscope, a new spirometer. Skilled in the art of medicine, yet he liked its science. His most absorbing interest was in the therapeutic properties of light. Long before

[1] Address on the occasion of the dedication of the Charles Denison Memorial Library and the inauguration of the Henry Sewall Lectureship in Medicine, University of Colorado School of Medicine and Hospitals, Denver, May 28, 1937.

its use was recognized in the treatment of tuberculosis, he felt that he had cured himself with sunlight. Far ahead of his time, he believed that light and electricity were one and the same, and that the time would come when light would be used and understood in the healing of disease. How he would now enjoy all that has been learned since his time—the use of the x-rays and ultra-violet light!

Having come to Colorado for his health (1873), he turned his attention to tuberculosis and gave up his former work on diseases of the eye and mechanical surgery. His papers show repeatedly that he had marked mechanical skill. He made extensive studies of the use of tuberculin in the treatment of tuberculosis and published several reports of his results. In one I was especially interested because he had had repeated blood counts made after the injections. These counts were made for him by Dr. A. M. Holmes[2] who, as far as I can ascertain, was the first one to find changes in the blood cells in tuberculosis. In 1896 Holmes found that with the advancing disease the neutrophilic leucocytes rise and the small lymphocytes decrease, and the converse with regressing lesions.

Dr. Denison became a profound student of climate, and most of his published work concerns the broad aspects of climate with reference to disease, interests that are only just now adequately before the public. With the opening of this library in his honor, I hope that an interest in the history of medicine will be strengthened and that the medical students will care to know of the work of those who have built up the medical profession in this community.

The memory of Henry Sewall is still so vivid with us that it will be almost as if we were speaking to him, but before we follow his work, it is fitting that we should pay tribute to two women who have contributed so generously to the life of this community. This library is not the only gift of Mrs. Denison to Denver. In the Fairmont School on West Third Avenue in this city is a children's library, the most charming I have ever seen. Its walls are covered with Copley prints of Abbey's paintings of the King Arthur legends and its shelves are well filled in the hope that many of the children may come to share one of Mrs. Denison's priceless possessions—a love of books. This is a memorial to her beloved granddaughter, Edith Swan. With rare vision Mrs. Denison has understood the value of research in the development of the medicine of our time. It was in memory of the ambition of her son to devote his life to medical research that she built a laboratory for this medical school while it was still in Boulder. It was in his honor that she has established the Henry Strong Denison Medical Foundation. This foundation has been active for thirteen years, seeking in the medical schools all over the country to find and to aid the group of young medical students who are especially gifted for research. Henry Denison was a student of mine, both in his early high-school years, when he showed himself to be a born naturalist, and later in the medical school, when his brilliant mind awoke to the joy of medical research. It has thus been one of the deepest gratifications of my life that Mrs. Denison asked me to share with his sisters, Mrs. Henry Swan and Mrs. John Jameson, the pleasure of finding the students for these awards. The awards have been given to students recommended by their teachers as those who should become the investigators and the teachers of the next generation. Indeed, many of our fellows are already on the faculties of medical schools. At the request of Mrs. Denison I have the honor to present to the Charles Denison Memorial Library these four bound volumes of the research of the students done under grants from this foundation. They are, of course, incomplete, for the work of these students goes on.

[2] A. M. Holmes, *Med. Rec.*, 50: 325, 1896.

This medical school is also deeply indebted to Mrs. Henry Sewall. It was her loving care that made it possible for Dr. Sewall to devote his frail body and his powerful mind to the work that made him one of the great medical men of our time. This school wins great distinction because he taught here. As the city of Denver found out during the world war, Mrs. Sewall has rare gifts in organization that could have brought her recognition in her own right, but she chose rather to devote her abilities to help his work and she has thereby made herself beloved by all his medical friends throughout the country. Now she has given to the students in this medical school a lectureship, that succeeding classes of medical students may find inspiration and example in the life of Henry Sewall.

Last winter, starting to read all Henry Sewall's work, my eye lingered on the title page of the journal to which he sent his first article, Volume 1 of the *Journal of Physiology,* which was started in London in 1878. You too will be interested in this title page, for it reads:

> The Journal of Physiology
> Edited by Michael Foster, M.D., F.R.S.
> Professor of Physiology in the University of Cambridge
> With the cooperation in England of
> Prof. A. Gamgee, F.R.S., of Manchester; Prof. W. Rutherford, F.R.S., of Edinburgh; Prof. J. Burton-Sanderson, F.R.S., of Oxford
> and in America of
> Prof. H. P. Bowditch, of Boston; Prof. H. Newell Martin, of Baltimore; Prof. H. C. Wood, of Philadelphia.

Thus, when Dr. Sewall started his work in physiology in the laboratory of Newell Martin (1876–1881), England and America united to see if the English-speaking nations of the world might have enough research to fill one journal on the newer scientific medicine; not perhaps a whole volume every year, for the second volume spanned two years and the next one, three, but still enough to make a creditable journal. What a development Henry Sewall saw in his lifetime! America was not without medical journals at that time. Indeed, there were thirty-five of them in all—sixty-four if the Canadian journals were included as well, some with quaint names, like the very first one, the *Medical Repository,* started a century earlier, 1797, or the *American Medical and Philosophical Register,* the *New-England Journal of Medicine and Surgery, and the Collateral Branches of Science,* or the *Medical Recorder of Original Papers and Intelligence in Medicine and Surgery,* but there was no journal at all to record the starting of the new era of the medical sciences initiated in the last decades of the nineteenth century. America, however, was not slow in transplanting the new European medical culture, as is made delightfully clear in Sewall's address on "The Beginnings of Physiological Research in America," published in 1923, in which he traces the lineage of Sharpey, Huxley, Michael Foster, Newell Martin, and we add Sewall.

Henry Sewall's first work was on the gastric glands, published a year before he received his degree, and I shall quote the first sentence in full. Mrs. Sewall will recall that one afternoon in early July, 1935, sitting in her lovely garden, we had both enjoyed Dr. Sewall's latest enthusiasm, namely, the discovery that all of us scientists write badly and that we all need to learn the art from the modern, the very most modern journalistic style. The memory of that delightful talk was with me as I turned his first page, and how glad I was that he had not made that last discovery too early but had rather inherited the gift of his father, who was called the "Silver-tongued Sewall," as well as the gift of his grandfather, who was a medical experimenter. These were Sewall's first words: "A prolonged investigation made on the stomachs of adult animals having failed in its object of giving me some insight into the functions of the different cells in the glands of the stomach, I determined to take up the question in another way; and by carefully examining the stomachs of embryos to seek if there was any correlation between the differentiation of certain cells in the embryo stomach and the first appearance of functional activity. This method, the results of which are here detailed, has not done all that I expected from it, but has nevertheless, I venture to hope, not been entirely fruitless." Then he proceeded to show that the power to split protein and to curdle milk was correlated with the appearance of the so-called chief cells, sound physiology of the present day. Sewall's first sentence really foretells the story of his life. The morning he died, he was still "seeking to gain some insight" into the processes of nature;—that phrase writes his autobiography and on that last day his experiments had not yet done all that he had hoped from them, but he was still in the joy of the making of new plans for his next steps.

To return to the young student of medicine. After winning the doctor's degree in Baltimore he went to Europe and worked with Kühne in Heidelberg, with the great physiologist, Ludwig, in Leipzig, and with Michael Foster at Cambridge. Kühne had only just made the brilliant discovery of the visual purple which developed in the retina during the intervals of darkness. With him Sewall published two papers on this remarkable pigment; this work laid the foundation for his interest in the physiology of the special senses, to which he returned again and again in studies on the eye and on the sense of equilibrium.

When an instructor in Baltimore, for he assisted Newell Martin from 1876 to 1881, while getting his degree (1879), Sewall worked not only on the physiology of gastric secretion but also on muscle-nerve preparations, the universal introduction to physiology at that time. He found that a stimulus not of itself strong enough to cause a reaction nevertheless modifies the reaction to succeeding stimuli. This is a part of every course in physiology to-day. In Ludwig's laboratory he continued to work on this subject with Professor von Kries, and in Cambridge he worked on the evidences of function in the cells of the gastric glands with Professor J. N. Langley.

Returning from Europe after two years, Sewall was appointed professor of physiology at the University of Michigan (1882–1889). In the brief time he was there, but eight years, Sewall made two major discoveries in physiology, work of such significance that, according to Dr. William H. Howell, it placed him in the front rank of physiologists. The first of these discoveries was on the sensory mechanism of the heart. Trained by Newell Martin and then by Ludwig, it was natural that Sewall should turn his attention to the heart. What a description Sewall has given of Martin's discovery of the method of isolating the mammalian heart! He wrote, "I very well remember one morning, I think that it was in the fall of 1880, Martin said to me in effect, 'I could not sleep last night and the thought came to me that the problem of isolating the mammalian heart might be solved by getting a return circulation through the coronary vessels.'" Later, of course, Sewall saw Martin carry the experiment through (SCIENCE, 1923).

Starting at Michigan, Sewall worked on the action of the nerves of the heart, and in an article on the depressor nerve, published with his assistant, D. W. Steiner, he showed that the heart has to be considered not only as a motor mechanism but "as a sensory organ which might appreciate changes of pressure and in turn set into action a reflex apparatus" through the brain to be returned as motor impulses to the heart muscle. Dr. Howell has told me that this work foreshadows in everything but name and the precise location of the sensory endings the discovery of the sensory functions of the carotid sinus and the arch of the aorta. This work, while known to physiologists, has not yet been sufficiently realized by the medical profession as a whole.

Sewall's second beautiful discovery was acclaimed in the recent award of the Kober Medal (1931). In 1887 Sewall published an article in the *Journal of Physiology,* entitled "Experiments on the preventive inoculation of rattlesnake venom," in which, for the first time, he described the immunization of an animal to a foreign protein. The tablet erected at Ann Arbor in honor of this discovery reads as follows:

Commemorating
The pioneer work of Henry Sewall
Professor of Physiology
At the University of Michigan
from 1882 to 1889.
His work in immunizing animals against snake venom
demonstrated the principle
of antitoxin production.

This demonstration by Dr. Sewall anticipated by a half dozen years the discovery of antitoxic immunity by Behring and Ehrlich. The year that Sewall announced this work, 1887, was the year of his marriage to Miss Isabel J. Vickers, of Toronto, Canada, and one can not but wonder how clearly either of them realized what undying fame this work was to bring to Sewall. We shall now be able to show that these two major discoveries of Sewall's have run like a silver thread through all the research of his mature years.

Shortly afterward the symptoms of tuberculosis, which had developed as early as 1885, made Dr. Sewall resign his professorship at Michigan (1889) and go to Saranac with Trudeau. One misses, however, a record of any such period of rest as Dr. Sewall would later have imposed upon his own patients, for he at once became resident physician at the Cottage Sanatorium and there was apparently no interruption to his research. While at Saranac, Sewall started to work with the tubercle bacillus on a problem which was suggested to him by the late William Henry Welch of Baltimore. It was to compare the form and the staining characteristics of tubercle bacilli from the sputum of rapidly advancing cases with those from more quiescent cases, and in turn to compare these findings with bacilli from cultures known to be highly virulent and attenuated. He found that the organisms from advancing cases, like those from highly virulent cultures, were short rods, staining uniformly, while from the regressing cases the bacilli were long and markedly beaded. This has been fully confirmed and is in agreement with the most advanced bacteriology of to-day. Have you noticed that the words, exactly as they are known to-day, occur again and again like a refrain in regard to Sewall's work?

After a brief stay at Saranac, indeed less than a year, the Sewalls came to Denver. Here Dr. Sewall became professor of physiology in this medical school, the Denver and Gross, as it was then called, and started in the practice of medicine. In that day training for the pratice of medicine, as far as it was based on the underlying medical sciences, reflected pathology. This was true of the training of the elder Janeway in New York and of Osler in Baltimore. Sewall came into clinical medicine, as it were, by accident, and through physiology, and he therefore represented a type of clinician only just now coming to the fore through the newer discoveries centering around physiology and biological chemistry. Thus he was ahead of his time and it is exceedingly interesting to follow the clinical work of this physiologist turned physician. He published in all twenty-one articles on the heart and blood vessels, together with six more on special diagnostic methods for heart and lungs. While still at Ann Arbor he made a study with Myra E. Pollard on breathing, in which he recorded carefully the accurately toned voice sounds heard through auscultation of the lungs. Miss Pollard was a singer, and from this article I should judge that Sewall had a musician's ear far beyond the average, sensitive not only to pitch but to fine gradations in the qualities of sound, a gift without which no one can ever become highly expert in those methods of diagnosis that depend on the sense of hearing. Evidence of this highly skilled differentiation of qualities of sound occurs again and again in his clinical papers, as, for example, in the article on analysis of voice changes in the auscultation of the lung for the diagnosis of early lesions in the lungs.

Directly stemming from his early studies on the heart is his work on the action of the papillary muscles as well as analyses of the action of the cardiac valves taken from observations on his patients. For example, he found evidences of slight leakages of the atrioventricular valves occurring so frequently and transiently that he concluded they are to be considered as a safety device for an over-distended ventricle, and thus as a physiological mechanism. Another illustration is his use of the variations in blood pressures with varying postures to evaluate the state of a patient.

In 1921 Sewall published a paper with Dr. Samuel Swezey on the effects of limiting respiratory movements of the chest in certain cases which had then been found refractory to pneumothorax. In discussing the technique of so restricting the chest, he referred to the work of Dr. Denison in these words: "In fact, a Colorado medical pioneer, the late Charles Denison, probably left little to be accomplished in this regard beyond his ingenious devices for unilateral immobilization of the chest." The success of pneumothorax and the development of chest surgery have supplanted this work of Dr. Denison, but no one can read his papers on the subject without admiring his really great skill. From the historical aspect it is interesting to record that when Denison first described his method of immobilizing the chest, before the twenty-ninth annual convention of the Colorado State Medical Society, in 1899, he referred to the demonstration of Forlanini's method of pneumothorax which had been made here in Denver by the surgeon, J. B. Murphy of Chicago, just the year before.

As the years went on, Sewall's mind became occupied more and more with the subject of tuberculosis, and here his research was based on his own discovery of the immunizing properties of foreign protein. His early experiments had been made with snake venom; now he turned to other proteins, especially tuberculoprotein, as sensitizing agents. With his friend, the surgeon Cuthbert Powell, Sewall carried on an extensive series of experiments on the sensitization to foreign protein, using the nasal route of instillation. In the last article in this series, published in 1925, Sewall wrote as follows: "Some twelve years ago I became impressed with the idea that the surface epithelium of the body, including the epidermis and the succulent coverings of the respiratory and alimentary canals, must have most important functions in mediating between foreign material brought in contact with it and the internal tissues which it covers. From either a physiological or pathological point of view, the surface epithelium forms the "first line of defense" of the body. Our modicum of knowledge respecting the protective attributes of this covering embraces two certainties—that it is a mechanical barrier intervened to the passage of foreign material, especially when particulate; and that, when part of a mucous membrane, it is a mobilizing organ, capable of chemically changing foreign substances in contact with it." Here I can not but digress for a moment to recall that Sewall's grandfather, who was graduated in medicine from Harvard in 1812, was the first to demonstrate absorption through the skin by immersing a part in a solution of madder and finding excretion of the dye through the kidney. Returning to the experiments of Sewall and Powell, they dropped minute doses of horse serum into the nose of guinea pigs, repeating this procedure daily first on one side and then on the other, and after an appropriate interval tested the animals with an intravenous injection of the same serum. Most of the animals died with typical anaphylactic shock, showing that they had been sensitized to the foreign protein; but a few survived, and of these they wrote that they might have considered them as mere failures of absorption of the serum had they not found that they did not react to a second intravenous injection of serum twenty-four days after the first. They concluded that the original injections had immunized instead of sensitized. With carefully graded doses they found that larger doses tended to sensitize, smaller to immunize. In these experiments some of the sensitized guinea pigs showed, on re-injection, bronchial spasms simulating asthma. Sewall concluded that in the case of the human disease, certain individuals had been subjected early to foreign protein in amounts sufficiently large to sensitize rather than to the smaller doses which might have immunized.

Sewall also made extensive experiments on the effects of re-breathed air on normal and tuberculous guinea pigs, putting them in jars, six in series. He obtained some evidence of a slight sensitization to a foreign protein. These results are at variance with the prevailing views, namely, that the ill-effects experienced in close rooms are due merely to moisture and to the still air. Sewall's experiments, on the other hand, show that tuberculous guinea pigs died sooner and with more extensive lesions after prolonged exposure to re-breathed air.

The thought of sensitization runs through all these experiments and finally led Sewall to a re-study of the Koch phenomenon. For fifty years this has been a crucial problem in tuberculosis, and thus for the benefit of the non-medical part of my audience I must define this phenomenon. Koch described the effects of a first injection of tubercle bacilli into the subcutaneous tissue of a guinea pig, saying that at first there was little or no reaction that could be seen or felt, but that after about two weeks there developed a hard nodule which increased in size slowly, then ulcerated through the skin and formed a draining sinus which never healed. Quite different, on the other hand, was the progression of events after a second inoculation; on the next day there was a marked reaction, with swelling, redness and induration; these signs then regressed and again a hard nodule developed which either did not break down or, if an ulcer formed, it healed promptly. These events of re-inoculation are called the Koch phenomenon and they show that a primary infection changes the reactions of the body toward the re-introduction of tubercle bacilli. In this phenomenon is bound up the question of increased resistance or acquired immunity to this disease, and thus the solution of the problem of the mechanisms involved has remained a major question in tuberculosis.

In 1934 Sewall, with two of his students, de Savitsch and Butler, made an important study of the time relationships between the two inoculations and found that there was an optimum period for the second inoculation, as shown by a decrease and a fibrosis in the lesions of the first infection. The lesions of the primary inoculations were visceral, it having been repeatedly demonstrated by many observers that there is a restriction of the invasion of the bacilli of the second injection. If the re-infection followed too soon, as in two or three weeks, Sewall found that the visceral lesions were enhanced, but between the fiftieth and ninetieth days the effects of re-inoculation were the most favorable.

At the time of his death Dr. Sewall, still working on this problem, was studying the effect of a re-inoculation done by the intradermal route in two different places at the same time, one near the site of the primary injection and the other on the opposite side of the body, far from the original point. He was led to plan this experiment in the hope that it might throw some light on the clinical finding that during periods of regressing lesions in one lung, lesions that advance may spring up in the other. In this study, Sewall, working with the last medical student who had the privilege of assisting him, namely, Gerald J. Duffner, had made exceedingly careful discriminations between the true nodule or tubercle in the dermal or subcutaneous tissues and the inflammatory reactions around the tubercles. They found that the true nodule or tubercle which formed near the primary lesion was smaller than the one on the opposite side and postulated that the processes to be summed up as immunity might be greater near lesions than at a distance from them.

Mrs. Sewall has entrusted me with the pleasant task of finishing these experiments, and I must now give a partial report of the work. In the introduction to the paper on this work which Dr. Sewall had started to write, are these words, "The question whether allergy favors, opposes, or has nothing to do with the development of specific immunity in tuberculosis still invites experimental observation." That states the problem. Then he continued, "When a guinea pig is inoculated with a virulent strain of human bacilli and examined post mortem after three or four months, there is a lack of quantitative relationship between the effects of a large range of doses and the extent of lesions produced. The pathologic lesions may fail to differentiate strongly between two infections of which one is one thousand times as great by weight of milligrams as the other." Here he states one of the difficulties which has been a block in all the experimental studies which have sought to evaluate measures which might increase or decrease resistance to tuberculosis, that is, the tremendous variations in the effects of a given dose of bacilli, no matter how carefully and accurately measured. Our results, which are like those of others, have given a spread in survival time from fifteen to 738 days in rabbits inoculated with the same weight of bacilli, bovine strain B-1; while in guinea pigs inoculated with the human strain H-37 the survival time has varied almost as widely. This difficulty has now been overcome by a young man in my department, Dr. Kenneth C. Smithburn. He has been able to reduce the spread in death rate of guinea pigs inoculated by the intracerebral route to a minimum. How I should love to have told these results to Dr. Sewall! They depend on the newer phase of bacteriology known as dissociation. That bacteria grow in two different forms was discovered in 1921 by Arkwright and independently by de Kruif and Northrop the same year. Petroff was the first to apply this discovery to the study of tubercle bacilli and, with his assistant at Saranac, dissociated the avian strain into rough and smooth forms and determined that they were of widely different virulence. They also made what now proves to have been a partial dissociation of bovine and human forms. Dr. Smithburn, using an exact adjustment of the hydrogen ion concentration of the culture media, made possible by a modification of the glass electrode by Dr. D. A. MacInnes at The Rockefeller Institute, found that tubercle bacilli are highly sensitive to acids and alkalis. For his purpose he found Dr. Corper's glycerol-egg-yolk medium the best, and by adjusting this medium to different pH values he obtained three different types of colonies from freshly isolated human and bovine strains. They are, first, smooth, glistening colonies that look like moth balls; second, the markedly corrugated colonies in which the bacteria climb over one another from the surface of the media in patterns long held typical of the growth of acid-fast organisms, and third, flat, spreading colonies. The flat, spreading colonies, and indeed the smooth ones, were seen as far back as 1909 with the acid-fast organisms that infect the cold-blooded animals, but their meaning was not then understood. Dr. Smithburn has shown that the bacilli of the smooth colonies are highly virulent, of the rough colonies attenuated, and then concerning the organisms of the flat colonies he has made the significant discovery that they are not composed of organisms intermediate in virulence but of mixtures of virulent and attenuated forms in different proportions. By analyzing our records of survival time and type of disease in rabbits inoculated with the undissociated tubercle bacilli, Dr. R. M. Thomas had found that the animals could be separated into three groups; one group that died within the first 100 days with an acute infection; an intermediate group that died during the next 100 days, and a third small group that survived about a year and showed chronic lesions. With Dr. Smithburn's dissociated organisms it is possible to separate these three groups at will. With the old undissociated strains it is as if one were drawing out of a bag handfuls of tiny balls, part white and part black; one might get a handful predominately black, or predominately white, or approximately about equally mixed, but the chances of drawing twice exactly alike would be extremely slight. Thus, with the old cultures, one could never have any two animals with the same dose of the kind of bacilli that really count, namely, the virulent ones. But with the dissociated strains, all the animals that receive the virulent organisms die in the acute phase; all with the attenuated survive into the later period, while those with the organisms from the flat colonies die in the intermediate phase with some tendency to overlap into the acute phase. Thus one difficulty in experimental tuberculosis has been eliminated. Under the old conditions we had postulated marked differences in the resistance of the animals; now we know this assumption to have been only partly correct because we did not take into account the haphazard selection of the virulent organisms in the dosage. These newer strains are probably not wholly pure, for there has been no selection of colonies, but they are sufficiently pure to enable one to detect real, if slight, differences in resistance because the spread of the death rate is proportional to the reduction of the dose. Thus this new knowledge eliminates one variable.

To return to Sewall's last work, his experiment has now been repeated by Dr. A. L. Joyner, in my department, and myself. We have confirmed the observation of smaller nodules on the side near the primary lesion which we call the "Sewall Phenomenon," but we have not yet been able to carry the work to a convincing conclusion. Sewall's descriptions of the reactions, as made out by feeling the nodules, were so clear that they were readily followed. We used the intradermal route, the dosage and time intervals recommended. The site of the primary inoculation, as is conventional, was in the right inguinal region; the distant secondary one was on the left side with its nearest drainage toward the axilla. When the primary nodule developed after the first inoculation, we removed it from one animal. It had developed in fourteen days; the wound healed promptly and never ulcerated. The nodule was made of two small intradermal tubercles, each of which contained in one section fifty to sixty tubercle bacilli. This number of bacilli in so small an area represents high virulence. The culture we used was the human strain H-37, which had been grown by Dr. Smithburn at pH 6.8 for eight generations. The secondary inoculations were made with reduced dose in ninety days.

We have plotted the curves of our reactions: There were immediate redness, swelling and induration, typical of the Koch phenomenon, somewhat larger on the left side than on the right. It was like a tuberculin test and faded at the same rate; it was practically gone in four to five days. Later, in about fourteen days, the true nodules, or tubercles, started and increased in size at about the same rate as had the nodules of the primary inoculations. Unlike the primary nodules, they never ulcerated. At the end of one month these nodules averaged a little larger on the left side than on the right. All these observations are in confirmation of those of Sewall and Duffner. They may indicate that there is slightly more resistance near the first inoculation, as Sewall postulated, but I must now tell you of the complications of our experiment. We sacrificed the animals at different intervals, but those that lived beyond a month began to show new accessory nodules around the primary inoculation. They were all true tubercles, as proved by sections of them, and ultimately they made the amount of tuberculous tissue on the right side far exceed that on the left. This is the phenomenon that makes the problem so complex.

We then began to study the two areas of skin, which Sewall had made so interesting to us, by means of injections of a soluble dye which was being used by Dr. Philip McMaster at the Rockefeller Institute for the study of lymphatic drainage. Dr. McMaster has found a dye, pontamine sky blue, so innocuous that he could use it in his own arm, for it caused no reaction and ultimately faded completely. We found, as had he, that every intradermal injection of this dye reveals lymphatics instantly. This is because the plexus of lymphatic capillaries of the dermis is so abundant that one can not introduce a needle to that level without puncturing them. This means that dye is injected into dermal lymphatics under such pressure that it drains quickly into the deeper subcutaneous plexus and spreads a considerable distance. When the needle enters the subcutaneous level, on the other hand, the lymphatics may or may not be punctured, and often the dye enters them by the slower physiological route through their walls. These experiments with the dye showed us that our intradermal injections of bacilli had forced some of them into lymphatics under pressure so that they had been quite widely dispersed at the moment of the injection. Thus the nodules that develop in the dermis at the point of the injection can not tell the whole story, and one must know what becomes of the bacilli rather widely scattered in the subcutaneous tissues. The reason that so many more of the accessory, late nodules develop on the right side lies in the fact that the right inguinal nodes, always massively caseous from the primary right inguinal inoculation, offer more of a block to the drainage of the bacilli of the second inoculation than the normal or more nearly normal left axillary nodes.

Numerous studies of the Koch phenomenon, made during the fifty years and more since Koch first described it, have shown that in the previously infected animal there is not only restricted dissemination of reinjected tubercle bacilli, but reduction in their numbers and some change in their form. This has been found by Rist and Rolland, Kraus, Willis and many others. We have counted the bacilli in the sections of all the secondary tubercles, both the early ones and the later, and have found but few bacilli, one or two, up to five, in tuberculous lesions many times as large as the original primary tubercle that contained fifty or sixty bacilli. Moreover, many of these bacilli have been long and beaded, as Sewall had described the organisms of healing lesions and attenuated cultures years ago. With the development of the multiple late lesions, there were ultimately many more residual bacilli on the right side than on the left, for every tubercle has shown at least one bacillus. The nodules were at varying distances from the primary lesion, but they complicate the experiment and we must devise a plan which will obviate this difficulty. The fate of the bacilli, either their death or their attenuation, seems to us the crux of the Koch phenomenon or the immune reaction.

Recent studies on the reactions of the body to acid-fast organisms have stressed the factors which are common to all these organisms. Tuberculous lesions form after the injection of acid-fast organisms whether the bacilli are virulent or avirulent, as well as whether the bacilli are living or dead. Lesions from living, virulent bacilli progress in animals that are susceptible to the strain. Lesions from attenuated, avirulent or dead bacilli regress. Similar lesions can also be produced by lipoids extracted from all types of tubercle bacilli, virulent or avirulent, or from bacillary residues. The tuberculo-proteins have also been shown to have much in common. An example of this is to be found in the fact that the tuberculin prepared by the government for the testing of cattle is made not from bovine strains with which the cattle are infected, but rather from three virulent human strains. It is probable that human strains were selected because they are less apt to show loss of virulence under cultivation than are bovine strains. When we come to know the materials that differentiate the strains from one another and the virulent from the avirulent forms, it may be possible to probe deeper into the mechanism by which the more virulent strains survive in the infection. We already know that even susceptible animals have some power to degrade the virulence of tubercle bacilli. The mechanism of this degradation of virulence is the enigma of the Koch phenomenon.

In the last manuscript of Dr. Sewall is another sentence which I wish to quote; it refers to this long, difficult and unfinished task of solving the Koch phenomenon. He wrote: "It seems important that discrete facts spontaneously occurring or artificially established continue to be assiduously collected and arranged in a way to establish the inevitable sequence and hence a meaning." How true these words, and how well they express the adventure which is research to which he devoted his energies with joy to the very last day of his life!

OBITUARY

SIGMUND GRAENICHER

DR. GRAENICHER died on September 16, having been in poor health for some years. He was a naturalist in the broad sense, especially interested in entomology. He was born at Natchez, Mississippi, on April 29, 1855, of Swiss parents. His mother and father died within a week of each other of yellow fever, when he was only three months old. In his early childhood he was in the loving care of an old Irish couple, but when twelve years old he was sent to Switzerland to be educated. His uncle, to whom he was consigned, wished him to be an engineer, and accordingly he attended engineering courses at Stuttgart and in the Polytechnikum at Zurich. On the death of his uncle, Graenicher felt free to give up the engineering, for which he had little inclination, and to devote himself to biological subjects. He studied marine life at Nice, and obtained his Ph.D. at Basel in 1884. Expecting to return to the United States, he entered the field of medicine and after working for a time at Bern, he took his degree "Summa cum Laude" at Munich in 1888. He had in the meanwhile been married, and the couple came to Milwaukee, where Graenicher took up the practice of medicine. Very soon, he became associated with the Museum of Natural History at Milwaukee, which in those days was especially known from the brilliant work of Dr. and Mrs. Peckham on spiders and wasps. Graenicher began by building up the collection of fishes, which he found to consist of only two specimens. For years he worked as honorary