SCIENCE

FRIDAY, JULY 28, 1916

CONTENTS

MSS. intended for publication and books, etc., intended for review should be sent to Professor J. McKeen Cattell, Garrison-on-Hudson, N. Y.

THE CONTRIBUTION OF MEDICAL SCIENCE TO MEDICAL ART AS SHOWN IN THE STUDY OF TYPHOID FEVER[1]

I INTERPRET the gratifying invitation of the Academic Senate to appear before you as faculty research lecturer for the current year not only as an opportunity of assembling and correlating a group of facts that I have been studying, but also as allowing me to attempt an explanation of the method by which such facts are obtained. I wish in particular to suggest how one of the more theoretic or so-called scientific branches of medicine is utilized in the practical problem of preventing and curing disease.

There is little reason that many of you should have attempted to differentiate between medicine as an art and medicine as a science. Public interest and concern in medicine deals with it largely as it is applied to the individual or community and little with the scientific and more theoretic investigations on which the progress of applied medicine depends. Medicine to the layman is typified in the physician who attends him and it is the noble and satisfactory function of this individual to ease the mind and body of his patient and frequently so to apply his knowledge of human structure and function in health and disease as to avert death and hasten recovery. The practitioner employs the art of medicine, that is to say he combines, modifies and adopts certain recognized means to

[1] The annual faculty research lecture at the University of California, delivered on Charter Day, March 23, 1916, on invitation of the Academic Senate.

effect a given end. There exists, however, a type of work in medicine with which the public comes less in contact and which concerns itself primarily with the fundamental understanding and elaboration of those very means of prevention, relief and cure which the physician applies.

It would naturally occur to you that the individual best fitted to discover means of understanding and thereby of combating disease, would be one fully conversant with its manifestations and results through constant and persistent contact with the sick. Such, indeed, was the development of medical science through many centuries. I need only mention categorically a few of the great discoveries that have been made during the centuries by practising physicians. Galen, in the second century of our era, showed that control of the muscles depends on integrity of the nerves that run to them, by the simple experiment of cutting certain of them in animals. In the sixteenth century Versalius not only founded the science of anatomy, but described the mechanism of breathing and introduced artificial respiration. Harvey in the seventeenth century experimentally demonstrated the mode of circulation of the blood in the animal body. Thomas Young laid the foundation of physiological optics and explained the principle of color differentiation. Jenner showed conclusively that inoculation with cowpox will protect against smallpox, and thereby laid the foundations of vaccination as a preventive of many infectious, parasitic diseases. Morton, in the last century, discovered the principle of anesthesia, which has made surgery painless.

You will notice that these examples consist entirely of contributions which may be regarded as fundamental principles rather than adaptations of such principles, however practically valuable; in other words, it is a list of discoveries rather than of inventions; on such basis I have omitted Lister's great application of Pasteur's principles of bacterial contamination in aseptic and antiseptic surgery. You may further observe that the contributors cited have worked on experimental rather than purely deductional lines; I have not, for instance, mentioned the important work of Auenbrugger, who associated certain percussion notes over the chest wall with diseased conditions in the lungs and heart. I trust I shall be able to convince you that essential advance in medicine, as in other biological sciences, lies in the development of principles through inductive experimentation.

In the popular mind and in popular fiction it is still the well-known practitioner who is the great contributor to medical science. As a matter of fact to-day, and for many years, the progress has been largely due to a group of workers who are concerned little, or often not at all, with the care of the sick. Many major discoveries have been made by men with no medical training at all. I may simply mention among the latter Pasteur and Metchnikoff, whose contributions we shall later consider in more detail. This differentiation in medicine of a group of medical or even nonmedical men from medical practitioners, is a specialization or division of labor that is unknown to or misunderstood not only by the general public, but even in the medical profession itself. Its development is, however, quite logical and tending toward greater efficiency.

Progress in medical treatment a hundred years ago, and to a great extent fifty years ago, depended almost entirely on deductions that were ingeniously made from personal experience with the sick. The greater such an experience was the greater and more complete the series of facts obtained, the more valuable the deductions from them. Nothing approaching a complete series of facts, and particularly of facts in their chronological order, was possible until experimental methods were employed. As Neuberger has stated, collection and observation of fact constitute the first step in science, but not science itself. With the application of the methods that had already been utilized in the sciences of physics and chemistry to biology and medicine, it has often been possible not only to reproduce in animals some particular stage of a disease that has been met with in man, but to study the preceding and succeeding stages in such a process with a completeness that could be afforded in the sick room only through unlimited experience. Any deductions from the haphazard data of spontaneous disease requires, moreover, unlimited skill in fitting each stage as it irregularly occurs, into its proper place. Deductions from a relatively complete and orderly series of experimental facts are at once more rapidly arrived at and more reliable than empiricism. They have the further advantage of suggesting in their genesis other questions that have perhaps never arisen in clinical experience, the answers to which may, however, greatly simplify the problems of medicine.

When once the fruitfulness of the study of medical problems by methods already employed in the exact sciences became evident to the thoughtful physician, innumerable questions arose in his mind which he felt sure could now be answered. He felt, let us say, that animal experiments could tell him the exact relation between a shrunken and diseased kidney, a thickening of the arteries and an enlargement of the heart, a combination frequently found associated, and once the exact relation was known, particularly as to which came first, he felt some method of arresting or preventing the process might finally be obtained. At first the more ambitious and able practitioners endeavored to answer these questions for themselves, working in their laboratories into the still hours of a morning that ushered in another day spent at the bedside and the operating-table. These giants exist even to-day and it is owing to their example, enthusiasm and aid, that some of us are now able to carry on their work with greater single-mindedness and under less heroic conditions of existence. As the facts have accumulated and the methods of these newer sciences have been elaborated, it has become increasingly more difficult for one with divided interest to understand and particularly to add to them. Twenty-five years ago the professor of anatomy was a surgeon; the professor of pathology a practitioner of medicine. These men were often able and brilliant teachers of subjects which were their avocations rather than their true professions. They were even contributors to sciences which in their incompleteness made the finding of new facts easy. As the mass of acquired facts became larger, the gaps between them shorter but more difficult to fill, and the stimulus to further discovery greater, men one after another slipped from the beaten track of practise to become laboratory workers, usually at a financial sacrifice, because the work appealed to them.

It became evident that the medical sciences require whole-souled devotion. As Dietl expressed it in 1851,

> As long as medicine remains an art it will not be a science. As long as there are only successful physicians there will be no scientific physicians.

It is the practitioner, however, who has created the field for this latter type of worker and who, to a large extent, has made his existence possible.

We have had then for a number of years, two types of workers in medicine—the laboratory man and the practitioner; the boundaries between them are by no means fast and one crosses readily from one into the other field, but with less and less frequency does one attempt to do both types of work at once. The relations between these workers are highly cooperative, and usually mutually appreciative. The practitioner, as the original patron of the medical sciences, was at first inclined to regard his laboratory colleague as a high-grade technical assistant, and, being closer to the source of human disease problems, he still at times assumes a somewhat ex cathedra attitude as to what problems the medical scientist should investigate. Concerning the actual method of investigation he has, through lack of experience, become tacitly acquiescent. The relation of these workers in regard to the problems themselves is an interesting one and worthy of fuller elaboration.

It is obvious that the practitioner, through constant contact with the sick, knows of more problems that need solution, but through failure to appreciate the limitations of scientific method he does not usually appreciate those problems which can be solved. The clinician is constantly asking the laboratory man for explanations or help that can not as yet be given, and is often surprised when he asks whether *A* and *B* in conjunction will produce a condition *C* to be answered evasively, or told that *D* equals *E*. The clinician has had the tables reversed on him and must perforce content himself with what is given him to apply and not ask for what he would like. A slight misunderstanding each in the other's point of view must arise when we consider the differences in the material with which each man has to deal. The clinician is interested primarily with the needs of individuals, with the problem of a case; the scientist with disease entities, with a complex composed of all the cases of a particular malady that have existed, or that may exist, or frequently with some more abstract line of investigation arising from them. In the first instance the problem, though acute, is a personal and passing one that in the particular case will disappear before the question that has arisen can possibly be answered; in the latter case the solution is acceptable however long it may be in coming. It is easy to understand the impatience of the clinician who wishes results in order that he may apply them to Mr. A, and on the other hand it is reasonable to appreciate the refusal of the laboratory man to be dragged from a promising problem of fundamental import to investigate superficially an ephemeral individual symptom. While it is still possible for the laboratory man to be influenced in choosing his problems, he travels fastest by following attentively those problems which his own work has suggested. It is often more profitable in the end to follow what appear to be irrelevant ramifications rather than to attempt direct determination, let us say of the cause of cancer, or a specific cure for tuberculosis. I venture to say that these questions will not be answered by what we consider direct attack, for it is the habit of nature to respond to our interrogations with apparent indirectness. The real indirectness of course lies in the way we put our questions and not in nature's response. We plan an experiment and await a result which shall be firmly yes or no; the answer is neither of these, but something that throws no light on the original inquiry. Blessed is the man who sees in this incomprehensible reply the starting-point of a new line of inquiry which may take him far afield from the goal he had first in mind. We scientists are like rag-pickers, some fumble through masses of rubbish looking for a certain coin, while the true investigator takes up each object that is turned over and asks himself what use he can make of it.

Let me illustrate the stages in the evolution of modern medical science from medical art by an outline of the development of our useful knowledge in respect to a single disease, namely, typhoid fever.

Typhoid fever has been, and still remains, one of the significant causes of death and disability. So far as can be shown from the necessarily incomplete statistics of the Public Health Service, there were over 17,000 deaths from this disease in the United States in 1913, which means there were over 170,000 cases, since the mortality averages ten per cent. It is a malady particularly prevalent in crowded groups of men, such as armies and asylums. Sixty per cent. of all the deaths in the Franco-Prussian War were due to typhoid, and in the Spanish-American War one fifth of all the enlisted men contracted the disease, and there were seven times as many deaths from it as from implements of war. And typhoid fever is important not only as a cause of death, but particularly owing to its economic waste; for an acute disease it has a particularly lengthened course and is followed by frequent sequels. It has recently been estimated that the economic loss in this country from typhoid is $50,000,000 annually, as a disease ranking second only to tuberculosis.

Our interest in typhoid fever is heightened by the fact that it is not only an important disease, but one which can and will eventually be obliterated. Recent reports from the Surgeon-General of the United States Public Health Service show that the incidence of this disease is probably not more than half what it was thirty years ago, owing in large part to improved sanitation alone.

Perhaps the one most significant line of advance in medicine has been the gradual recognition of disease entities. On the recognition of separate diseases depends all measures of quarantine, prevention and rational therapy. Diagnosis, the recognition of a disease entity, depends on the patient's symptoms and these symptoms are of two classes; subjective, or those the patient himself experiences as pain, chilliness, and the like; and objective symptoms which the physician can detect. Among the latter may be mentioned rapidity of the heartbeat, fever, eruptions, changes in blood pressure; changes in the blood and urine, and the like. Medical progress has been dependent on the methods of recognizing such constant variations from the normal as are found characteristic of a given type of disease. Such variations were detected at first by the unaided powers of observation, and later by the employment of instruments and methods of precision introduced in the evolution of the medical sciences.

One of the most important symptoms of the parasitic or infectious diseases is a rise in bodily temperature, or fever. A fever is a disease characterized by such a rise in temperature and some fevers continue over a period of days or weeks. The disease we now recognize as typhoid or enteric fever is one of these continued fevers and, although probably seen by Hippocrates, was for centuries confused with other lasting fevers of somewhat similar appearance. Recurrent fever, septic infections, and typhus fever in particular present pictures which even to-day in their beginnings and in their purely clinical aspects may be confused with typhoid.

We owe our first full description of what was probably typhoid fever to an English physician, Thomas Willis, who in 1643 described an epidemic of the disease that occurred in the Parliamentary troops. Early in the eighteenth century Strother, another Englishman, described ulcerations in the intestine and enlargement of the spleen in that slow nervous fever which we now recognize as typhoid. The effect of this disease in producing a cloudiness or aberration of the mind is what has given it its name, which is derived from the Greek τῦφος or cloud. Its particular nervous or mental effect was further observed by Huxham, who in 1737, on a purely symptomatic basis, separated cases of "putrid malignant fever" (or typhus) from the "slow nervous fever." The final separation of these two confused diseases did not come, however, until a century later and was dependent not only on the recognized differences in the contagiousness and course of the two diseases, but on the recognition of the characteristic and almost inevitable lesions or anatomical changes which are found in fatal cases of typhoid, but never in typhus fever. These lesions, ulceration of the intestine and swelling of the spleen, liver and lymph nodes, mentioned by Strother, were described by Riedel in Germany (1748), Baillie in England (1761) and in particular by Roderer and Wagler (1762). We owe further descriptions of the clinical characteristics of typhoid fever to Bretonneau (1826) who called it "dothienenteritis," or abscess of the small intestine, a name which it frequently bears in French literature, and to Louis (1829) who gave the name "fièvre typhoïde" to the malady.

It is to the great credit of a Philadelphian, William Gerhard, to have given in 1839 a convincing basis of separation between typhus and typhoid fevers. He based this differential diagnosis on accurate descriptions of the greater contagiousness of typhus, the presence of characteristic lesions in typhoid, and on careful comparison of symptomatic differences between the two maladies. His observations, later confirmed in Germany and England, gave us the first basis on which to regard typhoid fever as a separate and distinct disease entity.

The final chapter in the clinical or purely observational study of typhoid fever is represented by two important observations in reference to its transmission from one human being to another. The disease as contrasted with typhus fever was regarded, and properly so, as only slightly contagious, that is, directly transmissible from one patient to another. In 1856 Budd pointed out that the danger of transmission in typhoid, the poison of the disease as he expressed it, lies in the patient's excreta, and in 1873 Murchison actually traced an epidemic to a contaminated milk supply, and showed that the stools of typhoid patients are the principal source of danger in spreading the disease.

This brief statement then outlines the significant advances that were made over a period of centuries in the differentiation and recognition of typhoid fever by purely observational methods, confined to the patients themselves and made by practitioners of medicine. In so far as alleviation of the disease is concerned, there is little or nothing to report beyond purely symptomatic and palliative treatment, the most significant point in which was the introduction of hydrotherapy by James Currie in 1770 and its rediscovery by Brand a century later. The recognition of the danger of spreading the disease through contamination with typhoid excreta must be regarded as a great contribution to preventive medicine.

We come now to a period, which may be roughly defined as the year 1880, which ushered in the two most productive of the medical sciences, bacteriology and its twin sister, immunology. Whereas the experimental sciences of chemistry, physiology, and some aspects of experimental pathology, were already established and had made, and continued to make, valuable contributions to human welfare, bacteriology was destined to explain the causation of a series of diseases known as infectious, and immunology to utilize these discoveries in the specific prevention and cure of many of them. The infectious diseases are not only important in themselves, but are recognized as indirectly the cause of many of the chronic diseases, so called, which are slower in their course, but none the less health-destroying and fatal in their outcome. The growth of bacteriology has been coincident with the filling of the ranks of our present army of laboratory workers, many of whom have been primarily concerned in advancing this science. Bacteriology owes its stable beginnings to two men, Louis Pasteur, a chemist, and Robert Koch, for a brief time a country physician and later professor of hygiene in Berlin. Immunology, the science which explains natural protection to infectious disease and utilizes this knowledge in creating such conditions artificially, we owe first after Pasteur to Metchnikoff, a Polish biologist with no exact medical training. It is characteristic of these sciences that their problems, although arising in cases of human and animal disease, have been developed, in large part, away from the bedside, under the conditions of greater accuracy and completeness afforded by the experimental reproduction of the disease in animals. Such an experimental disease may be interrupted and attentively studied in its successive stages and its course may often be followed outside the animal body under conditions of greatest clearness.

It was the great service of Pasteur, and particularly of Koch, to show that each one of an increasing number of infectious diseases is caused by a separate and identifiable type of microorganism. Such a microorganism is always found in each case of the disease in question, but in no other instance, and will give rise again to the same disease when reintroduced in a healthy animal of the same species. The first instances of infectious diseases studied, anthrax, typhoid, chicken cholera, tuberculosis, and others, were found to be due to minute plants called bacteria. Later observers have described similar infectious diseases due to equally lowly animal parasites, particularly to those known as protozoa.

Typhoid fever was one of the first of the human infectious diseases to yield the secret of its parasitic cause. The typhoid bacillus, *B. typhosus,* was first described by Carl Joseph Eberth in 1880, who found it microscopically in tissues from a patient that had died of typhoid fever. It was grown outside the body in pure culture four years later by George Gaffky. This organism was soon recognized as the cause of typhoid fever, although the final postulate necessary to prove the etiological relationship to the disease was not fulfilled until 1900, when Metchnikoff and Besredka succeeded in producing the disease experimentally with pure cultures in anthropoid apes. Of great corroborative importance in proving the causative relationship of the typhoid bacillus was its presence in the stools and urine of cases of typhoid fever, which was demonstrated in 1885. In the same year Fraenkel and Simmonds found the microorganism in the circulating blood of a case of typhoid fever, a condition which was later shown by the work of Kühnan (1897), Castellani and Schottmüller to be fairly constant during early stages of the malady. This observation not only proved finally and conclusively the etiological relation of the typhoid bacillus to typhoid fever, but led to a gradual reconstruction of our conception of the disease itself so that we have finally come to regard it primarily as a septicemia or blood infection rather than an intestinal disease *per se,* as the striking lesions in the small bowel had led us to assume.

A scientific discovery may be considered worth while if it merely gratifies intellectual curiosity and adds an apparently insignificant support to a structure, the totality of which makes for human knowledge and welfare. It is a characteristic of the medical sciences in general, and of bacteriology in particular, that the discovery of new principles has led very rapidly to practical results of the greatest significance to mankind. In no instance is this characteristic more strikingly true than in the study of typhoid fever. The study of *B. typhosus* as the single and essential cause of typhoid fever led rather rapidly to important advances in the prevention and cure of the disease.

I have already referred to the valuable suggestions of Budd and Murchison that the potential danger of contagion in typhoid fever lies in the excreta from patients. In common with all empirical results arrived at by retroactive judgment between cause and effect, these suggestions were only partly convincing and led to only partial avoidance of the danger. Witness, for example the obstinate assertion of Pettenkoffer, the great hygienist, who insisted that the contagion in this disease must pass through a ripening stage in the earth, and that its spread is dependent on the level of ground water. The demonstration that the typhoid bacillus was not only the cause of the disease, but that it is present in the stools and urine of typhoid patients, at once led to more logical and far-reaching avoidance of these sources of contagion. It was accepted not only that typhoid patients are a source of possible danger, but it was soon suggested that even after their recovery they might continue to retain the germs of the disease in their urinary bladder or intestines (Horton-Smith, 1900; Koch, 1902). This led, at Koch's suggestion, to a systematic investigation of the stools of recovered cases of typhoid fever in certain parts of Germany where the disease was particularly prevalent, and showed that four per cent. of all recovered cases remain "carriers" of *B. typhosus* for varying lengths of time, some of them for years. In connection with this study Drigalski made the important observation that a few individuals may harbor the typhoid bacillus in their intestines without ever having suffered from the disease, "healthy carriers" as they are called. Repeated observations in all parts of the world have shown that through contamination of foodstuffs, these carriers may produce not only a chronologically extended series of cases, but actual acute epidemics. The obvious remedy consists in detecting the innocent but dangerous individual and isolating or curing him.

Food contamination occurs not only in its preparation by carriers, but sometimes through transfer of the bacteria by flies, as has been shown to be the case particularly in asylums and prisons where excreta have been left exposed in the neighborhood of kitchens. Reed, Vaughan and Shakespeare have particularly emphasized this danger of fly transmission in their careful study of the devastating effect of the disease among our troops in the Spanish-American war. Evidence of this sort has led to an appreciation of the necessity of proper, protected latrines which can be rapidly built even in temporary camps.

These and other real contributions toward the prevention of the spread of typhoid fever have been made by pure bacteriology. Let us now consider what the sister science of immunology has accomplished. I have only suggested how much the demonstration of the typhoid bacillus in the blood or stools of a suspected case of typhoid may aid in diagnosis of the disease. As a matter of fact no diagnosis is complete or indeed certain without such examination. An even simpler and almost as reliable method of laboratory diagnosis has been devised by Widal and by Gruber, depending on a principle that had been previously discovered in laboratory experiment. Bordet in particular is responsible for having shown that the blood serum of animals that have been given injections of a microorganism may be distinguished from the serum of normal animals by the fact that it clumps the microorganism in question. This fact was applied by Widal in his now famous test for typhoid fever, which depends on the presence of this agglutinating substance in the serum of those that are suffering from typhoid fever. This sign occurs in nearly all cases of the disease, although more frequently in its later stages.

Our present methods of protective vaccination against typhoid fever depend on principles that have been dimly appreciated but at times successfuly used by very primitive peoples throughout the centuries. It had been observed that those who recover from certain of the infectious diseases are thereafter protected from them. With this fact in mind the Orientals practised arm to arm inoculation with smallpox virus which usually produced only local evidence of the dread disease and was followed by protection from it. Jenner made this haphazard and dangerous method of prophylaxis a safe one by utilizing virus from a modified form of smallpox, namely cowpox, which is not only harmless, but gives equally good protection. Full understanding of the principle involved and its application to other infections, however, was dependent on the advent of bacteriology a century later. Pasteur not only separated out the causative agents of a number of diseases, but found that he could so modify their virulence that they no longer produced fatal or serious effects when reinoculated into animals. Those that had been treated with these modified germ cultures were found, however, to be protected against fully virulent original growths of the microorganism.

Facts such as these were early discovered in respect to the infections produced by the typhoid bacillus in small animals. Beumer and Peiper in 1887 found that mice that had recovered from a non-fatal dose of this organism would subsequently withstand doses that were fatal to their untreated brothers. Shortly after, following a very important discovery by two American scientists, Salmon and Smith, it was found that this same protection could be effected in animals by the previous injection of cultures of the typhoid bacillus that had actually been killed by heat.

In 1894 two German scientists, Pfeiffer and Kolle, on the basis of further theoretical studies, were led to try the effect of giving human beings small hypodermic injections of dead typhoid bacilli. They found that the doses they used produced certain uncomfortable but transitory symptoms, but that the blood of such treated individuals when subsequently examined contained antibodies which indicated that they were protected against typhoid fever. At the same time, and independently, A. E. Wright began similar inoculations in British soldiers who volunteered for the purpose. The inoculations did them no harm, and as larger and larger groups of these vaccinated men came into being and were subjected in war to the same dangers of typhoid infection as were untreated men in the same regiment, it became evident that they were much less likely to contract the disease than the uninoculated, and when such vaccinated men did at times come down with typhoid fever, the disease almost invariably ran a milder course than in the unvaccinated and the mortality among them was distinctly lower.

It took something over ten years to convince the thinking world that preventive inoculation against typhoid fever is harmless and that to a striking extent it does protect. The results attained in the German and English armies and among the personnel of hospitals have assured us that these classes of people, who are the most exposed to typhoid fever, become, when vaccinated, only one half to one sixth as liable to contract the disease as the untreated. The protection, then, under these unfavorable conditions, is not absolute, but very evident. Much better results have been obtained in the last few years in the United States army, where, in spite of objection, typhoid vaccination has been made compulsory since 1910 for all men under forty-five years of age. Whereas in the preceding nine years there were on the average 351 cases of typhoid annually, since compulsory vaccination the cases have sharply diminished until in 1913 and 1914 there were only four and seven cases, respectively, a truly remarkable showing. These last results have been enough to convince the most skeptical, and have led to widespread adoption of the method, not only in armies, but in civil communities. These results in our army, life-saving, convincing and valuable as they have been, are open to a very slight objection in my opinion; they have led the public, and particularly the medical profession, to a slight over-confidence in the efficacy of the method itself. These army results are essentially perfect, at least far nearer perfection than has ever been reached by any similar type of biological preventive or curative treatment, a fact which leads us to suspect that they are exceptional and due to the operation of a set of conditions which, in spite of their existence over a considerable period of time, are not to be counted on.

Among the conditions that have operated in making these conditions more perfect is the vaccine employed and the method used in its administration. Army officials are, in my opinion, inclined to attribute an undue importance to this factor. They use a certain strain or race of the typhoid bacillus derived from England, to which they are inclined to attribute particular properties of immunization. Results elsewhere have indicated, and we believe we have strong evidence from unpublished work in our own laboratory, to prove that a vaccine compounded of a number of strains of the organism is better. The army has introduced three instead of the two injections which were formerly used in England, and this is an undoubted advance.

The fact remains, however, that the army vaccine, or at least vaccines prepared by commercial firms from the army bacillus under identical and simple conditions, do not invariably protect in civil life. Recent reports from the continental armies, each employing a different method, show that in none of them is the protection afforded nearly absolute, in spite of the fact that in parts of the French army four or five injections have been given. I am inclined to believe with Sawyer that the superior results in our army are largely due to the fact that the entire body of men has been protected, that there has been no single unprotected spot for an epidemic to get a start and gain in violence, to use a vague and perhaps not wholly accurate simile. Some recent results in France certainly indicate that antityphoid vaccination is more effective in those groups with the higher percentages of assuredly vaccinated men.

I have gone somewhat fully into this discussion of the army typhoid vaccine for the purpose of indicating that their results, although exceptional, have by no means convinced other authorities that the methods they employ are in detail the best. Let me emphasize again that we are not now considering whether typhoid vaccination is of value, *that* you must accept as proved beyond peradventure, but just how valuable it is and in what way it may be further perfected. In other words I am leading you into those intricacies of detail which any scientific problem attentively considered must present, and from the unraveling of which new and important issues may arise.

Our former beloved professor of hygiene, George Reinhardt, came to me some three years ago and asked if I did not agree with him that the student body in this university should be offered the opportunity of being vaccinated against typhoid fever. With no hesitancy at all I answered "Yes." When he pressed me further as to the best method of preparing and administering the vaccine I felt unwilling to decide so important a matter on the basis of literary knowledge alone. In association with the late Dr. Edith J. Claypole we undertook to arrive at some conclusions on the subject. We found that nearly twenty different preparations of typhoid vaccine had been suggested, and each regarded by its author as the best. Data, however, on which to compare one vaccine with another were almost entirely lacking, that is to say a vaccine was approved because it had worked well under a given set of conditions with a more or less considerable number of men without any direct comparison with other vaccines.

Three distinct improvements in the vaccines in vogue seemed possible.

First: All vaccines were admitted to protect, at best, for only relatively short periods of time, say about two years.

Second: Many of the vaccines advocated were admitted to give rise, on administration, to rather uncomfortable transitory symptoms.

Third: The current method of administration, three injections over a period of three weeks or more, seemed an unnecessarily long period to wait for protection.

It was with these questions particularly in mind that we began our experiments. Out of them have arisen innumerable further questions, some of which have given rise to investigations of theoretical and practical interest. In the first place there had been no convincing experimental method of comparing the relative protective value of various vaccines. The only results of value seemed to be statistics from inoculated men obtainable only after years and under most uneven conditions. Certain experiments of Metchnikoff and Besredka with anthropoid apes were suggestive, but impossible to carry further, owing to the expense of these animals. We finally adopted an experimental procedure in rabbits that had been used for other purposes and which, with our modification of it, led us to conclusions that were rapidly obtained and apparently valid. It was found possible to compare several of the best typhoid vaccines in respect to the length of time they protected rabbits against infection with living typhoid bacilli. As a result of many experiments of this sort we came to the conclusion that a new type of "sensitized" vaccine, as it is called, gives rise to the most durable immunity. The word "sensitized" simply means that the bacteria in the vaccine have been treated with the serum of animals that have been highly immunized against them. It was furthermore found possible to remove certain toxic elements (endotoxins) from these vaccines with a further increase in immunizing property. The final product, then, a "sensitized vaccine sediment," as we call it, not only protects animals longer from infection than other vaccines, but is found when injected into human beings to produce little or no reaction.

Another improvement we have suggested is the administration of the customary three doses of vaccine within a week instead of the three weeks usually regarded as necessary. Here again careful experiments in rabbits showed us that this rapid method produces an equally efficient and lasting protection.

The final proof of the value of a preparation is of course in practise, that is to say, its actual protective value for human beings. The California State Board of Health has been supplying our vaccine for free distribution to physicians for the past two years. Dr. Sawyer, of this board, undertook to find out the results of typhoid vaccination in this state about a year ago. He obtained records from over 5,000 cases that had been treated with our vaccine, and something over half that number that had been treated with various other vaccines, mostly of the army type, as dispensed by commercial houses. There were about the same actual number of failures to protect in both series, that is, there were twice as many cases of typhoid fever per thousand among those vaccinated with other vaccines as with our own.

It is evident, then, from these results and from what I have said, that typhoid vaccination, at least in the general community, is relatively, but not absolutely, protective. It remains for future investigation to determine in what way the percentages of failures can be decreased.

It seemed to us very important, in our investigations, to devise a method by which the duration of protection could be determined in individual cases. It is all very well to know that on the average vaccination will protect for about two years, but what of the exceptional individual, who from sad experience we have learned is not protected even for two months? Dr. Force and I think we have a method for determining the actual presence or absence of protection in the individual at any given time. This tests consists in rubbing a small amount of material from killed typhoid bacilli on the skin. We have found that nearly all those who have had typhoid fever in the past, and who are known to be usually protected from it, react to this test with the formation of a slight reddish blush about the abrasion. Most people who have been vaccinated within the last two years also react positively. Normal people do not react. We feel justified in assuming that the presence of a positive reaction of this sort is evidence of protection. So far it has not failed us in practise, that is to say, no vaccinated person who has given a positive test has shortly thereafter had typhoid, and conversely in two vaccinated cases where the tests were negative and doubtful, respectively, the individuals have shortly thereafter contracted typhoid fever. It is too early to speak authoritatively about the absolute value of this "typhoidin test," as it is called, but at least we feel justified in urging our vaccinated students to be revaccinated when we find the test negative.

I hope I have somewhere in my remarks suggested to you that results of direct practical bearing are by no means always arrived at directly. In fact the experienced investigator comes to rely more and more on Pasteur's adage of "Chance and the Prepared Mind," and learns to seize chance happenings and turn them to his own ends. I think the evolution of a practical point out of theoretical studies may well be illustrated by some of our recent work. The efficacy of various typhoid vaccines has been tested, as already mentioned, by the ability of each to protect rabbits in a given dose for a given number of weeks against infection with a large dose of living typhoid bacilli. In unprotected animals, or in animals insufficiently protected, these injected bacilli go on increasing in numbers, and although the animal may live for a considerable period, the typhoid organisms persist in his blood; he has become, in other words, a permanent carrier. In perfectly protected rabbits the bacilli disappear from the circulation within a few hours. It interested us to trace the method by which the bacteria disappear in the protected animals, and we found that coincidentally with the disappearance of the infecting bacteria there occurs a sharp rise in the number of white blood cells in the peripheral circulation. These white cells, leucocytes, or phagocytes, as they are called, are known through the work of Metchnikoff and others to be associated with defense of the body against invading bacteria. This leucocytic crisis, then, would seem reasonably to be associated with protection in these immunized animals. A moderate grade of leucocytosis occurs in the normal unprotected animal, but is apparently insufficient for the purpose. In tracing further the cause of the extreme grade of leucocytosis in the immunized animal, we found it to occur only under specific conditions, that is, only when typhoid bacilli are injected in typhoid immune animals, and not when typhoid bacilli are introduced in normal animals, or other bacteria in our immunized animals. It seemed reasonable, then, to think it might be due to the action of the specific immune bodies which circulate in immune animals and are known to increase phagocytosis by their action on the bacteria with which they unite and which they render more attractive to the leucocytes. This hypothesis we were able to verify by injecting bacteria that had been previously treated with typhoid-immune serum into the circulation of normal animals. The same phenomenon of specific hyperleucocytosis also occurred under these conditions.

Since this hyperleucocytosis is coincident with, and apparently the cause of, the body's ridding itself of bacteria, it seemed possible that the artificial production of it in typhoid fever might cure or beneficially affect this condition, which is so characteristically accompanied by a proliferation of bacteria in the blood stream. We tried out this possibility in our carrier rabbits, those animals in which we had produced a septicemia by injecting living typhoid bacilli. In some cases we cured these animals of their septicemia, and then after testing the harmlessness of large doses of our sensitized vaccine in rabbits and monkeys, even when injected directly into the blood stream, looked forward to a cautious adaptation of our results in cases of human typhoid fever.

It was nearly a year before we had an opportunity to try this method on human beings. In the meantime the results of other writers in essentially the same direction came to our attention, and further encouraged our hope in the proposed method. It will be necessary at this point to go back a step and consider preceding work that had been done in attempts at a specific cure in typhoid fever, that is to say, a cure attempted in full recognition of the cause of this disease, namely, the typhoid bacillus. Striking success in combating bacterial infections has been met with in certain cases by the application of one or more of three pretty definite methods. Some bacteria, like the diphtheria bacillus, produce their harmful effect in the body by the liberation of poisonous substances known as toxins. In the case mentioned, the disease, when taken in time, can be cured in a really miraculous manner by injecting diphtheria antitoxin, which is simply the serum of horses that have been treated with repeated doses of diphtheria toxin and thereby made to produce antitoxins that neutralize the toxin. Other diseases produce their harmful results largely by multiplication of the invading microorganism. Such diseases, for example, as epidemic meningitis, can be cured by inoculating serum from animals immunized against its causative agent, the meningococcus. Still other diseases, principally local affections, as, for example, carbuncles, may be treated with considerable success by injecting the causative agent itself; in the example mentioned, staphylococcus. This latter form of treatment, or vaccine therapy, as it is called, builds up an active immunity and leads the animal so to muster his reactive, protecting, forces as to expel the invader.

It is this latter method of vaccine therapy which alone has been used with any success in the treatment of typhoid fever. I have already referred to the hopelessness of affecting the course of typhoid fever in any but a palliative way by the other methods of treatment that have been suggested; the fever may be favorably influenced by the continued use of cold baths, but the duration of the disease is little, if at all, affected by such means. In 1893 Fraenkel began the use of small doses of killed typhoid bacilli injected hypodermically in typhoid fever. For twenty years this treatment has been tried with varying success by many physicians, some of whom have published their results. These results, although at times encouraging, have never convinced the medical world that the method is strikingly successful. The best that may be said of it is that it does no harm, and in the hands of some physicians apparently shortens the disease and prevents some of the unpleasant sequels by which typhoid is so apt to be followed.

During the past two years two innovations have been made which, from the results attained by several observers, and in view of the theoretical studies on hyperleucocytosis to which I made reference, have thrown an entirely new light on the possibilities of vaccine therapy in typhoid fever. These two innovations are, briefly, as follows: First, the administration of the vaccine directly into the circulation, and secondly, the use of a sensitized or serum-treated vaccine instead of the plain bacterial growth hitherto used. These procedures, introduced into practise by Thiroloix and Bardon, and by Ichikawa, respectively, carried out the precise method of treatment that we had already suggested from our experimental results, and fully justified our expectations.

During the past year it has been possible for us to carry out the intended treatment in a number of cases in this vicinity, through the great courtesy of physicians who have allowed us to see their patients and have been willing to accept our suggestions in relation to their treatment. This confidence and cooperation has resulted not only in rapid amelioration in the majority of cases, but through comparative study of the successful with the unsuccessful cases has suggested improvements which may increase the percentage of favorable results.

Let us consider what happens when a killed preparation of sensitized typhoid bacilli is given intravenously in a case of typhoid fever. The introduction of something like one twenty-fifth of a milligram of the vaccine into the circulation is followed in a few minutes by a distinct shaking chill, which is accompanied by a rise of the fever of from one to two degrees. This shaking and fever, which is seldom extreme enough to be very uncomfortable, is accompanied by a fall in the number of white blood corpuscles. Following this reaction the fever rapidly falls so that in from six to twelve hours the temperature has reached normal, or even subnormal. This fall in the fever is accompanied by a rise in the leucocytes, profuse sweating, and a feeling of well-being. The severe headaches, beginning delirium, and other symptoms characteristic of typhoid, disappear, or are markedly ameliorated. Perhaps the most important result produced is that the blood usually becomes free from bacteria following a single injection. In forty per cent. of the cases, this return of temperature to normal is permanent, and the patient remains symptomatically, and to all intents and purposes, well. The temperature may fluctuate for a day or two and then become normal. This forty per cent. of aborted cases, as we call them, actually about twenty-five in our series, were restored to a permanent normal condition within a week after beginning treatment. About twenty-five per cent. more are markedly bettered, but not so rapidly cured; the course of these ameliorated cases is characterized by a permanent drop of say a degree in temperature following each injection, and the average duration of the disease in this category is distinctly shorter than is usual. There remain, however, a third of our cases, which total sixty-two, in which the intravenous vaccine treatment has produced no demonstrable effect. These cases are usually severe ones from the onset and it is impossible to say that the treatment did not prevent an even more serious course than the one observed. At least it may be said that the treatment does no harm in these cases, and is followed by temporary abatements of fever and symptomatic benefit. There is a significant blood picture in this class of unaffected cases; they are found to differ from those that are benefited by the treatment in the weakness of antibodies present in the serum. Mention has already been made as to the occurrence and diagnostic value of certain of these antibodies or agglutinins in typhoid fever. We believe from our study that a certain concentration of these antibodies is necessary to assure recovery or benefit after the vaccine injection which, as has been mentioned, produces an increase in the leucocytes. Our present conception of the mechanism of the rapid cure that is frequently produced is that it is due to the combination of these two factors, increased leucocytes and antibodies already present in the body. In other words, when the patient is fighting the infection successfully, a sudden call on his reserves, the phagocytes, finally routs the invader. It may be possible to supply these antibodies when they are lacking by serum from immune animals, and this is one of the many problems connected with this disease on which we are now engaged.

I have tried to lead you into full view of the firing-line of the forces attacking typhoid fever. You will perceive that much remains to be done in the line both of prevention and of cure, but you will not fail, I am sure, to share my belief that here is one of the major diseases which will eventually disappear. I have endeavored to show you the vulnerable points in its cycle of development. If individual cases be rapidly cured, much suffering and death will be prevented and great economic loss avoided; the period of dissemination of the disease germs will also be greatly shortened. Again, if comprehensive sanitary regulations safeguard the disposal of excreta from typhoid fever cases, detect and eliminate the carrier, and prevent the contamination of food and drink, the continuity of the disease will also be interrupted. Thorough prophylactic immunization of large or entire communities will not only protect most of the vaccinated individuals, but prevent foci for further spread of the disease.

You will appreciate the inequality in the utilizable knowledge of typhoid fever that has been acquired through the two different types of medical advance. The purely observational, bedside, clinical progress, resulted, after the lapse of centuries, in criteria on which a differential diagnosis could be made with considerable accuracy; in certain observations from which not wholly convincing conclusions were drawn as to the spread of the disease, and certain methods of palliative symptomatic treatment like hydrotherapy, and more recently, increased feeding. Contrast with this the advances during the last thirty-five years, which marks the era of bacteriology. The parasitic cause of the disease was determined. The demonstration of this microorganism gave us a means of certain diagnosis of the disease; threw light on the nature of the disease process itself; conclusively settled its method of spreading; and has given the only efficient means for specific prevention and therapy.

You will be convinced from this example that advances in applied medicine lie through laboratory investigation rather than through observations made at the bedside, at least in so far as the infectious or parasitic diseases are concerned. Equally persuasive data, from the laboratory standpoint, could be given in relation to the diseases of disturbed metabolism which involve the sciences of chemistry and physiology. You will further readily believe from the complexities of this one problem that I have tried to suggest, that successful prosecution of work of this sort may well monopolize the attention of a large group of workers. The number of these workers is limited only by the opportunities that are available; a reserve supply of eager and potentially productive minds is always at hand. The work itself is, however, not self-supporting, such advances as we may be able to make in the prevention and cure of disease bringing no pecuniary reward. It is fortunate indeed for our welfare that the contributions to human health are not patented as are contributions to human comfort and luxury.

The opportunities for advances in the medical sciences come, in part through private benefaction, in part through public funds wisely administered, when, as in this university, opportunities are given not only for the dissemination of acquired knowledge, but also for its advancement. This ulitization of public funds for any particular research is justified, apart from any preconceived notion as to its promise of practical reward.

Frederick P. Gay
University of California

CHARLES WILLARD HAYES

The geologist, geographer and explorer, known to colleagues and friends as "Willard" Hayes, died, after a long illness, at his home in Cleveland Park, Washington, D. C., February 8, 1916. He was fifty-seven years old, and in the twenty-eighth year of his professional career.

Hayes was born at Granville, Ohio, graduated at Oberlin (A.B.) 1883, and received his doctor's degree at Johns Hopkins University in 1887. His entry, in the same year, to the scientific staff of the U. S. Geological Survey was, as with most young men joining scientific bureaus of the government, a continuance of the student and research life. Hayes's studies were destined to contribute to a fuller understanding of the principles of geology and physiography; to better the methods of geological investigation and to make more practical, as well as more comprehensive and thorough, the application of geology to economic problems.

The first assignment of Hayes was as assistant to Russell, who, under the direction of Gilbert, then chief geologist, was making a general geologic section across the southern Appalachians. After a year of apprenticeship Hayes succeeded Russell, and began the areal geologic mapping, which he had satisfied himself was the only way to solve the complex structure of this region. It was in the course of this work that he demonstrated, in the folded strata, the existence of flat overthrust faults some of which have a horizontal dis-