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TWENTY-FIVE YEARS OF BACTERIOLOGY: A FRAGMENT OF MEDICAL RESEARCH[1]

IMMUNITY

JUST a quarter of a century ago, that is in 1895, the announcement was made at the 67th meeting of the German Society of Naturalists and Physicians that diphtheria, one of the most severe and fatal diseases of mankind, had been conquered by means of an antitoxin. This great event is a landmark, not alone in the history of medicine, but also in the history of the world, and it provides a high peak of achievement from which the growth of bacteriology may be viewed. In order that we may follow the growth with understanding, it is necessary, at first, to cast a glance backward before we begin on the narrative, the aim of which is to bring us to the state of knowledge of bacteriology existing in our own day.

Since disease is so universal a phenomenon and communicability from individual to individual so obvious an incident of its epidemic prevalence, the conception of a *contagium vivim* or *animatum* and hence of an invisible form of life as the initiator of the condition, can be traced far back in the written records of human events. And yet it was not until about 1850 that a microscopic body, which we would now call a bacterium, was actually detected in the blood of a sick animal. The anthrax bacillus, as it has since been named, which is now recognized as the inciting microbe of splenic fever, was destined to play a leading part in the development of the future science of bacteriology, but at this early period its full meaning was not perceived. When, however, in 1863 Davaine succeeded in communicating splenic fever to a

[1] Address of the president of the American Association for the Advancement of Science, Chicago, 1920.

healthy animal by the direct inoculation of blood containing the anthrax bacillus, the science of bacteriology may be said to have been born.

The dates are significant to one who wishes to follow the march of events which brought the greatest master of all, Pasteur, into the field of microbiology and led him on to the study of the infectious diseases, first of animals and then of man. For on looking backward we find that coincidental with Davaine's epochal experiments, Pasteur was already engaged on those studies of fermentation and putrefaction which were not only to set our conception of those processes on a secure biological foundation, but as an important side effect were to demolish, once and forever, the elaborately constructed but insecurely based doctrine of the spontaneous generation of microscopic forms of life.

For Pasteur it was but a step, although for us one of the highest importance, from the studies in fermentation and putrefaction to those on the infectious diseases in which, indeed, the great triumphs he achieved consist far less in the detection of new kinds of microbes to which the various contagious diseases might be described, than in his fundamental discoveries in immunology, or the science of the specific prevention of disease.

This work in the field of immunology, first opened to experimental investigation by him, is the aspect of Pasteur's labors to which I wish especially to direct your attention, since it forms the connecting bond between the earliest and thus the oldest, and the present and thus the latest discoveries in a field in which medical science has come to secure some of its most notable successes. There can be no doubt that the discovery in 1880 of the artificial immunity to fowl cholera came not as a direct incident, but rather as an accidental circumstance to the experiments being pursued. In after years Pasteur loved to point out the importance of the "prepared mind" as a requisite of the investigator, in order that he may seize hold of and utilize in respect to a question propounded by experiment what, viewed superficially, appears to be only an indirect and misleading answer. The advances leading rapidly from the artificially induced immunity in fowl cholera to the dramatic and historically and economically important immunity in anthrax and to the humanly important immunity in rabies, involved no strictly new conceptions on Pasteur's part. They consisted merely of the carrying forward of the ideas, often ingeniously modified, derived from the study of the sources of the condition of immunity in fowl cholera.

But should we inquire to what order of events already known this phenomenon of artificial immunity belongs, we should say at once probably to the order having to do with the Jennerian vaccination against smallpox. As every one knows, vaccination against smallpox consists in the utilization of human smallpox material which has become modified by passing through the cow, in which it sets up the condition named cowpox. When this modified microbic virus of the disease is returned to man, a mild form of smallpox is induced, which suffices through a term of years to protect the individual vaccinated, so-called, from infection with the more active or virulent smallpox virus.

The significance of the new observations was grasped by Pasteur and related to Jennerian vaccination. His great discovery then consisted in the determination that pathogenic or disease-producing microbes may be modified otherwise than by passing through foreign and relatively insusceptible animal species, and that such simple agencies as long cultivation *in vitro* (fowl cholera), high temperatures and therefore non-optimal conditions of growth (anthrax), and partial drying of the animal material carrying the microbe (rabies), would suffice so to modify and attenuate the respective microbes that upon inoculation they set up not the severe, but only mild states of infection, from which not only does recovery ensue, but the restored animal is enduringly protected from the ordinary and often fatal attacks of a disease.

Looking backward from our present higher position of vantage, we may discern certain minor imperfections in this fundamental work on artificial immunity. For example, it would now appear that the so-called attenuated cultures of the bacillus of fowl cholera, used for purposes of immunization, were not so much attenuated as actually dead, and that the material inoculated consisted of a mixture of dead bacilli and their metabolic and disintegrative products. In other words, it seems that Pasteur without perceiving it had discovered not only a principle of wide applicability in inducing artificial immunity, but a general method of utilizing dead bacteria as vaccines, and one which in more recent times has been widely resorted to in preventing outbreaks of typhoid fever, cholera, and some other diseases.

In 1882 antirabic inoculation was perfected. Pasteur had, of course, reflected deeply on the sources of the immune state and in explanation of it he inclined to the view that the basis of the phenomenon was a nutritive condition. He conceived that in the course of that form of microbic development within the body which came to a spontaneous end and left the individual protected, certain essential foodstuffs were consumed, in virtue of which the same variety of microbe could not later gain another foothold. Time has not upheld this simple conception; but when it was formulated the subject matter of bacteriology was still too fragmentary and scanty to point to the deeper underlying chemical and biological processes involved. Indeed, nearly ten years elapsed until Behring's discovery of antitoxic immunity brought about a revolution in the prevailing ideas and opened up new and fascinating vistas of research.

We have now reached the period at which the German school of bacteriology, led by Robert Koch, has arisen beside the French. Koch's career in science was meteoric. From an inconspicuous country practitioner he became, in the period beginning about 1880, the outstanding world figure in bacteriology. But his greatest work was completed in relatively few years, although that of his pupils has continued up to and is still potent at the present day. It is informing to reflect that just as Davaine made the first signal advance in the experimental inoculation of disease with the anthrax bacillus, and Pasteur the first dramatic demonstration of the practicability of protective inoculation with bacterial cultures also with that bacillus, Koch rose into fame through the study of its life history by direct observation under the microscope. But Koch's greater contribution to bacteriology consisted of a method of cultivation so perfected that pure growths of bacterial species were readily obtainable. The consequence was that in a very brief period of years a whole host of pathogenic bacteria or incitants of diseases of man and animals was secured, among which were the highly important bacilli of tuberculosis, cholera, typhoid fever, diphtheria, tetanus, dysentery, plague, meningitis and many others.

Up to the period we are now considering, all the diseases of microbic origin thus far investigated successfully belonged to the class in which the bacteria invaded the blood and the internal organs. But now we are about to learn of another kind of disease induced by a class of bacteria which are peculiar in that they do not migrate throughout the body but remain fixed in a special tissue or part, where they multiply and secrete a poison which finds its way first into the lymph, then into the blood and the organs generally. This latter class of microbes produces its effects to which we give the name of disease, and of which diphtheria and tetanus are examples, through the operation of a poison, peculiar to each, and in each instance attacking by preference certain definite organs or parts of them. Thus the poison elaborated by the diphtheria bacillus selects especially the lymphatic organs, heart and nervous system for its action, and the tetanic poison the nerve cells governing muscular contraction.

We have now returned by a route somewhat circuitous perhaps to the point from which we started, namely diphtheria and its antidote. But in the course of the journey we have taken, new points of view have been gained which, as will appear, are to transform entirely the outlook upon the problems that bacteriologists set themselves to solve.

Behring and Kitasato chose the task of inducing in animals immunity, to diphtheria on the one hand and to tetanus on the other. This was a logical undertaking and one clearly in the spirit of the times. Both men had a strong interest in the quest. The one (Behring) was deeply engaged in the investigation of the chemical disinfectants and conceived ideas of modifying bacterial growth through these agents, as Pasteur had succeeded in accomplishing with physical means. The other (Kitasato) had succeeded where his predecessor and the discoverer of the tetanus bacillus, Nicolaier, had failed in obtaining pure cultures of that microbe. Moreover, the restricted local development of the two bacilli and their generally poisonous or toxic effects aroused in them an eager interest intensified by the epochal discovery just made by Roux and Yersin that the toxin of the diphtheria bacillus was readily separable from the bacilli producing it and could be obtained by precipitation in, it is true, an impure state but one in which its poisonous action was preserved. Indeed, so appalling did its poisonous effect prove to be that these investigators could not imagine any other non-living substance than an enzyme which could exhibit such active properties.

The isolation of the diphtheria toxin, quickly to be followed by the similar isolation of the tetanus toxin, was an event of capital importance and reacted at once vigorously on the chemical aspects of bacteriology just struggling into the light. The immediate effect of the study of the new poisons, called toxalbumins, was to discredit a whole series of pure, crystalline basic substances obtained not long before from a wide variety of bacteria, to which the name of ptomaines had been given. Many of the ptomaines were possessed of poisonous properties; but what was disconcerting was that very diverse bacteria might yield identical chemical compounds which, therefore, lacked the property of specificity, an essential quality of bacterial activity. The toxalbumins, on the other hand, which even to this day have not been secured in a chemically pure state, exhibit in perfect degree the property of specificity and display all the power for evil and all the potential possibilities for good which their original and respective bacilli possess; and although no method of chemical identification of their special nature is available, yet their pathological effects and immunological activities serve readily and accurately to distinguish one from the other and to indicate their origin.

The rendering of animals immune to diphtheria, on the one hand and to tetanus on the other, proved a difficult but not impossible task. The method adopted was to admix disinfectant chemicals, of which the one finally selected was iodin trichlorid, with the bacilli to be injected under the skin of animals, or with the contents of the culture flasks at the end of the incubation period. Obviously, the intent was to moderate the poisonous action of the inoculated material, in the hope that a mild and not fatal infection would be induced from which recovery would follow leaving the treated animal immune.

The experiments were sometimes successful, and as such seem merely to illustrate a variation of the Pasteurian method of inducing immunity which, as we saw, was not distinct in principle from the Jennerian vaccination. But the break with the past was none the less imminent, for Behring's next act was not to speculate on the theory of immunity but to perform a decisive experiment. It is to be kept in mind that in the poisons or toxalbumins of diphtheria and tetanus, we possess the essentially active ingredients of the respective bacilli and that the body attacked does not succumb to the invading bacilli but to the action of the toxins. Hence, Behring turned to the blood of the immune animals and tested it for neutralizing power against the poisons, and discovered antitoxin; he injected the blood of an immune into the body of a normal animal prior to inoculation and discovered passive immunization; and finally, he injected the blood of an immune animal into animals previously inoculated with the bacilli of diphtheria and tetanus, and discovered serum therapy. The day for speculation on what constituted the immune state had now definitely passed, and the time had arrived for subjecting the phenomenon to experimental study.

The fluids or "humors" of the body, to employ a term made respectable by age, as represented by the serum of the blood, had been shown to carry the immunity principles, but what part did the cells of the body play in the process? Both fluids and cells were now submitted to rigid and ingenious scrutiny, and about them an immense literature has grown up. Soon the students in the field divided into two camps, namely, one led by Ehrlich, defending the humoral doctrine, the other led by Metchnikoff, urging the cellular or phagocytic doctrine. The conflicts which raged about these concepts were always animated and sometimes even bitter; but the ultimate effect was to extend rather than to retard and confound knowledge. We are moving now in more peaceful times, the heat of the earlier conflicts having largely subsided, and it may be stated that neither the one nor the other doctrine finally triumphed, but that the humors or fluids of the body on the one hand and the cells on the other have come to be recognized as the active participating factors in the immunity process, the one complementing the other. Where the phenomenon is one purely of the neutralization of a poison or toxin, the fluid portion of the blood suffices; where also the process is relatively the simple one of acting on and dissolving a bacterial cell, there also the fluid may suffice, although an essential element in the process may have been supplied by the white blood cells at the moment of their withdrawal from the body. But where the bacteria are not readily disintegrated and dissolved, there the phagocytes of the blood and tissues come into play and, through their power of engulfing these particles, operate as one of the body's main defenses against infection.

The unravelling of the intricacies of the immune state, following upon the work of Behring, has brought about a sudden and unprecedented enlargement of the scope of bacteriology, as well as supplied a wealth of new facts of which many have permanently enriched practical medicine and opened new territory to profitable exploration. It may suffice at this point merely to mention certain of the devices for diagnosis and means of preventing or of treating disease, which are the immediate heritage of studies in the field of immunity, of which many have come not as direct fruits, but as invaluable by-products of the search. In this manner have been secured the Widal test for typhoid fever, the Wassermann and allied reactions, the hypersensitive or Schick test for diphtheria susceptibility, the hypersensitive reaction as now applied to the detecting of the offending agency in hay fever and allied states, the refinements of bacterial vaccination in the prevention and sometimes in the treatment of disease, and so-called specific serum therapy. Moreover, these studies have placed in the hands of the bacteriologist a powerful instrument for detecting, through immunity reactions carried out in test tubes, or the animal body, new varieties of pathogenic or disease-producing bacteria and of investigating more closely and sorting out groups of pathogenic microbes not hitherto subject to analysis. Finally, the immunity reactions, as they are generically named, have been found not to be restricted to bacterial cells and poisons, but to apply to a wide variety of cells and their products. For it should be recalled that in the decade immediately succeeding the discovery of antitoxin, agglutinins, precipitins, bacteriolysins, cytotoxins, hemolysins, complements, chemotaxis, anaphylaxis, and the minutiae of phagocytosis were discovered and became the objects of animated and often feverish and sometimes controversial but always profitable investigation.

It happened also and quite naturally and logically that this should be the heyday of hypotheses concerning the biological basis of immunity and the manner in which interaction takes place between toxin and antitoxin inside as well as outside the body, and of the englobing of bacteria and other bodies by the blood and tissue cells, as well as the nature of the combinations and permutations and reactions between the more complex bacteria and cells in course of their immunological transformations. And thus there came to be elaborated the side-chain hypothesis of Ehrlich, which vied with the phagocytic theory of Metchnikoff as well as with the adsorption theory of Bordet and the physico-chemical theory of Arrhenius. And if in our busy lives of to-day we think less of receptors and amboceptors, of complements and complementoids, haptophores, and toxophores, and limit ourselves somewhat more closely, perhaps even a little too exclusively, to the observed fact itself, yet it is well that we do not forget how great at the time was the stimulus to research and how rich the booty which accrued from those labors tinged with the radiance of the real scientific imagination of an Ehrlich, a Metchnikoff, and a Bordet.

Not all the high expectations of practical benefit to follow from these discoveries have been realized, but sometimes the very failures have been turned to account in opening up new, or illuminating old, avenues of progress. In this connection it is instructive to recall the early pronouncement of Behring made two years after the discovery of antitoxin, and while he was under the influence doubtless of that great contribution:

"The present state of the immunity question," he says, "may be defined as follows: Thus far no generally applicable explanation for natural immunity has been forthcoming. But of the artificially produced immunity it may be said that the precise study of a number of examples has so far advanced our knowledge that we may assert with confidence that the immune state arises from a peculiarity of the blood and, indeed, of its cell-free portion; in no instance in which a sufficiently high grade of immunity has been attained in an animal species, easily susceptible to the infection in question, has the blood withdrawn from the body failed to show evidences of the presence of the immunity-conferring substances."

In this statement will be perceived the extreme humoral view of the origin of immunity, which subsequent investigators failed to uphold. But he continues in a prophetic vein, unfortunately likewise destined not to be wholly fulfilled.

"With the achieving of this standpoint the next step in the winning of specific curative agents for the infectious diseases is clearly outlined: all that is required is the induction in a susceptible animal species of a high degree of artificial immunity, and then to test the blood for the presence of protective and healing substances."

Time has exposed the fallacy of this over-confident attitude and taught the distinction between the two varieties of infectious disease and their corresponding immune states, according as their main effects and symptoms arise from the toxalbumins or poisons we have been considering, or the intimate presence within the organs of the microbes themselves. The former variety chances indeed to be in the minority, and hence it has come about that the diseases to be successfully combated by antitoxins are few in number, while those in which the microbes penetrate deeply into the body and which poison its tissues by means of so-called endotoxin, are far more numerous. The latter class includes such important diseases as tuberculosis, typhoid fever, meningitis, plague, cholera, the septicemias, and still others. And yet the failures have been only partial, and success has been and is still being won against odds which were once considered insuperable.

What is striking is the capriciousness with which the microbes themselves or their endotoxins lend themselves to the making of therapeutically effective serums, as contrasted with the ease and certainty of action in this respect of the toxalbumins. All the latter seem capable of yielding abundant antitoxins, and this independently of their precise source, since it happens that toxalbumins resembling those of bacterial origin exist also in the higher plants —as in the castor and jequirity beans—and in the venoms of reptiles and insects. On the other hand, it has not thus far been found practicable to fashion curative serums for tuberculosis, typhoid fever, plague, cholera, etc., while success has been achieved in the instance of epidemic meningitis, and very hopeful results have recently been attained in the case of pneumonia.

In meningitis the success is linked with the recognition of a second principle of action, namely the advantage to be derived from what may be called the local specific treatment of a disease, or the bringing of the healing serum into direct and intimate relation with the seat of the infection itself. Since in epidemic meningitis it is the membranes surrounding the brain and spinal cord and those more delicate ones lining the cavities of the ventricles of the brain which are the seat of infection, it has been found easily possible, through a simple and safe procedure, to inject the serum into the cavity of the spinal meninges, whence it is quickly distributed over all the membranes of the brain and cord. It may be of interest to remark that it is not practicable to reach the inflamed membranes with the serum by way of the blood, since nature, in order to protect the sensitive nerve tissues from injury by any chance deleterious substance in this fluid, has interposed an impenetrable barrier, the choroid plexus, between the circulation and the cerebrospinal fluid which bathes and sustains the nervous organs, and which is itself elaborated from the blood by this plexus with an accuracy of selectiveness highly remarkable.

In pneumonia again a beginning success has been achieved through a finer discrimination of specific kinds among the pneumococci, the inciting microbes of the disease. This distinction is independent of ordinary physiological and cultural characters displayed by the bacteria, which do not serve to bring out the underlying specific properties of each, and has been accomplished by means of the so-called immunity tests carried out in test tubes or in the animal body. The gain to practical medicine from the detection of the fundamental differences subsisting between the three main types of pneumococci existing in this country has been very great. Already a curative serum for one of the specific types of pneumonia has been secured, and through its application many lives have been saved; while beginnings have been made in respect to vaccination against the disease when, as sometimes happens in institutions and in communities, epidemics prevail and claim many victims, as occurred in the Army training camps during the measles epidemics of 1917–18.

Thus we have learned that the immunity reactions, or the effects on bacteria and their poisons, of the fluid and cells of the body as modified by the process of artificial immunization, provide more delicate and precise means of discriminating bacterial species than the qualities of form, growth appearances and physiological activities, and more accurate methods of distinguishing poisons than the most refined chemical analyses; and we shall learn a little later in connection with the distinct but related hypersensitive or anaphylactic state, that the prepared and sensitized animal body responds to infinitesimal amounts of protein matter according to its specific origin, in a manner not otherwise determinable and far beyond the most delicate laboratory test which the chemist has invented. The animal body thus artificially prepared, or as sometimes happens naturally sensitive, acquires an appreciation of the inner constitution of the protein molecule, classifying it, as it were, not only according to its ordinary chemical nature, but according to its species origin.

The immunity reactions we have considered are not artificial creations, since as we now know, they are the very processes which nature employs in her unaided efforts to abate infections, and when need be, to adopt the body to foreign proteins. The spontaneous recovery from infectious disease, by which is meant merely that the body by its own power overcomes the microbes and their poisons, depends upon the setting into motion of the series of operations through which immunity responses in fluids and cells are insured, precisely as has been described in the event of an artificial immunization. Hence in our efforts at serum therapy we aim merely to aid "nature," by introducing, as it were, into the beset body the finished immunity products artificially produced in healthy animals; and in protection by vaccination, success is assured only to the extent to which the healthy body has been compelled to prepare the specific immunity substances and to hold them ready at hand to combat the entrance through its outer gateway of, for instance, such microbes as those inciting typhoid fever and smallpox.

That it is through the prowess of the body itself, and not the skill and art of the physician, that recovery from infectious disease takes place, had already become evident to the ablest physicians of nearly one hundred years ago. It is true that they could form no real conception of the manner in which the cure was brought about, but in admitting the existence of a class of maladies which Jacob Bigelow in 1835 called the "self-limiting diseases"[1] this innate faculty of the organism to overcome infection was recognized. It may be of even more than historical interest to reprint here the pregnant paragraph in which Bigelow expresses this view:

> This deficiency of the healing art (he is now writing of the advances in knowledge of the structure and functions of the human body in contrast to the lagging behind of the science of therapeutics, or the branch of knowledge by the application of which physicians are expected to remove diseases) is not justly attributable to any want of sagacity or diligence on the part of the medical profession. It belongs rather to the inherent difficulties of the case and is, after abating the effect of errors and accidents, to be ascribed to the apparent fact that certain morbid processes in the human body have a definite and necessary career, from which they are not to be diverted by any known agents, with which it is in our power to oppose them. To these morbid affections, the duration of which, and frequently the event also, are beyond the control of our present remedial means, I have, on the present occasion, applied the name of the *self-limited diseases;* and it will be the object of this discourse to endeavor to show the existence of such a class, and to inquire how far certain individual diseases may be considered as belonging to it.

ANAPHYLAXIS

Allusion has several times been made to the hypersensitive state which is often regarded as the opposite of the immune condition. Because the latter is conceived as protective and hence is spoken of as being prophylactic, the former in turn has been named anaphylactic. The obvious distinction between the two conditions is simply defined by the statement that while the immunized animal shows a greater degree of resistance to a second inoculation of the materials used for immunization, the anaphylactized animal on the contrary shows a heightened susceptibility.

The history of anaphylaxis illustrates the manner in which the rapidly growing knowledge of immunity reacted on the appreciation of this condition. It now appears that the physiologist Magendi, who flourished in the first quarter of the nineteenth century, first noted that an animal which had borne without apparent effect one injection of a quite harmless protein such as egg white, reacted severely to a second injection of the same kind of material given after an interval of days. No further contemporary attention seems to have been given to this isolated incident, and it was not until 1894 that the speaker chanced again upon the phenomenon. He was engaged upon a study of the pathologic action of the toxalbumins, and his attention was attracted by recent experiments on the similar globulicidal (or red blood corpuscle destructive) action of certain alien blood serums, such for example as the serum of the dog for the red globules of the rabbit. Since animals could be rendered immune to the toxalbumins, the attempt was made to make rabbits immune to dog's serum, but without success. On the contrary, it was found that animals which had withstood one dose of dog's serum succumbed to a second dose given after the lapse of some days or weeks, even when this dose was sublethal for a control animal.

Again the observation fell on stony soil, as indeed subsequent ones were destined to do a few years later and, as it now appears, chiefly because knowledge of and interest in the general subject of immunity had not progressed far enough at that period to present to the contemplation of the "prepared mind," to use

[1] Jacob Bigelow, "Discourse on Self-limited Diseases," Boston, 1835.

Pasteur's phrase, the sharply contrasted hypersensitive state.

But the time for the systematic investigation of the phenomenon was approaching, for between 1902 and 1904, Richet and his pupils had their attention arrested by an extraordinary incident, as it then seemed. In undertaking to effect immunization with certain poisonous proteins of animals, they found that instead of inducing resistance, they induced hypersensibility. To this latter condition they applied the name anaphylaxis. Although as it subsequently turned out, the idea involved misconception of the nature of the process, yet these studies stand forth illuminatingly as recognizing for the first time the dependence of the hypersensitive state upon a preceding injection of a given protein substance and the necessity of an incubation period covering a number of days between the injections, in order that the sensitive condition might be ushered in. That the sensitizing effect was of the nature of a general biological reaction of the animal body to the parenteral introduction of natural proteins into the body, without reference to their primarily poisonous character, came to be appreciated a little later as the result of observations made on rabbits and guinea pigs injected and then reinjected with horse serum, as well as with other innocuous proteins. In order to arouse the reaction of immunity in the animal body, some degree of primary poisoning of the cells, as with bacteria, their metabolic products and similar substances originating in other varieties of living beings, must be accomplished; while the sensitive state arises from the interaction of the animal body with any native protein substance whatever which finds its way directly or indirectly into the blood.

From the many investigations which now ensued, it appeared that while many kinds of warm blooded animals are subject to the condition, yet the most striking, because most uniform and dramatic effects are yielded by the guinea pig, which has since become, as it were, the "classical" animal for observing and studying anaphylaxis. The reason for this choice arises from the circumstance that in the guinea pig a sensitization of the smooth muscle fibers occurs, so that on reinjection of the original protein, among other effects, a contraction of the lining membrane of the bronchi takes place, which by closing their lumina and excluding air, quickly causes death from asphyxiation. Moreover, the guinea pig has proved exquisitely responsive to sensitization, so that minute quantities, measured even in fractions of milligrams, of pure native proteins suffice to induce a specific hypersensitive condition, whence it has followed that the prepared guinea pig has been found suitable for the investigation of the ultimate chemical relationships, not otherwise observable, which subsist between native proteins.

Profoundly different as are the obvious features of the anaphylactic and immune reactions, yet certain of the fundamental conditions governing both coincide. It will be recalled that in arousing immunity in animals by artificial means, certain new substances of the general nature of antipodes, or as technically named, antibodies, are made to arise in the blood of the treated animal; and it now appears that in the course of sensitization of animals, antibodies to the proteins injected also develop. In both instances the material originally injected, whether primarily poisonous or not, if active, belongs to a class now called antigens, that is generators of antibodies. The expression of the immunity reaction, in its simplest terms, consists of a chemical or physico-chemical union between the original antigen and the manufactured antibody, taking place in the body or in a test tube, through which the primarily poisonous antigen is rendered innocuous. In other words, the immune antigen-antibody complex is a harmless compound.

In a similar manner the sensitizing antigen and induced antibody unite in anaphylaxis, but the product of the union is essentially different from the one just considered, in that it is highly injurious, and the effect of the antigen-antibody complex is not to protect, but to poison the animal. The basic distinction between the immune and the anaphylactic condition, as described, is further enforced when we recall that the original toxic protein used to immunize is detoxicated in the course of the immune reaction and the original non-toxic protein used to sensitize is endowed with the property of intense toxicity in course of the latter reaction.

As in the instance of the immune state, a still undecided controversy is going on as to whether the hypersensitive condition depends upon humoral or upon cellular factors. There is no doubt that the anaphylactic antibody exists free in the blood, and hence that a normal animal can be rendered passively sensitive by the infusion of blood derived from a sensitized animal. It is equally true that the anaphylactic response is in part a cellular one, as in the instance mentioned of the bronchial musculature stimulated to contraction. By appropriate experiments it can be shown that organs containing smooth muscle taken from sensitive animals, exhibit the equivalent of the anaphylactic reaction even outside the living body; and also that coincidentally with the appearance of the "shock" of the reaction in the guinea pig, the blood becomes incoagulable.

Hypersensitiveness may exist independently of purposive artificial sensitization, and some of the most important examples of that condition have been observed in man. Because of their size, perhaps for other reasons, human beings even when sensitive react to the parenteral injection of native proteins less severely than the smaller animal species. And yet lamentable instances, if very few in number, of serious or even fatal anaphylactic effects have been observed in man. These have occurred especially in connection with the therapeutic employment of curative serums derived from the horse. The greatest danger from this source is at the time of the first injection, for while severe effects do sometimes follow upon a second or subsequent injection, they have never been attended by fatal consequences. Luckily, means are known for anticipating these even infrequent accidents, and of guarding against their dangers without at the same time depriving those in need of the benefits of serum protection or therapy.

Beside the active state of sensitization another is known which may be termed negative. Thus it has been found that when a sensitive animal is given an injection of a protein which produces a certain degree of anaphylactic effect, but not a fatal outburst, the treated animal can for a time be rendered insensitive. And thus human beings who are sensitive, say to horse serum, may be desensitized by means of successive small inoculations of the diluted serum, and while in the refractory state thus induced receive without risk larger injections of the serum.

On the other hand, lesser states of anaphylaxis in man are by no means infrequent. To them belong the rashes of "serum sickness" following the injection of curative serums which while annoying are not dangerous, and the very disagreeable manifestations of hay fever and its allied conditions, now attributed to the action of vegetable materials, pollens chiefly, upon the sensitized mucous membranes of the nose and throat. Recent studies by Auer have shown that animals sensitized with harmless proteins, such as horse serum, develop severe local inflammations when from any local cause an extrusion of the antigen-containing fluid of the blood is enabled to penetrate the extravascular tissues; and on the basis of this observed fact he has suggested that functional disturbances of many organs of the body in sensitive human subjects may be brought about in a similar manner.

In a related field the hypersensitive reaction has been employed to aid in the diagnosis of important diseases of man and animals. It is apparent from what has been stated of the site of the fatal anaphylactic shock in the guinea pig, and as stated a moment ago of the sensitiveness of tissue cells in general to the circulating anaphylactic antigen, that a visible local reaction might be obtainable by introducing the protein to which the animal or person is sensitive into a visible portion of the body, as say the skin. In this way sensitiveness is looked for before serum injections are given, tuberculin is employed to disclose hidden foci of active tuberculosis, luetin is used to expose evidences of latent syphilis, and, in a modified manner, the Schick test is applied to determine whether exposed children do or do not carry in their blood, spontaneously as one might say, sufficient diphtheria antitoxin to afford them security without a protective serum injection. And beside the benefits accruing to human therapy directly from the working out of the meaning of anaphylaxis are to be placed those improvements introduced into veterinary practise, from which human preventive medicine also has derived great gain, namely, the application of the tuberculin test in clearing milch herds of actively tubercular cattle, and of mallein to the controlling of glanders among horses.

FILTERABLES

As we move from the contemplation of one achievement to another in bacteriology, we rarely pause to reflect how far circumstances almost accidental have favored the gains. The working out of the biological basis of fermentation and putrefaction, and a little later of the microbic origin of disease, is obviously bound up with the perfection of the compound microscope, and the usefulness of that instrument for the purpose is as obviously bound up with the ultimate size of bacteria and related organisms. And yet without the fortunate conjunction of an optical device and the degree of magnitude of living objects, we should still be groping in outer darkness in the search for the origin of disease, and still struggling with the phantoms of spontaneous generation. But the great men who proved the connection between microscopic life and the biological processes mentioned, including the source of the infectious diseases, did more than describe the phenomena revealed by the microscope and otherwise. They established methods with principles so clearly enunciated and rigidly based that it has been found possible to penetrate into an inhabited territory in which thus far the most powerful microscope has not always enabled us to discern the living forms.

Thanks to their labors we know now, first, that the faculty of setting up disease in successive individuals is a property only of matter which can itself increase indefinitely, and all matter thus constituted is possessed of life; and second, that certain disease producing parasites can be separated mechanically from the soluble products of their growth, by passage through earthenware filters, in which the interstices or pores are smaller even than the size of the microbes themselves. By varying the density or porosity of these filters, we arrive at a way of roughly estimating the size of the microbic cells.

Thus it came about that in 1898 two German bacteriologists, Loeffler and Frosch, who were engaged on the study of the very highly communicable foot and mouth disease of cattle, discovered that after diluting the contents of the unbroken vesicles which arise in that disease, with 20 to 40 times their volume of water and passing them through such earthenware filters, the filtrate not only would induce the disease on inoculation, but that the same series of events followed the dilution and inoculation of the vesicular contents of the experimental variety of disease through an indefinite series. Obviously the filtrate contained a living element which came to be called a virus, just as is the smallpox germ, for in neither instance, and notwithstanding laborious endeavors, has the living organism itself ever been seen under the microscope.

We now recognize a class of microbes or viruses which are so minute as to be regarded as ultramicroscopic, and yet so active as to be capable of setting up disease in animals and man. The precise limits of the class have yet to be defined. When we consider that there remain still to be detected the microbic incitants of some of the most contagious as well as common of diseases, our minds readily seize hold of the possibility of their being of this nature. Thus the microbes responsible for such contagious maladies as measles, scarlet fever, and chicken pox, and those inducing smallpox and rabies are not known, and not a little obscurity still surrounds the etiology, as we say, or immediate origin of epidemic influenza.

Inasmuch as the filterable microorganisms or viruses, or filter passers as the British prefer to call them, are known alone through their disease-producing propensities, no one can say whether, as is true of the bacteria, innumerable kinds exist in nature, among which relatively a small number has acquired parasitic or pathogenic qualities. Of the less than a dozen diseases known or on good grounds considered to be induced by filterable microorganisms, two attack human beings, namely poliomyelitis or infantile paralysis, and trench fever; and a third, yellow fever, which until very recently was believed to belong also in this category, has now been relegated to another class, with respect to which special devices suffice to bring into view its microbic incitant.

There exists, therefore, a degree of uncertainty in this field of research for which allowance must be made, since it may well happen that suddenly through a fortunate series of experiments or the opening up of new methods, a parasite hitherto regarded as invisible may be brought into microscopic view. Should, for example, complete evidence be brought forward to relate the Rickettsia bodies to certain specific infectious diseases transmitted especially by insects, as by the wood tick in Rocky Mountain spotted fever, and lice in trench and typhus fevers, then another group will have been transferred from among the ultramicroscopic to the visible parasites. A similar situation exists regarding the globoid bodies of poliomyelitis, the disease of man most convincingly established as induced by a filterable microorganism. By means of a highly specialized method of cultivation applicable especially to the class of spiral microbes, or spirochetæ, Dr. Noguchi and the speaker isolated from the nervous organs of cases of poliomyelitis, globular bodies so minute as to be just at the limit of visibility under the highest power of the microscope. With cultures of these bodies they induced experimental poliomyelitis in the monkey; but the culture method itself is so intricate that thus far few bacteriologists have been able to repeat the work, which therefore still awaits final confirmation.

Since the recent pandemic of influenza and the assault made upon the so-called influenza bacillus of Pfeiffer, isolated first in Germany during the influenza epidemic of 1889–1890, the inciting microbe of that disease has been sought among the filterables. The announcement of the finding of such a parasite in the nasopharyngeal secretions by Nicolle and Lebailly of Paris in the autumn of 1918, aroused high hopes which subsequent investigations have not served to sustain. The problem was approached in a somewhat different manner by two workers—Olitsky and Gates, at the Rockefeller Institute. Their studies embraced two periods, the epidemics of 1918–1919 and 1920, and the intervening (interepidemic) period, the latter serving as a control for the former. The essence of their investigations consisted in injecting through the trachea into the lungs of rabbits saline nasopharyngeal washings derived within the first 24 to 36 hours after the appearance of symptoms from influenza patients and observing the effects (*a*) upon the blood and (*b*) upon the lungs. The striking changes, in the successful experiments, relate to the white corpuscles of the circulating blood which suffer a numerical depression affecting chiefly the mononuclear type of cells, and to the lungs in which multiple hemorrhages and edema, but not pneumonia, arise. The effects are correlated: where no lung lesions are found no blood alterations occur. These objective phenomena are induced by filtered materials free of all ordinary bacteria (ærobic and anærobic) and they have not been secured otherwise than with materials derived from early cases of epidemic influenza; but when present, the rabbits affected very readily become subject to the action of various other bacteria (streptococci, pneumococci, staphylococci, influenza bacilli), to which they are otherwise resistant, but which then settle in the lungs and excite fatal pneumonic affections. The unassisted action of the influenzal material is not fatal; only when an ordinary bacterial lung infection is superadded does death follow. All who are familiar with the effects in man of pure influenza and then of influenza complicated with pneumonia of pneumococcal, streptococcal, etc., origin will appreciate this distinction.

What also characterizes the class of diseases incited by the true filterable parasites is their high degree of specificity and the enduring immunity which follows recovery from an attack. This is true among animals, for instance, of hog cholera and foot and mouth disease, and in man of poliomyelitis. This specificity is shown by the difficulty or impossibility of implanting the virus on specifically remote animals. In poliomyelitis, for example, only monkeys are subject to experimental infection, in hog cholera and foot and mouth disease, only swine and cattle. Bearing in mind Behring's dictum that to produce a therapeutic serum, it is essential to immunize highly susceptible animals, it becomes evident why success has not crowned the many undertakings to prepare an antipoliomyelitis serum in the horse or other large animal, and why it is only by the use of swine themselves that an anti-hog-cholera serum has been secured.

The investigation of this class of excessively minute or filterable parasites casts a sharp ray of light into a neighboring field of biological research which at the time aroused hopes of further rapid progress but which the intervening time and effort have not realized.

Perhaps no subject in experimental pathology has been pursued with more thought and energy than the one to which the name of cancer research is applied. The reasons are obvious. The nature of the source of the cancerous tumors is still shrouded in essential darkness. It is, of course, known that cancer sometimes follows upon prolonged irritation and inflammation of tissues variously excited. But what the immediate impulse is that calls forth the cancerous state is unknown. And yet advances have come from the study of the spontaneous and transplantable cancers in mice, rats and some other animals. A long series of biological conditions governing the growth and recession of the tumors have been uncovered, and by altering those conditions, on the one hand growth can be promoted, and on the other, retarded. In this way, Murphy and his coworkers have accounted for the influence of the action of the X-ray in affecting cancer growth; and by observing the correlative effects on the lymphoid structures of the body, which are very sensitive to the rays, and the changes corresponding to them in the circulating blood, they have so altered the scale as almost at will either to abolish or stiumlate the development of mouse cancers.

But these experimental results and others of a class in which the defensive forces of the body can be marshalled against the implanted cancer cells, throw no real light upon the series of events underlying the origin of cancer. The light referred to was shed by the studies of Rous, of the Rockefeller Institute, upon a sarcoma, or fleshy cancer, of the domestic fowl. This cancer, which arises at times spontaneously in fowl, is subject to successful implantation in other fowl. The specificity is accurate; it will not grow in other birds and grows best in the variety of fowl in an individual of which it originally appeared. Its growth is first local, as is cancer in man, and later metastatic, or, appearing at a distance and starting from microscopic masses of cells derived from the original tumor and carried by the circulation to remote parts of the body. The altogether new and unprecedented fact about this tumor, which has, however, not yet been found to be true of the cancers of mammals, is that it may be induced by the injection into the susceptible variety of fowls, of a cell-free filtered extract of the tumor. In other words, Rous has accomplished for this tumor what bacteriologists had effected for a certain refractory group of the infectious and communicable diseases, namely, relating it to a form of life not imagined by the founders of bacteriology, but which their discoveries in the field of the living microscopic, as opposed to the ultramicroscopic, universe brought within range of recent biological research.

SPIROCHETES

The vicissitudes of bacteriological science, like those of other sciences, have depended upon time and method, and sometimes the one and sometimes the other has served to promote discovery. When by a happy conjunction of circumstances, time and method happen to conjoin, then advances almost startling in nature may take place.

It is in this way that we may view the remarkable progress of events in connection with a class of special microorganisms or spirochetae, so called since Schaudinn's discovery in 1905 of the *pallida,* the microbic inciter of syphilis. The search for the microbe of syphilis had been unremitting since the early days of bacteriology, and not a few false claimants held the field for a brief space. Schaudinn's discovery was very soon confirmed, and has now been firmly established; and it is interesting to note that in fact it was itself a confirmation of an observation made a few years earlier by Metchnikoff and Bordet, who, however, because of the technical difficulties of the quest did not succeed in confirming their own findings. The unusual difficulties surrounding the detection of the living *pallida* in the body fluids, because of its extreme tenuity merely heighten the respect we must hold for the zoologist Schaudinn's perspicacity. Very soon staining methods were introduced to lighten the task of detecting the *pallida,* but so capriciously did they act and so baffling did the ordinary microscopic detection prove, that the great promise of the employment of the *pallida* for purposes of diagnosis and treatment was not at once realized.

None the less, a great advance in bacteriology had been achieved, and a new class of microbes potentially disease-producing was presented for study. Within a year a second spirochete, called *pertenuis,* was discovered in the lesions of yaws, a tropical disease having certain affinities with syphilis. The search for the delicate spiral organisms was not an easy one, and only the masters of bacteriological technique were likely to succeed in it. Then suddenly the labor was lightened and the road made smooth for a rapidly succeeding succession of discoveries in this field by the invention and application of the dark-field or ultramicroscope. This instrument was perfected for observing dispersed particles in colloidal solutions and, as many of you are aware, operates by projecting powerful rays of light in directions parallel to the surface of the microscopic slide. Such a field if optically empty will be dark and not luminous; but if particles are present in it, the rays of light will be intercepted and the particles illuminated. They in turn, and according to their size, will appear as bright objects, or when very small, give a diffuse luminosity to the field. The phenomenon is similar to the one described by Tyndall, in which a beam of light passed through a dark space containing suspended particles causes them to become visible. When the suspended matter consists not only of dispersed particles, but of microorganisms, these also become luminous, and when, as with the spirochete, they exhibit a wavy structure and independent motion, they at once arrest attention. To-day the dark-field microscope is found in every well-equipped clinic, and it has aided in adding many new species to the already considerable number of microbes known to be disease-producing.

The latest significant addition to this field is the *Leptospira icteroides,* or the jaundice-producing spiral, which Noguchi has recently detected in the blood and internal organs of cases of yellow fever. His extensive investigations carried on in Ecuador, Mexico, and Peru, as well as at the Rockefeller Institute, have rendered it highly probable that this spirochete is the microbic incitant of that severe epidemic disease.

Yellow fever, as you know, is an insect-borne disease and arises from the insertion into the blood of man of a virus carried by a particular mosquito—*Stegomyia calopus.* After the mosquito transporting the virus has bitten a healthy person, an interval of about five days elapses before his blood becomes infective, and the infectiousness endures about three days longer. During the latter period the blood serum can be passed through the finest-grained porcelain filters without losing its infectivity. On the other hand, a normal mosquito which has bitten a yellow fever patient, does not become capable of infecting other human beings until after about twelve days. Hence the insect acts not merely passively, as a needle might, as the conveyer of the virus, but is necessary in order to increase or otherwise modify the infective material withdrawn from the blood.

The discovery of the yellow fever spiral definitely removes the disease from the class believed to be provoked by ultramicroscopic organisms, and at the same time adds so well defined a microbe as *Leptospira icteroides* to the group of filter passers. The data so far secured regarding this spiral in relation to yellow fever fulfill the conditions arising out of Reed and Carroll's discoveries in connection with the disease in man. These are great gains for theoretical bacteriology. The rewards to practical medicine are even greater, since it has been found that *Leptospira icteroides* lends itself to the making of an active vaccine (killed organisms) and also an effective therapeutic serum. Hereafter yellow fever is to be combated (1) by removing the breeding places of the stegomyia, (2) through vaccination, and (3) by an antiserum.

The etiology, or causation, of yellow fever so long and fruitlessly sought seems to have been solved, and it may be of interest to inquire why just at this juncture? The answer is, through the conjunction of the "prepared mind" and animal experimentation. For nearly a decade Noguchi has been investigating this spiral class of microbes, in course of which he added materially to our knowledge of methods of study and of new species. He had first-hand knowledge of a related disease, infectious jaundice, transmissible to guinea pigs, which prevails endemically in Japan and sporadically elsewhere, and in which Inada had discovered a peculiar spiral organism (*Spirocheta icterohæmorrhagiæ*). In other words, the time was ripe and Noguchi peculiarly equipped to take up again and investigate with newer methods the problem of yellow fever.

The story is still incomplete, as recent developments have shown; for just as Metchnikoff and Bordet had seen the *pallida* before Schaudinn, so it now appears Stimson of the U. S. Public Health Service had previously observed the *icteroides*. He examined a series of sections of organs stained by Levaditi's method to show spiral organisms, taken from a patient having yellow fever who succumbed in New Orleans in 1907, and in the kidney found spiral forms to which he gave the name of *Spirocheta interrogans*, but the significance of which could not then be determined, and which Noguchi now identifies as the *icteroides*. Coming at this time and in this way, the observation is a welcome confirmation. Without the many data since supplied by Noguchi's experiments and studies of living cases of yellow fever, it possesses only suggestive value. The finding came too early in the development of our knowledge of the spirochete, and again the seed fell on stony ground.

There remains one further aspect of this incomplete discussion of spiral microbes in their relation to disease to be considered briefly, namely their separation into two classes according as the diseases induced by them respond to treatment on the one hand by curative serums, and on the other by so-called drugs or chemicals. It has just been stated that yellow fever can be combated by a serum of this kind, and the same is true of infectious jaundice. In this respect the two inciting microbes—*L. icteroides* and *S. icterohæmorrhagiæ*—behave as do certain bacteria. But the spirochete of syphilis and yaws and some others are not subject to serum influences, and hence they and the disease they induce must be attacked from another quarter, and in this instance with chemicals for which they evince an extraordinary selectiveness, as do the malarial organisms and certain parasitic trypanosomes which are of protozoal nature.

CHEMOTHERAPY

Chemotherapy is the name applied to the branch of experimental medicine in which chemicals, or drugs, are searched for, and when necesary and possible, fashioned to subdue a particular kind or class of infection. The beginnings of chemotherapy reach into the dim past; the science of chemotherapy is just being built up. The epochal discoveries of the curative value of cinchona bark in malaria and of mercury in syphilis, are examples of the early, and as we now say empirical working out of specific therapeutics.

But in emphasizing these two triumphs of the empiric period long antedating the experimental epoch in medicine, sight should not be lost of the essential point, namely that the virtues of those remedies were established also by experiment carried out over long decades and upon man himself, for in no other way could these active drugs have been separated from the thousands of innocuous or even harmful ones applied by man at all stages of his evolution to the alleviation of suffering.

In a strict sense, curative serums are examples of chemotherapy, and the most specific ones known, since they are so exactly adapted to combat a given microbe or its toxin, and because in the end the active component is chemical in character. But as usually employed, the term is applied rather to chemicals or drugs not produced by the animal body and of definite and ascertainable ultimate composition.

The beginnings of the experimental science of chemotherapy are very recent, and hardly more than a start has been made in exploring the field. The principle on which it is based can be expressed simply: microbic parasites on invading the animal body arouse defensive activities on the part of the host, which when of sufficient intensity serve to weaken and restrain, and ultimately to overthrow and conquer the invaders. These natural defenders, as we learned earlier, consist of fluid and cellular constituents of the body, sometimes preformed, sometimes only manufactured on demand, and in part especially adapted to the particular parasitic agent to be vanquished.

With this picture before them, of the manner of the body's defense against microbic invasion, bacteriologists could appreciate that the overcoming and healing of infection is never a mere passive process, and the action of healing agents in the body does not occur, as the older therapeutists believed, precisely as would happen if the parasitic agent could be exposed to the effects of drugs, say in a test tube. Moreover, it was always evident that such effective drugs as quinine and mercury must be employed sparingly, because while they were able to injure and thus to lead to the destruction of the microbes inducing malaria and syphilis, they were likewise capable of injuring the component cells of the body itself.

The outstanding instance in which experimental chemotherapy has registered a great success is in connection with the organic compounds of arsenic, which have been adapted to the overcoming of infection induced on the one hand by spirochetes and on the other by trypanosomes. That arsenical compounds possess therapeutically active properties against these two classes of parasitic diseases—as represented on the one hand by syphilis and on the other by African sleeping sickness—is not entirely a recent discovery; but until the systematic investigations of Ehrlich were instituted, which ultimately yielded salvarsan, knowledge was fragmentary, medical practise based on it ineffective, and the road to progress obscure. Now the outlook is wholly changed, and there is going forward an active and either already successful or at least highly promising search for new drugs or chemicals, directed against both the bacterial and the protozoal parasitic microbes. This territory so newly opened to exploration in which organic chemists and pathologists should pool interests in order to move forward, is of almost infinite possibility, since the number of chemicals is nearly limitless which can be produced and so fashioned as to injure and subdue as it were the parasitic invader, and at the same time, pass over and leave little influenced the adjacent body cells. But the conditions of the search are intricate since, as just indicated, a useful drug must exhibit high power of attack upon the protoplasm of a parasitic microbe and a low one on that of the cells of the blood and the organs, in order that the former and not the latter may be predominately affected. It is a peculiarity of chemicals as contrasted with serums that they can never be so accurately designed to their purposes as to remain entirely without effect on the cells of the host; but it is also recognized that when the drugs are effective, they do not carry on a single-handed combat, but serve best when they either assist or are assisted by the natural defensive mechanisms of the body, which also are roused into action to overpower the invader and the cooperation of which often insures protection against reinvasion, acquired at the end of, and in consequence of, the struggle.

INFECTION AND SURVIVAL

Infection and the mastering of infection are intricate biological processes in which contending forces are brought into play one against the other, whence a struggle ensues. We have seen that the host stands ready equipped with mechanisms of defense which may be quickly mobilized, and which undergo favorable modification during infection, when as we say, it proceeds toward a favorable termination. The bacteriologist has learned within the past quarter of a century to imitate nature's method of surmounting infection by supplying certain of the defensive implements artificially wrought to be brought to her aid in time of stress and need, and the chemist is learning more and more the manner of adapting drugs to the destruction of the microbic parasites of disease for a like purpose.

All the advantage is, however, not on the side of the body, since the parasites also possess powers of modification, through which the most elaborate obstacles placed in their way by the host may be rendered futile.

These adaptations consist in the acquisition of special properties of aggressive action or virulence, with which is associated the ability to produce and liberate substances paralyzing to the defensive processes of the host. Again, the parasites may surround themselves with a kind of mantle, protecting them from the potentially destructive effects of serum and phagocyte. Or they may undergo an internal change of constitution, through which resistance to injurious agencies not normal to the species is developed. The last condition is called "fastness" and has been observed especially among trypanosomes and spirochetes exposed within the body of the host to ineffective amounts of specific serums or chemicals.

With so many factors interplaying, it is not difficult to perceive that the problem of infection is a complex one, both as regards its occurrence and its issue. But our understanding of the conditions under which it arises has been immeasurably extended by the discovery of the insect and higher animal agencies in communicating infective agents to man, and of the part played by so-called microbe carriers, those unfortunate and innocent persons who have recovered from or merely been exposed to a communicable disease, or suffered a slight, abortive, or ambulant attack of which they are ignorant, and the discovery of the usual portals of entry into the body of pathogenic microorganisms.

Infectious diseases prevail in two more or less distinct, but at times interwoven ways, which we speak of as the sporadic and the epidemic. The former represents the ordinary manner of spread, the latter the occasional or periodic explosive outbreak or wave, such as has been experienced recently with the pandemics of poliomyelitis, influenza and lethargic encephalitis.

What has been sought in the past and is being assiduously looked for in the present is an adequate explanation of the transition from the sporadic to the epidemic type of disease. We possess already quite accurate numerical data which show the manner in which epidemics begin, how they reach their maximum or peak, and then how they fall away again. Indeed, we now construct easily and recognize readily the epidemic curves of different epidemic diseases. But it is to be hoped that a new era is appearing in the study of epidemiology in which experiment may play a part along with observation, statistical and other. Already beginnings are being made in the attempt to define the distinction between the potentially fluctuating grades or power of infectivity and degree of virulence, taking the former to mean the natural propensity which a microbe displays in penetrating the ordinary portals leading into the body and its ability to survive and multiply there, and the latter the capacity to overcome the natural defenses when artificially inoculated. This is a field clearly approachable by experiment, using small laboratory animals, among which arise from time to time, and much as happens with man himself, destructive epidemics induced by known microbes. Finally, there is the field in which not a single species of microbe is concerned but more than one, the first preparing, the other utilizing the prepared way for its more vicious purposes. Frequent examples of the last condition are observed among the lower animals, in which, of course, the opportunities for study are superior to those existing in man; but recent experiences in this and other countries during the influenza epidemic carry conviction of this relationship, since the original disease is recognized to be not of severe nature, while the pneumonia engrafted upon it is admittedly of highly fatal character.

My purpose in reviewing some of the notable events and tendencies in bacteriology which have come to light in the past twenty-five years has been to present to your consideration the achievements in one branch of modern medicine, and to indicate the relation subsisting between medicine and the more fundamental sciences of physics, chemistry and biology. Bacteriology has depended also for its development on its sister sciences of physiology, pharmacology and pathology, without which many of its phenomena could not be interpreted. It seems but proper to state that what has been attempted here for bacteriology could readily be equalled or even exceeded by spokesmen for those sister sciences, so surely has medicine grown scientific in recent times.

Simon Flexner

SCIENTIFIC EVENTS

MUSEUM OF THE BUFFALO SOCIETY OF NATURAL SCIENCES[1]

On October 16 the Buffalo Society of Natural Sciences opened its New Museum at 1231 Elmwood Avenue. This building is merely the inner court of a much larger museum which is to be erected by the society as soon as funds are available. The court measures approximately a fifty-five foot square. There is also a lobby, hall and office on the main floor and an office and two work shops on the second floor.

The entire idea of the New Museum exhibit is to give every man, woman and child who visits it the opportunity to understand the evolution of this earth from the time it was a part of a nebula arm up to the present decade. The hall of the building is devoted to astronomy and meteorology, many of the transparencies having just been obtained from the Mount Wilson and Yerkes Observatories.

The next exhibit is dynamical in nature, telling of what elements our earth is made and of the forces that have changed the earth's crust to form continents, oceans, rivers, lakes and mountains.

This is followed by an exhibit of paleontology which touches on the flora and fauna of the sixteen great geologic ages and ends with an evolutionary exhibit of man and one of the horse.

The last exhibit exemplifies the way in which man has utilized nature's products. It is truly marvelous how dyes have been made from coal tar; silk garments, alcohol, linoleum, tar and paper from wood; and the beautiful Deldare semi-porcelain ware from the commonest clay.

Among other interesting objects to be found in the museum are the relief maps of such localities as Mount Shasta, Mount Vesuvius, and the Grand Canyon of the Colorado. There is a very large relief map of Erie County which occupies a large space in the center of the floor. It was constructed by Frederick Burgie, of Rochester.

Two cases have been reserved as a display ground for especially beautiful objects owned by the society. At present these cases are filled with precious and semi-precious stones, many of them in the matrix.

Of especial interest to the children is the fine exhibit of birds and animals which have been mounted by Joseph Santens. Mr. Santens is at present completing a collection of native birds which will be studied by the school children under the new Nature Study Syllabus as published by the regents of the state of New York.

[1] From *The Museums Journal.*