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*SOME PROBLEMS IN THE LIFE HISTORY OF PATHOGENIC MICROORGANISMS.**

OUR knowledge of the profound influence which the microscopic organisms, known as the bacteria, exercise in the life of the globe, may be considered an acquisition of the last quarter century. The surmises and hypotheses of the half century preceding were then made over into well-attested facts.

The activities of microorganisms manifest themselves in many different ways. The functions carried on by the bacteria of the soil are known to be of fundamental importance to higher plant life. The work of the bacteria producing fermentation, putrefaction and decay is of similar importance in preparing the way for the soil bacteria and ministering to the wants of higher organisms. Out of this latter class there has arisen a group which has given these microorganisms all the notoriety they possess. It is a small group, but formidable in that it is in partial opposition to the higher forms of vegetable and animal life. It is these parasitic forms to which I shall devote my address, as it is they which have preoccupied my attention for some years. In thus passing over large groups of bacteria I simply register my inability to properly present their claims, and I trust that others here present will fully supplement my paper by dealing with them in deserving fashion.

While bacteriology, strictly speaking,

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deals only with a fairly well-defined group of unicellular plant-like forms standing near the limit of microscopic vision, medical bacteriology has been gradually widening its scope to a study of all unicellular and even higher parasitic forms, which multiply more or less indefinitely and continuously for a time in the invaded body. In addition to the bacteria proper, the protozoa, and those highly important ultramicroscopic organisms which seem to have certain characters not possessed by either of the other two groups, are now frequently gathered into medical bacteriology, because of certain underlying principles of action which they possess in common as parasites.

Bacteriology differs from the older sections of biology in several important particulars. In the first place, it has been developed under the stress of practical demands. The enormous economic and sanitary significance of bacterial life has pushed forward this study very rapidly, and the problems undertaken have been suggested almost wholly by considerations arising in agriculture and medical practise.

In the second place, bacteriology, at least so far as the parasitic forms are concerned, is essentially a study of two realms, that of the parasite and that of the host, of two organizations, widely different, acting upon one another and entering into complex, reciprocal relations. The older departments of biology do not present such a complicated aspect. Thus anatomy or morphology has, at least until very recently, dealt with structure and development without considering the relation of the individual to its environment. That was relegated to physiology and pathology. With the bacteria the morphologic aspect dropped nearly out of sight because of the difficulty encountered in analyzing structures so minute and relatively simple. Even the classification gradually evolved, as more and more forms were examined, is at present very largely a physiologic one, the characters being based on the action which the bacteria exert upon the medium in which they multiply.

Then again, there was no ulterior interest in the study of bacteria as such, which is a strong impulse in many other departments of biologic science. It is what bacteria do rather than what they are, that commanded attention, since our interest centers in the host rather than in the parasite. This tendency manifested itself in a peculiar way. As soon as bacteria could be handled in pure culture, the study prosecuted most actively was how most quickly to destroy them. Disinfection, sterilization and all agents which act destructively upon bacteria were diligently sought for. The first impulse of the youthful branch of bacteriology was thus to destroy, rather than to study and analyze. When, some years later, the antibodies were discovered, the rush toward the bactericidal serums was equally manifest.

Bacteriology in its scientific form was thus ushered into existence largely by medical men who had definite practical ends in view. It presented from its beginnings a dual aspect for study and its chief aim from the first was the destruction of one of the elements, the parasite. Slowly, however, the more impartial study of host and parasite in their mutual relation began to take root and to-day there is scarcely a department of physical, chemic and biologic science which does not have some share in the unfolding of this complex relation existing between plant and animal life, on the one hand, and the microorganisms acting as parasites, on the other. As a result of this rather unique state of affairs, bacteriology is not a self-contained, well-defined field of work, but one greatly subdivided by aims and methods of study. A realm as large as that of microorganisms

may well claim attention in many workshops of science.

The short time at my disposal does not permit a wide survey of the field of bacteriology, and I have deemed it best to discuss in a general way the parasitism of bacteria and to outline the probable results of any attempts of medical and sanitary science to modify this parasitism. In undertaking this task I have adopted the somewhat discredited method of presenting actual hypotheses, partly new, partly old, in a new dress. These furnish a definite point of attack, and are better suited for discussion than any presentation which boxed the compass with the views already well known.

Infectious diseases have frequently been portrayed as a battle between two organisms, the host, on the one hand, the parasite, on the other. There are few diseases even among those not strictly infectious in character in which this battle does not go on at some stage and in which the activity of bacteria may be ignored. For some years the analysis of this warfare has been the chief problem of bacteriology and pathology. What are the weapons of offense and defense on either side? Are the weapons simple or complex? Are they changed as the struggle progresses to suit the immediate state of the battle? Do the combatants themselves change during long or short periods of time, and does the character of the disease change as a consequence? Do the parasites act differently when posing for us in the culture tube than in the animal body? These and other queries may easily be read into the special literature of the last decade.

To realize the great complexity of this struggle we need but to review the gross facts of disease which express themselves in epidemics, on the one hand, in individual disease, on the other. We meet all gradations of severity, from rapid death to a mild transient disturbance, from a disease lasting hours to one lasting fifteen or twenty years, or even longer. Even the simplest generalizations concerning such a varied phenomenon must necessarily be subject to many exceptions, and perhaps gross inaccuracies. This is evident from the heated discussions which have been waged over the humoral and the cellular phenomena, the antitoxic and bactericidal forces of the blood and the phagocytic activities of certain cells, each party to the discussion claiming, at least for a time, that the opponent had no case. Though the brilliant researches of Metchnikoff and Ehrlich, and the fundamental discovery of Behring and Kitasato, have to a certain degree exposed the mechanism of warfare, the exposure is only fragmentary, and the hypothetic reconstructions based on it are leading as usual to further controversy. We do know that no two species of microorganisms carry on the warfare just alike, and that the same parasite finds a somewhat different situation in every host attacked. The problem of the immediate future is to determine where the brilliant discoveries of Metchnikoff, Nuttall, Behring, Bordet, Ehrlich and others belong in the life of each microbe, and to construct for each disease the exact nature of the contest.

In the following pages I do not intend to enter into any discussion concerning the intimate life of bacteria, but simply to point out certain biologic problems which seem to lie on the surface, as it were, and which illustrate the close relation existing between bacteriology and general biology. They have suggested themselves to me from the comparative standpoint, one up to the present but poorly cultivated in medical science.

The researches of Roux, Kitasato and Behring, Van Ermengen and others, have shown that certain species of bacteria secrete toxins during their vegetative period.

These toxins are soluble in the mediums in which these species multiply. Besides these physiologically well-defined poisons, there are others which are closely linked to the body substance of the bacteria, and which have become familiar to us in such well-known substances as tuberculin and mallein. According to the theory of R. Pfeiffer, this second class of poisons is liberated only by the disintegration of the bacteria, and the intoxication of the host, due to its destructive action on the bacilli, is a kind of post-mortem effect of the parasites. Other bodies, the so-called lysins, which act destructively upon red and white corpuscles, have also been demonstrated by Van de Velde and by Ehrlich and his pupils, but their significance in disease is not yet clear.

In the host, on the other hand, during the multiplication of microorganisms, there appear bodies known as antibodies, which have aroused the greatest interest. They neutralize the soluble toxins, agglutinate the invading bacteria and disintegrate them. They also precipitate or coagulate albuminous bodies. Their action is specific, being directed toward the invaders. These are the main weapons which thus far have been found. Are there other offensive and defensive bodies? What course do the bacteria pursue in the presence of the gradually accumulating antibodies of the host? Do they forge new weapons or not?

Professor W. H. Welch in his Huxley lecture presented the theory that the mechanism of the production of antibodies on the part of the invaded host was set in operation by the microorganisms as well, and that various tissue poisons might have their origin in overproduced bacterial receptors thrown off under special stimulation by host substances. This theory implies that bacteria may not unfold all their activities in the culture tube and that the latter give us no reliable clue as to their behavior in the living body.

On this point we may perhaps get some light by a consideration of the plasticity of microorganisms. It has long been known that the pathogenic power of bacteria is reduced gradually in artificial cultures. It is also well known that by a series of inoculations or passages through animals the virulence may be restored, and even raised above the natural level. Bacteria have been gradually accustomed to originally destructive doses of poisons in culture fluids. Very recently it has been shown that they may be gradually trained to multiply in strongly bactericidal serums and to refuse to be clumped in strongly agglutinating serums.

These adaptations persist for a certain time and are transmitted for a limited period, even in culture. In other words, the modifications are more or less gradually acquired and gradually lost. The same is true of the antibodies of the host. The antitoxin circulates in the blood of the horse long after the stimulation by toxins has ceased. In the immunized animal the agglutinating properties do not disappear at once. I am, therefore, inclined to believe that the bacterium freshly removed from its usual environment will, at least for a time, exercise all its functions, provided the special nutritive substances which may be needed to carry on those functions are present.

The theory of Professor Welch would then resolve itself into a question of nutrition. In the body of the host there are certain substances which give rise to special toxins when acted upon by special bacteria. If we could offer these special substances to freshly isolated bacteria there is no reason why the assumed toxin should not be formed. We must, therefore, take into account two possibilities, the adaptation of microbes to originally destructive agencies,

and the production of poisons from specific substances elaborated by the host.

I have entered into this much of detail concerning the mutual relation of microorganisms and host in order to make clear the hypothesis, which it seems to me accounts very well for the general phenomenon of infection. It is that the tendency of all invading microorganisms in their evolution toward a more highly parasitic state is to act solely on the defensive while securing opportunity for multiplication and escape to another host. By tendency I mean a general slow movement through long periods of time. The following data are in its favor:

1. The production of diffusible toxins survives parasitism indefinitely, and is readily brought about in cultures.

2. Where toxin-producing bacteria have become adapted to a definite species, as in diphtheria, the toxin itself acts upon a number of different species. In other words, the parasitic relation is far more specialized than the chief pathogenic product.

3. No strictly invasive bacteria have yet been found producing diffusible toxins which appear to be of any real significance in the disease process.

4. Those which produce such toxins are not strictly invasive bacteria.

5. The injury due to invasive bacteria is known to be due to the disintegration of bacteria and the setting free of poisons locked up in the bodies of the microbes.

6. Pathogenic bacteria manifest less biochemic activity than the related saprophytic forms.

7. The hemolytic and leukocidic toxins of bacterial filtrates may be due to autolysis of the bacteria. Jordan has shown that hemolysis is at least in part due to a change in the reaction of the culture fluid.

According to this hypothesis, microorganisms in slowly adapting themselves to the parasitic habit would gradually eliminate active toxin production and other aggressive weapons as of little use, and strengthen whatever defensive mechanisms they may accidentally possess the rudiments of. If these are capable of marked development, we may expect such types of disease as tuberculosis, leprosy, glanders and syphilis, in which the parasitic habit is carried to a high state of perfection. If their mechanisms of defense are not capable of much development they will soon be destroyed or else become adapted to live upon the skin, and especially the mucous membrane as opportunists and occasional disease producers.

In this adaptation the possession of somatic poisons set free during disintegration may play an important part. They may give rise to just sufficient toxin to produce a local protecting nidus of necrotic tissue, until the time for escape to some other host arrives. This assumption is supported by the fact that diseases of some duration are usually focal in character. The microorganisms multiply only in certain foci which sooner or later become evident as the visible seat of disease.

It may be claimed that defensive and offensive methods are practically the same, and that it is simply a play upon words to make any distinction between them. But reflection will convince us that offensive methods mean direct injury, whereas defensive methods simply mean a neutralization of the offensive weapons or else a condition which is invulnerable to them, such as an envelope made of a special substance.

According to Ehrlich and his pupils, the antibodies which appear in the course of disease are not new bodies, but overproductions of bodies present in minute quantities normally. The parasitic microbe is thus at the very beginning of the invasion confronted with these bodies. At the

termination of the disease there are no new bodies present, but the antibodies are on hand in relative abundance. The situation which the invader has to face is thus qualitatively the same at the beginning and at the end of the attack. How does he meet it by defensive methods?

Three possible fates await the invaders: (1) They are largely destroyed within the body; (2) they are excreted, or discharged through various channels; (3) they remain indefinitely in the body after the disease is over, to be eventually destroyed or eliminated.

That the microorganisms are largely destroyed within the body in the course of the disease is not open to dispute; this class is of no special significance to us. Of most importance are those that escape to continue their life cycle in another subject. The mechanism of elimination is of vital importance to the parasite. It assumes many forms, and is admirably adapted in the various specific diseases to perpetuate the existence of the species.

The survival of the microbes after the disease is over may be explained partly on the ground that in nearly all diseases some of the microbes pass their final stage near the surface of the skin, or mucous membrane, or in organs in direct or in indirect contact with the outer air, so that escape outward is readily effected through destruction of tissue, and hence protection from the bactericidal forces of living tissue. The small number which in some types of disease remain alive for some time after the disease process has subsided, may also be enclosed in small foci of necrotic tissue, and thus escape destruction temporarily.

I am inclined to believe, however, that among the problems of the future will be the elucidation of still another mechanism for the protection and escape of the microorganism. It is highly probable that in a certain number of species of bacteria after the active vegetative stage a latent stage follows, during which the parasite which has escaped destruction provides itself with some protective envelope which also aids it in its passage to a new host. This envelope, which may be some specific substance not recognizable with the microscope, or which may be represented by the capsules in some groups, may be a defensive body of the parasite stimulated to overproduction by the antibodies of the host. This body also interferes with the metabolism of the microbe and thus acts in the double capacity of stopping the disease and protecting the microbe at the same time. This hypothesis suggested itself to me while endeavoring to account for the peculiar behavior of tubercle bacilli under cultivation.

It is well known that tubercle bacilli from the diseased tissues of cattle grow very slowly, and then only upon certain culture mediums, such as blood-serum. After several years of continuous cultivation they multiply vigorously in glycerin bouillon and can hardly be distinguished in appearance from those human varieties of the bacillus which grow richly from the first or second transfer. There seemed to be no justification to assume that the bacillus had completely changed its metabolism under artificial cultivation. The more rational hypothesis seemed to be the one which assumed the existence of some protective substance only slightly acted upon by the serum, not at all in glycerin bouillon, and therefore a hindrance to multiplication. After repeated transfers, this protective substance was slowly lost either through a selection of bacilli or absence of stimulation on the part of the host, or both causes combined, and the growth became as luxuriant as with the more saprophytic human varieties. It is obvious that each group or species of bacteria would have its

own special protective device depending upon original capacities of the species which would be gradually developed in power and efficiency with the perfection of parasitic relations.

The formation of protective or defensive coverings, the strengthening or modification of the cell wall or the secretion of defensive fluids, would account for certain phenomena which are familiar to bacteriologists much better than the current theory which bases parasitism exclusively upon toxin production, active or passive.

In cultures we should expect a loss of power to form protective substances because the antibodies are absent. Hence the universal tendency toward the reduction and final loss of virulence, with apparently the metabolic and vegetative activities unchanged, and the frequently observed regaining of virulence by passages through series of animals.

In the evolution of parasitic bacteria I assume then that though the function of toxin production may have been the entering wedge toward a parasitic existence, there is a progressive loss of this function as of little use to the parasite after it has once acquired a foothold, for the action of toxins at a distance from the focus of multiplication does not aid the parasite, while it may destroy the host. In other words, with the invasion of the tissues of the latter it became necessary for the invader to concentrate its powers in its immediate vicinity, and for this purpose those poisons set free by the disintegration of the parasite may be of use in protecting the focus where the younger forms are, by necrosis of tissue, plugging of vessels, etc., and thereby keeping away the bactericidal forces until the bacteria have accumulated sufficient protective power to subsist in a latent condition and are ready to be discharged outward. With the loss of active toxin production according to this hypothesis and the loss of other, now useless, metabolic activities, there goes hand in hand a strengthening of the defensive functions. This strengthening I interpret as the gradual development of certain substances which the non-immune host is unable to act upon or at most only in a slight degree. This substance which, as it were, shoves itself between the parasite and the common bactericidal forces of the body, bears the specific pathogenic character of the microbe. It is the substance which, according to the nomenclature of Ehrlich, calls forth the amboceptor from the resources of the host to combine with it, and thus open the way for the usual bactericidal forces or complements according to Ehrlich. The existence of this specific protective body will account for the varied resistance of animals to the same microorganism and the relative difficulty to induce immunity. The more difficulty the body has in producing the amboceptor the greater the difficulty in acquiring immunity.

In the departments of preventive and therapeutic medicine, the isolation of this protective substance apart from the body toxins would be of prime importance in combating disease by inducing individual resistance. In fact, the theory that the so-called immunizing and disease-producing substances are separate is not new, but has been presented under various forms. The tendency to give up the toxic extracts of bacteria and use the latter in their entirety in immunization pays tribute to these unknown bodies. The most prominent example of this change was the abandonment by Koch of the old tuberculin, a boiled extract, and the utilization of the entire tubercle bacilli ground and uninjured by heat, in the production of immunity in tuberculosis.

The foregoing hypothesis, that the tendency of microbes in perfecting the parasitic habit is to act solely on the defensive, is to

a certain degree supported by a phenomenon of considerable biologic importance, which I wish to discuss very briefly.

If we examine the statistics of the various infectious diseases we are struck with the relatively low mortality of most of them. There are few highly fatal plagues now known. To be sure, the mortality of many infectious diseases is regarded as formidable by sanitarians, but if we disengage ourselves from the humane view for the moment and take the biologic standpoint, we will agree that the relatively high mortality of 25 per cent. to 50 per cent. indicates a very decided preponderance of the resisting powers of the human race. The odds are always against the invading microbe. This state of affairs appears for the moment to contradict the results of experimental bacteriology, which teach us that the virulence of microbes may be more or less rapidly raised by repeated passages through susceptible animals, or even through those which possess considerable resistance. The accustoming of bacteria to antiseptics, bactericidal and agglutinative serums, has already been mentioned. With this capacity for adapting themselves to the defensive mechanisms of the host, why should not the infectious diseases become more, rather than less, virulent? What is it that keeps their virulence on a low level? This problem has occupied my attention for a number of years, but only recently did a fairly satisfactory explanation present itself. Before entering upon it I have still one other phase of the problem to consider.

Of a given number of races of the same species of bacteria, the one which becomes parasitic on a given host species is not necessarily the most virulent for that species. This phenomenon impressed itself upon me during the study of a number of races of the bacillus of septicemia hemorrhagica, or, more familiarly, rabbit septicemia. Races of this species have been found very widely distributed among mammals and birds. Epizootics due to it have been described as occurring among cattle, carabao, game, swine, rabbits, guinea-pigs, fowls, geese, etc. It lives in the upper air passages of many domestic animals in health.

The rabbit may be successfully inoculated with any of these races. Some are very virulent, for the merest scratch of the skin inoculated with them will result in death within twenty-four hours. But the rabbit is not attacked spontaneously by them, although they are ubiquitous. The race which has fastened itself upon the rabbit is one of a very low degree of virulence for that animal. Similarly the highly virulent tubercle bacillus of cattle is encountered only occasionally in man, although the opportunities for a transfer from cattle to man are very good.

On first thought, it would seem to us that the most virulent race would be the one to crowd out any less virulent races and to finally predominate. But comparative pathology shows us that the contrary may be true.

The explanation for these apparently discordant facts readily flows from a consideration of the life history of parasitic microorganisms. This briefly consists of three phases, the entry into the host, the temporary multiplication therein, and lastly, the escape to another host. Each step in this life cycle must be carefully and deliberately worked out in the evolution of parasitic organisms, and each demands a special mechanism adapted to the purpose. One step is as important as the other. The parasite must find an unguarded entry or one which yields readily to its efforts. It must have a means of defense within the body and it must finally reach the exterior to enter a fresh subject.

As a result of these needs, each microorganism producing disease has one or sev-

eral avenues of entry and escape. In some of the protozoa there is but one avenue, and this is highly specialized and is through the body of some insect. Among the bacteria the channels of escape are less highly developed, and there may be several. As a rule, the microbe adapts itself eventually to a locus more or less in direct contact with the exterior, and in some instances the loci of entry, multiplication and exit have coincided. If we think over the various infectious diseases of man and animals, of which we have any definite information, we shall be surprised to find in how many the points of attack are in organs or tissues in direct communication with the exterior. In the most common type of tuberculosis, pulmonary consumption, the process is almost wholly limited to the respiratory organs. In typhoid fever the process is to a large degree carried on in the intestinal wall. In dysentery and cholera it is wholly so. Even in the very protracted disease of leprosy, the skin is the chief seat of the disease, while the discharge of bacilli from the ulcers of the nose is the rule in the tuberculous type. In that exquisitely parasitic, highly specialized group of microorganisms producing the eruptive diseases the final process is carried on in the skin. In these diseases the mechanism of escape is the most perfect.

On the other hand, among the spore-bearing pathogenic bacteria the means of escape is uncertain. Thus the anthrax bacillus betrays its saprophytic nature, as pointed out by Koch many years ago, in its inability to produce spores within the body. Were it not for the accidental discharges of blood from the mucous surfaces and the operations of man, the bacillus might not escape at all to sporulate. Similar conditions obtain for the bacillus of tetanus and of Rauschbrand. Both produce disease probably in an accidental manner and not as progressive parasites. Their continued existence is assured by vegetation and spore formation outside of the body, and it is highly probable that the species would continue to exist if they did not attack animal life, and that their incursions into the body are of no use to them. On the other hand, all attempts to demonstrate the production of spores in bacteria whose existence depends largely or wholly upon parasitism have thus far failed. The spore is evidently poorly fitted to parasitism and is replaced by other devices of more adaptability.

The mechanisms of invasion and escape bear a distinct relation to the pathogenic power or virulence. It is safe to assume that those varieties or species, no matter how virulent, will be eventually destroyed if these mechanisms are imperfect. In fact the more virulent the microbe, the more rapid the death as a result of invasion, the less the opportunity for escape. Hence there will be a selection in favor of those varieties which vegetate whence they can escape. The surviving varieties would gradually lose their highly virulent invasive qualities and adapt themselves more particularly to the conditions surrounding invasion and escape. That some such process of selection has been going on in the past seems the simplest explanation of the relatively low mortality of infectious diseases. These individuals or races of microbes which invaded the host too rapidly and caused death would be destroyed in favor of those which vegetated more slowly and in tissues permitting escape of the microbe after a certain time.

We may now return to the rabbit septicemia bacillus. The reason why the most virulent type of this group does not pass to rabbits is due to the fact that there is no satisfactory mechanism of entry and escape. This presupposes a lesion, a wound as a place of entry, and the excretion and

transfer into a wound in another animal. In the rabbit this difficulty is worked out in the way usual with this bacillus. The microbe adapts itself to vegetate upon the mucous membrane of the upper air passages. Under certain conditions it invades the lungs, pleural and pericardial, more rarely the peritoneal cavity, producing pneumonia and extensive exudates on the serous membranes, and causing death. The disease of the thoracic organs evidently follows some predisposing cause, which enables the bacillus to make a temporary invasion from the mucous membrane. This incursion into the body is not essential to the life of the race. In fact a little reflection will show that the bacteria which invaded are not likely to be transmitted, whereas those on the mucosa are readily handed down from old to young. The virulence of the bacillus is thus kept on a low level, so low that subcutaneous inoculation of pure cultures produces merely a local lesion. This type of disease is quite different from that produced by inoculation with highly virulent races. These multiply rapidly in the blood throughout the body.

We can now appreciate Pasteur's failure to exterminate the rabbits of Australia. He believed that with races of this bacillus on hand which destroy life very quickly, all that is necessary is to start the disease among rabbits, and it will tend to spread. The stricken rabbit with its blood full of germs does not offer the means for inoculating a second, and so the virulent race perishes.

We can understand, furthermore, why the bacteria associated with definite diseases in animals produce a diseased condition with difficulty after inoculation. The virulence of the specifically adapted microbe is of a relatively low order, and in the production of epizootics various conditions must be realized which assist the microorganism. The careful analysis of these conditions will form one of the great problems of pathology in the immediate future.

The phenomenon of the elimination of the most virulent races and the establishment of parasitic races of less invasive power I have portrayed in the simplest terms. But it is probably much more complex. The parasite, to be successful, must also stand in a definite relation to the tissue through which it enters. It is quite probable that the race of rabbit septicemia bacilli of high virulence would not be able to maintain itself in the mucus of the upper air passages. This ability to multiply in certain places is evidently an acquisition which gives the particular race its specific character. Without doubt the bovine tubercle bacillus, though of great virulence, does not possess the specific power of entering the human body, or it may be of maintaining itself after entry in certain tissues, such as the lymph-nodes, except under certain accidental, favoring conditions not yet understood. Perhaps the process of cultivating vaccine virus in the skin has deprived it of the capacity for entering through the respiratory tract, and has converted it into a purely inoculable virus.

In the study of pathogenic bacteria the relative ease with which pure cultures may be obtained from the blood and other organs only accessible by way of the blood has made this a favorite way of obtaining such cultures. But it may be asked whether we are not in this way obtaining bacteria of maximum virulence. May not the non-agglutinability of some typhoid bacilli immediately after isolation be accounted for in this way? In general, the bacteria thus obtained can differ but little from the type, as they are all recently descended from a single bacillus or a very few which caused the infection. It is different in the so-called passages through series of animals in which the usual portals

of entry and exit are circumvented and the bacteria injected into the body and withdrawn therefrom directly. As a result of such passages many species of bacteria have been made more virulent, and Pasteur was able to greatly modify the unknown virus of rabies.

Besides the maintenance of virulence and its occasional augmentation, a slow decline to complete loss of virulence may be looked for under conditions abnormal for the microbe. This probably goes on where the bacteria multiply, partly or wholly protected from bactericidal influences. The bacilli of tuberculosis, which multiply in cavities of the lungs or in muco-pus of the air-tubes in chronic cases, must be regarded as degenerating in virulence. And we actually encounter races varying considerably in pathogenic power. In the throats of well persons or those who had diphtheria months ago, bacilli without any power of toxin production, but with all the other characters of genuine diphtheria bacilli, are occasionally encountered.

During the elimination of the more virulent races of microorganisms, there goes on as well a gradual weeding out of the most susceptible hosts. In a state of nature in which medical science plays no part, there must occur a slight rise in the resistance of individuals, due to selection and perhaps acquired immunity, which meets the decline of virulence on the part of microbes until a certain norm or equilibrium between the two has been established. This equilibrium is different for every different species of microorganism, and is disturbed by any changes affecting the condition of the host or the means of transmission of the parasite. One result of the operation of this law is the low mortality of endemic as compared with epidemic diseases. Certain animal diseases, while confined to the enzootic territory, cause only occasional, sporadic disease, but as soon as they are carried beyond this territory, epizootics of high mortality may result. Climate in some cases enters as an important factor, but the most important, perhaps, is the slight elevation in virulence brought about by a more highly resistant host. The most susceptible animals are weeded out, and the rest strengthened by non-fatal attacks. The virulence of the microbe rises slightly to maintain the equilibrium. In passing into a hitherto unmolested territory, the disease rises to the level of an epizootic until an equilibrium has been established.

The same is true of human diseases, among which smallpox is a conspicuous example. The great pandemics of influenza, which seem to travel from east to west every one or two decades, soon give away to sporadic cases, and the careful work of many bacteriologists would indicate that the influenza bacilli found at present have fallen to the level of secondary invaders, and are parasites of the respiratory tract in many affections.

As pathogenic microorganisms differ not only in the degree of parasitism attained, but also in their essential nature, a great variety of diseases is the result. In a crude way they may be arranged into three classes:

1. Microorganisms which live upon the skin and the mucous membranes and invade the body only when lesions exist in these structures, or where the general resistance is impaired.

2. Microorganisms which appear only occasionally from some unknown but permanent focus. They produce epidemics often highly fatal, but they are successfully pushed back because the strain can not readily adapt itself to the new conditions.

3. Microorganisms which are most highly adapted for a parasitic existence and which produce diseases of a relatively fixed type.

As regards the first class, the conditions under which they produce disease rise more and more into prominence. The factor microbe becomes almost secondary to other factors. Many of our most common diseases obey certain meteorologic laws. Thus diphtheria and pneumonia are chiefly winter diseases, because the conditions of throat and lungs which favor them are largely due to cold weather, or we might say, the cold weather acting upon an indoor sedentary population or one subjected to untoward influences, injures the respiratory tract. Some microbes of this class depend upon the preparation made for them by others. Thus the exanthematous diseases, such as scarlatina and smallpox, are frequently associated with or followed by the invasion of streptococci, and the majority of deaths are due to such secondary invasion. The streptococci live upon the mucous membranes, and whenever the proper opportunity comes they invade more vital territory. This group of bacteria is the frequent cause of death in chronic diseases. Some years ago Professor Flexner pointed this out and denominated the invasion as a terminal infection. I think that they may also be appropriately styled the parasites of the diseased state.

Among the second group we may place such diseases as Asiatic cholera and the bubonic plague. The origin of the first is unknown. The definitive host of the second is probably the rat.

Among the third class we have such groups of diseases as tuberculosis, leprosy, syphilis and glanders, on the one hand, and the eruptive diseases, on the other. The former are very chronic, protracted, the widely separated but highly parasitic latter acute, rapid in their course. In the eruptive diseases the infection seems to depend solely upon the specific susceptibility of the individual, and immunity is easily brought about by protective inoculation.

In tuberculosis and leprosy the mode of infection is evidently very different from that of the group just mentioned. Prolonged exposure, as in family life, seems necessary to successful infection, and even then many exposed individuals escape. In tuberculosis, heredity plays a very prominent part in the eyes of the physician, because the disease appeared to propagate itself in families. This was probably due to the necessity for more intimate association and repeated exposure in order that the disease might appear. Here the disease is long drawn out, the parasite may become in a sense individualized, and the attack upon a new host may have to be made repeatedly. With these highly parasitic forms the necessity for a frequent transfer to another host is slight. In leprosy, the disease may last fifteen years to twenty years, and then death ensues, usually as a result of the attack of the secondary invaders.

From the biologic standpoint which I have endeavored to present, we may conceive of all highly pathogenic bacteria as incompletely adapted parasites, or parasites which have escaped from their customary environment into another in which they are struggling to adapt themselves, and to establish some equilibrium between themselves and their host. The less complete the adaptation, the more virulent the disease produced. The final outcome is a harmless parasitism or some well-established disease of little or no fatality, unless other parasites complicate the invasion. The logical inference to be drawn from the theory of a slowly progressive parasitism would be that in the long run mortality from infectious diseases would be greatly reduced through the operation of natural causes. But morbidity would not be diminished, possibly greatly increased, by the

wider and wider diffusion of these parasites, or potential disease producers. The few still highly mortal plagues would eventually settle down to sporadic infections or else disappear wholly because of adverse conditions to which they can not adapt themselves.

In this mutual adaptation of microorganism to host there is, however, nothing to hinder a rise in virulence in place of the gradual decline if proper conditions exist. In fact, it is not very difficult to furnish adequate explanations for the recrudescence and activities of many diseases today, though the natural tendencies are toward a decline in virulence. In the more or less rapid changes in our environment due to industrial and social movements the natural equilibrium between host and parasite established for a given climate, locality and race or nationality is often seriously disturbed and epidemics of hitherto sporadic diseases result. Typhoid fever will serve as one illustration of my thesis. It is ordinarily a sporadic infection, passing from the sick to the well by direct contact. Our knowledge that the infection of this and other diseases is contained in the discharges of the sick and a growing sense of cleanliness led years ago to the large systems of sewerage, which have made a crowded city life possible. But the removal of sewage from our immediate surroundings was the beginning of new trouble. The sewage was led into water courses from which drinking water came. Hence the great epidemics in place of sporadic disease. The direct transmission of the parasite on a small scale was largely checked, but the indirect transmission greatly favored. The dweller in cities with unprotected water-supply is still further endangered by the fact that the typhoid bacilli returned in the water may represent more virulent varieties than those handed down by his ancestors in rural communities. The motley population brought together by migrations from all parts of the globe bring the various races of bacilli with them to be redistributed on a large scale.

Conditions may even create diseases artificially. Thus in childbirth, the physician through want of cleanliness may in his examination actually inoculate a wounded surface with streptococci or other septic bacteria. In a hospital badly managed, such germs may be made to pass artificially through a series of individuals and their virulence raised. In nature this could not take place, because there would be no physician. Hence the transfer would not take place. The history of maternity hospitals before the period of asepsis in surgery is a sufficient proof for the theory advanced. Hospital erysipelas and hospital gangrene were diseases artificially bred. With the introduction of the principle of asepsis in medicine and surgery the artificially created diseases were destroyed, because the transportation facilities of the bacteria were cut off.

These illustrations indicate that so-called natural law does not stand in the way of our having highly virulent types of disease if we are ignorant enough to cultivate them. The microorganism is sufficiently plastic to shape itself for an upward as well as a downward movement. Among the most formidable of the obstacles toward a steady decline of mortality is the continual movement of individuals and masses from one part of the world to another, whereby the partly adapted parasites become planted as it were into new soil and the original equilibrium destroyed. These various races of disease germs become widely disseminated by so-called germ carriers, and epidemics here and there light up their unseen paths. Fortunately for us, the conditions under which these microorganisms may establish themselves are in

many cases so complex that they can not be realized. It is highly probable that the bubonic plague can not get a foothold or maintain itself among us, while Asiatic cholera might have a better chance, through our still greatly unsatisfactory water-supplies. Many tropical diseases would fail to take root in our climate. The mysterious rise and disappearance of leprosy in the middle ages has astonished many students of epidemiology. Possibly some slight bias of the microorganism may have accomplished what seems almost a miracle. Perhaps the right race or variety once introduced may repeat the history of the Middle Ages in our day or in that of the coming generation.

Another obstacle to the amelioration of infectious diseases is the rapid change going on in the habits of individuals and the ferment in our conceptions of health and well-being, which are continually upsetting any established equilibrium and making us more resistant to some diseases, more susceptible to others. Of great interest is the effect upon the human race of the assiduous care of those afflicted with certain chronic diseases which is just now expressing itself in the establishment of sanatoriums for the cure of the tuberculous. If this movement should gain great headway there may be a race of immunes gradually developed who may be able to stand the untoward conditions of indoor city life much better than the naturally robust and physically superior who have no so-called hereditary taint.

Of still greater interest is the vast vaccination experiment to whose beneficent influence the century just past bears ample testimony. The vaccinated individual is either wholly immune or else the disease contracted after exposure is abortive and the eruptive stage does not come to full development or maturity. The excretion of the infecting organism is thereby greatly interfered with and it is not improbable that in the mildest cases it may not reach that maturity necessary for the successful infection of others. In view of the adaptability of microorganisms in general, it is not beyond the range of possibility that a variety of the smallpox organism may through a chain of accidents arise as a result of successive passages through partly protected individuals. To-day it seems fairly well established that a single vaccination in infancy is not an adequate protection during life and at least one nation —a nation which not only cultivates but consistently utilizes science—prescribes two vaccinations as necessary to complete protection. Whether in the days of Jenner repeated vaccinations were deemed necessary I have not been able to verify; but we may assume without immediate fear of experimental contradiction that a century of incomplete protection may have worked some changes in the smallpox organism. In any case, it is obvious that our thesis implies in addition to the natural decline of virulence also a gradual rise in virulence whenever the resistance of susceptible individuals is raised on a very large scale. Either the microorganism if a true parasite will perish or else it will augment its invasive powers to meet those of its host.

Another problem has been created for the diphtheria bacillus by the extensive use of diphtheria antitoxin. Will the thorough protection of one group of human beings lead to the decline or to the increase in virulence of the diphtheria bacillus circulating among the individuals of this group? What effect will the transfer of such bacilli to unprotected groups have? These and similar queries may be answered not many years hence, for a generation of microbes represents a very short space of time.

It may not be out of place to call atten-

tion here to the bearing of my thesis upon the recent attempts to utilize parasitism in ridding us of undesirable or noxious animals. In bacteriology there have been attempts to destroy field mice and rats with certain species of bacteria. In entomology, parasitism is such a familiar phenomenon that it has been seized upon on a number of occasions to destroy otherwise unassailable insect pests.

Leaving out of consideration the presumptive dangers of introducing new species into a locality or country which must always be taken into consideration, although they may be of no significance, we have to consider the chances of success as compared with the cost of introducing and maintaining the parasites. In any event, we need not expect a destruction of the noxious species, for that is not the end of parasitism. A reduction in numbers is all that need be looked for. The new parasite will probably fail to become acclimated at first, and it may be necessary to reintroduce it for a number of years. During this period some few may become adapted to their environment and continue as parasites. Whether the equilibrium finally established will be of economic value, must be observed rather than predicted. In bacteriologic experiments of this kind the continued vigorous activity of the bacteria from year to year need hardly be expected. The disease will either die out or continue on a low level of mortality, in accordance with the general laws I have detailed, unless bacteria whose destructive powers are maintained and carefully gauged in the laboratory are distributed at definite intervals.

In conclusion, I will simply call attention to another problem affecting the future well-being of mankind, the possibility of new infectious diseases arising in the flux and change incidental to human progress. We have assumed that the capacity for a parasitic existence probably depends on some original offensive power of the microbe which it accidentally possessed, such as toxin production, or the presence of intracellular toxins combined with defensive powers. These, possessed independently of the host, were probably the entering wedges to be further developed or dropped, according to necessity. It is more than probable that all species of bacteria which possess these rudimentary invasive powers have already availed themselves of the opportunity to become parasites of animal life, on the one hand, of vegetable life, on the other, and that no startlingly new diseases will arise from saprophytic forms.

Subsidiary problems there are, however, concerning the modifications and readaptations of the parasitic forms already in existence. These may be grouped under two heads:

1. The transfer and adaptation of parasites from one host species to another.

2. The increase of invasive properties of parasites of the same host.

Are there any new diseases likely to appear as a result of the successful adaptation of parasites of higher animals to the human subject? This is a legitimate question, though difficult to discuss, for want of material at present. Among the more important possibilities I will simply mention the bovine tubercle bacillus and the hog cholera group of bacteria. The larger number of parasites on animals are so specialized, however, their receptor apparatus, according to Ehrlich, may have been so curtailed that parasitism on a relatively distant species may be impossible.

As regards the second problem, that microbes may gain in invasive power on the same host, the principle I have endeavored to establish would stand in the way of any rise in virulence because the most invasive forms of a varying species would have the

least chance for transmission. Whatever increase in disease-producing power may be acquired must be gained under special conditions, one of which is association with other microbes. Thus, if we could conceive of the same streptococcus, originally an inhabitant of the normal throat, as passing on account of some series of accidents through the bodies of a number of scarlatina patients, this streptococcus might thereby rise temporarily to the level of a serious menace to the throats and perhaps other organs of relatively healthy people.

Again, certain microbes like *B. coli,* the pneumococcus and meningococcus may, by living upon catarrhal mucous membranes and passed by case to case, acquire enough temporary pathogenic power to cause localized epidemics under favorable conditions. Any advantage thus gained would soon be sacrificed and the microbe return to the normal condition unless a satisfactory mechanism of transmission could be established.

It will be seen that there are many problems before the bacteriologist, problems which have something akin to those of the student of races, varieties and species among higher forms of life. These problems must be attacked with the same patience and pertinacity that were exercised by Mendel, Darwin, De Vries and many others in the effort to trace the rise of new species.

In dealing with the great problems of pathogenesis and parasitism as applied to the microorganisms in such a summary and hasty manner, and in endeavoring to trace the law of a declining virulence (and hence mortality) and an advancing parasitism, I may have left some doubts in the reader's mind concerning the ultimate value of medicine, preventive and curative, in controlling these diseases, since it might be assumed, according to the hypotheses presented, that they would take care of themselves. This impression will, I think, be dispelled by a little further development of the ideas presented.

The social and industrial development of the human race is continually leading to disturbances of equilibrium in nature, one of whose direct or indirect manifestations is augmentation of disease. In order to avoid this calamity or reduce its force as much as possible we must make special compensations or sacrifices to restore or maintain the normal balance. The more clearly the kind of compensatory action required is foreseen, the more promptly it is put into effect, the less disease there will be. It is the true function of medical science to discover and put into effect those compensatory movements which will counterbalance the temporary ill effects of what, for want of a more illuminating term, we call human progress.

It is largely through the phenomenon of parasitism that nature attempts to restore the equilibrium, and in this microorganisms play the most important part. As soon as the individual falls below a certain level he may become the prey of a microscopic, or even an ultramicroscopic, world. Hence the importance of bacteriology in medical science. Much has already been done in determining ways and means for the counterbalancing of the ravages of this microscopic world, but science can not rise above natural law, but must work through it. The optimism of the world frequently places science above natural law and believes it capable of correcting any and all excesses of individuals and races. We may be certain that it will never be able to eliminate the factor of parasitism. Its most important work will continue to be to analyze this factor into its minutest details and to devise means by which this analysis may be made useful in turning aside or at least in deadening the shock of disease.

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