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THE PARASITISM OF THE TUBERCLE BACILLUS AND ITS BEARING ON INFECTION AND IMMUNITY*

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THE present-day problems in tuberculosis which can be approached by experimental or at least by laboratory methods manifest themselves in three different ways:

1. In the somewhat chaotic condition of opinion concerning the avenues through which tubercle bacilli gain a foothold in the body.

2. In the wide divergence of opinion concerning the relation of bovine to human tuberculosis; and

3. In the general trend of studies toward the problem of specific immunity, with special reference to prevention and treatment.

These three problems, though distinct, are interrelated, and in a lecture of this kind, in which some freedom in the statement of theories and hypotheses and a rather broad treatment of the subject are not only permissible but desirable, it must be necessary to deal with each, to some extent at least. The most important of the three is the one dealing with immunity, and my statements will be grouped around and directed toward it as a focal point.

The method of treating the subject will be from a biologic standpoint which assumes as a basis for discussion a complex relationship established in time by a selective adaptation between two living organisms, of which one is a parasite of the other. Whatever pathologic processes of constant character are the expression of this parasitism, such as tubercle forma-

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tion, for example, are regarded as the result of an interaction of two organisms rather than the work of one alone.

Viewed from this standpoint, this tendency toward a state of equilibrium between host and parasite is disturbed by any change of condition which influences either parasite or host. It varies with the species, race, nationality or even family of the host and many other accessory conditions. It depends on the race of tubercle bacilli. In experiments such conditions as age of culture, total period of cultivation, character of the culture medium, condition of aggregation of the bacilli, mode of application and dosage are of great importance in determining the outcome of the experiment. Similarly the outcome will vary according to the species of animal on which we are experimenting.

Much of the experimental inquiry of the past has been along too narrow lines and with the conditions too poorly defined. We have lost sight of the general relations of bacteria to animal life. Our haste to take the animal and bacterial mechanisms to pieces and to test the individual tissues and components has crowded out the broader view that the host fights more as a unit. We had almost forgotten to take into consideration the flexibility and adaptability of the micro-organisms themselves.

In a recent lecture I presented in a somewhat new aspect the relationship between host and parasite by pointing out that in a stable parasitism the parasite is in command of a mode of exit from the body as well as one of entry. Both are necessary for the continued existence of the parasite as such. The evolution of this process has brought with it two related conditions: first, a lowered virulence or invasive power of the microbe; and, second, the tendency to attack mucous membranes, cutaneous surfaces or organs in direct communication with the exterior. The lowered virulence is only another expression for localization on the external surfaces among which mucous membranes and the respiratory tract may be placed for present purposes. As a result of this adaptation tuberculosis has taken largely the form of phthisis. That is,

the parasite has become localized in an organ in direct communication with the exterior, yet largely protected from miscellaneous bacterial and other parasites. Its modes of exit and of entry are identical. The bacillus may vegetate in the lung tissue and it may be easily discharged outwardly.

Phthisis, however, is only one, even if the preponderating type, of tuberculosis. Much has been made of the other manifestations. Among these, disease of the lymph nodes, bones, kidney, brain and spinal cord must be considered aberrant from the standpoint of the bacillus, for in these situations, with the possible exception of tuberculosis of the kidneys, the bacillus is doomed to an ignominious destruction, because there is no exit. These aberrant forms of parasitism are most frequent in childhood, because, perhaps, the tubercle bacillus being, as it were, keyed to adult life, is for that reason more invasive for childhood.

To the biologist these types of disease are of interest as suggesting problems in susceptibility and resistance which, as stated above, are the problems through which experimental medicine may deal practically with this disease.

In order to bring out in relief certain general biologic phenomena of tuberculosis, I shall discuss, first, very briefly the mode of invasion of the body by the tubercle bacillus, then sketch a theory of the interaction of the body and the bacillus. I shall then discuss the tuberculin reaction and the action of dead tubercle bacilli and the procedures suggested or used for producing an increased resistance of the body.

I. THE INVASION OF THE BODY BY THE TUBERCLE BACILLUS.

Bearing on immunity, the problem which deals with the primary seat of tuberculosis and its relation to the portal of entry deserves consideration, since it is, to a certain degree, an index of susceptibility. The theories concerned with the mode of invasion of the tubercle bacillus may be classed under four heads:

1. The inhalation of dried sputa, as laid down by Koch and elaborated by Cornet and others.

2. The inhalation of moist particles, or spray infection, as formulated and worked out by Flügge and his pupils.

3. Congenital tuberculosis, resulting from infection *in utero,* as defended by Baumgarten.

4. The infection through milk in infancy associated with a greater or lesser degree of latency until puberty and even later, the theory recently championed by Behring.

In taking some definite stand as to which of these theories, if not all, should have our support, we may gain some evidence from a study of the primary seat of the disease, *i.e.,* that place in the body where the presence of the bacillus is shown either by the existence of actual lesions or by animal inoculations.

In the largest number of cases of tuberculosis the lungs themselves have been regarded as the primary seat of the multiplying bacilli. In children, however, other conditions frequently prevail, and the primary seat of the active process may be in the cervical, the bronchial and the mesenteric lymph nodes; many authors have called attention to this fact. Weigert [1] referred to this over twenty years ago.

The most recent monograph of Harbitz [2] refers to it as follows: "The general rule in cases of children is that the lymph nodes are primarily attacked and that the lungs are infected from them. General experience teaches that isolated tuberculosis of bronchial nodes is quite common while isolated pulmonary tuberculosis, with or without a slight and plainly secondary lymph node tuberculosis, is a rarity in children."

Ribbert goes so far as to assume that pulmonary tuberculosis is mainly hematogenous in origin, the source of the infection being some lymph node primarily diseased.

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[1] Deutsche med. Wochft., 1903, p. 735. "In adults, for instance, we find so frequently the familiar tuberculous lymphatics issuing from ulcerations in the intestines while the lymph glands pertaining to them show comparatively slight changes. In children, on the contrary, we often encounter the reverse, pronounced caseous changes and swelling in the mesenteric glands while no morbid process can be detected in the afferent lymphatics, even in their trunk region." He refers also to similar conditions for the bronchi, the mouth and the skin.

[2] Jour. Inf. Diseases II, 1905, p. 143.

Petruschky, in his various publications dealing with the curative power of tuberculin, has identified himself so thoroughly with this view as to regard and to classify lymph-node tuberculosis as the first stage in tuberculosis generally.

Baumgarten [3] has contended and still contends that tubercle bacilli always produce some lesion at the point of entry into the body. In taking this position he relies on animal experiments; but there are objections to animal experiments, inherent in the difficulty of approximating natural conditions. The local lesion in animals may be due to a variety of causes, among which are local trauma, dead and attenuated bacilli and chemotactic substances due to autolysis in the cultures, and the want of adaptation of the bacillus to the species of animal used. Compare these with the entry of a solitary bacillus or perhaps several bacilli in a dried condition, without producing trauma or any chemotactic response, and we see at once the difference between the natural and the experimental mode of invasion.

The invasion of tubercle bacilli into the lymph nodes without causing disease at the point of entry has interested me since I began the study of bovine tuberculosis, in which disease such invasion is the rule, and I shall take this opportunity, therefore, of describing this phenomenon in the cattle disease more in detail. I will premise my remarks on this subject by stating that mammalian tuberculosis appears in two independent types—human and bovine. If either human or bovine type were suppressed the other would still continue. The best evidence on this point was presented by Kitasato, who demonstrated that in Japan the human disease existed in its usual activity, though the cattle disease was absent and milk formed no appreciable element in the food of children. Most other mammals at times have been found infected, either from human or bovine sources. In these a satisfactory mechanism does not exist to perpetuate a porcine or canine or feline type of disease. The bovine disease is the best, therefore, for study, next to that of man himself.

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[3] Berliner klin. Wochft., 1905, p. 1329.

Soon after the recognition of tuberculin as a valuable diagnostic agent, astonishment and consternation were created by the discovery that a very large percentage of the best dairy cattle of the world reacted to tuberculin. Under the influence of this discovery some ill-considered laws were passed to destroy all reacting cows and their flesh, for the purpose of eradicating the disease. During these few years of active warfare, beginning in 1893, I was able to make autopsies on about 350 head of cattle which had reacted to tuberculin. This enabled me to get a good composite picture, as it were, of the early stages of the disease and to determine the primary foci with considerable accuracy. A portion of the results of this investigation was published in 1894 [4]; the rest has remained in manuscript form.

In cattle, tuberculosis is an exquisitely parasitic disease, in which the chief seat of the lesions is in the lymph nodes. Next in order come the lungs, then the liver and serous membranes. Furthermore, it may occasionally be encountered in almost any other organ and tissue.

There are three portals of entry, the upper respiratory tract (mouth and nose), the lungs themselves and the small intestines. Very rarely the skin or subcutis has given entrance. The infection through these portals is indicated chiefly by disease of the corresponding lymph nodes. In the head, for example, the pair of retropharyngeal glands are the chief indices of infection. They are situated close together under the mucous membrane covering the dorsal posterior wall of the nasopharynx. The other lymph-nodes of the head are infrequently diseased and need not be considered here. The mucous membrane is free of disease; the tonsils are very rarely infected. The progress of the infection along the chain of nodes in the neck is slow, and the infection of the head glands has little, if anything, to do with the primary or secondary disease in the thorax.

Tuberculosis due to inhalation of tubercle bacilli is by far

[4] Bulletin No. 7, 1894, Bureau. An. Ind. U. S. Dept. Agric.

the most common. The lungs and associated lymph nodes may be infected or only the latter. The thoracic lymph nodes in cattle belong to three systems, the tracheal and bronchial nodes, closely attached to the trachea and its branches, and draining the peribronchial and perivascular lymphatics, the dorsal mediastinal chain or chains dorsal of and resting on the pillars of the diaphragm and on the esophagus, which probably drain the lymphatics of the lung tissue itself, and the anterior mediastinal glands situated under the first rib; that is to say, in the apex of the thorax. That the bronchial and dorsal mediastinal glands drain the lungs is shown by their similar structure, pigmentation and contents of very fine particles of mineral matter coming from the air. The third group has no pigment and probably drains the pleural cavities only. It may also stand in some relation to the cervical nodes.

In all herds which were examined there was a considerable number of animals in which the pulmonary infection resulted in lymph-node disease only. In one herd of sixty animals, for example, of which fifty-three were infected, twenty-seven had tuberculosis of the thoracic lymph nodes, but no lesions in the lungs.

Next in frequency comes disease of the lungs themselves. The chief seat is in the large caudal lobes. In man the upper or cephalic lobes are the preferred seat. In cattle the invasion is just where one might suppose it to be when coming from bacilli suspended in air; it is in the direct line of the current and in the lobe which goes through the widest excursions. That most of the infection lodges here I also infer from the fact that the one mediastinal gland which evidently drains this portion of the lungs is the most frequently infected lymph node in the whole body. The infection through the intestines shows itself exclusively in tuberculosis of the mesenteric lymph nodes and in disease of the liver. Lesions of the mucous membrane are extremely rare.

This very hasty and imperfect sketch of the primary foci of tuberculosis in cattle shows that the bacilli usually enter the system, first, in the inspired air or in the food through

the mucosa of the mouth or throat; secondly, through the lungs in the inspired air, and, thirdly, through the intestinal mucosa in bacilli swallowed in the food. The most striking fact is the passage of the bacilli through the mucous membrane or the air cells into the associated lymph nodes without leaving any trace visible to the naked eye or detected by manipulation. I am convinced, therefore, that Baumgarten's theory can not be maintained in the bovine disease and that tubercle bacilli may pass through at least one gateway of the body without being detained.

The tendency of the tubercle bacillus to settle down and to multiply in the lymph nodes in cattle is manifested in still another way. When the disease becomes generalized by the escape of bacilli from some primary focus into the general circulation, the secondary disease does not give rise to a miliary tuberculosis, but isolated foci may appear in various organs. Even these may be absent and the infection of the organ or the passage of bacilli through it indicated by marked affection of the corresponding lymph glands. Thus the evidence that bacilli have passed through the liver and kidneys is frequently indicated only by tuberculous portal and renal lymph nodes respectively. Evidence of udder infection is frequently presented only by tuberculous pubic lymph nodes. That submiliary tubercles may be found in these organs is not to be denied. I have found a few in the liver in an advanced stage of the disease, composed only of a giant cell and a few epithelioid cells around it. The fact remains that the lymph nodes act toward these organs very much as the lymph nodes of the lungs do in the primary infection.

There are a few other data derived from a study of the distribution of tuberculous lesions in cattle which are of interest here. In the disintegration of pulmonary foci the bacilli may pass in two directions, into the associated lymph node or outward by rupture into the air tubes, or both ways at the same time. Passage into the lymph channels is signalized by an enormous hyperplasia of the dorsal mediastinal and certain bronchial nodes. The bulk of these may be in-

creased from twenty to thirty times. The tuberculous process is in the same stage throughout, which indicates a sudden flooding of the gland. When the discharge is outward, yellowish, caseous masses are found at the autopsy in the smaller air tubes. Ravenel has demonstrated that these masses are actually ejected during coughing. The mucosa of the air tubes themselves is not infected primarily, and eruptions, ulcers and catarrh are subsequent to the discharge of caseous matter. The latter acts both as an irritant and an infecting substance. Infection of other, notably the cephalic or smaller, lobes is brought about by aspiration of the caseous masses. These smaller lobes are more dependent and subject to the gravitation of fluids and semisolid matter.

The careful noting at the autopsy of the approximate age of the tuberculous lesions led me to conclude that infection through one of the avenues mentioned has, as a rule, nothing to do with the others. That is, there seemed to be no connection between tuberculosis of the mesenteric glands and pulmonary disease. It was noticed, however, that the stage of disease in the thoracic and abdominal lymph nodes was in many cases the same. The inference was that the animal was infected at the same time through two or even three different portals. The theory of Behring that tuberculosis starts in early life through the digestive tract is inapplicable as a rule to the bovine disease.

Concerning the mode of invasion of tubercle bacilli in rabbits and guinea-pigs through the natural portals, without the infliction of a trauma, as by subcutaneous inoculation, or the circumventing of certain channels, as by injections directly into the peritoneal cavity or the blood, I have no data of my own. There is evidence, however, to show that in these animals also the lymph nodes form the earliest foci of multiplication in feeding and inhalation experiments, and that the bacilli soon break away through this barrier and are diffused in the blood current over the body.

In the pig the ingestion of infected milk leads at first to tuberculosis of the head and cervical lymph nodes and those

of the mesentery from which stations generalized infection by means of the blood takes place very soon.

A most important question is raised by this penetration of the tubercle bacilli to lymph nodes. How far may they penetrate before they settle down? Do they go beyond the first lymph node? Do they ever reach the blood directly from without? The conservative notions of twelve years ago would hardly admit the penetration of tubercle bacilli below the mucous membranes. To-day the extreme and radical notion of Behring that infection occurs early in life and may remain latent and that tuberculosis in later life largely dates from infancy is being seriously and widely discussed. This preparedness to receive and to discuss such a statement is partly due to the strides made in the study of parasitism. We have become accustomed to the complicated dual-host system of malarial and other blood parasites, the wanderings of the larvæ of uncinaria from skin to duodenum and larvæ of certain flies from œsophagus to skin. The revival of instructive studies in animal parasites brings back again the complicated life cycle of tape-worms and flukes. Among the bacteria it seems well established that glanders bacilli may enter the body of horses through the digestive tract. Nicolas and Descos [5] showed that in the dog tubercle bacilli may appear in the thoracic duct after a meal of fatty substances impregnated with them. Ravenel [6] confirmed their observations. There is good reason, then, for anticipating discoveries or theories which might greatly simplify our view of infection.

In my studies of the bovine disease I was unable to see anything more than the localization in the lymph nodes of the invaded part or perhaps a very slow creeping along to the succeeding nodes. I am not inclined to accept the extreme view that tubercle bacilli may penetrate very far into the system at the start. The view that they may enter the blood during invasion is derived partly from artificial inoculations.

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[5] Jour. de Physiol. et de Path. Gén., vol. iv, 1902, p. 910.

[6] Jour. Med. Research, vol. x, 1903, p. 460.

In such experiments more or less injury is always inflicted and the bacilli may enter both blood vessels and lymphatics. In the spontaneous infection, the bacilli enter the lymphatics only and the nodes act as a temporary or permanent barrier. The positive experiments with dogs quoted above can not very well be generalized to apply to the spontaneous disease until similar experiments have been made on other species with bacilli from various sources.

II. THE RECIPROCAL ACTION OF BACILLI AND THE INVADED ANIMAL TISSUES.

The passage of tubercle bacilli through mucous membranes and the alveoli of the lungs into the nearest lymph nodes is probably made in the same way and by means of the same agencies by which particles of soot, quartz and other mineral particles are conveyed, that is to say, as inert matter for the time being. The lodgment in the lymph nodes is probably due to mechanical agencies, the nodes acting as filters and barriers.

Here the bacilli begin to multiply and to set in motion that complex series of events leading to tubercle formation. Taking a tubercular focus in one of the thoracic lymph nodes of cattle, the first visible sign of the presence of the bacillus is the proliferation of epithelioid cells, with single nucleus or multiple nuclei. This new tissue undergoes central necrosis and caseation. The surrounding tissue proliferates to form a more or less dense capsule and the process comes to a standstill.

If we endeavor, with the aid and guidance of existing knowledge, to construct a sequence of the factors which are concerned in this process of tubercle formation, we shall find it extremely puzzling. It has occupied my attention for a number of years, yet even to-day with the help of the many currents of experimental data coming from so many laboratories I realize that we may choose several widely different interpretations without coming into violent collision with what we may regard as reliable experimental data.

At the outset it may be said that the tissue proliferation in tuberculosis is something specific in character, varying slightly

from host to host. In man and cattle it is much the same. In the smaller animals, either spontaneously diseased or inoculated, the tuberculous tissue is still characteristic, but giant cells are rare or absent. These, as a rule, are absent when the process is very rapid. In those species to which the bacillus has adapted itself, man and cattle, the cell proliferation is most uniform and characteristic.

The tissue reaction leading to the quiescent focus above described I believe to be a mechanism of defense for the body, even though imperfect. I also believe that it is a mechanism of defense for the tubercle bacillus—a mutual product, as it were. The structure of the tubercle interferes with the further dissemination of the bacillus by clogging the channels of escape. The bacilli become embedded in the proliferating cells and the necrosis protects the surviving ones from further attack for the time being. We can conceive that if this cell proliferation is somewhat delayed, the final result is a much larger focus. If it is still more delayed, the bacilli may be carried into other lymph nodes of the series and may establish several foci. The stimulus for such proliferation rests somewhere with the bacillus. It was shown many years ago by Prudden and Hodenpyl, by Straus and by many others later that dead, even boiled and washed, bacilli stimulate cell proliferation of a more or less specific type. We also know that such proliferation goes on in the presence of living bacilli, for an indefinite number survive the whole process.

In view of the fact that living, though very attenuated, tubercle bacilli are far more effective in producing immunity than dead bacilli, a fact brought out by Behring, Koch, Trudeau and others, we are safe in granting that the formation of the tubercle is stimulated by something given off from the living bacilli and not destroyed by heat. The simple stimulation of cell growth by the multiplying bacilli, however, does not fully explain the matter. There is an additional element which enters here, and this probably resides in the blood and to a less degree in the lymph. The blood is evidently an unfavorable medium, as indicated by the location of tubercles in the

various animal species.[7] In order to account for the facts as nearly as possible, the following theory has been evolved during the past seven or eight years:

The tubercle bacilli as they come directly from some discharging focus are provided with some protecting, more or less inert substance as an envelope. This envelope maintains a neutral chemotaxis until the bacillus reaches the connective and lymphatic tissue, where it settles down. The protecting envelope is slowly removed by the normal tissue fluids. When this has been accomplished the bacilli are able to multiply, but during multiplication they stimulate cell proliferation and, according to the activity of this process, the multiplication is checked. The bacilli are destroyed in part; the rest, through the protecting influence of caseation, remain latent, provide themselves with the protecting envelope, and if discharged outward are ready to infect another individual.

It will be noticed at once that the theory presented has much in common with the theory of opsonins which A. E. Wright has developed with so much skill and industry since 1902.[8] We may as well call the blood factor the opsonin, in deference to Wright, as the one who first called attention to it as a normal element. I do not agree with Wright, however, in attributing any special rôle to the blood leucocytes in body defense, for there is little or no evidence of this in the tissue reaction to the tubercle bacillus.

The many observations which refer to an early phagocytosis by leucocytes when bacilli are injected may be explained in two ways: First, as due to neglected factors inherent in the cultures used. These are the injection of too large numbers of bacilli, attenuated by long cultivation, and many of them dead, autolytic products, and the production of trauma during inoculation. The attenuated and dead bacilli fall a prey to

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[7] Maragliano states that he has been able to cultivate tubercle bacilli successfully only on guinea-pigs' serum.

[8] Bulloch: Practitioner, Nov. 1905; a general summary and bibliography of Wright's work.

the leucocytes, and as soon as these are disposed of the true tubercle appears. Second, it is possible that the virulent tubercle bacilli may be carried by leucocytes, as are inert particles of dust, pigment and mineral, and deposited in a favorable place. We should scarcely attribute much importance to the carrying of a particle of quartz dust from the alveolus of a cow's lung to a mediastinal gland as a protective measure.

Baumgarten justly calls attention to the errors lurking in the injection of large numbers of bacilli, and his theory that the elements of the tubercle are quite different from the wandering phagocytes has been fully sustained. The phagocytosis which appears to go on in the tubercle itself I regard as a hedging in, a suppression of multiplication rather than a destruction. Even the common appearance of bacilli in epithelioid and giant cells may be interpreted as a growing around the bacilli on the part of the proliferating elements rather than an actual ingestion. That destruction may finally occur is highly probable, but necrosis soon ensues to check this and protect the remaining bacilli. I am aware that this assumption of a protecting envelope which can be conceived of as a secretion may appear strained, but I have been unable to harmonize the facts with any other theory. In its support I presented in a recent paper facts observed in the cultivation of tubercle bacilli, some of which I quote here:*

> In the cultivation of tubercle bacilli the peculiar behavior of the bacilli first and last is best explained by assuming some change in the envelope or outer membrane of the bacilli. It is well known that it is very difficult and frequently impossible to obtain cultures of tubercle bacilli from tuberculous tissue in culture media in which they will grow readily after months or years of artificial cultivation. To obtain original cultures it is necessary to approximate as closely as possible the conditions obtaining in the animal body.
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> We can interpret this great change which the bacilli undergo in artificial cultures in two ways: 1. They make use of substances which at first could not be utilized as food. In other words, their metabolic

* Trans. of the First Annual Meeting of the National Association for the Study and Prevention of Tuberculosis. 1905.

functions have undergone a profound alteration. 2. The bacilli under artificial cultivation have eliminated something which has interfered with active absorption and assimilation.

I am inclined to accept the second theory and to assume that in the course of artificial cultivation a relatively impervious protective capsule has been gradually eliminated or modified, and, as a result, the growth and multiplication have become freer and more rapid. This elimination or modification of the envelope may go on by a selective growth of those bacilli which are most easily affected, or else the membrane may become modified in all bacilli because the active struggle with living tissue is in abeyance.

This theory also voices a condition which, I think, should be considered in any theory of immunity. I refer to the latency of tubercle and other bacteria in tissues. This latency of tubercle bacilli in lymph nodes has been demonstrated by not a few experimenters (Loomis, Pizzini, Harbitz and others). According to the theory here proposed, the tubercle bacilli are unable to multiply in the system when the opsonic power is too low, for the reason that the protecting capsules are not removed. Under such conditions the body is apparently immune, but really is in a state of hypersusceptibility. When the opsonic power rises the multiplication begins. This theory would also explain more rationally the greater activity of tuberculosis in certain decades of life.[9]

It is far from my purpose to apply this theory to all invasive bacteria. Each group or species possesses certain morphologic and physiologic peculiarities which are overdeveloped or suppressed in the evolution of parasitism. The work of Denys, of A. E. Wright and of Neufeld has shown that, while lytic forces may control typhoid and cholera bacteria, they do not govern streptococcus and other infections, in which cellular activity in the form of phagocytosis plays an important part. The more rapidly growing bacteria may possess quite a different mechanism of defense. As pointed out by Dr. W. H. Welch, they may secrete substances in the body which we do not sense in the

[9] This conception of a hypersusceptibility in the form given here is, I think, new. There are several other diseases in which this conception may prove explanatory and stimulating, and I hope to return to this subject in a later paper.

culture tube. These he calls toxins, while I should prefer to call them protective substances of the bacteria. According to either conception, they would be harmful, the toxin directly, the protective substance indirectly by neutralizing the protective substances of the animal body. Finally, the theory here presented holds only for the spontaneous disease of man and cattle, attacked by their own specifically adapted races of bacilli. In experimental work this mutual relationship is disturbed by the foreign character of the bacilli used, by the crude methods of causing infection and by the use of artificial cultures more or less modified.

III. THE PRODUCTION OF SPECIFIC ARTIFICIAL IMMUNITY TOWARD TUBERCLE BACILLI.

The overshadowing problem before society to-day is that relating to acquired immunity to tuberculosis in the individual and its influence on future generations. Can immunity be induced artificially and will the survivors transmit anything of value to their offspring? The relative mildness of endemic diseases has been at times referred to as indicating the inheritance of acquired immunity, but the increased resistance of the population to endemic diseases can be explained as a result of weeding out or selection. In a recent lecture I pointed out that, with the weeding out of the host, there goes on a weeding out of the parasite as well until two are eventually selected which maintain a kind of equilibrium toward each other. During the weeding out of the host the parasite must gain in power to keep up with the former. This selected race of bacteria or other parasites attacking a population hitherto unexposed to it may cause serious epidemics and lead to the belief that the permanently infected population had gradualllly inherited an acquired immunity, whereas selection may have done it. In spite of these discouraging possibilities, the face of medicine and of society in general is determinedly set toward the prevention and cure of consumption and every possible means will be tried to raise the resistance of the individual. To experimental medicine has fallen the task of seeing what

can be done to raise the specific immunity artificially by making use of the tubercle bacillus, or any of its component substances, or even of hypothetical antibodies.

Historically the most important factor in the study of immunity is Koch's old tuberculin. From this, logically and illogically, all other methods of inducing immunity have radiated. It will be necessary, therefore, to deal with this first of all. The administration of this substance demonstrated three remarkable phenomena: 1. The great sensitiveness of the tuberculous individual and the comparative indifference of the healthy body to it. 2. A distinct thermal reaction of the tuberculous individual, that is to say, a general effect, and 3, a hyperemia of the tuberculous focus. These can be readily demonstrated on tuberculous guinea-pigs.

My interest in the tuberculin reaction was aroused in 1898, when I was giving considerable attention to the immunizing effect of tubercle bacilli, killed at the low temperature of 60 degrees centigrade. I was very much surprised to find that some of the guinea-pigs which had been inoculated with heated bacilli and in which there were no signs of active tuberculosis after eight weeks succumbed promptly to small doses of tuberculin. Others lost considerable weight, but survived.

This tuberculin reaction is closely allied to another brought out by dead bacilli, injected into an animal which has already received a dose of dead bacilli. In other words, the first dose of dead bacilli sensitizes the animal to such a degree that the second arouses a violent reaction and may even prove fatal. This had already been pointed out by Straus. Since making these experiments I have asked myself the question again and again, Why does a single dose of the dead bacilli sensitize the animal, and why does not a corresponding dose of tuberculin do likewise? So far as I was able to examine the literature, no one had succeeded in making animals hypersensitive by the use of tuberculin alone.

This hypersensitiveness I looked on as an immune reaction. The animal had been taken out of a condition of neutrality or indifference into one of irritability and defense, however imper-

fect. In seeking an explanation of this peculiar difference between heated bacilli and tuberculin, it became necessary to determine what the tuberculin reaction means. It is well known to the special student that there are about nine or ten theories of the action of tuberculin in print, and it seems perhaps folly to add another. Fortunately the one I believe accounts best for the facts observed by others and myself is very much like one of these nine or ten as I shall point out.

In the tubercular tissue and its immediate vicinity the tubercle bacilli have induced certain tissue changes, and with them certain new functions of the tissue have been aroused, which are the result of immunization. These new properties are concentrated in the immediate neighborhood of the focus. The specific resistance is, as it were, chiefly focal and only secondarily generalized. When the tuberculin comes in contact with this focus, the former is acted on, with the result that the originally innocuous tuberculin becomes poisonous perhaps by the splitting off of some poisonous substance. An incomplete digestion I should prefer to call it. As a result of this action we have, first, the local hyperemia and, second, the constitutional effect. In other words, the tuberculin becomes poisonous by an immune reaction directed toward the tubercle bacillus. This reaction is defective and in so far dangerous to the host. The only way in which the danger can be met is for the body to produce an antibody to this second substance. So far there is little evidence to show that the body is able to produce this in any amount. The animal body has learned to protect itself by suppressing multiplication rather than by attempting to neutralize such poisons.[10]

This theory of the tuberculin reaction as stated above is similar to the one proposed by A. Eber[11] nearly ten years ago. According to him the action of the tubercle bacillus raises the physiologic activity of the tissue involved in disease to such a

[10] This secondary poison is probably of the same nature as the aggressins recently brought forward by Bail.

[11] Deutsch. Ztschr. f. Tiermed, XXI, p. 34.

height that it becomes capable of acting on the tuberculin and splitting off from it a toxic pyrogenic substance called by him tuberculopyrin.

My own interest in the tuberculin reaction was aroused by the query why a dose of dead tubercle bacilli can make the body sensitive while a corresponding amount of tuberculin does not. The reason why the injection of tuberculin as such does not lead to a subsequent tuberculin reaction as a result of one or several doses lies in the fact that tuberculin after injection is distributed throughout the body. Each cell receives but a brief exposure to a very minute quantity and probably much is eliminated unused. When dead bacilli (or even living ones) are introduced they soon settle down, and, the process of disintegration being very gradual, the tissues in which they are deposited receive a continuous, even though infinitesimal amount of tuberculin from the bacilli, and as a result of this persistent stimulus over a small area the tissue becomes focally active.

If this theory be true, the effect of the old tuberculin in establishing resistance appears in a new light. It would, first of all, exercise its chief function of being converted into a poison. During this conversion it uses up the antibody of the tuberculous focus. The benefit to be derived from it would be, first, in stimulating the reproduction of this antibody in the focus and around it, and, secondly, to accustom the body gradually to the action of the secondary poison set free from it. According to Koch, its action is antitoxic, but in a very roundabout way. Nevertheless, the use of the very minute doses now generally advocated may accomplish a kind of one-sided resistance, which large doses, as given in the past, might strain and even injure. This view would also oppose doses of tuberculin which set free enough toxin to cause fever, and this mode of administration has been interdicted.

This theory, furthermore, harmonizes with certain recent experiments which show that tuberculin reactions are diminished in severity when accessible foci are removed before injecting the tuberculin.

The gradual loss of the tuberculin reaction may be accounted for in one case by the tissues becoming gradually accustomed to the secondary tuberculin poison, in another by the subsidence of the active process and the gradual loss of the antibody production on the part of the healed or quiescent focus, in a third by a temporary exhaustion of the antibody which activates the tuberculin in the focus. It is well known that in cattle the reaction from a tuberculin injection following another similar one at a short interval appears earlier and is weaker and shorter in duration than the first or it may not appear at all. If twenty times the initial dose be injected reaction does occur, but here we may have other substances enter which were present in the small dose in insignificant amount. Just as in diphtheria toxin the toxon elements began to appear when we gave up the ten-minim fatal dose for the fifty or one one hundred in testing the strength of antitoxins.

That I should have given preference to heated tubercle bacilli as immunizing agents rather than to the old tuberculin is obvious from the theory of action of the latter which I have formulated. Fully a year before I began my experiments with tuberculin, Koch, in 1897, had issued his new tuberculin T.R., which consisted of the ground, unheated bodies of tubercle bacilli. This was a distinct theoretical advance on the old tuberculin and was abreast of the new views of immunity. The old conception of the direct curative action of tuberculin had been abandoned. The issuing of the bacilli *in toto* tacitly acknowledged that the body must become immune to the entire bacillus and its metabolic products, for as long as we do not know which substance of the bacillus plays the most important and decisive rôle in arousing the defensive reaction of the body we must inject all of them.

There have been many other investigators working along similar lines. Some have kept us regularly informed of their forward and backward movements in this puzzling territory; others have kept to themselves their wanderings. The literature has grown to stupendous proportions, and any one who enters this field with any suggestions or theories is certain to

do injustice to some precursor, for almost every possible interpretation has been stated somewhere before.

Among the more thorough and distinguished investigators a few may be mentioned. Maragliano has essayed immunity with the watery extract of tubercle bacilli and has studied assiduously the various toxins of the bacillus. Denys has tried to immunize with the bacteria-free filtrate of cultures. There have been notable contributions to the chemistry of the tubercle bacillus by Kühne, Ruppel, Levene, de Schweinitz and others. The noteworthy work of Trudeau, Baldwin and their associates has greatly contributed to the steadying of our advance in the knowledge of immunity and its bearing on clinical medicine. These observers have also been untiring in separating the wheat from the chaff of that which has come to us from abroad. Very recently Behring announced the use of tubercle bacilli for immunization or treatment which, according to brief reports, have been extracted with water, 10 per cent. salt solution and, finally, alcohol, ether and chloroform. With this bacillar skeleton, as it were, he expects to obtain better results. The details of the process are not yet generally known.

The attempts at the preparation of a therapeutic serum I shall pass over, since there does not yet appear to be a very satisfactory experimental basis for estimating its efficiency. It will in any case remain of merely theoretical interest in the cure of tuberculosis, owing to the difficulty of preparation and the probable cost.

In spite of this array of painstaking contributions to the biochemistry of the tubercle bacillus and the relation of its various component elements, secretions and metabolic products to the production of immunity, we still appear to be at the beginning. The recent studies of Koch, Behring and Pearson in bovine immunity produced by the intravenous injection of living human bacilli, and the same experiments of Trudeau on smaller animals, bring us back to the old principle first brought out by Pasteur in 1880 in his studies of protective inoculation toward fowl cholera. We have not only retraced our steps to the whole bacillus, but even to the living attenuated bacillus.

A very pertinent question, one which has undoubtedly been put by every physician and experimenter dealing with tuberculosis, suggests itself here: If immunity does not appear in the course of tuberculosis, why should we expect to produce it by artificial means? An answer to this question involves many factors, on only one of which I shall touch.

Immunity in tuberculosis consists of two elements, the focal or local immunity due to the multiplication of tubercle bacilli in a given territory, and a less pronounced general immunity due to the biochemical activities of the local process. If the general immunity becomes quite strong, or if the original resistance is so great that a little impulse makes it complete, then a second attack is not likely to occur. This, alas, is not ordinarily the case.

Granted that the first infection manifests itself, as a rule, in certain lymph nodes, two different results may be looked for. Either it leaves an immunity which promptly fixes the next invader, closes in on him so that multiplication is speedily checked, or else in the less responsive the second invaders, lodging in the lungs themselves, may prove disastrous, owing to the destructibility of the lung tissue itself and the chance for secondary infections. This would mean that in the first type of individual the early infection protects against a second; in the second type, the first apparently, but not really, predisposes toward a second, the distinction being due to a difference in the rousing of immunizing factors.

In cattle the short life of the individual does not enable us to realize much from a study of primary and subsequent infections, but the impression that I have gained from a careful repeated study of the autopsy notes is that old lymph-node tuberculosis is rarely associated with fresh pulmonary disease. Cattle, I believe, are nearly immune and it requires but a little to tip the scales in favor of the host.

The acquired general immunity following the first attack is shown in a variety of ways. Experimentally the second local lesion in the guinea-pig, as pointed out by Koch, is a different process from the first. Clinically, the lymph-node tuberculosis

of childhood later becomes an organ tuberculosis. The bacilli are literally held up in the portal of entry, and pulmonary disease becomes the type of the second stage or of later life. The first infection of the intestines lodges and multiplies in the mesenteric lymph nodes. When lung disease is established and the sputum is swallowed, tuberculous lesions of the mucous membrane are very common; those of the lymph nodes, slight or absent. Behring is quoted by some one as stating that this infection is due to a hypersensitiveness. I should say a partial immunity, for here also the bacilli are held up at the place of entry. These facts were noted long ago, but not explained, by Weigert, as stated at the beginning of the article.

To the physician this phenomenon of repeated infection meant no immunity. And, indeed, so far as the patient is concerned, it is as good as none. It is more dangerous owing to secondary infection, but it carries in it the germ of possibilities, namely, the immunization to a degree which will totally prevent the second attack. In the meantime it may not be amiss to point out here the true significance of protecting patients from repeated infection. I should place this among the most important of the details of treatment, and it is not to be denied that the careful protection afforded tuberculous patients nowadays in sanatoria may have a powerful influence in raising the percentage of recoveries. To this opportunity for repeated infection on which I would place much more responsibility than on diffusion of early or latent infection in the body itself, there must be added the chance of acquiring tubercle bacilli of much higher invasive powers and, therefore, more dangerous.

At this point I may be permitted to digress a moment to refer to the peculiar localization of tuberculosis in the upper or cephalic lobes of the lungs. Numerous attempts at explanation have been made chiefly on anatomic bases. Some would make pulmonary disease hematogenous in origin, the infection coming from some disrupted primary focus, probably a caseous lymph node. The following evidence offered by experimental and comparative pathology on this puzzling phenomenon is somewhat contradictory, but suggestive.

I have already stated that in the spontaneous disease of cattle the largest or caudal lobes are most frequently diseased primarily or else those lymph nodes associated with them. The smaller cephalic lobes are more often secondarily diseased from aspirated caseous matter. This is as we should expect to find it if the germ lodges and multiplies where we should expect most bacilli to lodge when carried in the air.

Some years ago I noticed in several rabbits which had been inoculated into the ear vein with human tubercle bacilli and kept a long time the following peculiar condition: The bacilli which ordinarily are deposited in every part of the lungs and which, if virulent, fill the entire lung tissue with tubercles, had been suppressed and destroyed excepting along the thin border of both cephalic lobes, which were solid and tuberculous. It is probable that this condition can be frequently induced if the tubercle bacilli are very finely ground before injection so that large masses may not lodge and inevitably produce foci anywhere. These two facts, the spontaneous disease in cattle and the induced disease in rabbits, both favor, one negatively, the other positively, the hematogenic origin of tuberculosis of the upper lobes in man; but there is a third element in the form of a general principle which, to my mind, holds the balance. This may be briefly stated as follows:

Bacteria multiplying by preference in certain localities as *loci minoris resistentiæ* will reach these places if they have access to them through the blood or through natural openings. For example, typhoid bacilli injected into the blood will probably cause ulceration of the intestinal lymph apparatus just the same as if ingested. Applying these various data to pulmonary disease, there is no more reason to assume the suppression of tubercle bacilli entering by one route, the air, than by the other, the blood. I am myself inclined to believe that the bacilli inhaled are suppressed and destroyed except in the apices in susceptible individuals.

To return to our subject of focal immunity. This, as contrasted with a general resistance, is probably the chief stumbling block to successful artificial immunization. To bring

about the latter the whole body has to be exposed to the immunizing (and toxic) substances, as there is no other way of reaching certain avenues or portals of entry which are exposed to invasion. We might, for instance, cause the inhalation of an impalpable dust or spray of ground tubercle bacilli to increase the resistance of the lungs in the healthy and the diseased, but then the greatest care would have to be exercised not to give an overdose to an affected lung; otherwise a very severe or even fatal congestion due to the local tuberculin reaction might result.

This problem of local immunity and its relation to a general immunity has occupied my attention for a number of years. Beginning in 1898 I carried out a long series of experiments on guinea-pigs with bacilli killed at 60 degrees and 100 degrees centigrade to see how far a focal or local immunity contributed to a general resistance. These experiments have been frequently interrupted and are still incomplete partly because the equipment needed to protect attendants has not been available. So far only dead bacilli have been employed throughout. The animals used were guinea-pigs. No striking results have been obtained, and hence the work has remained unpublished. The experiments bear, however, on the subject before us and I shall briefly refer to them here.

If we inject a certain amount of a suspension of tubercle bacilli in some indifferent fluid, and killed at 60 degrees centigrade, into the peritoneal cavity of guinea-pigs, no immediate effect is produced. There may be at first slight loss in weight or none at all. After four to eight weeks the guinea-pig, outwardly well, is sensitive to tuberculin. An ordinary dose may kill it or reduce its weight considerably. At this time the peritoneal cavity may or may not show any local proliferation. In the omentum some nodules may be found centrally disintegrated, soft, like pus, but consisting only of the usual fatty débris. The inner wall of the nodule is smooth, there are no signs of a progressive disease anywhere recognizable with naked eye or in sections with the microscope.

If we now inject a second similar dose, the guinea-pig within

twenty-four hours begins a prolonged tuberculin reaction associated with fever and rapid loss in weight. If we examine the peritoneal cavity after one or more weeks, we now find considerable hyperplasia of the omentum, more rarely eruptions on the peritoneum of the abdominal wall. The omentum may become very large and adhesions may bind it to various organs, especially to the upper small intestine and lead in some cases to intestinal hemorrhage and rapid diminution in weight, even death.[12]

This second severe reaction I regarded as due to the rousing of a local immunity by the first reaction. The bacilli first injected into a neutral territory were probably largely carried off into different tissues before any local reaction took place, for I found histologic traces of their presence in the liver, spleen and bronchial glands. The phenomenon is thus similar to the invasion of the lymph nodes in the neutral body. At the same time many bacilli remained in the omental tissue and in the immediate neighborhood of the abdominal cavity. The second injection caused a prompt reaction on the part of the tissues first invaded and the bacilli were largely held there; hence the great proliferation of the omentum.

This increased local reaction following invasion is a general phenomenon, not limited to tuberculosis. When animals of more than the usual resistance are inoculated with septicemic organisms, the local reaction is always more severe and the disease more prolonged than in the most susceptible. If very susceptible animals are first partly immunized, the local reaction following the test inoculation grows more severe, parallel with the immunity, up to a certain point.

The question now arose, How much immunity have other distant tissues gained by this intraperitoneal local vaccination? If more or less general resistance is gained, why not induce

[12] Since making these observations I have asked myself whether some of the tubercular eruptions of the peritoneum, cured by operation, may not have been due to dead or nearly dead bacilli discharged from an old focus on a promptly reacting, because partly immunized, membrane.

with dead bacilli local foci in the periphery of the body under the skin, for example, where they can be controlled and watched? To test this, the abdominal cavity and the subcutis were used. A long series of guinea-pigs were inoculated, some into the abdomen, some under the skin, some with bacilli killed at 60 degrees centigrade, others with those killed at 100 degrees centigrade. The cultures were all relatively young cultures, both human and bovine, grown on dog's serum. The conditions were made as uniform as possible. In order to estimate the relative reaction caused by the subcutaneous and the intraperitoneal injections the subcutaneous focus and the omentum were examined histologically. In general it may be stated that there was evidence that one injection had some influence on distant parts of the body, but this was distinctly below the influence imparted locally.[13]

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[13] In connection with these I tried to see if the injection of tubercle bacilli heated to one hundred degrees centigrade would produce any impression on a rapidly fatal infection with living bacilli. Eighteen guinea-pigs were used. In the first half of the experiment some received one injection of boiled bacilli into the abdomen, others, the same into the subcutis. After eight weeks they and controls received a surely fatal dose of living bovine bacilli into the abdomen. I knew that none would resist this dose and I simply wished to see what differences might appear. The abdominally immunized pigs lived longest, next came the subcutaneous cases and then the controls. The gain in prolonged life averaged only about seven days for the protected pigs. But the significant features of the experiment were exhibited in the course of the disease. The controls became feverish on the ninth day, yet even sixteen days later than this the vaccinated pigs were still well and active. Soon, however, they became ill and died suddenly. Here the immunity held the disease in check for a time, but when the resistance was finally overcome the process was very rapid. In the second half of the experiment, the guinea-pigs received two preliminary doses of boiled bacilli, one into the abdomen, the other under the skin. The same early checking of the disease was seen, a decided difference between treated and untreated being noticeable. All, however, succumbed; the average survival of the treated was about fifteen days longer than that of the untreated. The contrast would probably have been more striking if I had limited the test to a small number of fatal doses of bovine bacilli, rather than to the large dose actually given. Experiments similar to this have probably been made by many others before.

IV. SOME SUGGESTIONS CONCERNING THE PRACTICAL APPLICATION OF METHODS TO PRODUCE IMMUNITY.

The experiments made on cattle with human tubercle bacilli by Behring, Pearson, Koch and others have shown that a pronounced resistance to living bovine cultures may be established even in young animals. This procedure is, of course, inapplicable to man. In the immunization of cattle two factors operate very strongly toward the success of the process: First, the intravenous injection of the bacilli which carries them to every part of the body and especially to the lung tissue where we know the bacilli are likely to be held back in large numbers. Here they are most needed to produce a local resistance in the most frequently exposed and diseased organs (lungs and lymph nodes) of the body. It is doubtful that the bacilli multiply at all after injection.[14] In the second place, the postmortem examination of spontaneously and artificially infected cattle has led me to believe that cattle are in a fair state of equilibrium with their bacillus and that there is needed but a relatively slight impulse at the right place to establish a resistance which will promptly suppress the invaders.

The investigations of Nägeli, Necker and others which reveal a very high percentage of latent or arrested infection in the human subject also indicate that the normal human being possesses considerable resistance and that after infection only a slight impulse efficiently applied may suppress the disease at an early stage. This encouraging possibility leads me to believe

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[14] It is of interest here to note that according to Behring the intravenous injection of these human bacilli into adults may cause a fatal pulmonary edema, which we may explain as a local tuberculin reaction in infected animals. I described a similar condition in rabbits several years ago. After intravenous injection of certain cultures mid-way in virulence between the bovine and the human types, a fatal pulmonary edema and hyperemia may appear after four or five weeks. This is probably a true tuberculin reaction of the lungs, due to the extensive destruction of tubercle bacilli and the liberation of poisons. Similar pulmonary accidents in goats were described by Arloing.

that there is a great opportunity for some form of preventive inoculation before the disease has fastened itself on the predisposed subject, if such a process could be introduced. This vaccination should be equally applicable before and after infection. The general outcome of the investigation with bacilli killed at various temperatures has encouraged me to suggest their use for immunization. The very fact that they are so much more efficacious than the old tuberculin in rousing the antagonism of the body is significant. But it may be said the injection of dead bacilli will lead to a local focus, an objection which Koch tried to overcome at the start by extracting bacilli and so producing the old tuberculin. It may also be asked what advantage can there be over the ground and crushed bacilli which have been subjected to no heat whatever and which are now being used by A. E. Wright and others in the treatment of chronic skin affections. It may even be urged that immunity or increased resistance has been attained in exceptional cases by the repeated injection of the old tuberculin. Macfadyan and C. Sternberg refer each to such a case. A relatively high degree of resistance has been reported by Koch to be attainable with his new tuberculin TR. There can be no doubt that all the preparations emanating from tubercle bacilli or the culture fluids contain substances which induce some resistance. If the reaction of the body is made up of several factors, as I have endeavored to explain, then the strengthening of any one factor may favor the final resistance produced.

The advantages which, I believe, will flow from the use of bacilli killed at a low temperature, are twofold:

1. The creation of a local focus of ever so slight a character, let us say in the subcutis, may lead to the production of immune bodies which, radiating from the focus, may prove efficacious. These foci may be multiplied by simply changing the point of injection. It may be that the very objection urged by Koch against a local focus, namely, that the immunizing substances remain there, is the very essence of the whole process. At any rate, we have no reason for believing that the crushed or

ground bacilli or even the tuberculin TR. is diffused more rapidly after the reaction of the body has been roused. Levene found that even fats repeatedly injected subcutaneously finally led to a local reaction with induration. In looking over the literature recently I was surprised and gratified to learn that Maragliano had recommended some such mode of treatment in his Philadelphia address.[15] Such local foci can be watched and their behavior correlated with the general subjective and objective symptoms.

The second advantage to which I wish to call attention concerns the material to be injected. In the production of immunity the tubercle bacilli to be used should be as recently isolated as possible and grown on blood serum to which pieces of sterile animal tissues may be added if desirable. If the theory I have advanced be true, that the body first acts on some product of secretion in the bacillus which has taken the form of a protective envelope, then the more recently isolated the culture and the more nearly the culture medium approximates the living body the more likely the active production of this envelope. This, of course, should be present in the bacilli to rouse to greater activity the antibody or opsonin after injection. The products in the market are prepared on a large scale from actively multiplying bacilli. A long experience leads me to the inference that there is an inverse relation between virulence and activity of multiplication. I have also pointed out that the slow accustoming of tubercle bacilli to media on which they at first absolutely refuse to multiply suggests the throwing off of some restraint (such as an envelope) either by all bacilli gradually or through the selection of a few which more quickly adapt themselves. The use of such early cultures of tubercle bacilli, grown on appropriate media, carefully killed at 60 degrees centigrade and tested with proper precautions before application, is within the reach of every hospital or sanatorium dealing with tuberculous patients.

My reason for presenting a method which I myself have not

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[15] Medical News, lxxxiv, 1904, p. 625.

tried is because I have no opportunities for such trial, and I am convinced that the delicate methods of immunization can not be successfully tested on any animals, except perhaps monkeys and cattle, and there are obvious objections and difficulties to be met in the use of either species. I believe that this method should at least be given a trial, although its execution will require considerable personal care and the observance of minute details which the medical profession is inclined to throw on the commercial bodies who manufacture biologic products, but from whom such kind of work can hardly be expected. Of especial importance is the test that the heated bacilli are actually dead, for the temperature of 60°C. is the critical temperature, below which tubercle bacilli are probably not destroyed. Experiments still incompleted indicate that bacilli killed in this way possess properties approaching the living organisms.

CONCLUSIONS.

In conclusion, I wish to allude briefly to the struggle against tuberculosis from the point of view of the bacillus itself, for the slight changes which this parasite undergoes are writ large on the history of mankind. By spying about the enemy's camp we may learn much for our own safety.

The tubercle bacillus is undoubtedly open to modification, and we may safely believe that there are a large number of races or varieties in existence. Even among the small numbers which we are able to study carefully in the laboratory, there are constant differences indicated by biologic and pathogenic tests. These must be the result of natural selection and brought together perhaps by the great immigration movements of the present era.

The thesis which I tried to discuss recently is that the tendency of infectious diseases is toward a balanced parasitism, with a reduced mortality, but not necessarily a reduced morbidity as a result. This is due to the selective adaptation of both host and microbe. For the latter the most important need is the establishment of a definite mode of entry and exit. In the case of the tubercle bacillus the chronic infection of the

lungs is the most favorable type of disease for the microbe itself. This selective adaptation will go much farther, I believe, and we shall undoubtedly meet with bacilli of very low invasive power which find a favorable nidus for multiplication in bronchial secretions. There is already some evidence that tubercle bacilli in sputum do not always signify serious consequences.

The only way to determine the relation between pathogenicity and character of the disease would be a study of the bacilli themselves. This would throw such an additional burden on clinical medicine that we can hardly hope for much progress in this direction. These very attenuated forms may become, as it were, the parasites of the sick lungs rather than of the normal ones. They would take the same position which pneumococci, streptococci and staphylococci occupy in the upper air passages.

The influence which a possible immunization of the human race might have on the destiny of the tubercle bacillus is open to debate. In the first place, all immunization is a confession that the parasite has broken through barriers and has come to stay. The only way to suppress an infection is to do so rather than to establish a compromise by simply increasing our resistance. The latter is admirable from every point of view, but it is not by itself going to eliminate tuberculosis. The only way to accomplish this is to prevent the bacillus from attacking a new subject. Immunization, combined with isolation and other preventive measures, would probably place a decided check on the disease, while immunization by itself alone would lead eventually toward the selection of especially virulent races of the tubercle bacillus which, producing a mild disease in the partially immune, would probably cause a very severe disease in the unprotected or unvaccinated. If the method of immunizing cattle now made generally possible by the commercial exploitation of Behring's bovovaccine should become widespread, we would be treated to a most valuable object-lesson of the effects of this process on the protected and unprotected. With the introduction of such a method there is likely to come a slackening of the usual preventive measures and a more indis-

criminate dissemination of tubercle bacilli followed eventually by the appearance of more virulent races.

In this fragmentary exposition of the parasitism of the tubercle bacillus I have left many phases of the subject untouched, many statements undeveloped and certain theories quite unprotected. My purpose in presenting them is not so much to produce conviction as to stimulate others either to develop them further or else to rout them and to put something better in their place. They may be regarded as working hypotheses through which I have attempted to correlate existing data, my own studies serving merely as a guide through the Babel of theories.

The best that the laboratory worker can do is to suggest principles or laws which must be intrusted to the clinician, if he will accept them, to be developed and applied to the many variations which actual spontaneous disease manifests. It is also true that the working out of methods in the laboratory and their clinical application are two wholly different problems. Experimental and clinical medicine must work hand in hand, with the closest co-operation, if one does not wish to disappear in pitfalls known only to the other.