ALLERGY IN CLINICAL TUBERCULOSIS*

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INTRODUCTORY.

We have now reached a place in our understanding of tuberculosis in which we are able to interpret the disease and its manifestations more clearly than at any previous time. This position has been attained through diligent study of every phase of the subject. It has included careful clinical observation and much painstaking animal experimentation. The correlation of the data obtained in these fields has furnished a basis for writing the story of clinical tuberculosis anew and recognising the immunity reaction as a factor of prime importance in determining the pathology of the disease, its symptomatology, its diagnosis, its clinical course, and its healing or failure to heal. Without the consideration of allergy we can no more understand the pathologic changes and varied clinical manifestations in tuberculosis than we can understand its etiology without considering the tubercle bacillus.

In the early years of extensive study of tuberculosis our opinions were so largely dominated by deadhouse pathology that we could not understand living tuberculosis. We failed to grasp what it is that is occurring, changing and repeating itself, which makes up the ensemble of chronic tuberculosis as we meet it day by day in the clinic.

However, through an ever-increasing accuracy in clinical observation, and a more perfect technique in physical examination, with examinations repeated at frequent intervals on the same patient, and these supplemented by X-ray films taken by the most approved technique and by laboratory studies, we have learned that clinical findings are to be interpreted, if they are to be understood, in terms of immunological response in which the allergic inflammatory reaction is to be kept to the fore. By correlating the results of these methods with the data obtained from immunological investigations we have learned that tuberculosis is a very different entity from that which was formerly believed. We can now visualise and record the ever-changing interplay between the invading bacilli and the host in a much more satisfactory manner than was possible before the nature of the body's specific resistance to reinoculations of bacilli was known. In fact, we are now realising that it is the immunity reactions which make up the disease picture.

THE KOCH PHENOMENON.

The basis for this better understanding of tuberculosis has been within our grasp for nearly forty years. It was contained in one of Koch's early papers in which he announced the discovery of tuberculin; but, like most great basic truths, it has required a prodigious amount of thought and labor to clarify it

and make it understandable to the great mass of workers. His observation was the first recognition of the fact that an animal, immune to tuberculosis, that is, one whose specific immunity mechanism has been aroused by a previous inoculation with tubercle bacilli, reacts differently toward living or dead bacilli from one infected for the first time. This reaction to reinoculation has come to be known as Koch’s phenomenon. It was the first immunological approach to the study of tuberculosis, and has been made the basis not only of the modern immunological study of tuberculosis, but of the immunity reaction in other diseases as well.

Koch’s description of the immune reaction is as follows [1]:—

"When one inoculates healthy guinea-pigs with a pure culture of tubercle bacilli the inoculation wound closes up and apparently heals within a few days. In the course of ten to fourteen days, however, a hard nodule appears, which breaks down and forms an ulcer. This remains until the death of the animal. It is quite different, however, when a guinea-pig that is already tuberculous is inoculated. Animals that have been inoculated from four to six weeks previously are best suited to this purpose. In one such animal, however, the inoculation did not heal in the beginning, but small nodules appeared, and within one or two days showed characteristic changes about the point of inoculation. Around the point of inoculation it became hard and took upon itself a darker colour, which did not confine itself to the immediate point of inoculation but spread to the surrounding tissues for a distance of from ½ to 1 cm. When the succeeding dose is administered it shows very distinctly that the skin showing the alteration is necrotic; and it is eventually cast off, a small superficial ulceration remaining, which usually heals quickly and permanently without the regional lymph-glands becoming involved. The inoculated tubercle bacilli also act very differently upon the skin of a healthy guinea-pig from what they do upon one infected with tuberculosis. This characteristic action is not entirely confined to living tubercle, but also occurs when dead bacilli are used, whether the bacilli be destroyed, as I attempted in the beginning, through low temperature of long duration, or by boiling, or through the action of chemicals.

"After these characteristic effects had been discovered, I followed them in every direction and I found that pure cultures of tubercle bacilli that had been killed, ground up, and mixed with water could be injected under the skin of healthy guinea-pigs in large amounts without producing anything beyond a local suppuration. Tuberculous guinea-pigs, on the contrary, were killed by the injection of very small amounts of such cultures of dead bacilli within from six to forty-eight hours after the dose had been administered. A dose that is not sufficiently large to kill an animal often produces an extensive necrosis of the skin in the neighborhood of the site of injection. If the solution of dead cultures of bacilli is diluted still further so that it appears only slightly opalescent, then the animal remains alive; and if the injections are carried on with intervals of one or two days, a remarkable improvement in the condition of the animal takes place.

"The ulcerating inoculation wound becomes smaller and eventually forms a scar such as never occurs without such treatment. The swollen lymphatic glands become smaller, the nutrition of the animal improves and the diseased
process becomes quiescent if it is not too far advanced and the animal does not go rapidly down to death as is usual.

"These observations furnished me a basis for producing a remedy against tuberculosis."

We owe much to von Pirquet's [2] explanation for the changed reaction of body cells toward bacilli and bacillary protein as we find it in the immune animal as compared with the primarily infected. He called the phenomenon met in the reinfected, "allergy," and carefully studied many phases of the reaction. In tuberculosis we speak of it simply as "allergy" or as "tuberculo-allergy."

What is Allergy?

If we undertake to define allergy we are at a loss to know how much of the body's reaction toward bacilli and bacillary protein to include in the term, and how much to exclude. Allergy is a result of a hypersensitiveness to bacillary protein and manifests itself in the cells throughout the body of the host whether they have come in immediate contact with the invading bacilli or not. Therefore it must depend, for its existence, upon bacillary products which are elaborated within the disease focus, and which wander out from it and are disseminated through the blood-stream to all body cells. We cannot separate allergy from hypersensitiveness nor can we divorce it from immunity. After the first implantation of tubercle bacilli has gotten well under way, these three reactions, as far as is now known, represent the most important factors in tissue defence.

Krause [3], whose studies on allergy in experimental tuberculosis are among the most important so far made, in discussing the subject of pathogenesis in a recent paper suggests that allergy is the body's reaction against tuberculo-protein while immunity is the reaction against bacilli, thus: "For our purpose immunity is regarded as that condition of increased specific resistance to implantation and extension of tubercle bacilli, and allergy as that state of tissue hypersensitiveness to tuberculo-protein that comes into existence with the earliest formation of specific anatomical tubercle. Both immunity and allergy continue to work within the body as long as tubercle, with its tubercle bacilli, persists."

Allergy is established by the primary inoculation. Its rapidity of appearance in experimental tuberculosis varies with the dosage of bacilli, coming on after a few days when relatively large quantities of bacilli cause the infection and after two or three weeks when few are responsible for it. We assume that the same holds for man.

Allergy is a varying force. It is inflammatory in character. The power to react allergically may be studied in animal experimentation. It may be increased many fold by repeated inoculations. Roughly speaking, the larger the inoculation that the animal is able to overcome the higher will be his ability to react allergically. This subject has been studied and developed by many workers in many countries. Among the early workers in this field we would especially point out Römer, [4], [5], [6], [7], [8], [9], and Hamburger, [10], [11], [12], [13], [14], while among recent workers, no one has done more than Krause [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], to give us an adequate understanding of this important subject.
We are able to observe the building up of allergy following successfully withstood reinoculations in the course of clinical tuberculosis, either following many small reinfections unattended by recognisable symptoms, or one or more severe ones. From our knowledge of the incompetent wall which surrounds the tuberculous focus and its bacillary content during the time when the disease is active we are forced to assume that small reinoculations, unrecognisable though they may be, take place at frequent intervals; it may be minutes apart; it may be hours. But that they take place without making their presence known by symptoms is not only a possibility but a probability. That these are followed by small, probably often microscopic, allergic reaction, and result in an ever-increasing efficiency in the workings of the immunity mechanism, and further that they stimulate the reticular elements to form new fibrous tissue and thus become potent forces in the healing of the disease is also probably true. Allergy is favoured not only by a suitable reinoculation but by a satisfactory structural and functional state of the cells on the part of the host.

Should an excessive dose of bacilli cause reinoculation, the body may not be able to respond with a competent immunity reaction, and so allergy may be depressed at least for the time, or it may even be caused to vanish. So may it disappear under stresses to which the body is subjected, such as those during pregnancy and in the presence of such disease as influenza, measles and scarlet fever. It may be depressed when the host is undergoing severe stresses of whatever kind.

The severity of the reaction of the body to reinoculations of tubercle bacilli depends to a large extent upon the degree of allergy present. The more marked the allergy the more severe the reaction. Allergy can be taken as a measure of immunity; for the resistance to bacillary invasion and the reaction of the body cells to circulating bacillary protein seem to go hand in hand. In the clinical course of tuberculosis I have learned that as a rule those patients who possess the greatest resistance to the disease show most marked local reactions to tuberculin.

The presence of allergy, as was pointed out by von Pirquet [29], hastens the body's reactions and also makes them more violent. It is a determining factor in the further course of the disease in every reinoculation that takes place in tuberculosis; in fact, it is such an intimate part of clinical tuberculosis that we cannot think of active tuberculosis apart from the allergic response. While allergy is primarily defensive it may at times become injurious by causing so severe a reaction that the host is either harmed or destroyed. This has been shown in animals where a fairly large dose of bacilli or of tuberculin is withstood by the healthy pig without any immediate reaction taking place, while the same dose of bacilli or tuberculin, injected into a tuberculous animal, may cause death within a few hours or days.

Koch [30] found that 20 to 30 mg. of tuberculin would kill most guineapigs suffering from a tuberculosis of four or five weeks duration, and that 50 mg. would prove fatal without exception in from six to thirty hours.

It seems that tuberculo-protein in lethal doses produces its most acute effects on the blood-vessels, death being due to a paresis or paralysis of their walls.
The opinion that this is a form of allergic reaction is favoured by the fact that the same dose given to a non-allergic pig fails to produce any serious inflammatory response. This reaction in vessels must be borne in mind in accounting for certain hemoptyses which occur in the course of tuberculosis.

**THE ALLERGIC REACTION DIFFERS IN INFECTED AND NON-INFECTED TISSUES OF THE BODY.**

The body cells which possess the power of allergic reaction to the greatest degree are those in active and unhealed tuberculous foci, although all body cells in the infected organism are rendered allergic. The fact that the skin; the conjunctival, nasal, vaginal and rectal mucous membranes, the subcutaneous tissues, the muscles, the testicles, in fact, all tissues will react to the application of tuberculin when it is held in prolonged and intimate contact with them, but do not react to the tuberculoprotein which is set free into the circulation from a tuberculous focus within the body, as the cells about the tuberculous process do, indicates that the perifocal cells are the more sensitive to bacillary protein.

The allergic (auto-tuberculin) reactions met in the course of active tuberculosis are confined to those tissues which harbour living tubercle bacilli, particularly unhealed lesions. There is a continuous kaleidoscopic change going on in such tissues as a result of tuberculoprotein coming in contact with the cells in varying amounts at varying intervals of time. Sometimes the reaction is microscopic; at other times it may be severely exudative in character.

It is necessary to understand the relationship of the focal tissues to the allergic reaction, in order to comprehend the clinical aspects of the disease. The focus in which the newly inoculated bacilli settle is naturally most affected because here the chief contest between the invading bacilli and the cells endowed with specifically developed defence takes place. Here tuberculoprotein is set free as a result of the destruction of bacilli and is found in greatest concentration, whether the amount be small as in minimal reinoculations, or large, as in massive ones. Therefore, it is evident that the conditions favourable for severest reactions, viz., largest quantities of tuberculoprotein and most highly allergic cells, are present at the site of reinoculation, and in the tissues immediately surrounding it. It is also evident that small reinoculations will be accompanied by comparatively slight reactions in the focus of implantation, while massive ones will be accompanied by violent exudative inflammatory change.

While the conditions in the tissues at the point of new bacillary implantation are favourable for the production of the severest reactions, it is clear that all unhealed foci in the body contain highly sensitised cells which are capable of reacting with the circulating tuberculoprotein which contacts them. In comparison with that in the original focus, however, this reaction is of milder degree, because it is caused by relatively minute quantities of tuberculoprotein playing upon the sensitised cells of unhealed tubercle wherever they may be found in the body and are to be considered as important factors in the healing of the disease. Even reactions followed by extensive exudation and necrosis carry with them the power to stimulate the reticulum in the tubercle to the
formation of new fibrous tissue. Necrosis in the centre of tubercle and fibrosis at the periphery are phenomena not uncommonly found simultaneously in tubercle; in fact, they go hand in hand, as a rule.

The Importance of the Allergic Reaction in Diagnosis.

Tubercle bacilli may enter the body of a non-infected individual in fairly large numbers, and not make their presence known for several days, because they have no way of showing their effects clinically until the specific immunising mechanism, with its cell sensitisation, and the ability of the tissues to react allergically, has been established. When this has occurred, the entire picture changes. When tuberculo-protein is again brought into intimate contact with the body cells they show a condition of increased sensitisation toward it. This is shown at the site of inoculation as an inflammatory reaction when the tuberculin is applied locally, or as a general reaction with clinical symptoms appearing from within a few hours to one or two days, when the dose is administered subcutaneously.

Koch, in 1890, recognised this allergic reaction, although not by the name, as the basis of tuberculin diagnosis. He found that a tuberculous animal or man reacted to the subcutaneous injection of tuberculin with the same symptom complex which follows reinoculation of bacilli, while a non-tuberculous individual did not. He therefore suggested its use as a diagnostic test for tuberculosis. After considerable experience in administering the subcutaneous tuberculin test, he came to the conclusion that a reaction or failure of a reaction to 10 mg. of tuberculin could be taken as deciding the presence or absence of tuberculosis. Koch's method of administering the tuberculin test was first to give 1 mg. If no reaction occurred, he gave 5 mg.; and then if no reaction occurred, 10 mg. The reaction of the test at the site of injection was not heeded. It was the general reaction, accompanied by symptoms such as chill, rise of temperature, increased pulse-rate, increased cough and expectoration, and general malaise, that was taken to mean a positive reaction.

Focal reactions were also taken into consideration in all areas of visible tuberculous involvement. Later, in the presence of râles in the lung, following the injection, when they had not been present before, or an increase in those that had been present, was taken to mean a focal reaction. When X-ray examinations began to take part in diagnosis it was found that focal reactions appear as increased exudative (parenchymatous) phenomena. Later, it was shown that, in the tuberculous, the cells of the skin, subcutaneous tissue, conjunctival, nasal, vaginal and rectal mucous membranes all possessed increased sensitiveness to tuberculin. This gave a new meaning to the Koch phenomenon. Several new methods of applying the tuberculin test were suggested, such as the cutaneous of von Pirquet [31], the intradermal of Mandel [32] and Mantoux [33], the percutaneous of Moro [34], and the conjunctival of Wolff-Eisner [35] and Calmette [36].

Some of these tests were so simple, and the effects on the patient were so slight, when compared with the subcutaneous method, particularly in that they were not accompanied by the discomfort of a general reaction, that they came into general use and were employed in testing very large groups of individuals.
of all ages. This applied particularly to the cutaneous and intracutaneous methods.

It was a great surprise to find that nearly all children reacted to tuberculin, while comparatively few of them were suffering from active tuberculosis. From this it was learned that there is a difference between being infected with tubercle bacilli and suffering from tuberculosis. The important fact was also established that being infected is sufficient to cause positive reactions. Therefore, it became evident that the tuberculin reaction must be interpreted as cell hypersensitiveness to tuberculo-protein, due to prior infection with bacilli and not be taken as evidence of tuberculous disease.

In making a diagnosis in borderline cases, the fact of the absence of Koch's infection can be utilised to great advantage [37]. This is particularly true when examining nervous and psychical individuals, and those individuals with endocrine imbalance, who have symptoms simulating tuberculosis, also those suffering from post-influenzal, and subacute and chronic bronchitis, in whom it is necessary to consider the possibility or probability of a tuberculous disease. In such cases a tuberculin test should always be given as one of the first procedures in diagnosis, because of the value of a negative reaction. A negative test in a healthy individual is presumptive evidence that no tuberculosis is present, or at least no tuberculosis of an active form.

There are certain conditions, however, under which immunity may be markedly depressed and the reaction fail to appear, or appear but feebly, even though active disease be present. Such are pregnancy; the acute infections, particularly influenza, measles, whooping-cough and scarlet fever; cachexias; and extremely low states of general strength; also active advancing tuberculosis with relatively massive reinoculation.

Skin sensitisation, as found in the application of the tuberculin tests, is not the only use of allergy in diagnosis. The acute symptoms in tuberculosis, those of the toxie as well as those of the reflex group, and some of those due to the local action of the disease, are dependent upon the inflammatory allergic reaction for their existence. The disease may come on slowly after weeks or months of increased fatigability and loss of vigour; or, on the other hand, a patient may feel perfectly normal, with tuberculous infection slumbering within his body to-day. A reinoculation may take place, and to-morrow, as a result of his allergy, he may be suffering from the symptoms of acute disease. He may have temperature, malaise, increased pulse-rate, and the other symptoms belonging to the toxie group. He may further have a cough with expectoration. Or, if the disease should be in the pleura, he may have an acute pleurisy. The rapidity of the reaction is due to the shortening of the incubation period as a result of previous inoculation. Without allergy, as in the non-immune, the individual would not develop symptoms until he had gone through the incubation period and the bacilli had had time to fix themselves in the tissues and start in motion the immunity mechanism. Therefore, these important diagnostic symptoms are but an expression of disturbed function on the part of the host, brought about by the sensitised cells reacting to the presence of tuberculo-protein set free from active foci, particularly those at the seat of reinoculation. Bacilli destroyed by the host probably furnish a second source of supply.
The diagnostic importance of the X-ray in early tuberculosis is also based partly on the allergic reaction—not only the allergic reaction but a fairly marked allergic reaction in which considerable exudation takes place in the tissues. An allergic reaction may be of any degree from that of the mildest proliferation of cells, or the slightest exudation of serum into the tissues, to the most severe exudative process in which serum, cells and fibrin pass into the tissues and, in case of the lung, into the air passages; or even necrosis may take place. The reactions are all the same qualitatively, that is, they are all allergic, but they differ quantitatively. In order to get the increased flaky effects about a focus in an X-ray plate, as a result of a tuberculin injection, one must have exudative phenomena of a fairly marked degree.

The so-called parenchymatous lesion, as shown in the X-ray plate in early tuberculosis, is nothing more than an allergic reaction, sufficiently marked to produce more inflammatory changes and a greater amount of exudation into the tissues than that which usually accompanies the slightly exudative or the predominantly proliferative process.

**PATHOLOGIC CHANGE PRODUCED BY TUBERCULO-ALLERGY.**

The allergic reaction has a varied and varying pathology of injury, hyperemia, proliferation, exudation and necrosis. While tubercle is the normal response of the tissues to primary infections, it is also present, but as a secondary process, in reinfections.

Reaction to reinoculation always means some degree of inflammatory response. It may be only a hyperemia or a mildly proliferative reaction, or, on the other hand, it may be a severe predominantly exudative or necrotic one.

At the present time there is an unfortunate tendency on the part of students of tuberculosis to accept the classification of tuberculosis into the proliferative and exudative, suggested by Aschoff [38], as a basis not only of pathologic study but also as a basis for clinical consideration. This classification is a purely anatomical one and leads to faulty clinical conception. (Pottinger [39].)

The proliferative is suggested as the benign type, favourable for healing; and the exudative type as the severe type, unfavorable for healing. These are not different types of tuberculosis, nor even different types of reaction. They are both reactions of the tissues towards tubercle bacilli and tuberculo-protein in infected individuals. The reaction is the inflammatory allergic response of the tissues. One is a mild response, the other a severe response, but neither in itself can be made a basis for prognosis.

Neither proliferative nor exudative reactions exist alone as distinct pathologic entities. They are both found in the same pathologic picture. In fact, one cannot conceive of inflammatory reaction without hyperemia and some degree of exudation of serum or cells; and, furthermore, one finds in the severest reactions to bacillary disease a proliferation going hand in hand with exudation and destruction [40]. Even necrosis is not separated from and unattended by proliferative reaction.

Proliferative tuberculosis is not an exclusively proliferative form, patho-
logically, but only one in which the formation of new tissue, only predominates. Cell proliferation is present to some degree in all lesions, for it is the normal response of the cells to injury. It goes hand in hand with exudation as the two regular responses of the body tissue to bacillary reinoculation or to tuberculo-protein.

At times in the course of clinical tuberculosis the allergic reactions are so mild that the response on the part of the tissues seems to be almost wholly proliferative. There are reticular cells in every tissue in which tubercle formation takes place. These are a very important part of the cellular defence in tuberculosis. They take part in the allergic reaction, are irritated as a result of it, and as a result of the irritation proliferate and form new tissue. These cells are present in greatest numbers in the periphery of tubercle, but are found in less numbers in the center of the focus itself. As a result of the irritation produced by the allergic reaction new cells are formed which push inward and often obliterate the entire tubercle, converting it into a fibrous mass. Even caseous tubercle may be replaced by fibrosis as a result of this proliferating process.

All tubercles containing viable bacilli are subject to allergic or auto-tuberculin reactions, as long as reinoculations occur, or as long as tuberculo-protein escapes from unhealed foci. The effect of such reactions, except at the site of reinoculation, unless they be severe, is most evident in the perifocal cells, where they cause increased fibrosis, and may produce encapsulation and healing. The larger reactions produce a more profound effect. They are followed by exudation, sometimes severe, affecting any unhealed tubercles that may exist in the body at the time. But even in the severest exudative reactions, stimulation of the local reticular cells takes place producing an increase in fibrous tissue. Both proliferation and exudation are a part of all allergic reactions.

Exudation may be so slight as to be microscopical, in which event its main effect is to favour proliferation of fixed cells. It may be more severe and result in the watery elements of the blood passing into the tissues, or the exudate may contain cells and fibrin. The tissues may be literally engorged with exudate and, in case of the lung, the alveoli and bronchi may be filled with it.

In many such instances necrosis becomes an important part of the process.

It readily can be seen that the exudative process, when it results from a severe reaction, is pregnant with most serious damage to the tissues, and, if it were not changeable, it might result disastrously. But it is subject to change. In case reinoculations cease, the exudate may resolve and after a time the entire process take upon itself a mild character in which proliferation becomes the most important part of the picture.

The exudative process per se is not serious. The fact of its existence in the course of clinical tuberculosis in a severe form, however, indicates that bacilli are escaping in fairly large or very large numbers from existing foci to form new implantations, and that much tuberculo-protein is gaining access to the blood-stream. This may be taken as presumptive evidence that large quantities of bacilli may continue to escape; and, if they do, the resulting allergic reaction will cause an increase and a prolonged continuance of the exudative
process which may cause not only serious damage to the tissues, but may even prove to be inimical to life.

It is of the utmost importance that clinicians should hold the classification of tuberculosis into proliferative and exudative types as being without definite prognostic importance. An exudative process does not mean a bad prognosis, nor does a proliferative process mean a favourable prognosis. A predominantly proliferative process may be transformed into a predominantly exudative one inside of twenty-four hours through a fresh invasion of tubercle bacilli. A predominantly exudative process may, on the other hand, in the absence of a repetition of too many and too severe reinoculations, be transformed, in the course of a few weeks or months, into a process which is predominantly proliferative. We often see these changing effects during the course of clinical tuberculosis, quickly in the one case, even over night, slowly in the other, requiring weeks and months. Where the exudative process disappears particularly slowly we are justified in assuming that repeated reinoculations are taking place, which keep up the allergic reaction, even if they are not sufficiently severe to produce an elevation of the temperature curve with other accompanying toxic symptoms.

It required the labour of two genuises, that of Laennec in pathology, supported by that of Koch in bacteriology, to establish for all time the etiologic unity of all tuberculous processes. Now we have reached the stage in our study of tuberculosis when our conceptions of the various pathologic reactions and clinical responses to reinoculation should be unified; for they are all, in truth, only various degrees of response of cells, which have been rendered allergic by previous infection, to bacilli and bacillary protein, the degree of response being particularly determined by the quantity and quality of previous infections, the character of the tissues involved, and the reacting stability of the patient at the time of the infection and thereafter. Let us hope that it will not take so long to establish this unity.

One form of tissue response, or rather lack of response, is now recognised, in which tubercle bacilli may lie in the tissues without calling forth any recognisable response from the body cells (Bartel [41] and Opie [42]). This fact is difficult to explain on the basis of any of our notions of immunological or pathologic response, and requires future study for its elucidation. One may well speculate on the possibility of such bacilli taking upon themselves pathogenic qualities at times and being the sources of re-infections.

Necrosis, with its death of tissue, fits into the picture as a phase of the response of hypersensitive cells.

In attempting to unify the body's reactions on the basis of immunological response, we meet many factors which are followed fairly consistently by more or less definite response; but there are so many of these factors, such as numbers and virulence of bacilli, the inherited structural peculiarities of tissue, the nerve, hormone and psychic balance of the host, factors of environment, both physical and emotional, which enter into the body's response, that there is no way of determining in any given individual what his particular reaction to a particular reinoculation will be. We do assume, however, that the more serious the infection, and the lower the physical state of the host, the more
severe the disease, and the less the infection and the more perfect the physical state of the host the less severe the disease. The term "more serious" as used here means more widespread, as a result of the immunological mechanism of the host being unable to function adequately. It must not, however, be confused with a more violent body response, which is found in case the host's specific immunologic mechanism is highly developed. The most serious thing that can happen to a tuberculous patient is to have a given reinoculation fail to be met by an adequate immunological response.

Caseation and necrosis are the common destructive changes which take place in tissues which are subjected to allergic inflammatory reaction. Confusion in assigning to them a satisfactory explanation arises from the fact that contradictory conditions seem to be followed by necrosis. Primary tubercle caseates, even though the infection be relatively mild; and the regional lymphatic glands which receive drainage from the primary nodule usually show marked caseation. Again marked caseation with loss of much tissue rarely takes place in chronic tuberculosis except as the result of severe reinoculation, and then the necrosis is most evident at the point where the reinoculation has taken place. Frequently the first severe reinoculation that takes place when the disease becomes active is followed by a fairly large cavity, after which the disease may spread and subsequent reinoculations occur without other large cavities appearing.

From the standpoint of allergic reaction the conditions seem to be markedly different in these three instances. In the primary nodule caseation seems often to occur quickly before marked allergy has developed; the glands caseate under much the same condition. Ranke [43] has described this method of developing sensitisation as the period of the primary complex. Caseation with marked loss of tissue and cavity formation occurring as a result of the implantation of large numbers of bacilli early in the course of the disease, or following large reinoculations later in the course of the disease, seem to be favoured by a relatively low specific defence; or the correct explanation may be that the tissues are highly sensitised and the antigen is set free in large quantities. While the specific defence of the host as a whole may be lowered, it may actually be very high at the point of inoculation.

The facts do not seem quite clear enough to warrant a dogmatic statement. But it is generally accepted among students of immunology (Long [44], Krause [3]), that caseation is due to an excessive reaction in highly sensitised tissues. Caseation with cavity formation in the lung performs a protective service to the host in that large numbers of bacilli are cast out by the body with the expulsion of the cavity contents. These otherwise might spread and overcome all natural and acquired resistance and produce a rapidly fatal disease.

Several factors may contribute to caseation, some of which may be only incidentally a part of the immunological ensemble. Thus it has long been suggested that necrosis may be due to a failure of the cells to respond with a granulation tissue carrying the necessary new blood-vessels (Huebschmann [45]), or to a poisoning and destruction of local cells by toxins which are set free by the infection while the specific protective factors are held more or less in abeyance (Pagel [46]).
CLINICAL TUBERCULOSIS AND ALLERGY.

An acute infectious disease, such as measles, whooping-cough, diphtheria, scarlet fever or small-pox, represents one inoculation and one immunity response on the part of the host. The symptom complex which ushers in the disease with temperature, rapid pulse, and so forth, is the immunity reaction. This does not appear until the infecting micro-organisms have been in the tissues sufficiently long to set in operation the specific immunity mechanism of the individual. The result of the disease is either a sufficient and usually permanent immunity, and freedom from attacks by that particular micro-organism thereafter, or a failure of immunity and death. There is only one episode of infection and immunity response.

Tuberculosis, on the other hand, is different. The first infection with bacilli, after a period of incubation, calls forth an immunity response, and the disease may heal if the response is competent; it may be held in check so that further extension does not occur, in cases where healing is not accomplished; or, in case the immunity is inefficient the disease may spread, producing an immediate widespread disease. Where healing fails to occur, each new spread calls forth an immunological tissue response, and if the immunity is finally raised to a sufficient competency, healing may be brought about, even in relatively severe primary infections. Failing this, however, the disease progresses with a gradual lowering of specific resistance until death occurs [47].

Chronic tuberculosis is tuberculosis which develops in an immune individual, that being one whose immunity mechanism has been excited to action by a previous infection; and, usually, one in whom the immunity was sufficient, at least for the time, to cause the early infection to become quiescent.

Active tuberculosis is not brought to a close by the destruction and eradication of bacilli from the body, as is the case in the acute infections mentioned above, but bacilli remain in the tissues ever ready under favourable conditions to spread, multiply, and cause a reinoculation. The inability of the host readily to destroy the bacilli is due to their peculiar waxy content which makes them particularly resistant.

The course of chronic tuberculosis is, as a rule, punctuated by several or many episodes of reinoculation and immunity reaction [48]. These continue to take place in cases which heal until all avenues of escape from existing foci are closed and the bacilli are walled in. Except in instances in which all of the bacilli forming the infection are destroyed, a competent encapsulating fibrous wall is the determining factor in healing, and also in maintaining healing when attained. An incompetent wall is always a danger because it furnishes the point from which reinoculating bacilli may escape to set up new activity. The competency of this wall depends upon the production of fibrous tissue by the perifocal reticular cells, in response to stimulation by tuberculoprotein (tuberculin) which escapes from certain foci surrounded by incompetent investing walls. Thus, there comes a time in the healing of tuberculosis when the tuberculoprotein necessary to stimulate the perifocal cells to completely envelop the bacillus-containing tubercles may be lacking in amount, and so healing may be incomplete. This is probably a very common cause of incomplete healing and relapse in clinical tuberculosis.
The allergic inflammatory reaction which is called forth by the spread of bacilli is probably the cause, directly and indirectly, of nearly all of the symptoms attendant upon active tuberculosis, as may be judged from the following classification, which I first offered in 1913 [49], but which has been slightly modified as follows [50]:—

**Etiological Classification of Symptoms of Pulmonary Tuberculosis.**

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms due to toxins and other causes acting generally</td>
<td>Symptoms due to reflex cause</td>
<td>Symptoms due to the tuberculous processes per se</td>
</tr>
<tr>
<td>Malaise</td>
<td>Hoarseness</td>
<td>Frequent and protracted colds (tuberculous bronchitis)</td>
</tr>
<tr>
<td>Lack of endurance</td>
<td>Tickling in larynx</td>
<td>Spitting of blood</td>
</tr>
<tr>
<td>Loss of strength</td>
<td>Cough</td>
<td>Pleurisy (tuberculosis of pleura)</td>
</tr>
<tr>
<td>Nerve instability</td>
<td>Digestive disturbances (hypo-motility and hyposecretion), which may result in loss of weight</td>
<td>Sputum</td>
</tr>
<tr>
<td>Digestive disturbances (hypo-motility and hyposecretion)</td>
<td>Circulatory disturbances</td>
<td>—</td>
</tr>
<tr>
<td>Metabolic disturbances resulting in loss of weight</td>
<td>Chest and shoulder pains</td>
<td>—</td>
</tr>
<tr>
<td>Increased pulse-rate</td>
<td>Flushing of face</td>
<td>—</td>
</tr>
<tr>
<td>Night sweats</td>
<td>Spasm of muscles of shoulder girdle</td>
<td>—</td>
</tr>
<tr>
<td>Temperature</td>
<td>Diminished motion of affected side</td>
<td>—</td>
</tr>
<tr>
<td>Blood changes</td>
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</tr>
</tbody>
</table>

There are probably three sources of toxins which are responsible for the general or toxic symptoms of tuberculosis: (1) Broken-down focal tissues; (2) the serous, cellular and fibrous exudate; and (3) broken-down tubercle bacilli. We must assume that any and all of the products of a tuberculous focus, or of a tuberculous exudate, as a result of the changes which they undergo as they are subjected to the action of the defensive forces of the body, may produce toxins which are capable of causing toxic symptoms.

The reflex symptoms can readily be seen to be caused by the inflammatory process in the lung, which irritates the nerve-endings of the vagus and sympathetic afferent neurons which carry the stimuli to the centres in the medulla and cord and transfer them to other efferent neurons to complete the reflexes.

The local symptoms, or those due to the tuberculous process per se, originate in the tissues which are the seat of the disease; thus the hemorrhage from the injured vessels, the expectoration from the diseased focus or from the exudate in the air passages, the pleurisy from the tuberculous involvement of the pleural leaves; and the "cold," tuberculous bronchitis, from the inflammatory exudate or ulceration into the bronchi, may all be expressions of allergic reactions.

Not only the individual symptoms, but the course which the disease takes is determined by the degree of competency of the immunity mechanism which we may measure fairly well by the allergic reaction.

As mentioned above, proliferation and exudation go hand in hand as parts of the same process; necrosis, too, often accompanies. A predominance of the proliferative phenomena denotes mild reaction and indicates at that particular
time a disease process of relatively slight degree; but through a severe reinoculation an allergic (auto-tuberculin) reaction might be precipitated, which would within a few hours cause exudative phenomena to predominate. A preponderance of exudation, on the other hand, denotes at the time a more severe process. But this, too, may change, and after a time assume a predominantly proliferative form.

There are also varying degrees of reaction which occur with relatively the same amount of infection, the difference being on the part of the host and the degree of allergy with which his tissues are endowed.

We can best illustrate the pathologic changes as well as the clinical manifestations in their relationship to allergy by a clinical illustration. A patient with an advanced tuberculosis involving the upper half of both lungs has been relatively free from symptoms for two months. He has gained in weight and feels relatively well. He has no temperature, normal pulse, good appetite and digestion, and a satisfactory degree of physical strength. He coughs and raises 30 c.c. of bacillus-bearing sputum per twenty-four hours. Suddenly he feels toxic and aches, his appetite fails, his temperature starts to rise, and on the third day reaches a maximum of 102° F. His pulse increases in rate. Cough increases. Expectoration reaches 60 c.c. per day and the numbers of bacilli per microscopic field treble. He feels prostrated, is irritable, and fails to sleep. In one week temperature has again attained normal. He is regaining his nerve balance; appetite returns, and he rapidly regains his usual well-being. Cough and expectoration, however, continue more severe than before for some days.

The cause of these clinical phenomena was that the patient gave himself a reinoculation of quite a large number of bacilli. Some exit in the defensive wall which had been thrown around his tuberculous foci was unguarded; or, it might be that some new break occurred, allowing the walled-in bacilli to escape and attempt a new infection.

The cells which contacted the migrating bacilli, being allergic, reacted quite violently. The bacilli were in part destroyed and tubercle protein was set free which, circulating in the blood-stream, caused further inflammatory allergic reaction in other unhealed tubercles in the body. So there was widespread allergic reaction of varying degree called forth throughout the infected lungs.

Pathologically, changes from a proliferative and a mildly exudative process to a markedly exudative process took place. The pulmonary tissues and air spaces were filled with exudate. The exudation which took place in the air-passages caused an increase in expectoration and also an increase in the cellular content of the sputum. Ulcerated surfaces were stimulated and cast off an increased number of bacilli in the sputum.

Physical examination showed an increase in moist râles throughout the areas of active disease, being much greater in some areas than in others, the difference being in part at least caused by the state of healing of the affected tissues. The X-ray showed an increase in exudative reaction, being most marked in the areas in which the disease was most active.

The effect of the immunity reaction in this instance was to exert protective influence against the invasion of new tissues by the bacilli and also to exert a beneficial influence by promoting healing in former foci. The first purpose
was carried out by an attempt at destruction of the bacilli which had escaped from their former foci, and failing this an immobilisation of them to prevent their spread. The second purpose was effected through stimulating unhealed foci containing living bacilli, thus increasing the fibrous tissue about them and causing them to assume more and more of a proliferative character. Incidentally, the patient's immunity was raised by the process, and he became better able to oppose future attempts at reinoculation.

A few weeks later the acute symptoms had disappeared. The cough had lessened and the expectoration had dropped to an amount slightly below its previous level. Examination revealed a lessening of râles and the X-ray showed a diminution of the exudative inflammation which had characterised the picture taken at the time of the reaction, and an increase in the proliferative phenomena, showing that healing had been promoted by the reaction.

THE PROTECTIVE AND HEALING EFFECTS OF ALLERGY.

From the fact that allergy is a manifestation of immunity, it is necessary for us to assume that it is a necessary part of the body's defence-reaction. It is profitable to inquire what its defensive properties are and the manner in which they may be exerted to the greatest advantage of the host. Particularly is this true since we can follow it through the course of the disease from the time that the sensitisation of cells takes place, a few days or a few weeks after the primary infection, until healing has been accomplished, or death has occurred.

Every case of chronic tuberculosis shows throughout the stage of activity a continuous play of allergic manifestation. When in a strong and healthy individual all traces of allergic inflammation are gone and the body cells no longer react to tuberculo-protein, then the individual is no longer tuberculous. Krause [51] reports such a case and I have seen numerous such who have been free from disease for years.

It is very important to understand the relationship of proliferative and exudative processes to allergy, for otherwise the changes which take place during the clinical course of tuberculosis and the process through which healing is effected must remain unintelligible. The basis of this understanding lies in the fact that the allergic reaction is inflammatory. A part of every tuberculous inflammation, whether it results in tissue formation or tissue destruction, is exudation. The exudation differs in character according to the strength and character of the exciting cause.

The allergic reaction may be so slight as to cause only minimal exudation. There may be only a slight amount of serum and only a few cells poured into the tissues and this effect may be transient. On the other hand, it may be so severe that the tissue spaces and natural channels, such as bronchi, may be filled, literally gorged, with serum, cells and fibrin. In the case of the lungs there is a true pneumonic process.

Allergy, other factors being equal, increases with the repetition of successfully combated reinoculations. The summation of effects from repeated minimal reinoculations, such as we conceive of as taking place regularly and frequently—it may be hourly, it may be daily—in chronic tuberculosis in which
the bacilli are not walled in, is a well established allergy. The same may be brought about much more quickly and probably more surely by the host overcoming a severe reinoculation, or several severe ones.

From the time of the primary inoculation and the early reinoculations up to the time the disease has become well established as a chronic process, allergy is built up to such a height and with it the immunity of the host is raised to such a point, that millions of bacilli may pass over the mucous membranes of the bronchi daily without producing infection.

The allergic reaction renders certain very important services to the host, thus: (1) Allergy enables the individual who receives a reinoculation to withstand much greater numbers of bacilli without becoming infected, than are required to produce a primary infection, and furthermore it is further increased by each successive reinoculation which is successfully combated; (2) it aids the host in destroying many bacilli, both before and after implantation has occurred, causing many infections to be abortive in character; (3) it detains bacilli at the point of inoculation and prevents their spread throughout the body; (4) it heals lesions when once formed by causing a proliferative process in the reticulum in the periphery of tuberculous tissue by which a fibrous network gradually displaces inflammatory tubercle and necrotic tissue.

Before entering upon a discussion of these protective characteristics of the allergic reaction it is necessary to understand that the body's immunity mechanism can also be set in motion, though less efficiently, by the injection of dead bacilli (Koch [1], Petroff [52], Lowenstein [53], and Baldwin, Petroff and Gardner [54]), and probably to a minimum extent by tuberculo-protein (tuberculin) (Stewart and Rhoads [55]).

I have discussed this phase of the subject quite fully in recent papers [56], [57], [58].

It further must be understood that while the greatest degree of immunity is established by living bacilli, the stimulation of immunity reactions and the increase of the immunity itself after once established can be brought about by either living or dead bacilli or any bacillary substance containing specific tuberculo-protein. This is the basis of the natural healing process in tuberculous lesions and for the curative effects produced by tuberculin when administered therapeutically (Koch [1], Pottenger [56], [58]). "Every tuberculous patient treats himself with tuberculin whether he wishes it or not" (Long [59]), and without so doing, his lesion would doubtless fail to heal.

In order to make clearer the protective and healing qualities of allergy we shall discuss these protective properties in greater detail, realising that they cannot be wholly separated but that they will dovetail into each other and overlap, because they are all parts of the same reaction.

(1) Allergy enables the individual who receives a reinoculation to withstand much greater numbers of bacilli without becoming infected than are required to produce a primary infection; and furthermore, allergy is further increased by each successive reinoculation which is successfully combated. This has been shown experimentally by many observers. The reports of Römer, Hamburger and Krause previously mentioned are conclusive. It is also evident to those who observe their clinical cases closely. Oftentimes a reinocula
tion is attempted with bacilli sufficient to produce a severe reaction with fever, aching, increased cough and expectoration. An X-ray plate taken at the time will show a general exudative process throughout the areas of active tuberculosis, due to the auto-tuberculin reaction. Sometimes it is impossible on account of the generally increased density of the shadows to tell where the inoculation occurred; but at other times it can be determined quite readily. Plates taken at comparatively frequent intervals thereafter may show in the course of a few weeks the entire reaction to have faded away and even the field of reinoculation to have cleared, indicating that permanent implantation had either failed to take place or that it had been limited to a small focus.

It is generally recognised that the infection which takes place by way of the air-passages, when a bronchus becomes plugged with infected cavity contents or material from a caseating bronchial gland, results in one of the most serious forms of tuberculosis; yet bacilli in large numbers may pass over the same bronchus day after day, provided the lumen is free, without producing infection. This is definite proof of the specific resistance of the immune tissue to the tubercle bacillus.

Many abortive infections occur in the course of chronic tuberculosis when bacilli escape from previously infected areas into the immune tissues of the host. While no one can tell how many such occur in the lung, because of our inability to determine accurately, they are frequently observed in the eye, larynx, lymphatic glands, and testicle during the course of chronic tuberculosis. Inoculation occurs; allergic reaction follows; and after an inflammatory course of a varying period of time the seat of infection clears. The body has been able to withstand the bacillary invasion with no resulting harm because of its well developed specific defence.

(2) Allergy aids the host in destroying many bacilli both before and after implantation has occurred. It is generally accepted that the bactericidal effects of the tissues of the immune is much greater than those of the non-immune. Wolff-Eisner [60] maintains that lysis of bacilli is an important factor in the immune. Metschnikoff [61] and Wright [62] based important immunologic studies upon the increased phagocytic power of body cells in the presence of immunity.

Bacilli injected into the blood-stream are quickly destroyed, often without being responsible for new implantation. Krause and Hofer [63] noted the destruction of bacilli within twenty to thirty minutes when injected into the peritoneal cavity of pigs infected with tuberculosis. The fact that infection does not always follow moderately large doses of bacilli in the immune is evidence that lysis takes place.

(3) Allergy detains bacilli at the point of inoculation and prevents their spread throughout the body. This fact was first observed by Koch and described as a part of the immunity response. He noted that in the immune animals the bacilli were detained at the point of injection by an inflammatory process; that ulceration took place in an attempt to eliminate the bacilli from the body, if the inoculation were in the superficial tissues, and that the neighbouring lymph glands took little part in the picture, showing that passage through the tissues was interfered with, as compared with the rapid involvement of lymphatic glands which takes place in primary infection.
The same thing has been shown clinically. In chronic disease of the lung, or larynx, or intestines, the lymphatic glands into which the affected parts discharge their lymph take little part in the process. Quite different is it in the primary lesion. A small nodule in the lung is often followed by enormously enlarged and necrotic mediastinal glands. Ghon [64] learned that by examining the mediastinal glands and determining what ones, if any, were involved, he could follow back into the areas in the lung which drained into the particular gland and find the primary focus.

Krause and Willis [20] have performed a most important service by comparing experimentally the different rates with which bacilli make their way through the tissues of the immune and non-immune. Their results show that:

"(1) In normal non-immune guinea-pigs tubercle bacilli, inoculated intracutaneously or subcutaneously, are carried almost immediately (within an hour) from the portal of entry by the lymphatics.

"(2) Within three or four days they have made the circuit of the body.

"(3) In immune (allergic) animals their transmission is greatly retarded.

"(4) They remain fixed at or near the portal of entry for about seven days.

"(5) They do not reach the regional lymph nodes (superficial, inguinal and axillary) until two weeks after infection.

"(6) They do not become generalized throughout the body until three or four weeks after infection."

These experiments can only be interpreted as meaning that the tissues of the infected animal develop a defensive property that renders passage of bacilli through them very difficult. If we inquire into the nature of this defence we find that it consists of an inflammatory response. When bacilli enter immune tissues, an irritation, followed by inflammation with accompanying exudation, the degree depending on the severity of the response, takes place very quickly. The bacilli are hindered in passing through the tissues by this protective process which manifests itself in each new group of cells into which the bacilli find themselves carried by the phagocytes.

There is no doubt that this localizing power of the allergic reaction is one of the greatest defensive forces of the immune host. When this power has once been established in an animal or man, small reinoculating doses of bacilli are probably held regularly at the point of inoculation and destroyed without permanent harm being done to the host. We assume that this must occur during the course of clinical tuberculosis, and if we are right in our interpretation of our physical findings and X-ray plates, we see definite evidence of it. Larger reinoculations are not regularly restrained so easily, but even they frequently are cared for by the specific defensive mechanism without permanent harm resulting to the host.

(4) Allergy heals lesions when once established, by causing a proliferative process to take place in the reticular cells in the periphery of tuberculous masses by which a fibrous network gradually displaces inflammatory tubercle and necrotic tissue. This effect of the allergic reaction is the most important one in the healing of tuberculosis. The first three aids rendered by the allergic reaction are directed particularly toward protecting the organism from new
invasion of bacilli, but the fourth is particularly directed toward healing the
disease when established.

The fact that the infected animal is able to withstand larger doses of bacilli
without serious harm than the healthy one, the fact that he is able to destroy
more bacilli than the healthy one, causing implantations to fail or infections,
if they occur, to heal, and the fact that bacilli pass through the tissues of the
immune more slowly are all evidence that resistance to tubercle bacilli is
conferred upon the host by previous infection.

A specific inflammatory reaction occurs at the site of invasion as a result of
each reinoculation. Furthermore, a reaction occurs in other unhealed foci in
the body if the numbers of bacilli engaged in the infection are sufficient to
cause more than a minimal amount of tuberculo-protein to gain access to the
blood-stream. These two reactions are of the greatest importance in healing
tuberculous lesions.

The allergic reaction which is called out by the tuberculo-protein which
escapes from foci and from the bodies of bacilli which go into solution as a
result of the bactericidal properties of the immune tissues, is responsible for
the inflammatory reaction which has as its sequel the formation of fibrous
tissue, in and about tubercle, changing the tubercle into fibrous scar and
encapsulating bacilli where they cannot be destroyed.

Without this effect the probabilities are that tuberculosis would not heal
save in exceptional instances; but, with it, nearly all tuberculous foci in the
body of the immune host show some tendency to heal, and even those that at
times seem most serious show healing along with their destructive processes.

In order to understand the allergic, inflammatory, reaction, it is necessary
to recall the fact previously stated, that the action of tuberculo-protein is,
relatively speaking, a quantitative one, the more concentrated the product the
more severe the reaction. And further, it is just as important to know that
the cells of the immune host are endowed with different degrees of ability to
react allergically, and that cells in and adjacent to foci which contain living
bacilli possess this power to the highest degree.

So it is evident that there are three different reactions to tuberculo-protein
possible in the tuberculous individual: (1) The severest one at the site of
reinoculation because the bacillary products are most concentrated and the
cells are most sensitive at that point; (2) a less severe one in other tuberculous
tissue containing living bacilli; and (3) a possibility in all the tissues of the
host, in case the protein is introduced artificially in the tissues. This latter
has diagnostic import, aids one in forming an opinion of the degree of allergy
present, and aids healing should infection occur.

Taking into consideration the effect of the allergic reaction, one can visual-
ize what this inflammatory exudative and proliferative process means in the
course and cure of tuberculosis. It is primarily protective, protecting against
spread of infection and healing existing lesions.

The slighter stimulations cause a minimum of inflammatory signs and
favor healing, the larger ones produce more marked evidence of inflammation
and may be harmful. But no matter how severe the reaction, and no matter
how marked the accompanying exudative phenomena, a very important part
of every reaction is the stimulation of local reticular cells to the formation of fibrous tissue and healing of lesions by encapsulation.

What the further course of an inflammatory exudative reaction about unhealed tubercles will be, depends on future reinoculations. If they are of only mild degree, the exudate will resolve, leaving the area with an increase of fibrous tissue which was formed as a result of the stimulation. If, on the other hand, severe reinoculations continue, the exudative phenomena do not disappear, in fact, may increase in severity and be accompanied by destruction in the most densely infected areas.

Thus the combat goes on in every individual suffering from active clinical tuberculosis. If immunity can be kept at a high level, very large quantities of bacilli may escape from previous foci, provided they do not escape too frequently, and still serious new infections may be prevented; and, as a result of the stimulation of fibrous tissue, after the acuteness of the episode has passed, the field of infection may clear, leaving the host in a better condition than he was in before and after a number of such episodes a satisfactory healing may be brought about.

While tuberculin has not been used generally as a therapeutic measure, yet there are certain clinicians who have never ceased its employment after once beginning. They have always felt that it had a definite effect in healing. Now we are beginning to understand the nature of tuberculosis better, and to realise that both the pathologic and clinical variations of the disease consist of a series of reinoculations and immunity reactions, and that these reactions are produced by tuberculo-protein acting upon the specifically sensitised body-cells, and are an intimate and necessary part of the protective mechanism developed to guard the host from the dangers of the tubercule bacillus. We are further, as a result of this, forced to recognize that tuberculo-protein (tuberculin) is Nature's own protective and curative substance, because it raises immunity already established, and calls forth allergic reaction without which the body would not be protected against the spread of bacilli, and without which healing could not occur. When we realize further that small doses are wholly curative and only large doses are harmful, we have at our command the principle of its administration. Long [59], who, with his associates, has done so much to clarify our opinions of the nature of tuberculin, accepts its value with the following statement regarding its influence on the disease focus: "The focal reaction occurring at the site of disease, on the other hand, is of the utmost importance. Mild focal reactions are beneficial, and severe ones detrimental." Again, he states [65]: "All patients are under tuberculin treatment spontaneously, if not by actual therapeutic use. Sometimes this spontaneous tuberculin treatment is harmful, much of the time it is certainly beneficial. It is inevitable in any event." Tuberculin, too, has the advantage over the tuberculo-protein produced by reinoculation of favoring healing without the danger of a reinfection.

If one understands tuberculosis and the part tuberculo-protein plays in its cure, he can administer tuberculin therapeutically to the great advantage of the patient. Severe and dangerous reactions may be avoided if only the physician will study sufficiently carefully the sensitiveness of each patient to the remedy.
MacCullum [66] recently reviewed the status of our present knowledge of tuberculin and ventured the following prediction: "From all this it is evident that very great advances have been made in our knowledge of the chemistry of tuberculin and of the tubercle bacillus, and it is not too much to hope that in the next few years we shall be in a position to combat tuberculosis fundamentally and effectively."

With the present increased knowledge of tuberculin and its importance in the production of the allergic reaction, the most promising field for addition to our present-day therapy of tuberculosis seems to be the production of mild allergic reactions about tubercle by supplementing tuberculin in measured doses at appropriate intervals and suited to the patient’s tuberculoprotein sensitiveness for the haphazard doses and haphazard intervals which characterise spontaneous therapy.

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