WHAT CAN BE DETERMINED BY THE TUBERCULIN TEST*

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No matter what his specialty there comes a time in the practice of nearly every physician when it is of great importance to know whether or not a patient has a tuberculous infection within his body, and, if present, whether or not it is active. Because of my long use of tuberculin I am frequently asked the question whether it is possible by the character of a given reaction to tell anything beyond the fact that an infection is present. It seemed to me that the interest in this subject was sufficiently great to discuss it in the light of our more recent studies.

When Koch found that a tuberculous and a non-tuberculous individual reacted differently to an injection of tuberculin, he suggested that the fact might be utilized in diagnosis. Thus was established the subcutaneous tuberculin test. At that time a difference between tuberculous infection and tuberculous disease was not known to exist. In the minds of clinicians a person either had tuberculosis or he was free. It was not until the work of von Pirquet was reported that the basis for our present day conception of the primary infection and adult tuberculosis was laid.

Through careful clinical and pathologic study Koch and his co-workers established 10 mg. of tuberculin as the limiting dose between tuberculous and non-tuberculous individuals. All who reacted to 10 mg. or less were tuberculous, and all who required a larger dose to cause reaction were considered free from tuberculosis. Koch found that practically every one tested reacted when 40 to 50 mg. were employed, but thought it was possibly due to other substances in the tuberculin. The reaction which was required to be brought about by tuberculin in order to prove the presence of tuberculosis was a toxic one consisting of aching, tiredness, elevation of temperature, decrease in appetite and nervousness. It is the reaction which has been described as a "general reaction." Later, however, a focal reaction was also looked for. The local reaction was frequently encountered, but it was not recognized as evidence of immunity until local cutaneous sensitization was interpreted in terms of allergy by von Pirquet.

Subcutaneous Test.—The subcutaneous test is administered by injecting tuberculin into the tissues, under the skin, as its name implies. While called "subcutaneous," little or no distinction is made between injecting the solution under the skin and into the muscles. From the very beginning it was observed that different patients reacted differently to different doses. Some who were excessively sensitive might respond to doses as low as 1. mg. or even 0.1 mg., while others would not respond until 10. mg. were given. The dosage suggested by Koch was 1. mg. to be followed by 5. mg. after a couple of days, and this by 10. mg. a few days later if the patient failed to react to the preceding dose. It was later learned that the three phases to the reaction: (1) a local, at the place of the injection; (2) a focal, at the point of the infection, and (3) a general, which consists of a toxic reaction, are all important parts of the immunity mechanism.

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The local reaction, which is evidence of a general widespread sensitization of body cells, was not so interpreted at first. The focal reaction is evidence of the increased permeability of the vessels and probably increased sensitivity of cells at the point of infection. The general reaction is due to the fact that the cells of the host are endowed with substances which quickly break down the tuberculin into other substances, some of which are toxic. It is similar to other toxic syndromes. Each of these reactions depends upon the degree of sensitization of the body cells present, since that determines the degree of allergic reaction which will follow the injection of a given quantity of tuberculoprotein. Whether various classes of cells in the body acquire different degrees of sensitization to tuberculoprotein as a result of a tuberculous infection is not quite clear. But that there are at least three different degrees of allergic response observed in clinical practice, based on the intimacy with which the cells come in contact with bacillary protein, is quite evident.

Tuberculin on entering the blood stream of an individual suffering from tuberculosis circulates freely throughout the body, but causes an allergic response only in unhealed foci of disease. There is a distinction, too, in different foci, the reaction being quite marked in the markedly active foci and less marked in those less active and quiescent. When the tuberculoprotein gains access directly to the blood stream, non-focal tissues take no part in the allergic response; but if it is brought into direct contact with non-focal cells and is held there, as in case of subcutaneous or intramuscular injection, then local allergic reaction will ensue in these tissues. Increased vascular permeability is a part of inflammation. This permeability is such that it will permit many circulating substances to enter inflammatory tissues which do not enter normal tissues. Menkin has recovered many substances from inflamed lymph glands, including salts of iron, and horse serum, which he used experimentally in order to prove the permeability of the vessels of inflamed as compared with those of normal tissues. This experimental work throws much light on the focal tuberculin reaction, and makes possible a satisfactory explanation of the difference in the reactivity of tuberculous and non-tuberculous tissues. Increased permeability follows active cell injury caused by the inflammation; and biophysically means increased sensitivity of cells.

A positive focal reaction to the subcutaneous test injection is the most reliable evidence of active tuberculosis that can be attained by the employment of tuberculin. There seems to be ample theoretical and clinical data to justify this opinion. In this test one is not depending on the general sensitization of cells, but upon the increased sensitization of the perifocal cells, and the increased permeability of the vessels in the inflamed focal and perifocal tissues, which permit the tuberculin to pass through their walls in large quantities and come in contact with the cells to cause reaction. Focal reaction in the lung may show as cough and expectoration when not previously present, or an increase in same if previously present. It may also, though rarely, bring out râles on auscultation, and appear as an increased exudative shadow on an X-ray film. In visible lesions, such as those in the larynx or on the tongue, focal reaction may be noted as a hyperemia. In lymphatic glands, and in the testicle, it may show as increased swellings, which means increased exudative phenomena. The relation of the general reaction to the focal reaction is not thoroughly understood. It would seem that the general reaction is caused by the rapid splitting of the tuberculin,

with the setting free of massive amounts of toxins. Massive, of course, must be recognized as a relative term, for no great mass of toxins could be expected to result from the splitting of 1., 5. or 10. mg. of tuberculin, yet each of these doses is sufficient at times to cause a general reaction. Whether the rapid accumulation of the tuberculin in the focus causes a more rapid splitting of the tuberculoprotein or not can only be assumed. Yet such an assumption does not seem unwarranted. General, focal and local reactions may occur with a certain degree of independence. We conceive that a local reaction may occur without a focal or general reaction; a focal reaction without a local or general; but we can not conceive of a reaction sufficiently marked to quickly split tuberculin into its toxic fractions and cause a general reaction, without the same causing reactive phenomena either locally or focally.

General experience will bear out the assumption in early suspected but unproved cases of tuberculosis, that nearly all cases of active disease will react to a maximum dose of 10. mg. of tuberculin. One must always bear in mind, however, that a lesion long existent, which has resulted from repeated reinoculations of bacilli, may have so desensitized the cells to bacillary protein that 10. mg. of tuberculin may fail to call out either a local, focal or general reaction. This must be evident to any student of tuberculoimmunity as he follows the course of the disease in the clinic, for if the same degree of sensitization of cells, and the same degree of allergic inflammatory reaction, should continue to take place late in the disease, as occurs during the early stages of infection, there would be no hope for the patient. All patients would die of acute destructive lesions. But such far advanced cases rarely require a tuberculin test.

Subcutaneous and Other Tests Depending upon Allergy as Developed in Non-focal Cells.—When, in 1907, von Pirquet announced that the reaction of the cutaneous cells to tuberculin could be used as a method of determining the presence of tuberculosis, a new era in the investigation of tuberculosis was ushered in. This was soon followed by proof of the capacity of other body cells, in fact of all body cells, to react; and the entire subject of diagnosis was subjected to a new understanding, as a result of which has been evolved our present-day conception of: (1) the time of infection, (2) the establishment of the disease through reinoculation, (3) the dependence of the pathology upon the allergic response, and (5) the cure of the disease as an immune response of the host to the stimulation of bacilli and bacillary protein. The reaction of all body cells, outside of the foci of disease, must be considered as being a part of the same phenomenon; for no matter what cells are involved, whether it be those of the skin, subcutaneous tissue, muscle, conjunctiva, mucous membranes, or of some organ such as the testicle, the reaction depends on the one hand on the fact of the general sensitization of the cells of the body which has been brought about by previous infection, and on the other hand on the fact that tuberculin is brought in immediate contact with the sensitized cells and held there until reaction can take place. These cells lack the cumulative factor that holds for the cells in the area of inflammation where the permeability of the vessels is increased, as has been shown by Menkin, so require contact with the tuberculin to be more prolonged than could come from the tuberculin in circulating blood of a tuberculous patient.

From the standpoint of diagnosis reactions may be considered as focal, general and local, in all the different methods of applying the tests. The

only regular method of producing a focal reaction is by bringing a relatively large dose of tuberculoprotein into the tissues in such a manner that it will be readily absorbed and pass quickly into the blood stream, so as to be screened out through the more permeable walls of the vessels in the inflamed tissues of the active focus. The surest way is by the intravenous or subcutaneous route, although it may now and then follow cutaneous and intracutaneous administration. While a general reaction follows intravenous and subcutaneous administration oftener than any other, yet I have on a few occasions seen a marked general reaction follow cutaneous and intracutaneous administration of the test dose. The necessary condition for a general reaction seems to be the rapid breaking down of the tuberculoprotein into toxic molecules, with quick absorption, which rarely occurs except when tuberculin is administered intravenously or subcutaneously. The local reaction can be called out by living or dead bacilli, or by bacillary protein. All tissues of the body, as far as tested, have been found able to give a local reaction. We are best able to understand the nature of the reaction by the fact that it will not occur in non-infected individuals, but does take place regularly in those infected. Again, the condition responsible for it may follow very quickly, even in a few days, and regularly in two or three weeks after the bacilli or bacillary protein have gained access to the tissues. In case of living bacilli we assume that the reacting substance must be set free through either metabolic activity or death. In case of dead bacilli or tuberculoprotein, metabolic activity is out of the question, yet much the same process must follow for the reaction occurs in about the same time. So we assume that in all instances, no matter in what form the bacillary substance enters the tissues, or what tissues it enters, the reaction is probably produced in a similar manner; yet it is known that bacillary protein alone will produce cell sensitization only feebly, while living and dead bacilli will produce it to a marked degree and of a lasting nature, and further that the most marked and most permanent sensitization is brought about by living bacilli. All have the property of exciting the tissue response, which is known as the tuberculin reaction, when sensitization has been once established. The fact that living and dead bacilli produce the allergic state readily, while tuberculoprotein produces it feebly or not at all, indicates that the allergic state is connected with the early cellular response, which is associated with tubercle formation. Bacilli, living or dead, quickly find their way into leukocytes, some of which are favorable to their growth and multiplication, others of which destroy them. It is apparently due to the intracellular reaction that takes place, that some fraction, or fractions, of the bacilli are set free which are responsible for the production of cell sensitization and the allergic state. What these fractions are we do not know, but we are fairly safe in assuming that they are different from the protein fractions which call forth the allergic response when brought in contact with the sensitized cells.

Interpretation of Tuberculin Reactions.—Given a reaction, how are we to interpret it? What does it mean beyond the fact that the tested individual is sensitive to tuberculoprotein? Is there any difference in reaction at different periods or stages of the disease that can be relied upon? Is there any difference in reaction in different types of disease? These are the questions of greatest moment in practical experience, and if the last three questions could be answered, we would have the answer to the first. The answer to these questions establishes the value or the worthlessness of

the tuberculin tests in differentiating active from inactive lesions. Is any difference in reaction of the patient's cells found at different periods or stages of the disease that can be relied upon? This question in a broad general way must be answered in the negative; for any disease which is chronic in nature, and subject to repeated reinoculations of immunity stimulating substances, must be accompanied by waves of increased and decreased immunity. If the tuberculin reaction is an immunity reaction, and upon this point there seems to be a general agreement, even though different observers interpret the protective nature of the reaction differently, then it must of necessity vary with the immunity waves in the host. This is confirmed by the experience gained by those who treat tuberculosis with tuberculin. Every patient with active tuberculosis who is treated with tuberculin has two independent sources of stimulation of his immunity mechanism: (1) his own re-inoculations of bacilli and bacillary protein, and (2) the tuberculoprotein administered artificially. Such patients show a varying local reaction to the dosage administered therapeutically, showing a marked response with extensive inflammation to one dose and probably no reaction, or only a mild one, to the same dose administered at the next injection period; or, vice versa, showing no, or only a mild, reaction to a given dose several times repeated, and then a large reaction to the same dose at the next injection period. The important inference from this is that the degree of sensitization of the cells varies from time to time, even from day to day. Another pertinent observation is that some patients, but not all, can be brought to such a state of desensitization that they will fail to react to several hundred milligrams of tuberculin (I have given 500 mg. therapeutically), although earlier in the course of treatment the patient would show local reactions to one one-hundred thousandth (0.00001 mg.) of a milligram. Patients are frequently met who are so markedly desensitized that they fail to react to the usual test doses used in diagnosis, although they have been known previously to have had active tuberculosis. Such individuals might react if the tuberculin had been increased rapidly to a higher dosage, for complete desensitization must be a rare accomplishment in one who had a previously active disease.

Experience, then, shows that the hypersensitivity of the patient's cells to tuberculin applied locally oscillates from time to time during the course of the disease, and this probably means that his focal cells must show different degrees of activity from time to time, but we can not correlate these phenomena with any degree of accuracy; so, if this local reaction were the only factor to be considered, the only interpretation that could be put upon any single positive reaction would be that it shows the presence of a tuberculous infection without any regard to its activity.

As to the second question, involving the difference in reaction in different types of the disease, according to our knowledge of the principles of immunity in tuberculosis early in the course of the disease sensitization is greater than it is later, and the corresponding allergy brought about by reinoculation of bacilli or bacillary protein is greater. At this time the cells become so highly sensitized that if a reinoculation happens to be caused by a large number of bacilli, and the patient has been previously relatively free from inoculations, either a markedly exudative reaction, or even caseation and cavity, may quickly follow. On the other hand, if repeated small reinoculations take place, while sensitization may be as great at first, yet the allergic response is milder and the stimulation of the tissues takes the form

of mild hyperemia, or a very slight exudation and a preponderantly proliferative disease. Patients with preponderantly proliferative lesions may attain such a degree of desensitization that they fail to react with a destructive process until large areas of pulmonary tissue have become involved. That sensitization is still present is evident from the fact that sooner or later, when larger reinoculations take place, as they do in nearly all such cases, they are followed by an exudative process and even necrosis with cavity. Rarely, however, do we see the extensive exudative phenomena which are regularly observed in the preponderantly exudative lesions.

From these observations it is plain that one must be careful in drawing conclusions as to the state of a chronic tuberculous disease by a given reaction to tuberculin. Regardless of this opinion we are still justified in attempting to apply the facts brought out by these observations in aiding the early diagnosis of tuberculosis. It is necessary to recognize that cell sensitivity and the allergic reaction which depends upon it on the one hand, and the reinoculations of bacilli with their numbers and virulence, on the other, are varying phenomena. There are other causes of variation which are noted on the part of the host that are generally recognized. Such are stresses through which the patient passes, such as those resulting from malnutrition, various diseases, particularly the exanthemata, influenza, pregnancy, cachexias and the depression of immunity which follows a rapidly spreading tuberculous infection, as is seen in miliary tuberculosis and in the spread which takes place during the terminal stages of the disease. All of these may abolish the power of the cells to respond to bacilli and bacillary protein for the time, and add to the difficulties of interpreting the response or failure of response to the tuberculin test, when administered under these circumstances.

By knowing these factors which produce variation in response, there come forth well recognized conditions under which the patient should give a response that may be interpreted as meaning far more than the mere presence of an infection, as follows:

1. From the discussion of the factors which are responsible for, and those which modify the tuberculin reaction, we are justified in concluding that there is a time in the early period of the development of adult tuberculosis when the tuberculin test might afford information as to the nature of the process which is responsible for the individual's reaction to the test. That part of the body's early response to tuberculous disease which is marked by a high degree of hypersensitivity of the cells to tuberculoprotein is responsible for a relatively marked allergic reaction when tuberculoprotein comes in contact with them. This hypersensitivity and hyperallergy seems to be a necessary protection during the stage when the disease is spreading to new tissue. A patient with limited but active tuberculosis may and is most likely to respond with a local, a general, and even with a focal reaction, when the subcutaneous test is given; and with a prompt, marked local reaction when the tuberculin is brought in contact with the tissues at any point, whether it be in the skin, subcutaneous tissue, muscles, or conjunctiva, as it is employed in the various tests. In advanced tuberculosis the same type of reaction may occur, but it should not be expected to be so constant. In the old obsolete infections which have become thoroughly quiescent the reaction is prone to be much milder. Since the tuberculin tests are not needed as diagnostic measures in frank lesions in adults, but only in suspicious cases, and since such lesions are usually limited, the

tuberculin tests may afford valuable information as to whether activity or quiescence is present. Any patient who responds quickly and markedly to any local test should be given a thorough examination for active tuberculosis, and if no evidence is found should be kept under surveillance and given repeated examinations every one or two months until his status is satisfactorily determined.

2. A child showing a quick and marked response to a tuberculin test should be considered as having an active infection which is at the time, or has in the recent past been, giving off sensitizing substances into the circulation. This is evident because the primary complex in the child produces sensitization of the cells which may be maintained or increased until calcification takes place. For any degree of desensitization to take place in the natural course of infection we predicate that either quiescence or healing of the lesion is necessary.

3. Children who are in normal health and react positively to the tuberculin tests, need no special care beyond observation, and a check-up of their health at intervals of three to six months, at which time the test should be repeated.

4. Children who are below par and show signs suspicious of tuberculosis, and give a marked reaction to a tuberculin test, should be given such attention as will help them to secure a complete healing of their foci. In the less robust even a faint reaction should be repeated after the child has been restored to a more satisfactory physical state. Negative reactions in this group of children may mean a state of health too poor for a positive response and should call for a repetition of the test when the child's health has improved.

5. All children who react to tuberculin should be X-rayed, remembering that while 85 per cent of children have their primary infections in the lung, and the peribronchial and peritracheal glands, yet many of them are so located that they may not be visualized on the film; and above all else remembering that they may not be visualized no matter if they are favorably located unless they are partially or wholly calcified. A fully calcified node is not so serious as the partially and particularly the wholly uncalcified one; let these latter may not be shown on the film at all.

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