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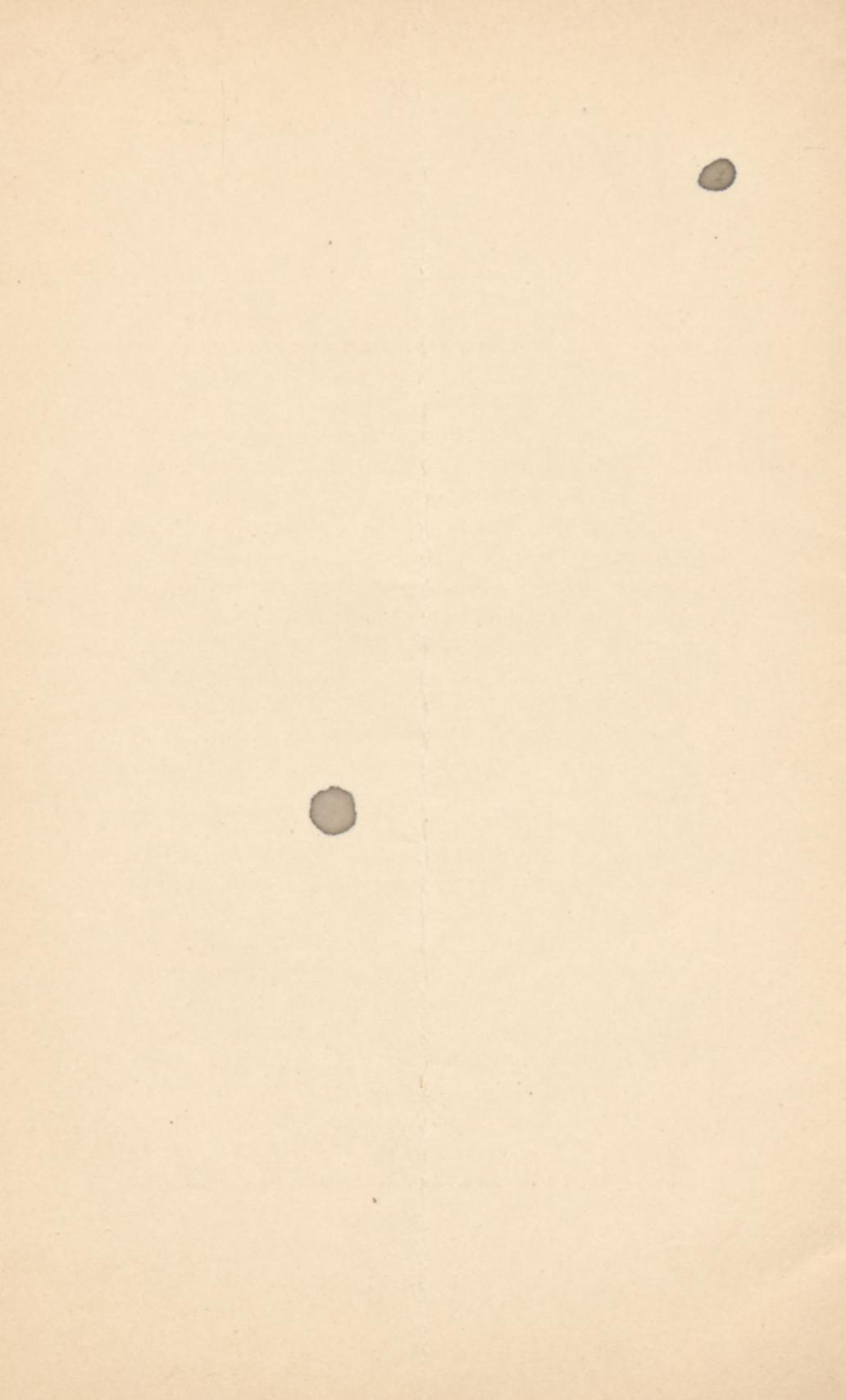
BY

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OF SARANAC LAKE, N. Y.

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**THE TUBERCULIN TEST IN INCIPIENT  
AND SUSPECTED PULMONARY TUBER-  
CULOSIS.**

BY E. L. TRUDEAU, M.D.,  
OF SARANAC LAKE, N. Y.

THE importance of making an early diagnosis in cases of tuberculosis cannot be too strongly emphasized. While studies in the autopsy-room have shown how often incipient tuberculosis is healed in man without its presence having even been suspected, clinical observation teaches daily how powerless we are to deal with the disease in its advanced stages, and how a latent pulmonary tuberculosis may be transformed into a hopeless and rapidly fatal disease when the unrecognized tuberculous process has gone on to ulceration, and when secondary infection has supervened.

The diagnosis of incipient and latent pulmonary tuberculosis, though often surrounded by many difficulties, can generally be made by a careful consideration of the history of the case, the rational symptoms, and the physical signs collectively, aided by a microscopic examination of any expectoration obtainable from the patient. Often at this stage of the disease, however, no expectoration is obtainable, or the bacillus has not yet appeared in it, and a most thorough examination of the chest and study of the symptoms fails to afford sufficient evidence to enable the examiner to reach a positive conclusion. He is therefore obliged to wait for the

well-known symptoms to appear, and waiting means to jeopardize the patient's best chances of recovery. The application of the tuberculin test to such cases will often throw much needed light upon them, enabling the physician to reach a positive conclusion, and will give the patient all the chances of recovery that lie in the detection of the disease at such an early stage, before extensive lesions have developed, or secondary infection has occurred.

Besides its value in detecting latent tuberculosis, the tuberculin test may be found, in future, to have a wide range of usefulness, not only to the physician, but to the surgeon as well, in the differentiation of many morbid processes which simulate tuberculosis, and the nature of which cannot be positively ascertained. The differentiation of an inflammatory bronchitis of chronic type from pulmonary phthisis, of tuberculous pleuritis from the other forms of the affection, of an unresolved pneumonic process from a cheesy pneumonia, of simple inflammatory pyelitis and cystitis from the tuberculous variety of these diseases, and of a gonorrheal or rheumatic from a tuberculous synovitis, is often very difficult, and much light as to the exact nature of the process under observation may be expected by a careful application of the tuberculin test to such cases. In view of the demonstrated accuracy of this test when applied to cattle and to other animals artificially inoculated in the course of laboratory research, where its correctness can be controlled by autopsy, it is remarkable that a method which has proved itself so generally reliable in detecting the disease in animals, and which offered such possibilities as a diagnostic

agent when applied to man, should have been so almost universally neglected and generally condemned on scant evidence as utterly worthless and dangerous. This, no doubt, has been due, in a great measure, to the bitter disappointment which followed the acclamation of tuberculin as an infallible specific, and to the unquestionable evil effects of its indiscriminate and injudicious application to the treatment of human tuberculosis. To those, however, who continued quietly the study of tuberculin, it soon became apparent that while its beneficial influence as a therapeutic agent could be exercised only within certain very restricted limits, its undoubted diagnostic value steadily became more and more evident in the light of slowly accumulating experience in its use. So general in this country has been the condemnation of the use of tuberculin for any purpose, when applied to the human being, that but little evidence in regard to its diagnostic value, except as applied to cattle, has thus far been presented.

Among European observers the opinions are somewhat divided, but tend to show that while it is not infallible, it cannot any longer be ignored as an aid to diagnosis in obscure or latent cases. Von Jaksch (*Verhand. der Congress f. Innere Med.*, 1891), after using it in twenty-eight cases, concludes that tuberculin has a high diagnostic value. Guttsdat has collected figures from German clinics which show that a well-defined reaction occurred in eight per cent. of apparently healthy individuals, in ninety-five per cent. of cases known to be tuberculous, and in twenty-seven per cent. of cases sus-

pected of tuberculosis. Maragliano (*Berlin Klin. Woch.*, No. 19-20, 1896) obtained a reaction in nine per cent. of apparently sound individuals, and in twenty-three per cent. of patients suspected of tuberculosis, but without any well-defined symptoms. Maragliano carried his tests to doses as high as ten to twenty-five milligrams in cases which failed to react to smaller doses. Grasset and Vedel (*Semaine Médicale*, Feb. 26, 1896) obtained slight but nevertheless well-defined reaction in ten out of thirteen patients suffering from various maladies, the tuberculous nature of which was suspected, but could not be affirmed, while in three cases of undoubted pulmonary tuberculosis with bacilli in the expectoration no appreciable reaction occurred. Grasset and Vedel used minute doses, not exceeding .0002 to .0005. De Renzi quotes Pieper, Rietzkow, Senn, and Verneuil, who reached the conclusion that Koch's injections are not a sure method of diagnosis in tuberculosis of the internal organs, and also Von Jaksch, who thinks Koch's method has a high diagnostic value. De Renzi himself says, "Nevertheless, it must be admitted that tuberculin in a majority of cases can be used as a diagnostic agent." R. Koch (*Deutsche Med. Woch.*, No. 14, Vol. I., April, 1897), in his recent publication on a "New Tuberculin," states that Dr. Nietner will soon publish the results of the application of the tuberculin test to one thousand cases.

Sarcoma, carcinoma, syphilis, and actinomycosis have been said to react to tuberculin, but in the instances quoted the presence of tuberculosis in conjunction with the above-mentioned diseases was



usually not excluded. Before condemning the test as at fault when reaction occurs in apparently healthy individuals, it should be borne in mind that autopsies made on persons dying of other diseases show some unsuspected tuberculous focus to exist in from thirty to forty per cent. of those examined.

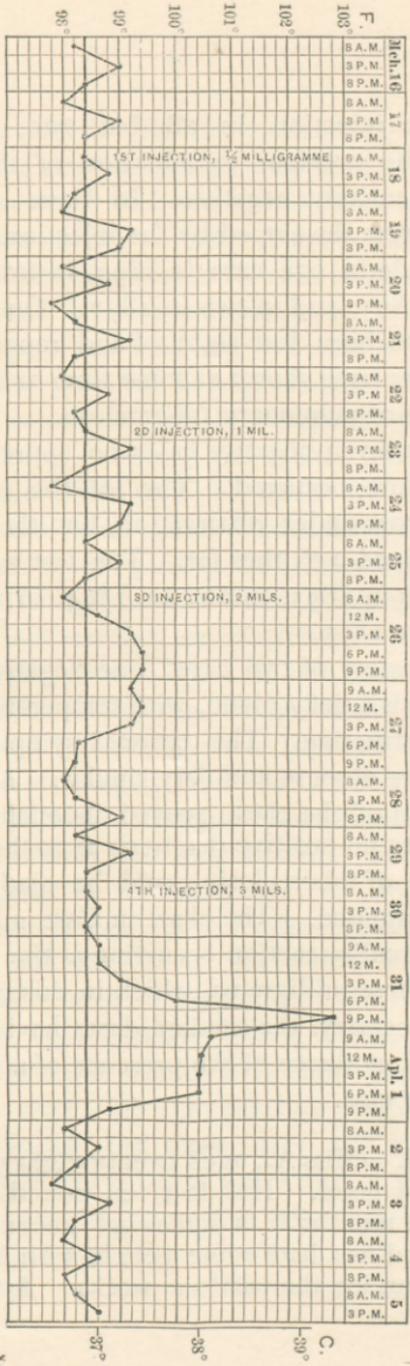
My own experience with the tuberculin test during the past five years has been principally in the direction of its occasional use to determine the presence or absence of suspected pulmonary tuberculosis when diagnosis could not be made by ordinary means, and has been limited to fourteen cases, seven of which were positive and seven negative. The highest dose given was three milligrams. In the positive cases reaction was obtained in six with a dose of two milligrams or less. In one, however, an injection of three milligrams was necessary before a well-marked and typical reaction took place. The temperature in six ranged from  $100.2^{\circ}$  to  $102.5^{\circ}$  F. at the height of the reaction, and the symptoms were of moderate intensity and soon abated. In one case only the temperature reached  $104.2^{\circ}$  F. Symptoms indicating reaction came on in six cases within twelve hours, and in one they were not well defined until twenty-two hours after the injection. In six of the cases the fever had entirely abated within twenty-eight hours; in one it lasted forty-eight hours. In all of these after the temperature returned to normal no unusual rise took place, and the general condition of the patients was within a week apparently the same as before the tests were applied. What slight physical signs were present seemed accentuated for a time within twenty-four hours

after the injection in all but two, in both of which the previous examination of the chest had proved entirely negative. In these no abnormal sounds were developed by the injections. The tests were made in one case in 1893, in two in 1894, in two in 1895, and in two in 1897. One of these patients has been lost sight of and reported as dead; the others have shown at some time or other clinical evidence of pulmonary tuberculosis.

In the seven negative cases no appreciable rise of temperature occurred. Two of the patients have passed from under observation, but the others have all remained well thus far. The test was applied in two cases in 1893, in one in 1894, in two in 1895, in two in 1897.

The history of two cases, one negative, the other positive, is briefly given, with temperature charts, as being instructive. The rational symptoms in both cases were obscure and very similar. A physical examination of the chest proved inconclusive, and in both cases no positive diagnosis as to the presence or absence of tuberculosis could be made before the test was applied. The chart in Case 2 shows a typical tuberculin reaction occurring at the fourth injection of three milligrams, which in this case was rendered necessary, the smaller doses having given but equivocal evidence of the presence of a latent tuberculous process.

CASE I.—Miss A., aged twenty-eight years. Family history good. Has lost ten pounds during the last three months. Is somewhat anemic, tires very easily, and has had some cough with but little expectoration for the past six weeks. Appetite poor,



CASE 2.  
 Temperature chart showing reaction after four injections of tuberculin had been given.

and digestion at times troublesome. Has no fever, but has occasionally perspired a little at night. Expectoration repeatedly examined shows no bacilli. Physical examination of chest inconclusive. The vesicular murmur is very faint, and expiration somewhat prolonged at right apex. This patient was sent to the mountains as a case of suspected pulmonary tuberculosis. The test was made in 1893, and the three injections given produced absolutely no rise of temperature. The cough disappeared within two weeks, and the patient was allowed to return to New York, where she is now living in excellent health.

CASE II.—Mr. B., aged nineteen years. Father died of phthisis; two brothers and a sister are well. A year ago began to notice that he tired easily and lost some weight. Has never been up to his usual standard of health since, though he has had no marked symptoms. Has no cough except at times when he catches cold; has no expectoration except at such times. Expectoration examined then showed no bacilli. Temperature when he gets tired or has a cold reaches  $99.5^{\circ}$  to  $100^{\circ}$  F., otherwise generally normal. Had typhoid fever in 1890. Lungs examined several times by specialists, but nothing found. Came to the mountains seven months ago, and has gained nearly ten pounds. At present is up to his normal weight. Still tires easily, but is desirous of entering college if no serious disease exists. This test was made in March, 1897. The first two injections produced no effect whatever. The third, of two milligrams, was followed by a little discomfort, and it will be noticed that the temperature, which stood at  $99.6^{\circ}$  F. twelve hours after the test, did not fall as usual the next morning, but remained above 99 until 6.30 P. M. As this seemed suspicious, a third injection of three milligrams was given four days later. A typical reaction ensued. At 6 P. M. he was a little chilly, had some

pain in the limbs, and went to bed of his own accord. At 10 P. M. his temperature stood at 102.8° F. It fell during the night to 100.6°, but did not return to normal until 6 P. M. on the day following the injection. Within two days he said he felt as well as ever; no rise of temperature has taken place since, and he seems in his usual health. A careful examination of the chest during the reaction was negative.

In the absence of any well-defined rules founded upon the experience of others at the time I began to use the test, the method I adopted has been a purely arbitrary one and I make no claim for its being the best or the most reliable, although as far as my own personal experience goes I have as yet seen no objection to it or any reason to modify it.

The range of the patient's temperature is ascertained by taking it at 8 A. M., 3 P. M. and 8 P. M. for three or four days before making the test. The first injection should not exceed five-tenths of a milligram and if any fever is habitually present should be even less, and is best given early in the morning or late at night as the typical reaction usually begins, in my experience, within six or twelve hours. Such a small dose, while it will often be sufficient to produce the looked-for rise of temperature, has under my observation never produced unpleasant or violent symptoms. An interval of two or three days should be allowed between each of the two or three subsequent injections it may be necessary to give, as reaction in very rare cases may be delayed for twenty-four or even thirty-six hours. On the third day a second dose of one milligram is given, and if no

effect is produced, a third of two milligrams three days later. In the great majority of cases of latent tuberculosis an appreciable reaction will be produced by the time a dose of two milligrams has been reached. If no effect has been caused by the tests applied as above I have usually gone no further, and concluded that no tuberculous process was present, or at least not to a degree which need be taken into account in advising the patient, or which would warrant insisting on a radical change in his surroundings and mode of life. If some slight symptoms, however, have been produced by a dose of two milligrams, it may be necessary to give a fourth injection of three milligrams in order to reach a positive conclusion. Nevertheless, it should be borne in mind that in a few cases the exhibition of even larger doses may cause reaction and indicate the existence of some slight latent tuberculous lesion, and the test should not, when applied within the moderate doses described, be considered absolutely infallible.

No evidence in connection with the tuberculin test as applied to man and animals has been forthcoming thus far from those who have made use of it which would tend to sustain the general impression that this method is necessarily dangerous and tends invariably to aggravate the disease, and my own experience has developed nothing which would seem to confirm this impression. It is evident that the size of the doses given has much to do with the limitations of this method for usefulness and the correctness of the conclusions reached by its application. The tuberculin used is also a matter of some impor-

tance in determining the dosage, as different samples vary considerably in their efficiency. The minute amounts adopted by Grasset and Vedel, *i.e.*, from .0002 to .0005, while they have the advantage of absolute safety, may lead into error, as they are insufficient, on the evidence of these observers themselves, to cause reaction in cases proven to be tuberculous by the presence of the bacillus in the expectoration. If, on the other hand, the test be pushed to the injection of such large amounts as 10 milligrams or more, as advocated by Maragliano, such doses are by no means free from the objection of occasionally causing unpleasant and sometimes dangerous symptoms; and even if the amount given be not carried to the dose of 10 milligrams, which is known to produce fever in healthy subjects, it is likely that, on account of individual susceptibility or the presence of some other morbid process in the body, reaction will be found to occur with the larger doses when no tuberculous process exists. The adoption of an initial dose so small as to guard against the absolute possibility of producing violent reactionary symptoms, and the graded increase of the subsequent doses within such quantities as are known never to produce reaction in healthy individuals, would seem to afford the best protection against unpleasant results and misleading evidence.

It is greatly to be desired, however, that more light should be thrown by additional studies on these points, and that the best method to be employed in making the test and its limitations be more accurately defined by evidence derived from a more extended and varied experience in its use.

NOTE.—Since the above was written, and while it was in the publishers' hands, a paper on the Diagnostic and Therapeutic Value of Tuberculin was read by Dr. James T. Whittaker before the Association of American Physicians, and although I was not present at the meeting, and have as yet seen only abstracts of his communication, it is evident that Dr. Whittaker's extended experience with tuberculin has been in the main similar to my own. The doses he has made use of are larger than those I have employed, but his experience as to the value of the test when intelligently applied, and its freedom from injurious effects, has been the same as mine.









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