S. Doubtful signs of phthisis pulmonalis; no tubercle bacilli in sputum; splenic extract iv. Strong suspicion.

Dr. Heredia's case. Suspected tuberculous peritonitis; splenic extract iv. Strong precipitate in six hours.

Dr. Surveyor's case of obstinate fever; suspicion of pulmonary tuberculosis; no tubercle bacilli in sputum; splenic extract iv. Strong reaction in eight hours.

Dr. Purshotum's case of phthisis pulmonalis; six months improving; tubercle bacilli found in sputum; splenic extract iv. Strong reaction in six hours.

From the cases in the above list and others not quoted here, it will be noted that, although the test had been applied to blood serums coming from undoubted cases of tubercle, there are a few which either give a partial reaction or no reaction at all. This want of uniformity in the reaction may be partly because the microbe causing the disease may not be identical, although of the same race; or the proper vehicle to extract the most potent precipitating material, so as to bring out the reaction, is not yet found; or, again, the optimum period when a patient's blood serum is best suited for the test has not yet been determined; or, further, as in the cases where a negative result is noted, the patients being quite well for two or three years, no agglutinins are now produced in them; although the sputum in these cases does show tubercle bacilli, these are probably no more active in them than *B. typhosus* in the so-called "typhoid carriers," or streptococci or *B. coli* in healthy individuals. But all these and other questions will have to be solved only by further study. It is on this account that I desire to designate the results embodied in this paper as only preliminary observations, and have brought them before you as such.

Although the general result of the serum reaction in cases of tubercle is positive, yet when we use the splenic extract I have been able to notice an equally potent reaction in certain cases of sprue, where the patient's blood is hydraemic and slightly haemolytic, and in all cases of leprosy (about twelve) tested. It may be that in these diseases the blood is loaded with agglutin or allied substances having a definite action on the tuberculous splenic extract or the reaction product in these diseases is closely allied to that of tubercle. I have tested the value of the reaction by its giving negative results with malaria, enteric infection, dysentery, meningitis, bronchitis, and a few other septic conditions. Fuller details and the important bearings of these reactions in the study of allied diseases I reserve for a further communication.

REFERENCE.

¹ Max Beck, in *Koch's Festschrift*, p. 611-624.

A STUDY OF THE TUBERCULIN REACTIONS IN SKIN AND EYE:

A SERIES OF ONE HUNDRED AND FIFTY-THREE CASES.

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THE following local tuberculin reactions were obtained in 153 consecutive cases. In all, the skin reaction test (v. Pirquet) was performed, and in 78 of these the conjunctival test (Wolff-Eisner or Calmette) was also employed. The investigation was mainly to test the value of the v. Pirquet reaction in children up to the age of 13, and also to compare it in a representative number of cases with the Calmette test.

Technique of the Skin Reaction.

The method recommended by v. Pirquet¹ and practised by him and his assistants in Vienna is to place a drop of tuberculin solution on the skin and to rub it into a skin abrasion by boring the skin through the drop with a blunt instrument—for example, a steel knitting needle. Another similar abrasion, without the use of tuberculin, serves as a control. This method is fairly satisfactory. It is superior to the method of scarification, as in vaccination. In my experience it is also better than the method recommended by Emmett Holt,² which consists in scratching the epidermis with a sharp point and inoculating one portion of it with the reactive fluid.

But I obtained the best results by the following modification of v. Pirquet's technique. With the sharp point of a straight surgical needle I chafed off the epidermis, exposing

a small circular patch of the pink cutis vera. Bleeding or oozing was expressly avoided. On this vascular surface the tuberculin solution was placed, and rubbed in by rotation of the head of the needle. A control surface was similarly prepared and inoculated with 50 per cent. glycerine in water. The original method of v. Pirquet and the modification described were tested against one another in 9 cases. Of these, 7 gave a positive reaction with the modified technique. But with v. Pirquet's method only two positive reactions were obtained; the remainder were negative. It should be said that most of the cases tested were of advanced tuberculous disease, and so belonged to the class in which v. Pirquet admits occasional failures of reaction. Nevertheless, they tested fairly the respective merits of the two methods, and showed emphatically the superiority of the modification. It was therefore employed throughout the series. A positive reaction was defined as a red papule which persisted for seven days. Sometimes, both in the control and the tuberculin-inoculated area, a narrow red ring appeared round the puncture after twenty-four hours. This had always disappeared by forty-eight hours, and was never regarded as a positive reaction. Two characteristics were required for a positive reaction—a papule of peculiar deep livid hue, and its persistence for not less than a week after its appearance. So defined, no positive reaction was obtained in any of the controls. The strong solution of "old" tuberculin of Koch was employed.

Analysis of Results, v. Pirquet Reaction.

Disease.	No. of Cases.	Positive.	Negative.
Joint affections	15	10	5
Enlarged glands of neck	17	14	3
Affections of bone	5	5	0
Pleural effusion (serous)	14	13	1
Pulmonary fibrosis and bronchiectasis .	6	4	2
Tuberculous peritonitis	12	9	3
General tuberculosis	4	0	4
Tuberculous meningitis	4	1	3
Non-tuberculous meningitis and cerebral tumour	7	1	6
Marasmus and chronic diarrhoea ...	9	2	7
Bronchopneumonia	12	3	9
Lobar pneumonia	10	0	10
Empyema	11	0	11
Chorea	3	0	3
Rheumatism	5	0	5
Miscellaneous	14	1	13
Skin diseases	5	2	3

Results.

The accompanying table gives the results. In the group of diseases of bone, lymphatic glands, and joints, the reactions were very clear, either emphatically positive or negative. It will be seen that a large proportion of the cases of enlarged or suppurating neck glands gave positive reactions. The test was of great value in obscure joint conditions where the clinical diagnosis was doubtful, and especially in cases of slight but persistent joint disablement after injury. If the v. Pirquet test can be absolutely relied on, its positive or negative findings in such cases must be of unique assistance to early diagnosis.

Perhaps the most significant group is that of the simple pleural effusions. In adults their close association with pulmonary tuberculosis is recognized. In children the association is not generally regarded as equally inevitable. But in the above group, 13 out of 14 cases gave a positive reaction. If this test is a true indicator of tuberculosis, these results must mean that already there is a systemic infection by the bacillus. Whether the pleural effusion is a chronic tuberculous inflammation of the serous membrane, or the skin reaction is a response to tuberculous infection of deep lymphatic glands, say, at the pulmonary roots, it is, of course, impossible to say.

The cases of tuberculous peritonitis for the most part reacted well. Three failed to react. They were all severe cases with great general prostration, and two of them have already proved fatal.

The groups of tuberculous meningitis and general tuberculosis illustrate well how in very severe or general infections the test, like the ophthalmic reaction, breaks down. In all the cases of these groups the clinical diagnosis was confirmed *post mortem*.

In the group of non-tuberculous meningitis and cerebral tumour, the single case that gave a positive reaction was of unusual interest and may be specially mentioned.

A girl, aged 3 years, was admitted with fever, deep coma, and marked head retraction and general rigidity amounting to opisthotonos. The clinical picture was that of epidemic cerebro-spinal meningitis. The v. Pirquet reaction was intensely positive. Lumbar puncture yielded abundant clear fluid, remaining clear after boiling and containing very few lymphocytes. This fluid also gave a positive skin reaction on inoculation. In four days the child was well, fully conscious, without fever or muscular rigidity, though lumbar puncture again gave excess of similar fluid.

A fortnight later, just before dismissal, the v. Pirquet test was repeated and was again markedly positive. In a month the child returned to hospital with measles, and the v. Pirquet reaction was now negative. This is consonant with Holt's statement that a superposed intoxication interferes with the tuberculin reaction.⁸ But the original positive reactions with the clinical signs would indicate a tuberculous focus in the cerebro-spinal axis. Meningitis can be ruled out, both by the fact of recovery and by the characters of the spinal fluid. The probable diagnosis is therefore a tuberculous mass in the cerebellum setting up temporary pressure and causing the clinical phenomena described.

Of the skin conditions, two were clinically tuberculous—lupus and tuberculous ulceration—and gave positive reactions. The remaining negative results were in cases of eczema.

The numerous control cases were taken from cases of lobar pneumonia, empyema, chorea, and other miscellaneous conditions. They were all negative, with the exception of a very healthy-looking girl, aged 13, who gave an intense reaction.

The important question is, Is the cutaneous tuberculin reaction reliable? The above results show that it is not so in advanced tuberculous disease. But in such the diagnosis is usually evident. In early or chronic conditions the results obtained are very strongly in favour of its reliability. Absolute proof is impossible. If a positive reaction is obtained in an apparently healthy subject, the only other evidence is that of the conjunctival and hypodermic reactions; and that if it confirms, is only confirmatory—it is not fresh evidence.

It is, however, certain that the reaction is specific, and, though local, an index of a general blood condition. If the reaction is repeated, it is always confirmed, *provided the general condition of the patient remains the same*. In 18 of the above series, I repeated the test after a varying interval. Of the original results, 11 were positive, and 7 negative. The repeated tests confirmed these in every instance. So far as proof is in the meantime possible, a positive v. Pirquet reaction may be regarded as a certain index of tuberculous disease, whether it is clinically manifest or not.

Late and Negative Reactions.

It is very necessary to make the proviso that, in a repeated test, the condition of the patient in general vigour and vitality must remain approximately the same. The recital of the following case makes the point very clear:

B. W., aged 4, a well-developed, but thin little girl, was admitted on April 15th for whooping-cough. No physical signs of tuberculosis in lungs, abdomen, or lymphatic glands. On April 17th she gave a marked v. Pirquet reaction. She steadily lost weight and strength, and on May 25th was very weak and emaciated; the test then repeated was negative. A few days later she developed measles. On June 8th the test was repeated, and was negative. Now there were signs of consolidation at the right apex and both bases. Death occurred on June 20th, and *post-mortem* examination showed enlarged lymphatic glands at the lung roots, hard, caseous and pigmented; extensive caseating tuberculosis in both lungs, and recently enlarged peritoneal glands, with numerous tubercles in the peritoneum.

Such a case is a striking illustration both of the strength and weakness of the von Pirquet test. It is capable of detecting tuberculous disease where clinical manifestations are completely wanting. It is a very delicate test in early

conditions. And yet in advanced stages of the disease it may completely fail.

The two following cases illustrate the same point, the alteration of the reaction with the altered condition of the patient. The change is here less extreme, but no less interesting.

Name and Age.	Disease.	Development of First Reaction.	Change of Condition in Interval (Several Weeks).	Development of Second Reaction.
H. C., 10 years	Tuberculous hip	24 hours	Retrosession	48 hours
R. L., 10 years	Enlarged cervical, inguinal, and axillary glands	Absent	Improvement	24 hours

These results lead up to the cases of late reaction—that is, where an abnormally long period elapses before the appearance of a reaction. Any period over twenty-four hours has been regarded as a late reaction, and the limit is stated to be forty-eight hours. In several of the following cases this limit was exceeded. Where two periods of time are given the first refers to the earliest appearance of a flush or areola, the second to the development of a definite papule, which completes the reaction.

Name.	Disease.	Time of Reaction.
A. C.	Abdominal tuberculosis	36 hours.
D. B.	Spinal abscess and gangrene of lung	48-72 hours.
J. W.	Tuberculous hip	48 hours.
H. C.	Tuberculous hip	48-72 hours.
V. T.	Bronchopneumonia	48-72 hours.
M. M.	Abdominal tuberculosis	72-90 hours.
V. L.	Abdominal tuberculosis	72-120 hours.

Holt states that the appearance of the areola is rarely later than twenty-four hours; and yet in the above series, which is much less numerous than his, 6 cases did not show reaction till forty-eight hours or later. In 2 cases the areola only appeared after three days, and in one the papule did not develop until after five days. Possibly these very late reactions have been overlooked in other investigations. It is more probable that they did not occur, because of the different technique employed in the performance of the test, and that their appearance in the above series is due to a superior technique. The modification of v. Pirquet's technique employed in this investigation may seem very trifling, but the tough epidermis is a serious barrier between the capillary circulation of the skin and the outside. And refinements of technique are not unimportant if they ensure contact of the toxin with the local circulation. That this modification is highly important has already been demonstrated by the results of a short series of cases in which it was compared with the original technique of v. Pirquet. It is also extremely probable that it accounts for the very late reactions shown in the above table.

These late reactions all occurred either in cases of widespread tuberculous disease, or where the local disease was complicated by another infection, as in the two cases of hip-joint disease. They form a group intermediate between those of vigorous reaction in early or moderate cases and those of negative reaction in advanced cases. Such negative reactions in my series were obtained in the following conditions:

Condition.	Negative Reactions.	Number of Cases.
General tuberculosis	...	4
Tuberculous meningitis	...	3
Tuberculous peritonitis	...	3
Bronchiectasis	...	1

All these were cases of very active or very widespread tuberculosis, in which the general prostration and weakness was profound; but of the 11 cases 10 have already died, and in every fatal case the clinical diagnosis of tuberculosis was confirmed *post mortem*.

The conclusion to be drawn from these cases of late and negative reaction to v. Pirquet's test is that the vigour of the reaction varies directly with the vigour of the patient and inversely with the amount of tuberculous infection. Where the general vigour is only slightly impaired a rapid and intense reaction is obtained. The most intense reactions I obtained were among the cases of osseous and joint tuberculosis, and also of pleural effusion. But where the vigour of the patient is low and the disease is widespread or complicated, the reaction is late in appearance and feeble or is absent altogether. With regard to the same point in the ophthalmic-reaction there is some difference of opinion. That will be discussed later. But in v. Pirquet's reaction the whole evidence strongly points to the conclusion just reached.

Comparison of the Conjunctival and Skin Reactions.

In 78 cases the Calmette and v. Pirquet reactions were tried in the same patient. The v. Pirquet test was performed as already described. In the Calmette test the dried tuberculin was used in 0.5 per cent. solution in distilled water. The solution was only employed freshly made up. The results were as follows:

	Positive.	Negative.
V. Pirquet	31	47
-Calmette	21	57

I should say that these cases are not new, but have already been included in the v. Pirquet series. Out of the 78 cases, the v. Pirquet test was positive in 31; it was negative in 47. In these 47 negatives the Calmette reaction was also negative in every case. It was positive in 21 of the cases in which v. Pirquet was positive, but it failed to react in the remaining 10 cases in which v. Pirquet was positive. That is to say, out of a total of 78 cases, the Calmette test either coincided with the v. Pirquet or contradicted it negatively. It did not contradict positively in a single case—that is, it never gave a positive reaction where the v. Pirquet was negative. A closer analysis of those 10 cases may be useful.

Name.	Condition.
G. B. ...	Tuberculous ankle.
D. W. ...	Tuberculous spine.
J. W. ...	Simple pleural effusion.
W. B. ...	" "
F. G. ...	" "
A. S. ...	Chronic bronchopneumonia.
C. W. ...	Tuberculous peritonitis.
R. S. ...	" "
H. C. ...	Tuberculous hip-joint (mixed infection).
J. A. ...	Tuberculous meningitis.

(V. Pirquet's reaction was positive and Calmette's reaction negative in all these cases.)

These conditions may be said to include all degrees of severity of tuberculous infection, so that in this list the v. Pirquet test is superior to the Calmette over the whole range of tuberculous conditions. The superior delicacy of the skin reaction is not partial or in one direction. It is total and in all directions. In these 78 cases it undoubtedly failed in some cases of widespread tuberculosis; it may have failed also in some incipient cases. But in each of these extreme directions it gave some reactions where the conjunctival test did not; and in neither of these groups did the Calmette test succeed where the other failed.

At the last meeting of the British Medical Association Calmette held that the conjunctival reaction was more useful than the skin reaction, because of the failure of the former to detect healed or quiescent tubercles.⁴ That is really an admission of the greater delicacy of the v. Pirquet test. Moreover, it is a difficult matter to say when a tubercle is healed. So long as the blood reacts to the skin test the tuberculous focus is potentially active. In the adult the limitation of the focus is more thorough; but in the child the activation of a buried tuberculous lymphatic gland may in a few weeks cause a general dissemination of tubercles, so that in children the power of the v. Pirquet test to detect latent or quiescent tuberculosis gives it an important advantage.

It must be noted that in the above cases a weak solution

of tuberculin (0.5 per cent.) was used for the eye test. Again, the subjects were all children, and though the solution could always be dropped on to the eye, it was often much diluted by a flood of tears. But these difficulties are inherent: stronger solutions in the eye are sometimes unsafe, and children will not cease to cry. Dealing with the skin much stronger solutions are used and can there be brought more effectively into contact with the local circulation. In a comparison of these two forms of tuberculin reaction, their essential similarity must be admitted. Both are vascular reactions depending on the close contact of toxines with the capillary circulation. But their practical application is different. With the skin it is safe to sensitize the local circulation by some form of scarification or abrasion. With the conjunctiva it has from the first been recognized as dangerous to employ the test where any degree of inflammation is already present. We aim at producing an abraded cutis. We deliberately avoid an injured conjunctiva. In that contrast lies the cause of the superior delicacy of the v. Pirquet test.

But it is needful to point out that the superficial circulation is much less accessible in the skin than in the eye. Therefore a proper technique in preparation of a vascular surface on the skin is highly important. Neglect of that may turn the balance in favour of the eye reaction, and may throw away the advantage in delicacy and safety which the v. Pirquet test undoubtedly possesses.

One final point is worth mentioning. It is much disputed whether severe conjunctival reaction means an active tuberculous process or the reverse. Wolff-Eisner holds the former view.⁵ Calmette, in his statement that the severity of the reaction corresponds with the number of antibodies present in the blood, inclines to the latter view.⁴ The evidence seems to be conflicting; but in the v. Pirquet test it has already been shown that the severity of the reaction varies inversely with the severity of the disease. In the skin the conditions almost approximate to those of an exact experiment by a definite abrasion. In the conjunctiva, the local vascularity, and therefore the local sensitiveness, must vary much even within the range of health. That fact probably explains the discrepant results obtained.

In conclusion, I would cordially express my thanks to the members of the staff of the East London Hospital for Children for their permission to use the abundant material of the hospital for the purpose of this investigation.

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¹ *Deut. med. Woch.*, May 23rd, 1907. ² Report upon 1,000 Tuberculin Tests in Young Children, *Trans. Amer. Ped. Soc.*, vol. xx, 1909. ³ *Ibid.* ⁴ *BRITISH MEDICAL JOURNAL*, August 28th, 1909. ⁵ *Berl. klin. Woch.* 1908, vol. xiv, p. 365.

A CASE OF DISSEMINATED TUBERCULOSIS TREATED WITH MARMOREK'S SERUM.

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THE results of treatment by Marmorek's serum in the following case seem to me sufficiently striking to render its publication desirable.

The patient was a schoolboy, of Spanish nationality, aged 15. He was first seen on December 14th of last year, when he was suffering from severe haematuria of more than six months' duration. His temperature was 103° F., and the abdomen was distended. There was an operation scar in the right kidney region. The case rapidly assumed a typical typhoid condition, with evening temperature about 104° F. and slight morning remissions. The following is a summary of the symptoms at this time:

The pulse was very rapid and feeble, the abdomen distended, with thickening in the right kidney region; pale yellow diarrhoea with much mucus and some blood; profuse haematuria but no pyuria; rapid emaciation. Widal's reaction was repeatedly negative, and so was the Ehrlich-Diazo test. The blood counts showed distinct paucity of leucocytes.

We were a little baffled at this stage by misleading information to the effect that the operation scar was due to a successful nephrolithotomy, but we now obtained a more veracious account from France which made it obvious that the case was tuberculous. We ascertained that the right kidney had been removed in the previous June for tuberculosis, and the bladder and prostate were found cystoscopically to be tuberculous.