THE QUANTITATIVE INTRADERMAL TUBERCULIN TEST AS AN AID TO PROGNOSIS IN TUBERCULOSIS.

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HISTORY OF THE QUANTITATIVE INTRADERMAL TUBERCULIN TEST.

The possibility of discovering a reliable test for the detection of tuberculosis dates from the publication in 1890 of Koch's[1] first article on tuberculin, called at that time lymph by its discoverer. Although noting the diagnostic possibilities of his discovery, Koch was more interested in tuberculin as a therapeutic agent. Nevertheless, the subcutaneous test, the first of the tuberculin reactions, was introduced by him. In this test, what would now be regarded as a large dose for diagnostic purposes, was injected under the skin. This large dose produced local, focal and general reactions in the susceptible. Subsequent workers endeavoured by reducing the quantity of tuberculin injected to produce a local reaction only, the smaller amount being insufficient to cause focal and general reactions.

The first cutaneous test, as distinct from the subcutaneous introduction of tuberculin, was described by von Pirquet[2] in 1907. This test, by introducing a small quantity of tuberculin into the skin, usually succeeded in avoiding the focal and general reactions.

Mantoux[3], in 1908, described the intradermal tuberculin test which is frequently named after him. Riviere[4] states that this test was first discovered by Mendel but is named after Mantoux, as the latter was the first to bring it into prominence.

Mantoux obtained diluted tuberculin from the Pasteur Institute and made a further dilution to 1 in 5,000 with normal saline. He then injected a small quantity (une goutte) into the skin on the anterior surface of the thigh, taking care that none would enter the subcutaneous tissues. The quantity injected he estimated as 0.01 milligrammes tuberculin. General symptoms he described as being normally absent and the typical positive reaction was at its maximum in 48 hours.

The von Pirquet test was, of course, known to Mantoux at this time and he compared his intradermal method with the cutaneous method. His conclusions were that the intradermal tuberculin test was equally simple and harmless, and had the advantage over the cutaneous test of a greater clearness in results and a greater sensitivity.

It will be noticed that Mantoux did not stress the fact that his test was quantitative, no doubt because he was using it for diagnosis only.

D'Arcy Hart[5], after reviewing the work of a considerable number of workers on the relative sensitiveness of the von Pirquet and Mantoux tests, considers that the intradermal test is 1,000 or more times as sensitive as the cutaneous test, if concentration be compared with concentration.

While subsequent investigators have changed the intradermal test of Mantoux, the principle of it has remained unaltered. The main modifications used by various workers will be described later.

REASON FOR THIS INVESTIGATION.

It is not surprising that, with the discovery of a tuberculin test which was more sensitive than the previous ones and at the same time lent itself better to quantitative administration, some attempts should have been made to find if there was any relationship between the reaction and the course of tuberculous disease. Relatively little work has been done on the use of the test in prognosis, but a great deal has been done using the test as a diagnostic agent.

A paper by Lobban[6] suggested this present investigation. Lobban's conclusions were that (1) "as the (tuberculous) disease advances the patient fails to react to the greater dilutions, (of tuberculin) and lesser dilutions are necessary before a positive reaction can be obtained".

(2) "That the intradermal tuberculin test in tuberculosis, when repeated at intervals, shows a more marked reaction when the case is improving, and fails to appear or become positive when a lesser dilution is employed, when the case is retrogressing".

Other writers[7], however, say that any relationship between the reaction and the progress of the disease is not sufficiently constant and accordingly is not of practical value.

The idea then occurred to the writer of testing the value of the Mantoux intradermal injection in prognosis on lines somewhat similar to Lobban, but using a larger number of cases, and endeavouring, especially with pulmonary patients, to arrive at a more accurate estimate of their clinical improvement for comparison with their reactions to the test. An attempt was also made to measure the reaction to the test in a more concrete manner.

The repeated intradermal injections of tuberculin necessitated by this investigation, naturally brought up the questions of positive sensitization and negative sensitization by tuberculin.

Some writers[8] maintain that after a positive reaction there occurs a variable period of increased sensitivity, during which a similar injection to the one producing the first reaction, would produce a considerably greater reaction.

Another writer[8], however, found that there was a period of decreased reactivity which lasted for a few days after a positive reaction. A similar injection to the one producing the first reaction, given during this period, would give a much weaker response.

These phases of sensitization if they are present and persist would naturally interfere very markedly with any investigation involving repeated injections as, for example, an increased reaction to a similar quantity of the same dilution of tuberculin as was injected before, might be due

to the presence of a positive sensitization phase, and a wrong conclusion might be drawn from it.

The negative sensitization phase is easier to deal with as it is only supposed to last a few days and, accordingly, if the interval between the injections is sufficiently long, no difficulty should arise.

There is thus some doubt as to the value of repeated tuberculin tests as an estimation of the progress of a patient suffering from tuberculosis. Also, some workers by describing a period of super-sensitivity, following an injection of tuberculin would naturally conclude that any increase in reaction to a similar quantity of tuberculin injected later was due in part, if not wholly, to this factor.

The writer has considered that owing to the differences in opinion and the different issues involved, the subject of repeated tuberculin tests in patients suffering from tuberculosis is worthy of investigation.

VARIATIONS OF THE INTRADERMAL TUBERCULIN TEST.

The quantitative intradermal, or intracutaneous, tuberculin test as its name implies consists in the injection into the skin of a measured quantity of tuberculin. The injection into the skin is the only common feature of this test as used by various workers. The volume of fluid injected, the dilution of tuberculin used, the kind of tuberculin, and the method of reading the reaction all vary.

1. VOLUME OF FLUID INJECTED.

Burhans[9], Gaisford[10], Daw and Lloyd[11], and D'Arcy Hart[12] all inject o.1 c.c. into the skin raising the usual wheal but regardless of its size.

Cummins and Walker[13], on the other hand, watch the formation of the wheal as they inject the dilution of tuberculin and aim at producing one the size of a threepenny

piece. The amount injected is, on the average, 0.1 c.c. but their main object is the raising of a wheal of a certain size, regardless of the amount of fluid injected.

Lobban[6] injects 0.2 c.c.

2. DILUTION OF TUBERCULIN USED.

As most workers investigate the test as a means of diagnosis they tend to inject a fairly low dilution of tuberculin. Thus Smith[14], Gaisford[10], and Burhans[9] use a dilution of 1 in 1,000 as a routine first injection. Burhans in an exceptional case if he has reason to expect a marked reaction would use 1 in 10,000. These workers do not retest with a lower dilution those who do not react.

Other investigators start with a higher (i.e. weaker) dilution of tuberculin and retest with a lower (i.e. stronger) dilution if there is no reaction. The range of dilutions which these workers use show a wide variation.

D'Arcy Hart[12] starts with 1 in 10,000 and goes down by multiples of ten to a dilution of 1 in 10.

Dow and Lloyd[11] starting at the same dilution do not go further than 1 in 100.

Cummins and Walker[13] commence at 1 in 100,000 and go to 1 in 500. They consider that lower dilutions in tuberculous patients might cause constitutional symptoms.

Lobban[6], who it will be remembered injects 0.2 c.c., has ranges in multiples of ten from 1 in 1,000,000 to 1 in 1,000

It is said[7] that there are workers using dilutions of 1 in 10,000,000 and 1 in 1000,000,000.

3. KIND OF TUBERCULIN.

Old tuberculin appears to be used by most of the investigators and it is prepared according to the method used by Koch. Muir and Ritchie[15], describe old tuberculin as consisting of a "six-weeks-old culture of tubercle bacilli in 5 per cent glycerin bouillon, evaporated down to a tenth of its original volume, killed by heat, and filtered".

Both human and bovine types of tubercle bacilli can be so cultured, consequently there are two types of old tuberculin.

In all probability, human old tuberculin is most commonly used by investigators but often the type is not mentioned. Gaisford[10] in an analysis of 500 cases injected both types in the first 50 cases, until he found that there was no difference in the reactions.

In 1927 an International Standard for concentration of tuberculin was established as the brands of tuberculin were varying in potency.[16]

4. METHODS OF READING THE REACTION.

(a) TIME. The great majority of workers seem to favour 48 hours after the injection as being one of the best times to read the result. They do not agree, however, that this should be the only reading. Gaisford[10] and Burhans[9] take readings also after 24 hours, while D'Arcy Hart[12] takes readings at 48 and 96 hours and states that if one reading only be required it should be taken at 72 hours. D'Arcy Hart disapproves of 24 hour readings as a typical non-specific reaction may still be present. It must be remembered that he uses lower dilutions than most investigators and is therefore more likely to obtain these reactions.

48 hours after injection, according to most workers, is the maximal stage of reaction.

(b) MEASUREMENT. Most investigators as they were using the test as a means of diagnosis or at least not for purposes of comparison with an identical test to be repeated later on the same patient, are content to state merely if the test is positive or negative. If the skin shows the typical signs then it is classified as positive, and some workers in addition, fix a minimum diameter of hyperaemia for a positive test. If the diameter of hyperaemia is under this extent or if there are no signs at all, then the reaction is classified as negative.

At least two workers have devised methods of measuring the reaction more accurately.

Lobban[6] measures the diameter of the area of hyperaemia surrounding the site of injection in inches, and calls a reaction with a diameter of 1 inch, one plus, 2 inches, two plus, and 3 inches, three plus.

Cummins and Walker[13] ignore the area of hyperaemia and measure the diameter, in millimetres, of the central wheal. It will be recalled that these workers when injecting tuberculin concentrate on raising wheals of uniform size.

(c) AMOUNT OF TUBERCULIN. It is not sufficient to say that a patient is a positive reactor to the intradermal tuberculin test; some measure of the amount of tuberculin to which the patient reacts must also be given. Several methods are in use for this purpose.

(i) DILUTION METHOD. This consists in stating after the result of the reaction the dilution of tuberculin with which it was obtained.

(ii) WEIGHT METHOD. On the assumption that 1 c.c. of old tuberculin weighs 1 gramme or 1,000 milligrammes, then 0.1 c.c. of 1 in 1,000 dilution tuberculin would contain 0.1 mg. tuberculin, 0.1 c.c. of 1 in 10,000 dilution would contain 0.01 mg. tuberculin, and so on. The weight of tuberculin causing the reaction could then be stated.

(iii) SYSTEM OF MARKS. Both the above methods are very cumbersome and Cummins and Walker[13] devised a scale of marks, ranging from 40 to 100, with each dilution of tuberculin they used having a range of 20 marks, the actual mark given depending on the size of the reaction to that dilution. This method will be alluded to again.

THE USE OF CONTROLS.

Practically all workers with intradermal tuberculin tests agree that injection of a control solution is

unnecessary. D'Arcy Hart[12] considers a control advisable if a lower dilution than 1 in 100 is used but as 1 in 1,000 dilution was the lowest used by the writer no controls were required. In addition, the highest dilution of tuberculin to which a patient would react was the object, so that there was very little chance of confusion arising as the result of the initial injection.

CHOICE OF TEST FOR THIS INVESTIGATION.

It will now be realised that there is no hard and fast form of the intradermal tuberculin test; the method depends upon the choice and personal preference of the investigator. Therefore, the writer, although the object of his investigation was similar to that of Lobban, felt that he was justified in not doing the test in exactly the same way.

A range of five dilutions of tuberculin from 1 in 1,000,000 to 1 in 100 in multiples of ten, was considered sufficiently large to obtain a reaction in all cases.

0.1 c.c. of the selected dilution was in each case accurately injected into the skin. The size of the wheal raised was not considered, as the test being a quantitative one, the amount injected could be more definitely measured than the extent of a wheal. As 0.1 c.c. was the amount injected by most workers this amount was chosen for the investigation. Also, from the point of view of the patient, 0.1 c.c. injected intradermally is much less painful than 0.2 c.c.

In an investigation of this nature more than one reading of the reaction is impracticable. At 48 hours after injection is the maximum stage of reaction and this would appear to be the optimum time for the reading, especially as small reactions are to be expected owing to the high dilutions used. As the wheals raised were only approximately equal to each other and, in fact, only used as an indication that the

injection was given intradermally the reaction was measured by the extent of the zone of erythema surrounding the point of injection.

A similar system of marking as that used by Cummins and Walker was found to be necessary for evaluating the various results, for although it is only the difference in reaction of each patient to a given quantity of tuberculin repeated at monthly intervals which is required, difficulty arises when the patient fails to react to the same dilution of tuberculin. A lower dilution has then to be used and there is difficulty in correlating the two reactions.

The method of Cummins and Walker has been adapted to suit this investigation and is as shown in Table 1.

It will be seen from this table that one number indicates both the extent of reaction and the dilution of tuberculin used. One mark represents o.5 cm. of reaction and by taking the measurement of the reaction to the nearest half centimetre decimals are avoided. This appears to the writer to be sufficiently accurate as differences of a few millimetres in the extent of reaction would not be of any practical value.

DESCRIPTION OF TEST AND TECHNIQUE OF INJECTION.

1. TUBERCULIN.

Human old tuberculin, Wellcome Brand, as supplied by Burroughs Wellcome & Co. was used. 5 c.c. undiluted tuberculin (series T.16401) was obtained at the commencement of the investigation and this was sufficient for the whole series of tests. It was kept on ice in a dark chest and sufficient was drawn out periodically to make the dilutions. The rubber stopper was replaced and a wisp of cotton wool soaked in 1 in 20 carbolic lotion placed round the junction of rubber with glass, before replacing in ice-chest.

2. DILUTIONS.

The diluent used was 0.5% pheno-saline. 5 glass

bottles each capable of holding 60 c.c., with fairly wide mouths, and rubber caps to fit were used to hold the dilutions. The necessary pipettes, the saline, the bottles and the rubber caps were all sterilised.

Into the first bottle 49.5 c.c. of the diluent were pipetted and into the remaining four, 45 c.c. 0.5 c.c. old tuberculin was then transferred to the first bottle and the contents thoroughly mixed. The dilution of tuberculin resulting was 1 in 100. From this dilution the other dilutions used were successively obtained by the transfer of 5 c.c. from one bottle to the one next in order. The sterile rubber caps were then fixed to each bottle and appropriate labels attached.

The dilutions were also stored on ice and were discarded after two weeks at most, and usually after one week.

Before using them the rubber cap was cleaned with 1 in 20 carbolic lotion, then pierced by a sterile hypodermic needle and the fluid withdrawn by a syringe. The small puncture was sealed afterwards with collodion.

3. SYRINGE.

The one used was a well fitting two-piece 1 c.c. tuberculin syringe graduated in tenths and twentieths and had a metal piston. The glass barrel was sterilised by leaving in 1 in 20 carbolic lotion for a few hours before use while the metal piston was sterilised by boiling.

The same syringe was used throughout the investigation. It held sufficient for ten injections and before being used for injection of a different dilution it was cleared a few times with sterile water.

4. NEEDLES.

Summit No.20 hypodermic needles were used. This is a fine needle with a short point and no difficulty was experienced with it in confining the injection to the skin. The needles were sterilised by boiling but once attached to the

syringe charged for ten injections it had to remain there until all ten injections were given. It was flamed between each injection while still attached to the syringe.

5. INJECTION.

The site of injection was almost invariably the front of the forearm, a different area being selected for each test. The skin was cleaned with methylated ether and the needle, attached to the syringe, introduced with the bevel upwards. The needle was held lying almost flat along the surface of the arm and pushed into the skin until the bevel was completely covered. This ensured that all the fluid injected entered the skin. The skin was kept tense by means of the left hand and not pinched up when inserting the needle.

When the needle was correctly placed, 0.1 c.c. of the appropriate dilution of tuberculin was inserted slowly into the skin. The needle was then withdrawn smartly and the patient told to leave the arm uncovered for a few minutes before drawing down the sleeve. The skin was not again treated with methylated ether or a dressing applied as no blood should be observed at all.

6. NORMAL EFFECTS.

A. LOCAL.

(i) IMMEDIATE. As the fluid was being injected into the skin a dead-white wheal was raised, which showed the hair follicles as little dark pits on the surface. The diameter of the wheal was usually about 0.6 cm.

(ii) 1-3 DAYS LATER. If a negative reaction resulted, the wheal had disappeared and there may have been a faint mark where the needle had entered the skin.

If a positive reaction resulted, there was at the site of injection a circular, sometimes oval, wheal composed of two concentric areas. The inner area was small, of darker colour than the outer, oedematous, and brawny to the touch. The outer zone was purely erythematous.

(iii) 3-5 DAYS LATER. The outer erythematous layer had faded, leaving the smaller brawny layer with signs of desquamation.

(iv) 14 DAYS LATER. The brawny desquamating layer was seen now as a brown discolouration which persisted sometimes up to two months or more.

B, GENERAL.

There were no general symptoms seen normally after an intradermal injection.

7. COMPLICATIONS OF TEST.

A. LOCAL.

(i) IMMEDIATE. If the skin was held taut and the needle was sharp, no pain was experienced by the patient when the needle was inserted into the skin. A sharp pain during the injection of the tuberculin dilution as the skin was stretched was, however, a frequent complaint. Its duration was exceedingly short, it did not last as long as the time taken to raise the wheal, and no more persistent pain followed.

(ii) 1-3 DAYS LATER. Vesiculation, which is regarded by many workers as a normal result of the test in an acute reaction, was seldom seen in this series owing to the use of high dilutions for initial injections. The vesicle in the few cases in which it appeared, burst spontaneously and all the treatment required was the application of sterile dressings. The duration of the brown discolouration did not appear to be any greater in these cases.

Irritation and a desire to scratch the part were frequent complications especially if the hyperaemic area was extensive. No treatment was ever required.

Pain in the arm was complained of on only one occasion and examination revealed no cause.

(iii) AFTER 3 DAYS. No complaints were made.

B. GENERAL.

Two patients complained of general symptons.

One E.M. No.21. Appendix 1, with a small reaction to 1 in 10,000 dilution complained on two occasions of shivering and a feeling of sickness on the morning following the injections. She did not vomit and the shivering was not observed by the staff. She had received intramuscular injections of tuberculin at another institution some time previously.

The other, R.C. No.54, Appendix 1, complained of headache and a tired feeling the day following an injection. His reaction for that injection was about 2 cm. less than his others, which suggests that the injection was not entirely intradermal.

8. READING THE REACTION.

The arm was examined for a reaction 48 hours after the injection. The positive reaction had a definite brawny centre with a surrounding area of erythema. This erythematous zone was usually circular, or slightly elliptical, in shape and it was the extent of this area which was measured. By means of a straight edge, marked in centimetres, the greatest diameter was found and measured to the nearest 1/10 cm. The result was noted down along with the name of the patient, the dilution of tuberculin used in the test, and the date of injection.

If there was no reaction, this fact was also noted.

As no soothing applications, such as lotio calaminae, were ever required for treatment of irritation at the site of the injection, the reaction showed up clearly against the normal surrounding skin and no preparatory cleansing had to be done before measurement.

THE INVESTIGATION.

In general, the plan of this investigation was to obtain reactions in patients, at definite intervals, and find by comparison with their clinical condition whether there was a relationship between the two.

It has been explained previously that higher dilutions, 1 in 1,000,000 for example, of old tuberculin were used in order that the highest dilution to which the patient reacted should be found. This entailed giving a large number of fruitless injections as every patient received an injection of 1 in 1,000,000 dilution old tuberculin as their first injection and only a very few reacted to it. Those patients whose reaction was negative to 1 in 1,000,000 were left for a week and then retested with 1 in 100,000 dilution. If still negative they were given an injection of 1 in 10,000 dilution after a further 6 or 7 days rest, and if again negative an injection of 1 in 1,000 a week later. Lower dilutions than 1 in 1,000 were not required in this investigation to obtain a reaction.

The dilution of tuberculin, with certain exceptions, which caused the reaction was then injected in the same amount (0.1 c.c.) every month for 4 months, and the extent of the reaction, in each case, was measured as described above and noted.

If the injection of the same amount of the same dilution of tuberculin given four weeks before produced a very much larger reaction, then this fact was noted and a higher (i.e. weaker) dilution of tuberculin was injected at the next test.

On the other hand, if the reaction was very much smaller than the previous one a lower (i.e. stronger) dilution was injected at the subsequent test.

If no reaction was obtained at all then the patient was retested with a lower dilution after a week. In all instances the patient reacted to this dilution.

A series of four tests was chosen as being sufficient to show a change in the clinical condition of a patient. A longer series would, of course, have been better, but there is a limit to the number of injections which a patient will bear without demur. Also, in a longer observation period, the

number of patients in the investigation would decline owing to deaths and dismissals.

Although there are roughly 600 tests which are pertinent to this investigation of 150 patients, in all 1,354 injections were given to nearly 200 patients. The difference in numbers is due to two main factors.

1. Relatively few reactors to the dilutions 1 in 1,000,000 and 1 in 100,000, necessitating a large number of retests.
2. Dismissal of patients, who had reacted, either irregularly, discharged fit or by death. It was not found practical to continue injections on patients discharged owing to the expense involved of two visits to the hospital, one for injection and one for reading the result in two days' time.

As explained above the old tuberculin when diluted does not retain its potency if kept indefinitely, and so during the investigation fresh dilutions were made on six occasions.

5 dozen Summit No.20 needles were used; as 1354 injections were given the average life of a needle was approximately 22 injections.

The injections to which the patient reacted and which, therefore, were relevant to the investigation, were numbered 1, 2, 3, 4, and not dated. The reason for this is that all patients were not tested on the same day and though each patient was tested over a period of four months it was not always the same four months. The tests were, however, completed in a period of six months so that any variation, which might be attributed to season would be negligible.

With few exceptions each patient had four tests to which they reacted.

The results of each reaction were entered on a separate sheet for each patient and at the same time certain clinical details were also noted. These will be more fully explained in the discussion of the results later and in the method of

assessing the symptoms.

An example of the sheet on which the details were entered is seen in Table 2.

PULMONARY PATIENTS.

NUMBER AND TYPE OF CASE.

The pulmonary patients tested were all chosen at random from those in Robroyston Hospital and Sanatorium at the time of the investigation. The total number who had the complete series of four tests performed was 76. It will be seen from Table 3 which gives the age and sex distribution that the great majority were females under the age of 30 years. As mentioned before, there is difficulty in an investigation of this kind in following up to the end all the patients who react to the test, and one of the reasons for the large percentage of female cases is that women and particularly young girls, are more phlegmatic than men, accustom themselves sooner to hospital life, and have a longer average period of residence. Male patients, on the other hand, perhaps because they are the breadwinners of a household, tend to be unsettled in hospital and desire to leave at the earliest opportunity, frequently on their own responsibility. As a result, a number of readings on men had to be discarded as the four tests could not be given before they left hospital irregularly. Another reason for the preponderance of female patients was that the writer was in charge of practically all the cases of female pulmonary tuberculosis in the hospital and therefore was more constantly acquainted with admissions; naturally, also, facilities for doing tests were greater in wards under his own charge.

All tuberculosis cases admitted to Robroyston Sanatorium are classified according to the Ministry of Health recommendation. Briefly this system has four main classes for pulmonary tuberculosis.

1. Class T.B. -. Those in which tubercle bacilli have never been found. Class T.B. + can never revert to this class.

2. Class T.B. + Group 1. Slight constitutional disturbance. Disease limited to size of one lobe. No grave complications.

3. Class T.B. + Group 2. Those not in Class T.B. + Groups 1 or 3.

4. Class T.B. + Group 3. The advanced cases with profound systemic disturbance and grave complications. A patient with both pulmonary and non-pulmonary lesions is classified as pulmonary. Several such cases are included here.

Table 4 gives the number in each of the above classes of the cases comprising this investigation and also the percentages.

The cases in Class T.B. - were considered tuberculous by clinical and radiological examination.

As was to be expected more than half the cases belonged to Class T.B. + Group 2, both on accounts of its larger range and because it represented a type of patient who tended to have a longer residence in hospital. Class T.B. + Group 1 is not represented at all in this investigation because in the experience of the writer it is rare in hospital and does not remain for sanatorium treatment very long. Class T.B. + Group 3 with 25% is well represented and would undoubtedly have been larger but for the difficulty of completing the series of tests before death in patients who were steadily failing. As it is, a number with only three tests before death are included.

The patients were all classified according to their condition at the time of commencing the investigation.

METHOD OF CLASSIFICATION FOR COMPARISON.

The above figures are given and this classification used only to give some idea of the different types of cases which were tested. This investigation is not concerned with showing that advanced cases of tuberculosis as a class react to a different dilution of tuberculin than early cases; its purpose is to find out if the reactions elicited in one particular patient can be used as a guide to that patient's

progress.

The difficulty now arose of finding a method of classifying the condition of a patient suitable for comparison with the results of the intradermal tests and with other classifications at monthly intervals.

All the usual classifications are unsuited for this as they do not tend to show the slight variations which may take place in progress in a month.

Cummins and Walker[17] when assessing one hundred cases of pulmonary tuberculosis used a system of marks. They assigned 50 marks for the lesions as shown by an X-ray film and 50 marks for the systemic state of the patient. The latter 50 marks were made up of temperature 20 marks, weight 20 marks, and general characters such as pulse, duration of disease, existence of other tuberculous factors, 10 marks.

The writer decided to use a similar method for assessing a case at the time of the intradermal injection. In this way four numbers would be obtained, representing the state of the patient at the time of the test; these numbers could easily be compared with each other to show whether the condition was improving or getting worse; they could be compared easily with the numbers representing the extent of the reaction to the test; they would show small variations in the progress of a patient as they would be derived from items such as temperature, weight etc., which could vary definitely from month to month.

Table 2 shows the information which was collected for each patient at the time of the tests to which they reacted and which had to be put into a form suitable for comparison.

Most clinicians believe that the temperature rate, the pulse rate, gain or loss in weight, and amount and bacillary content of the sputum are all of use in estimating the activity or quiescence of pulmonary tuberculosis.

Fishberg[18] states that "there is no active phthisis without fever, cough, tachycardia, langour, night sweats, haemoptyses etc. Some or all of these symptoms are found soon after the

patient becomes actively phthisical".

As regards temperature, Sir James Kingston Fowler[19] states that "by observation of the temperature in a case of pulmonary tuberculosis it is possible to determine the nature of the changes in progress in the lungs". Burrell[20] states more definitely that "the temperature is, however, the best guide to the activity of the disease".

With regard to pulse rate, some authorities also consider this an indication of activity of the pulmonary lesion. Referring to persistent tachycardia in pulmonary tuberculosis, Wingfield[21] says "it is sufficiently frequent to make a pulse record an essential examination in establishing a diagnosis and, like the temperature record, may be of great value in estimating the severity of a case".

Fishberg[22] also states "that excepting in heart disease and hyperthyreoidism, no disease can be valuated prognostically with the same degree of accuracy by the pulse rate as chronic phthisis".

The weight of a patient at any given time is of no value in estimating the extent of tuberculous disease in that patient or the prospects of recovery. But a series of weights of one patient showing a steady gain or a steady loss in a known period is of value in estimating the degree of systemic disturbance due to disease.

Simiarly with regard to sputum examination. The amount of sputum and whether it contains tubercle bacilli or not is only of value when there is a change in the amount of sputum over a known period or if the bacillary content changes definitely from negative to positive or positive to negative. Fishberg[23] states "there are cases which show but few bacilli in each specimen yet they run an acute and progressive course, while others with numerous bacilli pursue a slow chronic course terminating in recovery..... On the other hand, the complete absence of bacilli from the sputum for several weeks coupled with improvement in the general condition of the patient is

undoubtedly a favourable sign".

As mentioned above Cummins and Walker in their investigation made an assessment of the disease from the study of an X-ray film. It must be understood that they were making only one such assessment. It would have been impossible for several reasons in an investigation such as this to have plates taken of each patient every month for four months, no matter how desirable and convenient it might be. As a matter of fact, Cummins and Walker found in their comparisons that the systemic assessment appeared to be more successful than the X-ray assessment. The writer has, however, made use of one X-ray photograph in each case in connection with the relationship of the extent of X-ray markings and the intradermal tuberculin reaction. This subject will be discussed later.

According to the classification used in this hospital a patient even with an active tuberculous surgical lesion and a quiescent pulmonary condition is classified as a pulmonary case. Nine cases with a surgical tuberculous lesion are included here under the pulmonary classification on account of also having a tuberculous lung condition. The progress of the non-pulmonary lesion is taken into account in the assessment of these cases. This appears justifiable first, because these cases are definitely classified and secondly, because the test is being tried for its value in the prognosis of tuberculous disease. The number of such cases does not justify having a separate group for them.

The following scheme of marking was used for assessing the condition of a patient.

Temperature.	Ambulant afebrile.	0-4
	Resting afebrile.	5-12
	Resting febrile.	13-20
Pulse rate.	Below 100 per minute.	0-5
	Over 100 per minute.	6-10
Weight.	Gaining steadily.	0-4
	Stationary.	5-12
	Losing markedly.	13-20

Sputum.	0 - 5oz. daily.	0-5
	Over 5oz. daily.	6-10
	- to +	0-5
	++ and over.	6-10
Tuberculous complications.	Peripheral glands, organs, abdomen, bones and joints, depending on site and presence of abscesses and sinuses.	0-30

It will be noticed that the maximum number of marks is 100.

In assessing temperature and pulse rate, the average peak temperature and pulse rate for a few days before the injection was taken to avoid any increase due to the test.

Tuberculous complications appear to have a very large range but in practice, the mark given for them does not vary much over the series of four observations. An initial mark is given according to the location of the tuberculous lesion, disease of bones and joints getting a higher mark than disease of peripheral glands. This mark then only varies very slightly as the complication progresses.

The subdivision of the marks, as shown above in the scheme, for temperature, pulse, weight and sputum is to facilitate the assessment. Before a mark can be given for any one feature all four observations have to be studied to obtain the trend. This is particularly so in regard to weight and bacillary content of sputum but it also applies to the assessment of temperature and pulse rate.

Bearing this in mind and with the subdivisions ready to hand, it was very easy to arrive at a definite mark under each main heading. The sum of these marks will be called the "general assessment". It cannot be too strongly emphasised that these general assessment marks are only for comparison with marks deduced from observations on the same patient at a different time. In other words they show the progress of a patient by the difference in the marks either by gain or by loss, the total mark by itself is of no value, and is not intended for comparison with those of other patients.

METHOD OF COMPARISON.

To facilitate the comparison of the marks for the general assessment and the marks for the reaction the results were grouped together in the manner shewn in Appendix 1. The first three columns, giving the serial number, initials and age of patient were merely for identification purposes. Four columns are devoted to the general assessment marks and these are numbered, as explained before according to the time of injection, and not dated, for naturally all the dates do not correspond. Four columns are used also for the marks given for reaction. The numbers 1, 2, 3, 4, are given in order of time and correspond with the numbers 1, 2, 3, 4, under general assessment. Thus the marks under column 1, general assessment, refer to the general assessment at the time when the reaction mark is as stated under column 1 Reaction. It was thought more convenient to keep the ranges of general assessment and reaction marks separate as in this way the trend of each could more easily be appreciated. The final column, X-ray assessment, will be referred to later.

In the case of pulmonary tuberculosis where temperature, pulse rate, gain or loss in weight and amount and character of sputum are of importance in estimating the progress, favourably or otherwise, of a patient, the marks in the general assessment columns can be regarded as a fair guide to that progress. The object of this investigation is to show whether or not, the intradermal tuberculin reaction is also a guide. This can be done, therefore, by finding out whether the trend or variation in the marks for general assessment corresponds to a similar trend or variation in the marks for the reaction.

It will be realized from the method of awarding marks for the general assessment shown above that the smaller the mark the better is the condition of the patient. In consequence, if the marks given for the general assessment tend to increase then the condition of the patient is deteriorating, while if the

marks tend to fall, then the condition is progressing favourably. On the other hand the marks given for the extent of the reaction fall as the reaction gets less, and if a lower dilution of tuberculin has to be used. Therefore, if the reaction corresponds to the progress of the patient in the manner described by Lobban, the marks for the reaction and the marks for the general assessment will vary inversely.

EXAMINATION OF RESULTS.

The general assessment marks, which the writer is taking as guides to the progress of a patient, fall into four main groups. First, there are those in which the marks fall steadily, indicating, as explained above, that the condition of the patient is improving. Second, there are those in which the marks are rising steadily, thus indicating that the condition is not improving. The third group contains those marks which are irregular in the sense that they show no definite trend, and yet are subject to fluctuation. The fourth group is composed of those general assessment marks which are more or less steady, indicating that the condition of the patient is stationary.

To facilitate their more detailed examination, the pulmonary cases in Appendix 1 have been grouped according to the trend of their general assessment marks.

Group 1. Condition improving.

The cases in this group are numbered 1 to 26 inclusive in Appendix 1. Their general assessment marks will be seen to fall steadily. By this is meant that the first mark is greater than their fourth marks and their second and third marks lie between these two, the second being not less than the third. In this way, cases are included whose marks show a downward trend but yet may have two marks of equal value.

The cases in this group have falling general

assessment marks so that the reaction marks to show agreement should be steadily rising. As in allocating cases to this group steadily rising means that the marks tend to increase; there may be two of equal value together, but each mark is not less than the one preceding it.

By examination of the cases in this group, it can be seen that all the reaction marks are steadily rising except two, numbers 19 and 23.

In case No.19, the disagreement is very definite, for the patient was undoubtedly improving at the time the injections were done, and in fact, was dismissed shortly after, while the extent of her reaction was steadily falling and indeed a lower dilution was required to produce a response.

Case No.23, except for the third injection, shows agreement with the general assessment marks. This reaction mark, is, however, higher than the first, and it is only on account of the definition of "steadily rising" given above which prevents this case being considered as in agreement.

Ignoring for the moment the question of amount of variation, it will be seen that of 26 cases with pulmonary tuberculosis who are improving, 24 or 92.3% show an increasing extent of reaction to the tuberculin test, when it is repeated at monthly intervals.

Group 2. Condition deteriorating.

The cases in this group are numbered 27 to 36 inclusive in Appendix 1. The common feature of this group is that the general assessment marks are all steadily rising, thus indicating that the condition of the patient is deteriorating. That this is so can readily be seen from the list of patients, for out of the ten cases, five were dead when the fourth injection was due. In this group to show agreement with the general assessment marks, the reaction marks should be steadily falling. In nine cases these marks are falling. The exception is case No.35.

This patient is suffering from chronic phthisis with low activity and her condition is more or less stationary with no prospect of ultimate recovery. Her reaction marks would agree more nearly with this grouping of the case but owing to her general assessment marks showing a steady increase according to the definition of the writer, the case has been included in this group.

Again omitting to take into account the extent of variation, it is seen that 90% of the reaction marks agree with the findings of the general assessment marks.

Group 3. Irregular.

The cases in this group number nineteen and are numbered 37 to 55 in Appendix 1. The general assessment marks of each case, while showing variation, have no decided trend either upwards or downwards. This means that the condition of the patient is unstabilised. The general assessment marks could vary for a number of reasons; the temperature after being normal for months could suddenly show elevations; the weight might fall after a period of steady gain; the sputum might increase in amount and contain tubercle bacilli. Any of these happenings would increase the general assessment mark and if in four weeks' time there was a reversion to the original condition this would again be shown by a change in the general assessment mark. Similarly a temporary improvement in the condition of a patient would be shown by a temporary fall in the general assessment marks.

The reaction marks of cases in this group to show agreement with the condition of the patient should vary in the inverse direction to the general assessment marks.

As before, the extent of the variation is not taken into account but only the direction of the variation, when a comparison is being made.

It will be seen from an examination of the cases in

group 3, Appendix 1, that the reaction marks agree in 14 cases with the variations of the general assessment marks. The five cases not showing agreement are numbers 37, 40, 44, 48, 54. These cases quite definitely do not agree, but it will be noticed that their reaction marks all show variations although these variations do not correspond to those of the general assessment marks. None of these cases have reaction marks which are steadily rising, steadily falling or remaining unaltered.

14 cases agreeing out of 19 cases in the group gives a percentage of 73.7%.

Group 4. Stationary.

The 21 cases comprising this group will be found numbered 56 to 76 in Appendix 1. They have general assessment marks which either do not vary at all throughout the series or else have three marks identical, and the fourth not very much different. The reaction marks, if they are going to correspond to the condition of the patient, should be steady also. If two marks are allowed as a maximum difference between the lowest and highest reaction marks as still qualifying to be called a steady reaction then it is found that 11 cases in this group show agreement between the reaction to the test and their reaction to the disease. This gives a percentage agreeing with the general assessment of 52.4%.

DISCUSSION.

The figures for the four groups given above seem to show that there is a considerable degree of agreement between the reaction to the tuberculin test and the progress of a patient suffering from pulmonary tuberculosis.

In the first group, that is where the patients are steadily improving, it is found that 92.3% of the patients show

a steadily increasing extent of reaction to the same quantity of tuberculin.

The second group contains the cases which are steadily going downhill. The numbers are much smaller than the first group for this reason, but here again the agreement is very close as 90% of these patients have a steadily decreasing extent of reaction to tuberculin.

The figures are small but as regards a patient steadily improving or steadily deteriorating, it would appear that there is a very close relationship between the course of the disease and the extent of the reaction to similar quantities of tuberculin.

Groups 3 and 4, which contain cases with no decided trend, have smaller percentages of reactions agreeing with the progress of a patient. Group 3 has a percentage of 73.7 and group 4 of 52.4.

Group 3 has these cases which show some monthly change in their progress, though it is not in a constant direction, and this suggests that the reaction to the test is influenced by a change in the activity of the disease. The group 3 cases which do not agree, five in number, all show variations in the extent of their reactions and it is possible that the agency which causes the clinical manifestations of tuberculosis to change takes a different time to act than the agency which causes the reaction to tuberculin to change. In this way although both general assessment and reaction marks are irregular, they may not be in exact agreement at the same time, as the period of one month between each observation may not allow each to react to the change in the condition of the disease.

This difficulty does not arise in the cases comprising groups 1 and 2, for in them the patients are showing a steady trend in one direction, which trend in all probability had lasted, or was an indication that it was going to last, for some time,

so that at any time during the investigation the general assessment marks and the reaction marks should show agreement.

Group 4 is composed of cases which are all clinically stationary and it is in this group that the smallest percentage of agreement between the condition of the patient and the extent of the reaction is shown. Agreement is only present in slightly over half the cases. Compared with the first two groups this is small and it is difficult to find a reason for it. It may be that there is a certain amount of variation in the reaction normally present when the disease is inactive just as D'Arcy Hart found an increased reaction to tuberculin present in non-tuberculous subjects on re-testing after an interval of a fortnight. This increase was attributed to hypersensitisation. This, however, does not seem a likely theory as all the cases in this group, which do not show agreement, have not got rising reaction marks, showing increased response to tuberculin. Also the tests in this investigation were done at monthly intervals and Lobban found no change in the reactions to tuberculin in non-tuberculous patients on re-testing after this period.

Whatever the reason, it would appear that there would need to be some activity present in the tuberculous manifestation for the reaction to the intradermal tuberculin test to be influenced in a way which would be of value in indicating the prognosis. Thus in the group 1 cases, there is steady improvement probably due to diminishing activity of the disease and a high proportion of these cases have a steadily increasing response to the test. Similarly in group 2, these cases are going downhill, some of them rapidly, owing to increasing activity of the tuberculous infection. Again there is a high proportion of these cases with their reaction to tuberculin agreeing with the progress of the patient; in this instance, the response to intradermal tuberculin injections is steadily less.

In group 3, where the patients all show an irregular course of progress, the percentage of cases with agreement between the course of the reaction extent and clinical progress is again

higher than group 4, comprised of stationary cases. The reaction marks of groups 3 and 4 are, unfortunately, too similar in form for any value to be obtained from them in estimating the prognosis of a patient. Group 3 is composed entirely of cases with irregular reaction marks but group 4 has such a small percentage of cases with steady reaction marks that without knowing the clinical progress of a patient, the course of the disease in a patient reacting irregularly to tuberculin could not be deduced.

It is not so with the cases in groups 1 and 2. For if a patient has a steadily increasing response to intradermal tests then it can be concluded with a fair expectation of success that the patient is improving and that the prognosis is good; and on the other hand, if there is a steadily decreasing response to the tests it suggests with almost equal probability that the patient is not improving and that the prognosis is bad.

If it is admitted that, at least in certain cases, the intradermal quantitative tuberculin test is of value in indicating improvement or otherwise in pulmonary disease the question arises "Is the test an indication of the extent of change?". An attempt has been made to answer this question in respect of the cases in groups 1 and 2.

THE TEST AS AN INDICATION OF EXTENT OF CHANGE.

If the difference in the general assessment marks is taken as a measure of the improvement in the condition of the patient over the period of four months, then this can be compared with the increase in the extent of the reaction as shown by the reaction marks. The information is obtained from Appendix 1 and tables 5 and 6 show the results. Those cases which do not show the reaction agreeing with the trend of the disease are, of course, omitted; the cases whose progress has necessitated the giving of a different dilution of tuberculin have also had to be omitted on account of the system of marks tending to show too large a difference.

The tables have been arranged so that the cases with a difference in general assessment marks of five and over are shown in a different column from those with a smaller difference. The implication is that those cases showing a wider change in their general assessment marks have altered more than those with a smaller difference. Five marks is chosen as a dividing line merely as a convenience to approximate the numbers in each group.

It will be seen from Table 5 that there are 10 cases in Group 1 with general assessment marks decreasing by 5 or over. These 10 cases have increases in their reaction marks amounting to 49, giving an average increase of 4.9 marks. Also it will be seen that the 11 cases in this group with a decrease of less than 5 marks in their general assessment figures have a total increase in their reaction marks of 60, giving an average increase of 5.4 marks.

Table 6 similarly, gives the figures for the Group 2 cases though it must be remembered that the difference in the reaction marks are decreased. The average figures are 3.7 marks for those cases with a difference of 5 or over in general assessment and 2.75 marks for those with a difference under 5.

DISCUSSION.

In the group 1 cases there is no relationship shown between the extent of the variation in reaction and the extent of progress of the patient. The average increase in reaction marks, indeed, for those cases showing the greatest improvement in their condition is less than for those showing less improvement.

With the group 2 cases, on the other hand, there is an increase of the average amount of decrease in the reaction marks in the cases showing the greatest amount of deterioration. The numbers in this group are small in comparison with those

in group 1 and no definite conclusion can be drawn from them.

The theory put forward above in connection with the group 3 cases would also explain the non-agreement of the extents of variation in reaction and progress. It was suggested that the general assessment marks and the reaction marks on one particular date might not both refer to the actual condition of the patient on that date. In other words, the variation in the reaction may agree with the clinical variation of some other period.

EXTENT OF REACTION TO THE INTRADERMAL TUBERCULIN TEST COMPARED WITH EXTENT OF X-RAY MARKINGS.

The suggestion has been put forward by Dickey[24] that there is a relationship between the sensitivity to the test and the extent of the markings in radiograms. An attempt has been made by the writer to prove or disprove the suggestion in the case of pulmonary tuberculosis.

Even if an X-Ray film had been taken each time a patient was tested, it would seem unnecessary to compare a series of films with a series of reactions. Accordingly, one reaction was chosen and the X-Ray film of the same, or near, date was compared with it. The reaction chosen was the first to which the patient reacted as there was invariably an X-Ray film available for a previous and not too far distant date.

Cummins & Walker[17] in their investigation of 100 pulmonary cases made use of a system of marks for the lesions shown in X-Ray films. This system with slight modification was used by the writer and was as follows:-

100 marks were allowed, divided in this manner: 40 marks for extent of disease, making 20 for each lung and 5 for each quarter of a lung; 40 marks for density, the grades being:-

Caseous	30-40 marks.
Fibro caseous	15-30 marks.
Fibrous	0-15 marks.

20 marks were allowed for character of the lesion, for example, presence of cavities, exudate, or adhesions.

In practice, it was found easy to assess in this way the lesions seen in an X-ray film, and in the last column of Appendix 1, the results of the examination will be found. Those cases having collapse treatment, either by artificial pneumothorax or thoracoplasty were not assessed owing to the natural difficulty in estimating the various characters of the disease. There are 22 such cases in the appendix and they are clearly indicated.

The method of comparing the extent of the reaction and the extent of the X-ray marking was to find the average X-ray mark for the cases reacting to the different dilutions of tuberculin for the first time, namely 1 in 1,000,000, 1 in 100,000; 1 in 10,000 and 1 in 1,000, and compare the figures. The dilution of tuberculin used was easily found from the first reaction mark given in Appendix 1 as over 80 marks indicated a reaction to a dilution of 1 in 1,000,000, over 60 marks, a dilution of 1 in 100,000, over 40 marks a dilution of 1 in 10,000, and over 20 marks a dilution of 1 in 1,000.

Table 7 gives the result of this investigation. As was to be expected, the groups are uneven owing to so few cases reacting to the higher dilutions of tuberculin, but the closeness of the averages of the X-ray marks to each other is striking. It is true that the group reacting to the lowest dilution of tuberculin, 1 in 1,000, has the highest average but the difference of one mark is negligible.

SUMMARY.

The pulmonary cases have been investigated under three main heads.

First, it has been shown that cases which are steadily improving have an increased response to repeated tuberculin injections in over 90% of instances. Also patients

whose condition is deteriorating show a diminishing response in 90% of instances to the repeated tests. The other pulmonary cases whose condition is either variable or stationary do not show such high agreement between their progress and the variations in the repeated tests.

Second, the results of the investigation into the extent of the variation in reaction being a measure of the change in the condition of a patient are inconclusive.

Third, the investigation into the relationship of sensitivity to the tuberculin test and the extent of the X Ray marking showed definitely that the dilution of tuberculin to which a patient reacted was not a guide to the character of the disease as shown in an X Ray film.

NON-PULMONARY PATIENTS.

Number and Type of Case.

The non-pulmonary patients, who received the series of four injections, numbered 74 and all were selected at random from the patients in Robroyston Hospital and Sanatorium at the time of the investigation. Table 8 gives the age and sex distribution of these cases. It will be seen that the majority of the patients are between the ages of 10 and 30 years and that female patients predominate though not so markedly as in the pulmonary patients.

The classification used for non-pulmonary cases of tuberculosis is that recommended by the Ministry of Health and recognises four classes. These are briefly

1. Tuberculosis of bones and joints.
2. Tuberculosis of abdomen.
3. Tuberculosis of other organs.
4. Tuberculosis of peripheral glands.

Multiple lesions are classified in the one group which is highest.

Tuberculosis of bones and joints by far predominates over other manifestations of the disease in hospital, and it is necessary to subdivide this class to get an idea of the type of case investigated. Table 9 gives the numbers of the different classes of case with the percentages. By the subdivision of the cases with bone and joint tuberculosis it is seen that no one type of case has an overwhelming majority over any other. These figures are only given to show that there was a variety of cases under investigation and that any results obtained were not due to one particular type of case.

METHOD OF COMPARISON.

As with the pulmonary cases, the difficulty of assessing the change in the condition of a patient again arises. With pulmonary patients changes in temperature, pulse rate, sputum and weight afford efficient guides. In the

case of non-pulmonary Tuberculosis patients, however, these are of little or no value. Temperature may sometimes be a guide, but the vast majority of non-pulmonary patients have a steady normal temperature for long periods, once it has settled after admission. Pulse rate by itself is of little significance and like temperature it tends to show very little change over a four months period. Unfortunately, or fortunately, there is no such definite guide as amount of sputum and its bacillary content, and while change in weight is probably present, the nature of the illness usually precludes this from being measured.

In non-pulmonary cases improvement is judged, among other things, by the drying up of abscesses, the healing of sinuses and the lessening activity of the disease as seen in radiograms. When the conditions of a patient is deteriorating new abscesses may form, sinuses continue to discharge, paraplegia become evident and a radiogram show activity. These methods are not, of course, all applicable to each type of non-pulmonary tuberculosis and even if they were, they would not be of much value in an investigation of this kind where very little change might be evident over a period of four months.

Accordingly, no definite numerical assessment, as in the case of pulmonary patients, appearing possible to the writer, a more general method of classification has had to be used.

After observation over the period of four months during which the tests were performed each case was allocated to one of four groups, according as their condition showed marked improvement, improvement, deterioration or remained stationary. The change in each patient was estimated by considering those symptoms and signs applicable to the type of case, and the particular manifestation of tuberculosis from which that patient was suffering. The cases in the four groups thus formed have now to be compared with the changes in their

reaction to the tuberculin test over the same period. The method of measuring the extent of reaction requires no alteration and will be the same as that used in the case of pulmonary patients.

In Appendix 2 will be found a list of the non-pulmonary patients tested. The first three columns are only for identification purpose, while the next four under the heading "Reaction" contain the appropriate marks, according to the method explained before, for the result of each test and are arranged in order of time. In the next column the site of the lesion is noted and in the last column under the heading "Remarks" any definite change in the manifestations of the disease or in the treatment is recorded. If there is no such change this column is left blank. For convenience the cases are grouped together according to the change, if any, in their condition and these divisions are clearly shown in the Appendix.

EXAMINATION OF RESULTS.

Group 1. The first group consists of 16 cases all of which showed marked improvement in their condition during the four months which they were observed. On examination of the reaction marks of these cases it is found that in 14 a steady increase is shown. The two exceptions are numbers 13 and 16. Case number 13 very definitely does not agree as the reaction is steadily decreasing but case number 16 shows an increase at the third test only to fall again at the fourth.

Agreement with the clinical condition is thus present in 87.5% of the cases in this group.

Group 2. This is the largest group as it comprises 36 cases and all the members are classified as showing improvement. The patients in this group differ from those in group 1, in that the improvement shown is not so marked. In the group 1 cases the improvement shown by the patient is definite and there is no mistaking the clinical improvement in the disease.

The patients in group 2, however, resemble rather those in group 3 of the pulmonary cases. Their condition is not stationary, it may show variation, yet taken over a period of four months it can be fairly said that there is some improvement. Accordingly when the reaction marks are examined for those showing agreement with the clinical findings, provided the extent of the reaction is greater in the second, third and fourth, than in the first, then the marks are taken as agreeing. It will be seen from the marks in Appendix 2 that this condition is fulfilled in 26 out of the 36 cases, the exceptions being numbers 18, 24, 27, 34, 35, 37, 43, 46, 51, 52.

The agreement between the clinical condition and the variation in the extent of the reaction to the test is therefore 72.2%.

Group 3. This is a very small group as the number of non-pulmonary cases which can be definitely recognised as deteriorating over a period of four months is limited. All the patients included in this group were such cases, four had spinal disease with radiograms still showing activity, one had active disease of the sacro-iliac joint, and one died of abdominal tuberculosis before the four tests were completed.

In all of these cases the reaction marks, as shown in the appendix, were steadily decreasing.

Group 4. There are 16 cases in this group, numbered 59 to 74 inclusive in Appendix 2. The condition of these cases remained stationary throughout the investigation. If a difference of two marks is permitted in the reaction marks for unavoidable errors then the extent of reaction has remained stationary in only 7 cases. These cases are numbered 60, 63, 64, 66, 68, 69 and 71. None of the other cases show a steady trend in any direction, but show variations greater than two marks.

43.7% only of the cases in this group have steady reactions to the tuberculin test.

DISCUSSION.

The results obtained for non-pulmonary cases are very similar to those for pulmonary cases. There are again two groups out of four showing considerable agreement between the variation in reaction to the tuberculin test and the clinical change in the patient. Owing to the nature of the disease the groups are differently named but in the main they correspond.

Group 1 contains the cases showing marked improvement and this group corresponds fairly closely with the cases in group 1 of the pulmonary cases. These cases are all definitely improving and there is a high percentage (87.5) of these with an increasing sensitiveness to the intradermal tuberculin test.

The cases in group 3 comprise those which are steadily going downhill and in each case, without exception, they show a decreasing response to the test.

The group 2 cases though taken as showing improvement over the period of investigation, are rather similar to the unstabilised cases comprising group 3 of the pulmonary cases. The percentage of those showing an increase in sensitivity to the test is 72.2, which is relatively high but not of much practical value.

The stationary cases in group 4 show very poor agreement between the clinical condition and the test. Less than half have a constant reaction.

The results for non-pulmonary cases of tuberculosis seem to bear out what was found in the pulmonary cases, that the test to show agreement with the clinical change requires some change, either lessening or increasing, in the activity of the disease.

The question of whether the extent of variation in the reaction is an indication of the amount of change in the condition of a patient again arises and is more easily decided

owing to the simpler method of classification.

In Appendix 2, it can be seen that in every case in group 1 with steadily rising reaction marks the difference is never less than five while in the cases in group 2, showing a slighter improvement, only six have a difference between their first and last reaction marks of more than four. The group 3 cases, which were all deteriorating markedly, all show a difference in their marks of at least six.

SUMMARY.

The 74 non-pulmonary cases of tuberculosis were divided into four groups according to their clinical change.

87.5% of the cases with marked improvement showed an increasing sensitiveness to similar intradermal tuberculin tests at monthly intervals. Of the cases showing improvement only 72.2% had an increased sensitivity. Those cases whose condition was steadily deteriorating all showed a decreasing sensitiveness to the repeated tests. Only 43.7% of the cases showing no clinical change had constant reactions to the tests.

The extent of the change in the reaction would appear to be greater when the condition of the patient is also changing more markedly.

SUPERSENSITIZATION BY TUBERCULIN.

It is very important in an investigation such as this, where repeated tuberculin tests have been given, to consider the subject of super-sensitization before drawing conclusions from the results.

D'Arcy Hart[8] states that "in a primary positive reactor an increase of response, due to sensitization, frequently occurs if the test is repeated" and quotes other workers, using the intracutaneous test as agreeing. The same writer also found evidence of a period of decreased reactivity lasting for a few days after the first intradermal test.

Referring to the use of tuberculin tests in prognosis D'Arcy Hart[8] states "when tuberculin tests are repeated at intervals during the course of clinical tuberculosis, an increase or decrease in intensity of the response may be obtained. These changes may be due to positive or negative sensitization by the previous dose, as occurs in clinically non-tuberculous individuals; or they may be dependent upon variations in the patients resistance, in the activity of the disease process, or in extrinsic factors such as intercurrent infections; or, finally, if an inaccurate method is used, they may be merely the result of a chance or deliberate variation in technique".

Let each of these possibilities be examined in connection with this investigation.

1. Positive or negative sensitization by the previous dose, as occurs in clinically non-tuberculous individuals.

The reference to non-tuberculous individuals is due to D'Arcy Hart finding 13 out of 18 such cases having an increased reaction to an identical intradermal test repeated in a fortnight. Lobban[6], on the other hand, found that 53 non-tuberculous individuals out of 66 retested at monthly intervals with the same test had identical reactions. This

would appear to show that hypersensitization, if it exists, does not persist for one month, at least in non-tuberculous cases.

In this present investigation it has been shown that practically all the patients with increasing reactions to repeated tests at intervals of one month show clinical improvement. Also, practically all the patients who have decreasing reactions to the tests are deteriorating. To the writer it appears logical to conclude that, if positive and negative sensitization exist, positive sensitization occurs in those patients who are improving and negative sensitization in the patients who are deteriorating. On the other hand, it is probable that with the high dilutions used in this investigation to obtain a reaction, hypersensitization has disappeared by the end of one month.

2. Variation in the patients resistance, in the activity of the disease process, or in extrinsic factors such as intercurrent infections.

It is difficult to differentiate between the first two factors as a cause of variation in reaction, as the resistance of a patient may depend very much on the activity of the disease.

Intercurrent infection was not present in any of the cases during the period of investigation.

Seasonal variation is an extrinsic factor which is mentioned by Burhans[9], who quotes the work of Hamburger and Pezer. These workers found that children showed stronger reactions in the Spring than they did in the Autumn. Another worker, Schniffenkötter, also quoted by Burhans, found that adults had less intense reactions in Winter and early Spring. These results do not agree but in any case the question of seasonal variation scarcely arises in this investigation as each patient was tested over a period not exceeding four months and all the tests were done within six consecutive months.

3. The result of a chance or deliberate variation in technique.

It must be remembered that the quotation referred to any skin test. The intradermal tuberculin test which was used throughout this investigation, is a quantitative one and accurate repetition of a previous test can be carried out. The possibilities of chance or deliberate variation can, therefore, be disregarded.

As it has been shown that extrinsic factors do not enter into this investigation at least: that chance, or deliberate, variation in technique was not possible or attempted: that positive and negative sensitization, if they exist, are related to the clinical change in a patient: it would seem that a reasonable cause of change in the intensity of the response to repeated tests is variation in the patients resistance which would most likely be caused by variation in the activity of the disease process.

CONCLUSIONS.

1. The prognosis in a case of tuberculosis, pulmonary or non-pulmonary, is good if the patient shows an increasing response to quantitative intradermal tuberculin tests repeated at intervals of one month.
2. The prognosis in a case of tuberculosis, pulmonary or non-pulmonary, is grave if the patient shows a diminishing response to quantitative intradermal tuberculin tests repeated at intervals of one month.
3. The extent of variation in response to the tests appears to be a guide to the extent of steady change in the condition of a non-pulmonary case, but not definitely so in a pulmonary case.
4. Unstabilised cases of pulmonary tuberculosis tend to have an increased response to the intradermal tuberculin test as they improve and a decreased response as they deteriorate.
5. Non-pulmonary cases of tuberculosis showing slight improvement tend to have an increased response to the

intradermal tuberculin test as they improve.

6. Pulmonary and non-pulmonary cases of tuberculosis showing no change in their condition do not tend to have unvarying responses to repeated intradermal tuberculin tests.

7. The highest dilution of tuberculin to which a patient reacts is not a guide to the character of the tuberculous disease as seen in an X Ray film.

TABLES.

TABLE 1. Showing marks given for reactions to different dilutions.

Dilution.	Size of Reaction in c.m.	Marks.
1 in 1,000,000.	10	100
"	8	96
"	6	92
"	4	88
"	2	84
1 in 100,000.	10	80
"	8	76
"	6	72
"	4	68
"	2	64
1 in 10,000.	10	60
"	8	56
"	6	52
"	4	48
"	2	44
1 in 1,000.	10	40
"	8	36
"	6	32
"	4	28
"	2	24

TABLE+2. Form of table used for collecting results.

NAME		WARD.		AGE	OCCUPATION	
DATE						
DILUTION REACTION						
TEMPERATURE PULSE WEIGHT SPUTUM (1) Amount (2) Bacilli						
TREATMENT. General Sanatoria Surgical Art. Pneumothorax						
X Ray						
ABSCESS SINUS PARAPLEGIA						
REMARKS						

TABLE 3. Age and sex distribution of pulmonary cases.

	0 -	10 -	20 -	30 -	40-60 yrs.	TOTALS.
Female.	1	21	31	5	4	62
Male	4	5	1	2	2	14
Totals	5	26	32	7	6	76

TABLE 4. Classification of cases with percentages.

Class	No.of Cases.	%
T.B. -	14	18.4
T.B. + Gr.1	0	-
T.B. + Gr.2	43	56.6
TB. + Gr.3	19	25.

TABLE 5. Comparison of progress of pulmonary patients (group 1) with extent of variation in reaction to tuberculin test.

Case No.	Diff. in general assessment marks.	Diff. in reaction marks.	Case No.	Diff. in general assessment marks.	Diff. in reaction marks.
1	11	5	2	3	5
3	5	6	7	2	4
4	6	6	8	4	4
6	5	5	11	2	7
10	8	2	13	4	4
12	5	2	15	3	8
14	6	9	16	2	2
17	5	5	18	3	6
21	6	3	24	2	4
22	5	6	25	2	10
			26	4	6
Totals	10	49		11	60.

TABLE 6. Comparison of progress of pulmonary patients (group 2) with extent of variation in reaction to tuberculin test.

Case No.	Diff. in general assessment marks.	Diff. in reaction marks.	Case No.	Diff. in general assessment marks.	Diff. in reaction marks.
27	10	3	29	3	6
28	8	5	30	3	2
36	5	3	33	4	1
			34	3	2
Totals	3	11		4	11

TABLE 7. Comparison of X Ray markings with dilutions of tuberculin.

First reaction mark.	No.of cases in group.	Total X Ray marks of group.	Average X ray marks of group.
Between 80 and 100 (1 in 1,000,000)	3	145	48
Between 60 and 80 (1 in 100,000)	3	140	47
Between 40 and 60 (1 in 10,000)	36	1710	48
Between 20 and 40 (1 in 1,000)	12	590	49.

TABLE 8. Age and sex distribution of non-pulmonary cases.

	0 -	10 -	20 -	30 -	40-60 yrs.	Totals.
Female	2	17	20	7	2	48
Male	1	13	10	0	2	26
Totals	3	30	30	7	4	74.

TABLE 9. Classification of non-pulmonary cases with percentages.

Site of lesion.	No.of cases.	%
Spine	24	32.3
Sacro-iliac	14	19.0
Knee	15	20.3
Other bone or joint	9	12.2
Abdomen	6	8.1
Other Organs	2	2.7
Peripheral glands	4	5.4

APPENDIX 1.

General assessment, reaction and x-ray marks of all pulmonary cases. They are arranged in four groups according to the trend of general assessment marks. A.P. denotes artificial pneumothorax treatment and Thor. denotes thoracoplasty operation.

Number.	Initials.	Age.	Gen. Assessment 1	2	3	4	Reaction. 1	2	3	4	X Ray Assessmt.
			Group 1.		Improving.						
1	M.C.	15	21	14		10	44	48		49	A.P.
2	M.G.	17	21	21	20	18	30	30	34	35	45
3	N.B.	14	35	33	32	30	27	30	30	33	A.P.
4	E.B.	15	30	29	26	24	46	49	52	52	A.P.
5	M.G.	16	8	8	7	6	34	38	45	50	A.P.
6	J.T.	19	23	23	18	18	43	45	48	48	A.P.
7	M.A.M.	18	19	19	18	17	48	48	49	52	40
8	B.R.	17	14	13	12	10	44	44	46	48	50
9	S.B.	22	16	15	14	14	33	34	46	46	A.P.
10	M.B.	22	25	24	18	17	45	45	46	47	40
11	J.B.	22	14	13	12	12	46	50	52	53	60
12	B.B.	28	23	21	19	18	44	44	45	46	45
13	N.C.	21	31	30	27	27	45	48	48	49	65
14	J.M.	27	36	24	30	30	26	28	32	35	25
15	E.O.D.	29	16	15	13	13	26	29	34	34	40
16	E.H.	23	55	55	53	53	26	26	27	28	50
17	M.G.	25	23	20	18	18	25	29	30	30	45
18	M.M.L.	23	20	20	19	17	25	26	29	31	40
19	Mrs.A.	27	17	15	15	14	45	40	36	29	45
20	M.J.	26	24	22	20	18	45	52	52	72	35
21	E.M.	34	27	26	26	21	43	44	45	46	Thor.
22	I.McD.	42	50	48	45	45	44	48	50	50	55
23	R.D.	9	36	36	35	34	47	51	48	53	45
24	B.K.	7	12	10		10	48	51		52	35
25	J.F.	14	16	15		14	50	54		60	55
26	J.A.	41	41	41	39	37	45	47	48	51	65

Number.	Initials.	Age.	Gen. Assessment 1	2	3	4	Reaction. 1	2	3	4	X.Ray Assessmt.
			Group 2.		Deteriorating.						
27	M.McA.	18	30	35	40		49	49	46	Dead	60
28	M.W.	19	32	36	40		45	44	40	Dead	65
29	M.W.	22	41	41	42	44	30	28	28	24	70
30	C.McA.	20	45	46	48		26	24	24	Dead	A.P.
31	S.C.	24	18	18	21	22	83	66	64	60	35
32	M.McL.	28	30	30	32	37	45	45	40	28	A.P.
33	M.Q.	29	33	34	37		46	45	45	Dead	75
34	Mrs.G.	39	36	38	39	39	46	46	44	44	A.P.
35	M.B.	39	35	35	36	36	48	49	48	50	60
36	Mrs.F.	43	48	50	53		27	25	24	Dead	A.P.
			Group 3.		Unstabilised.						
37	M.A.	19	15	17	17	15	49	46	54	51	55
38	M.F.	16	9	8	14	20	64	70	60	48	A.P.
39	I.H.	18	33	25	26	22	46	49	46	51	A.P.
40	M.P.	17	44	39	45	42	31	29	30	31	60
41	C.S.	15	22	19	19	26	45	49	49	45	A.P.
42	E.C.	16	35	32	30	34	64	68	71	66	65
43	H.O.	15	39	36	40	40	29	36	30	30	60
44	M.W.	19	20		22	21	63		68	65	50
45	E.R.D.	29	37	35	30	33	24	28	34	31	Thor.
46	A.K.	24	46	47	44	44	45	44	46	46	70
47	M.M.	24	20	17	15	18	30	32	40	30	Thor.
48	B.W.	23	42	40	43	43	25	26	29	26	80
49	R.S.	24	40	40	38	39	44	44	46	45	40
50	N.C.	40	13		14	13	50		48	50	A.P.
51	A.K.	31	40	41		38	30	28		29	A.P.
52	W.T.	30	19	16	19	17	46	52	46	48	35
53	T.McQ.	14	27	29	27	25	48	46	48	50	50
54	R.C.	22	34	33	32	34	50	50	45	49	50
55	H.M.	57	15		22	15	49		44	49	40
			Group 4.		Stationary.						
56	P.B.	8	15	15	15	15	66	73	70	64	25
57	E.G.	14	21	20	20	20	44	46	44	44	45

Number.	Initials.	Age.	Gen. Assessment. 1	2	3	4	Reaction 1	2	3	4	X-ray Assessm't
58	M.P.	18	19	19	19	19	46	47	47	47	25
59	M.R.	17	12	12	12	12	46	50	51	51	A.P.
60	Mrs.H.	29	15	15		15	45	47		46	A.P.
61	E.M.	23	15	15	15	15	46	47	40	45	A.P.
62	E.R.	24	19	19	20	19	86	88	86	87	50
63	M.C.	26	32	29	29	29	27	29	30	25	A.P.
64	S.F.	25	21	21	21	23	30	36	25	33	25
65	M.G.	24	20		20	20	44		45	44	65
66	M.McF.	29	15	15	15	15	84	76	70	46	60
67	M.G.	20	13	13	13	13	45	45	46	47	35
68	M.H.	26	22		22	22	44		44	44	50
69	Mrs.B.	49	39	40	39	39	24	26	29	26	50
70	J.McQ.	7	13	13	13	13	54	52	52	52	35
71	R.B.	8	13	13	13	13	48	51	53	48	35
72	A.C.	13	14	13	13	13	48	48	47	49	35
73	W.T.	12	12	12	12	11	48	51	54	59	35
74	D.T.	11	15		15	15	55		50	52	35
75	J.I.	35	20	20	20	20	45	44	43	44	50
76	J.M.	35	38	38	38	38	44	44	44	45	30

APPENDIX 2.

Reaction marks of all non-pulmonary patients. The cases are arranged in four groups according to the change in their condition.

Number.	Initials.	Age.	1	2	3	4	Site of Lesion.	Remarks.
	Group 1.		MARKED IMPROVEMENT.					
1.	A.C.	16	48	52	53	54	Spine	
2	K.C.	24	45	46	48	52	Spine	Psoas dry.
3	J.McC.	20	65	65	70	70	Spine	Plaster jacket.
4	G.F.	9	45	47	54	54	Spine	Up in plaster.
5.	H.Y.	16	45	48	53	53	Spine	Abscess dry.
6.	M.H.	21	63	63	64	71	Sacro-iliac	
7.	L.F.	29	63	63	70	70	Sacro-iliac	
8	A.D.	16	48	52	54	56	Sacro-iliac	Sinus scraped.
9.	J.McG.	20	46	46	48	52	Sacro-iliac	Centalmid jkt. Up.
10.	L.B.	17	46	51	54	55	Knee	Splint removed.
11	C.H.	15	46	47	48	52	Knee	
12	R.F.	11	46	54		54	Knee	Certalmid Jkt.
13	N.B.	20	84	80	63	66	Ankle	
14	B.C.	19	44	45	47	49	Abdomen.	
15	C.S.	15	44	49	50	50	Abdomen.	
16	J.B.	17	50	49	53	49	Abdomen	
	Group 2.		IMPROVEMENT.					
17.	M.McC.	7	84	84	86	87	Spine	
18.	B.D.	16	84	80	65	68	Spine	
19	Mrs.M.	26	47	47	49	50	Spine	
20	I.T.	29	64	65	70	66	Spine	Certalmid Jkt.
21	Mrs.McD.	50	46	48		49	Spine	
22	W.B.	11	48	50	54	51	Spine	Plaster jacket. Up.
23	J.B.	12	45	48	48	49	Spine	
24	J.F.	43	48	50	42	46	Spine	
25	P.G.	28	46	52	47	50	Spine	
26	E.McG.	24	45	50	48	48	Sacro-iliac	Albuminuria cleared
27	A.S.	22	44	42	29	32	Sacro-iliac	Abscess dry

Number.	Initials.	Age.	1	2	3	4	Site of Lesion	Remarks.
28	J.M.	12	47	49	48	51	Sacro-iliac	
29	S.S.	33	45	47	50	48	Hip.	Sinus healed
30	J.McC.	26	64	65	70	65	Hip.	
31	A.C.	15	46	50	52	49	Hip.	Appendicectomy
32	R.W.	14	48	50	52	51	Hip.	Abscess dry
33	B.McD.	22	44	47	50	48	Knee	
34	J.N.	27	70	68	73	67	Knee	
35	M.McM.	47	68	62	49	50	Knee	Excision of knee
36	P.McC.	18	48	50		52	Knee	
37	A.K.	23	54	50	52	51	Knee	
38	A.L.	25	48	64	70	60	Knee	Abscess dry
39	W.McF.	23	44	48	47	48	Knee	
40	D.M.	49	47	52	70	65	Knee	
41	A.K.	18	46	53	49	56	Knee	
42	M.L.	16	64	68	65	69	Wrist	
43	H.G.	16	52	53	47	54	Wrist	Sinus healed
44	G.Z.	16	68	68	77	69	Hand	Sinus healed
45	P.B.	25	46	47		48	Ribs	Sinus healed
46	G.M.	19	66	62	66	68	Abdomen	
47	M.B.	17	51	51		55	Abdomen	Sinus of neck healed
48	Mrs.McM.	38	29	33	32	33	Kidney	
49	B.McK.	6	44	52	52	49	Face	
50	R.McC.	16	48	54	52	54	Neck	
51	E.Y.	17	68	64	69	68	Neck and Axilla.	Abscess dry.
52	T.D.	16	67	64	70	67	Wrist	Sinus healed.
	Group 3. DETERIORATION.							
53	S.M.	16	84	80	70	60	Spine	Disease active
54	F.McI.	21	68	60	51	49	Spine	Disease active
55	F.L.	29	63	60	49	52	Spine	Disease active
56	Mrs.McM.	33	68	62	50	51	Spine	Disease active
57	A.C.	23	46	46	45	40	Sacro-iliac	Disease active
58	B.M.	32	45	40	24		Abdomen	Died

Number.	Initials.	Age.	1.	2.	3.	4	Site of Lesion.	Remarks.
		Group 4.	STATIONARY.					
59	E.S.	24	65	62	66	66	Spine	
60	K.McI.	37	47	48	48	47	Spine	
61	Mrs.H.	31	26	30	27	27	Spine	
62	I.McL.	16	50	50	46	51	Spine	Plaster jacket.Up.
63	J.W.	20	50	52	52	52	Spine	
64	A.McD.	12	84	83		84	Spine	
65	C.K.	21	27	24	27	27	Sacro-iliac	
66	Mrs.L.	28	48	50	49	48	Hip	
67	S.G.	21	64	62	67	66	Knee	
68	J.S.	23	50	50	50	52	Knee	Abscess dry
69	M.D.	20	84	84		85	Knee	Leg amputated.
70	J.C.	16	51	46		50	Elbow	
71	I.C.	18	66	64	66	65	Ankle	
72	J.Y.	18	50	46	50	54	Ankle	
73	H.R.	24	88	84	87	88	Glands of Neck.	
74	C.C.	37	49	47	54	52	Glands of Neck.	

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