THE PRESENT VALUE OF THE TUBERCULIN TEST. WITH PARTICULAR REFERENCE TO ITS CLINICAL AND EPIDEMIOLOGICAL APPLICATIONS.

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PREFACE.

Tuberculin tests have, in recent years, come to be used with increasing frequency. Our knowledge of the test has been enlarged and the scope of the test widened. In this the Tuberculosis Officer is particularly concerned. He may use the tuberculin reaction in three ways :- in clinical diagnosis of individual patients, in tuberculosis "contact" examinations, and in the estimation of the level of tuberculous infection in selected groups of the population.

These three aspects of tuberculin testing will be discussed later, but it is obvious, without further comment, that the value of the first two procedures depends essentially upon the frequency of tuberculous infection, with its resultant tuberculin sensitivity, in the group of the population to which the patient or "contact" belongs. Partly for this reason, and partly to estimate the tuberculosis problem confronting the health services, many tuberculin surveys of groups of persons, and communities, have been undertaken. The vasy majority of these epidemiological surveys have been made on the Continent and in the United States.

It has appeared to the writer that a review of the relevant literature, and a discussion of the results of recent tuberculin testing in English areas might be useful in estimating the value of the tuberculin test in this country at the present time. It was also desired to ascertain whether any change had occurred in the frequency of tuberculous infection and sensitisation.

As part of the work, the relative values of the various tuberculin tests in common use were investigated.

This preface would not be complete without an acknowledgement of the considerable help obtained by the

author from the writings of Dr. P.D'Arcy Hart, whose report on the tuberculin test to the Medical Research Council in 1932 has remained the most important work of its kind performed in the United Kingdom.

C O N T E N T S .

DEFINITIONS.

Some terms used in the following pages require explanation. The definitions given are not beyond criticism, but may help to make clear the sense in which the terms are used.

"Clinical" or "manifest" tuberculosis means significant tuberculous disease with evidence of activity.

"Infection" refers to infection by the tubercle bacillus. It does not in this work usually imply the presence of an active focus or of clinical tuberculosis.

"Tuberculisation" is the state following upon infection by the tubercle bacillus, in which sensitisation to tuberculin may be demonstrated.

"Infected population" includes clinical cases, and those persons merely infected, and not suffering from clinical tuberculosis.

"Incidence of tuberculous infection in a community" is the percentage of the population that is infected.

"Attack-incidence of tuberculous infection in a community" is the percentage of the population that has at any time been infected.

"Incidence of tuberculin sensitisation, or sensitivity in a community" is the percentage of the population capable of producing a positive tuberculin reaction.

Dosage of Tuberculin.

0.1cc.	of	1:100,000	Old	Tuberculin	= 0.001 mg.	Old	Tuberculin
"	"	1:10,000	"	"	= 0.01 mg.	"	"
"	"	1:1,100	"	"	= 0.1 mg.	"	"
"	"	1:100	"	"	= 1.0 mg.	"	"
"	"	1:10	"	"	= 10.0 mg.	"	"
"	"	1:1	"	"	= 100.0 mg.	"	"

0.1cc. of 1st strength Purified Protein Derivative
= .00002 mg. Purified Protein Derivative.

0.1cc. of 2nd strength Purified Protein Derivative
= .005 mg. Purified Protein Derivative.

CHAPTER I.

The Positive Tuberculin Reaction.

It is generally agreed that the positive tuberculin skin reaction is the result of an existing state of hypersensitivity of the tissues to the products of the tubercle bacillus. The characteristic features of the skin reaction are the production, after injection of very small amounts of tuberculin, of a comparatively large area of erythema and oedema. The onset of the reaction is usually delayed, the maximum findings being present forty-eight, or seventy-two hours, after the injection.

Under ordinary conditions this hypersensitivity of the tissues is due to a previous tuberculous infection of the subject, with a resultant state of allergy.

In this country Old Tuberculin is commonly used to elicit reactions. This is a heat-concentrated filtrate of the products of growth of tubercle bacilli in a synthetic medium, and is standardised against an International Standard tuberculin.

The Structure of Tuberculin.

The structure of tuberculin has excited continued interest since its introduction by Koch fifty years ago. It has been hoped that knowledge of its chemical structure would provide a key to its biological activity, and a solution to many problems in tuberculosis. Tuberculin has proved to be highly complex, and various substances have been isolated by different workers. These can conveniently be discussed under two headings (a) Protein, and (b) Non-protein constituents.

(a) Protein constituents.

Koch himself suggested that the specific toxic substance he was introducing was protein in nature. He was followed by Hammerschlag (1891), one of the first to isolate protein as a constituent of the tubercle bacillus.

Many attempts at analysis of tuberculin followed, and various proteins were claimed to have been isolated, e.g. albumen, globulin, mucin, nucleoprotein, and proteose.

These protein fractions were characterised by being more or less potent tuberculins. Indeed it was found that the protein content was associated with the tuberculin activity, and in synthetic protein-free culture media, tuberculin activity could only be demonstrated about the same time that protein appeared, elaborated by the tubercle bacillus in its growth (Long,1926). If the protein were removed from the preparation by precipitation, the tuberculin activity was associated with the precipitate. In purified protein fractions, the potency was parallel with the nitrogen content, and digestion of the protein by pepsin and trypsin destroyed the potency, as the protein molecule was broken down (Seibert,1941).

Seibert, in particular, has "isolated" many substances, or mixtures of substances, using ammonium sulphate, and trichloracetic acid to precipitate unheated culture filtrates. These preparations, of a protein-like nature, were highly potent and, in addition to their tuberculin activity, were able to produce the "Arthus phenomenon" in guinea pigs, and precipitins in rabbits. They were therefore antigenic in character, and were able to produce sensitisation in non-tuberculised subjects (Seibert,1933).

Some controversy exists on this question of the sensitivity produced by antigenic tuberculins. It is not usually conceded that these can produce genuine specific hypersensitivity, identical with that following upon infection, or the injection of heat-killed tubercle bacilli (Rich,1944).

In a personal communication, W.Pagel suggests that the sensitisation produced by antigenic tuberculins, is anaphylactic in nature, and restricted to the particular protein contained in the tuberculin preparation that is used.

The molecular weights of the protein substances obtained by Seibert varied, the smaller the weight, the less marked being the antigenic character. Since it is desirable that tuberculin preparations should be unable

to produce sensitisation to themselves, but be capable only of detecting the specific hypersensitivity following tuberculous infection (Aronson and Nicholas, 1933), Seibert developed the use of a protein-like fraction obtained after trichloracetic acid precipitation of a steamed evaporated culture filtrate. This preparation, a crystalline, water-soluble powder, was the substance of lowest molecular weight, which would produce a tuberculin reaction in man. Having lost its antigenic properties almost completely during its treatment, "it was incapable of producing sensitisation". In structure, it was probably a complex polypeptide. As Purified Protein Derivative (Seibert,1934), it has been widely used in the Mantoux test, particularly in the United States, and in the tuberculin testing of cattle.

Using advanced techniques, Seibert et al. (1938) succeeded in isolating protein fractions, which appeared to be practically homogeneous in character, with no admixture of other substances. A new preparation of Purified Protein Derivative, twice as potent as the old one, was developed as a result of this investigation.

It is now probable that a very complex system of protein molecules exists in tuberculin. Differing methods of preparation and isolation produce differing protein fractions, which vary in the proportions of active protein, inactive protein, and non-protein constituents, and in their potency, toxicity and antigenicity. The separation of particular fractions can be repeated, if the same technique is used, and the same method of culture. Different protein fractions vary in the proportion of active protein contained, and in the amount of "denaturation" of the protein which has occurred during isolation (Seibert,1941).

(b) Non-protein constituents.

This account of the non-protein constituents is based mainly on the work of Anderson et al.(1943). They consist largely of phosphatide, acetone-soluble fat, and a so-called wax. All these contain a number of chemical compounds specific to the tubercle bacillus and unknown elsewhere. Although of interest, it is unlikely that these substances play much part in the tuberculin reaction, and their description will therefore be brief.

The phosphatide contains a new type of glucoside linked with fatty acids. The glucoside on hydrolysis yields mannose, inositol, and hexose, and an organic phosphoric acid, possibly glycerophosphoric acid. The fatty acids are composed of ordinary fatty acids, with two new ones, tuberculostearic acid, and phthioic acid.

The acetone-soluble fat is composed of fatty acid esters of the disaccharide, trehalose, and also contains the pigment phthiocol.

The so-called wax is a mixture of several compounds, the principal being an ester of a specific polysaccharide with mycolic acid.

These lipoid fractions on injection into animals produce cellular reactions similar to tuberculous lesions. The phosphatide and phthioic acid in particular produce monocyte and epithelioid cell reactions. These reactions however, have been attributed by McCarter and Watson (1942) to protein contamination. The skin reaction produced by the polysaccharide fraction is identical with the tuberculin reaction, and the large amount of polysaccharide required contains sufficient protein to produce an ordinary tuberculin reaction. The close association of these non-protein constituents with the protein in tuberculin, was the reason for the variety of proteins which were claimed to have been isolated in earlier years.

It will be seen from the above description that our knowledge of the structure of tuberculin is extensive, and has progressed much in recent years. The main difficulty in the analysis of the highly complex system composing tuberculin is the fact that since substances cannot be obtained in the absolutely pure state (Rich, 1944), investigation of properties is hampered by the presence of potent contaminants. There is no doubt however that the main factor in producing the tuberculin reaction is protein in character.

Relation of Old Tuberculin to tuberculin-protein.

Since the various forms of tuberculin-protein may be derived from Old Tuberculin, it might be thought that the latter also showed their characteristics. In particular, it might be thought that Old Tuberculin was antigenic and could sensitise an uninfected individual to subsequent injections of tuberculin. The graded tuberculin test would then, of course, become useless, if not sometimes dangerous.

Some workers have succeeded in obtaining a cutaneous reaction to Old Tuberculin after repeated injections of large amounts of the preparation into uninfected animals (Zinsser and Tamiya,1926). These reactions were inconstant and slight in character, and distinguishable from the typical reaction due to true hypersensitiveness,(Baldwin et al.,1927). Most writers agree that true tuberculin allergy, with its typical skin response, has not been produced by the previous injection of Old Tuberculin into uninfected subjects (Tytler,1930).

This discrepancy between the properties of Old Tuberculin and some of its derivatives is probably to be explained on the ground of dilution, the quantities of the various protein constituents injected in a usual test dose being so small that they fail to act as antigens and do not produce sensitisation. In addition the heat concentration of the culture filtrate in the preparation of Old Tuberculin may "denature" the protein substances, changing them into simpler bodies lacking antigenicity.

Mode of origin of Tuberculin.

The mode of origin of tuberculin has always been doubtful. It was unclear whether tuberculin was a metabolic or disintegration product of the tubercle bacillus in its growth, or whether it was present as such in the intact bacillus.

Wong (1940) therefore prepared a tuberculin from autolysed bacterial bodies. (A special technique was used to promote rapid autolysis of the culture). The

autolysate consisted mainly of bacterial proteins, without the metabolic products which occur in solution in ordinary culture, and partially compose ordinary tuberculin. The autolysate tuberculin proved to be as potent as Purified Protein Derivative, and to have comparable physical, chemical, biological and antigenic (complement-fixing) properties.

It seems likely then that tuberculin-protein is identical with the protein composing the body of the bacillus (tuberculoprotein) and is produced as an autolysate. This was also the opinion of Corper and Cohn (1943) who suggested that intracellular enzymes might be responsible for the autolysis.

CHAPTER 2.

Tuberculin Tests.

In the years since Koch introduced the subcutaneous tuberculin test, (1890,1891), using the allergic response of individuals infected by the tubercle bacillus as an aid in the diagnosis and treatment of tuberculosis, very many tuberculin tests and modifications have been described.

It is proposed here to discuss only the more important of these, giving particular attention to the more recent methods.

Koch himself had great faith, fully justified, in the future of the tuberculin test. Wilkinson (1912) quotes him as saying "I believe I am not going too far in assuming that tuberculin will, for the future, constitute an indispensable agent in diagnosis. By means of it, one will be in a position to diagnose doubtful cases of incipient phthisis even when, on account of the absence of bacilli, or elastic fibres, or regular physical signs, we cannot obtain certain information concerning the nature of the lesion".

The Subcutaneous Method.

Koch injected very small amounts (0.001 - 0.0001 cc.) of Old Tuberculin subcutaneously. A tuberculin-sensitised individual responded by showing a local inflammatory swelling, a general reaction, characterised by malaise and pyrexia, and occasionally a focal reaction around tuberculous lesions, shown by cough, increased expectoration, increase of moist sounds in the chest in cases of phthisis, or reddening of areas of lupus vulgaris.

The test depended for its interpretation on the production of pyrexia, and was therefore difficult to use in febrile subjects.

In view of the fact that it was unwieldy and difficult to interpret, and there was danger of exacerbating tuberculous disease, the method was

gradually abandoned, except by a few enthusiasts. Although considered by some workers to be a very sensitive method, Klopstock (1919) did not think it more sensitive than graded intradermal tests. In cattle testing the subcutaneous test has been displaced by the intradermal test, as a result of investigations by the Medical Research Council (1925,1928).

Local Subcutaneous Test (Escherich).

Shortly after Koch's test was introduced, the Stichreaktion, or needle-track reaction, was developed (Epstein,1891; Escherich,1892).

This was a variation of the subcutaneous test, a dose of tuberculin not large enough to produce a general reaction being used. The test was modified by Hamburger later (1908,1912), and became known as the Local Subcutaneous Test. It was used to supplement the von Pirquet test, mainly in Austria and Germany.

Cutaneous Test (von Pirquet).

In 1907 von Pirquet introduced the cutaneous test. This procedure was much safer than Koch's subcutaneous test. The skin, usually of the flexor aspect of the forearm, was cleansed with ether, and allowed to dry. Through two drops of undiluted Old Tuberculin a small metal borer scarified the skin. A small spot, not covered by tuberculin, and used as a control, was also scarified. A positive reaction was shown by an inflammatory papule, at its maximum in forty-eight hours, surrounding the sites of tuberculin inoculation. The control spot showed only a slight traumatic erythema.

In widespread use for a long time, the von Pirquet test has now been displaced by the intracutaneous test of Mantoux, except in Scandinavia, particularly Norway, where Ustvedt and others still favour it, and some other continental countries.

The Intracutaneous Test (Mantoux).

Mendel in 1908 was apparently the first to suggest the infiltration of the skin with tuberculin as a delicate diagnostic test. This procedure, however, was to be associated with the name of Charles Mantoux (1908), who very quickly established the test, which is, of course, the most widely used today.

Put very briefly, the technique is as follows: 0.1 cc. of Old Tuberculin or Purified Protein Derivative is injected into the skin of the flexor aspect of the forearm. A long 1 cc. syringe is often used, for its accurate graduation. An infected individual reacts by producing erythema and oedema at the site of injection, maximal at 48 or 72 hours.

It is usual to start the test with a dilution of 1:10,000 or 1:1,000 Old Tuberculin, and repeat in negative reactors, with 1:100. A dilution of 1:10 or undiluted Old Tuberculin is rarely used. Purified Protein Derivative is used in two strengths (0.00002 mg. and 0.005 mg.).

There is disagreement about the minimal limits of a positive reaction. Cummins and Walker (1931) thought an erythematous area 2 mm. in diameter was sufficient. Hart (1932) required at least 5 mm. erythema with infiltration. Opie and McPhedran (1926) required 10 mm. erythema with infiltration, as did Kayne (1935), Ustvedt (1932), and Wallgren (1928). Using synthetic medium Old Tuberculin, Holm (1934) recommended a "papule" of 7 mm. at 48 hours in the first test, and of 10 mm. at 48 hours in the second and third tests. Different dilutions, as Holm and Arborelius (1932) suggest, may require different criteria as to a positive reaction.

The present writer, using synthetic medium Old Tuberculin, laid greater stress on oedema than on erythema, and usually, unless the reaction was not in doubt, required 10 mm. erythema and oedema before reading a reaction as positive.

The stronger concentrations of Old Tuberculin do, of course, produce more reactors, though most cases of

clinical tuberculosis are discovered by dilutions of 1:10,000 or 1:1,000. Only 4 per cent. of a series of cases of tuberculosis failed to react to a Mantoux test using 1:1,000 (Hart, 1932). This does not apply to tuberculin surveys in non-tuberculous subjects, as will be discussed later.

In previous years the von Pirquet test was preferred to the others on the grounds of safety. In the Mantoux test, freedom from dangerous or unpleasant reactions is obtained by using a dilution of Old Tuberculin calculated not to produce an excessive reaction either locally or generally. In this way, dilutions of the order of 1:100,000 are occasionally used to produce positive reactions in highly sensitive subjects, e.g. cases of primary infection, or of pleural effusion. Because of the reserve of strength which it possesses, the Mantoux test is highly effective in demonstrating reactors. Most observers agree that 0.1 cc. of Old Tuberculin 1:1,000 injected intracutaneously (0.1 mg. O.T.) is approximately equal in sensitivity to the von Pirquet test, using undiluted Old Tuberculin. It has even been said that the Mantoux test is a million times more sensitive than the von Pirquet (Schnippenkötter, 1926).

In addition to being safe and highly sensitive, the intracutaneous method is reasonably exact, permitting the use of a definite amount of tuberculin, and giving a reaction easily assessed in the majority of cases. Because of this, it can be used quantitatively, and reactions can be compared with a fair degree of accuracy. Opie (1927) felt it was the only means by which successive tuberculin reactions could be measured and compared. This is valuable in clinical and epidemiological work.

The Mantoux test has of course, certain disadvantages. Sterility must be maintained. Dilutions, made in phenol-saline, have to be renewed after four weeks or so, as deterioration occurs. Dilutions in water can be used for only one day. For strict accuracy, syringes should be set apart for each dilution, since tuberculin adheres tenaciously to glass (Parish, 1935), and may thus produce false or misleading reactions. Fry (1938) attributed a series of anomalous "Schick" reactions to tuberculin adhering to syringes.

The Schick tests were also tuberculin tests.

In dispensary and survey work, the real difficulty is the fear and pain produced in many by the act of injection. A case of hysteria has been recorded, and nervous reactions are particularly likely where numbers of children are being tested together. Occasionally patients may refuse to be tested because of this fear.

Although simple, the technique has to be acquired, and the test must be performed by the medical attendant himself and cannot be delegated to a nurse.

Percutaneous Tuberculin Tests.

The various difficulties attendant upon the intracutaneous test, particularly since the use of the tuberculin test in clinical and survey work became more common, have revived interest in the percutaneous tests. These are of two main kinds, inunction and plaster tests.

Inunction Tests.

In 1907 the Moro test was described. The test material was an ointment of 5 cc. Old Tuberculin in 5 gm. anhydrous wool fat. A piece "the size of a pea" was rubbed into the skin, the finger of the person applying the test being protected by a fingerstall. A positive reaction was shown by an efflorescence of papules.

The method was unreliable and often failed even in "clinically tuberculous" patients. It did not have wide use outside Scandinavia. Widowitz in 1922 used ether to "defat" the skin before the ointment was applied. Later, more concentrated forms of tuberculin were introduced, with a corresponding increase in the accuracy of the test (Hamburger and Stradner, 1919).

The test was still not sufficiently reliable, however, and had only a limited use. Price in Dublin still favours Hamburger's ointment, prepared in two strengths. Negative reactions should be confirmed by the injection of 1 mg. Old Tuberculin intradermally.

Plaster or Patch Tests.

Owing to the defects of the various modifications of the inunction tests, many attempts were made to carry tuberculin on some medium calculated to absorb, dry or concentrate it, or limit the area of reaction. Gauze, cotton, blotting paper, filter paper, plain paper, paper towelling, have all been tried. Too absorbent a medium may not leave enough available tuberculin, excessively concentrated tuberculin may produce a violent reaction.

The plaster or patch test was therefore gradually evolved. The history of the more important stages is as follows: Lautier in 1908 conceived the idea of drying a drop of tuberculin on sticking plaster which was then fixed to the patient's skin. The tuberculin, dissolved by the insensible perspiration, penetrated the skin and produced a reaction. The plaster kept the tuberculin in contact with the skin for as long as was desired, and also obviated the necessity of inunction.

Various disadvantages were found in the early plaster tests, e.g. the tuberculin sometimes spread irregularly or appeared at the edges of the plaster. If liquid tuberculin were used, the doses could not be measured. As a result, the method was unreliable, and fell into disuse for some years.

Vollmer later revived the test. He used filter paper saturated with tuberculin and strapped to the skin. He was followed by Malmberg and Fromm (1931) who mixed the tuberculin with the adhesive coat of sticking plaster, and used a control plaster without tuberculin. Grozin (1933) revived the method of applying liquid Old Tuberculin to adhesive plaster. He found his test, compared with the von Pirquet test, to have an error of less than 10 per cent. Meanwhile, Vollmer (1937) produced his Patch Test. This consists of thin filter paper, saturated with Old Tuberculin, dried in a dust-free room, cut into small squares, and placed on pieces of adhesive tape. A square of filter paper, soaked in bouillon, is also placed on the tape as a control. A strip of "crinoline" gauze protects the squares and is easily removed before use. This test acquired a wide

popularity, partly because it was introduced when tuberculin surveys were being made on a large scale in the United States. Similar patch tests have been produced in this country (Evans Sons, Lescher & Webb).

The patch test is now fairly well standardised. The skin of the forearm, chest or back, is cleansed with ether or acetone, allowed to dry, and the plaster applied. After two days, during which the plaster is kept dry to prevent tuberculin being spread over the body, the plaster is removed. The reaction is then read. If negative, it is usual to see the patient again in a further 48 hours, as late reactions occur.

The reaction is described as a "sharply defined reddened indurated square, with lichenoid follicular elevations", but may vary from a few papules to a confluent elevated rash spreading beyond the squares, with vesicle formation in the centre. The best sites are the sternum and the trapezius muscles. The criteria for a positive reaction must not be too rigid as feeble reactions are fairly frequent. The writer, at times, has accepted one papule as evidence of a positive reaction.

It is necessary, of course, to use adhesive plaster that will not itself produce a non-specific rash by irritation. If a plaster rash does occur, the test however, can still be read. In a true negative reaction, the area covered by tuberculin filter paper remains white, while in a true positive reaction, this area is more red than the surrounding skin. A plaster rash usually fades quickly, only the tuberculin reaction being visible 24 or 48 hours after removal of the plaster.

The patch test is of course a blind test, the area of reaction being concealed under the plaster. If the plaster be removed too soon, a positive reactor may be missed; if left on too long, the patch may produce severe reactions. Repeated patch tests have been known to cause pyrexia (Schwartzman, 1942). Grozin (1943) therefore cut incomplete circles over the patches, leaving hinged flaps which, when raised, allowed the skin to be inspected. The plaster could therefore be removed as soon as a reaction occurred.

The plaster test used by the author, has three filter

paper squares saturated respectively with human tuberculin, synthetic medium (control), and bovine tuberculin. A solution of purified tuberculin protein is used, "two or three times as potent as standard tuberculin". Reactors to bovine tuberculin usually react to human tuberculin and vice versa. This is not surprising since the tuberculin produced by both types of organism is the same. Occasionally, only one square reacts. This is probably due to the lack of reliability of the test, rather than to any specificity in the allergy produced by human and bovine infections. The control square was rarely required, in the author's own experience.

In view of the fact that dilutions of Old Tuberculin gradually deteriorate, it is interesting that an investigation (Schwartzman,1942), of the effect of variations of technique showed the Vollmer patch test to be very stable. Slight reduction in accuracy of the test was found when the skin was not cleansed, or when the patch was immersed in alcohol, acetone or water before use. Marked deterioration,however, occurred if the patch were heated in an autoclave. The present writer has used patches two years old, with no evidence of deterioration, although there has been some feeling that since 1939 the patches have had a tendency to dry and thus lose their potency.

Comparison of the Patch and Mantoux tests.

A large literature has arisen around the various patch tests, concerned with their reliability as compared with the Mantoux test. It is proposed now to review some recent work on this question.

All the surveys quoted were made in the United States, except when stated otherwise.

Vollmer and Goldberger (1937) first showed that their patch test, in a series of 209 tuberculous children, gave more positive reactions than the von Pirquet test. Later, in 1939, using a stronger tuberculin, produced from a synthetic medium, the patch test succeeded in producing reactions even in unfavourable conditions, e.g. winter temperatures, or

in the presence of ichthyosis or myxoedema. The new patch was then tested against the Mantoux test (0.1 mg. Old Tuberculin) in 417 children in hospital. Of four cases of disagreement, three were patch positive, and Mantoux negative.

A further 261 tuberculous children were also tested, the Mantoux test being repeated with 1 mg. Old Tuberculin or second strength Purified Protein Derivative if negative. Only two cases of disagreement were found.

To determine whether the patch test was likely to miss patients with active lesions, 2,000 children were studied. It was found that of 763 positive reactors the patch test missed only three cases of active tuberculosis, two of these being "anergic". (Vollmer,1940).

In 1943 Vollmer made a survey of ten reports by various authors, dealing with 6,104 cases; 1,819 reactors were found by the patch test, as compared with 1,833 by the Mantoux test (including the use of 1 mg. Old Tuberculin or second strength Purified Protein Derivative).

This result seemed satisfactory, for the whole series. In addition, on comparing the Mantoux test using 0.1 mg. Old Tuberculin or first strength Purified Protein Derivative with the patch test, complete agreement was found to have been reached in these cases. The patch test could therefore be used to replace the Mantoux test in these dilutions.

To lessen reactions in subjects suspected of high sensitivity, patches may be applied for only 3, 6, 12, 18, or 24 hours. Negative reactors should be retested with the usual patch test.

The patch test has been used as an "allergometric" test, and Vollmer and Ripps (1943) published the following figures :-

Reactors to 0.01 mg.O.T. are patch positive after 24 hrs.
" " 0.001 mg." " " " "12 or 18 hrs
" " 0.0001 mg." " " " "3,6,or 12 hrs

A simpler way of using the "allergometric" patch test is to decrease the amount of tuberculin applied. It can then be shown that children reacting to the Mantoux test (0.01 mg. O.T.) will, in the majority of cases, give a positive reaction to patches containing one-twentieth or one-hundredth of the usual amount of tuberculin (Vollmer, Zelson and Rubin, 1939).

In a similar study in 1941, Furculow found the sensitivity to the patch test directly parallel to the sensitivity to the quantitative intracutaneous test. The severity of reactions was also parallelled.

Wolff and Hurwitz (1937) tested 964 children. There was no discrepancy between the Mantoux and patch tests in the cases of active tuberculosis, but there was a discrepancy of 1.8 per cent. in the series as a whole.

Because of the reluctance of college students to suffer injections, Rice (1939) investigated the value of the Vollmer patch test. Of 256 subjects, 23 per cent. were found to be negative to the patch test, while positive to the Mantoux test (P.P.D.). The patch test therefore seemed unsuitable for young adults. (The concentration of tuberculin was later increased in the Vollmer patch test and the method made more sensitive).

Grant Taylor (1940) tested 744 nurses, students and patients in a hospital. He found the Vollmer patch test to be slightly more sensitive than the Mantoux test in young adults, but less sensitive in adults over 50 years.

Taylor's findings, as regards the use of patch tests in adults, have been widely quoted, although the number of adults who failed to react to the patch test was only 15, 12 being over 50 years. Justifiably or not, the patch test has not been used much in adults.

Testing children in a sanatorium, Stewart (1939) found the Vollmer patch test as sensitive as the Mantoux test (1:1,000).

Crimm et al. (1941) examined 1,556 subjects, aged 13 to 16 years, of native (American) stock, with the Vollmer patch test and the Mantoux test (0.001 mg. P.P.D.) The series as a whole gave almost 99 per cent. correlation

between the two tests. It is interesting to note that of the 500 reactors, 14 reacted only to the Mantoux test, while 7 reacted only to the patch test.

In a study of another large number of subjects, Kerr and Winograd (1940), using the Vollmer patch test and the Mantoux test (first strength P.P.D.), found 98 per cent. correlation.

Investigating 1,000 dispensary patients, ranging from infants to the aged, of whom 300 had active pulmonary tuberculosis, Narodick (1942) found the Vollmer patch test agreed with the Mantoux test (first and second strength P.P.D.), in 98.5 per cent. of the series as a whole. Of the 671 cases reacting to the Mantoux test, 10 (i.e. 1.5 per cent.) were patch negative. Agreement in detecting active cases was almost complete.

Savage in 1941, compared the Vollmer patch test and the Mantoux test, using for the latter Purified Protein Derivative and two different preparations of Old Tuberculin (O.T[1]. and O.T[2].). Marked variation was found in the numbers reacting. The patch test produced 40 per cent. reactors; the Mantoux test (P.P.D. and O.T.[1] and O.T.[2]) gave respectively 46.5, 60, and 47.6 per cent. reactors. The Vollmer patch test appeared least sensitive, but did not miss any clinical cases. These marked variations, particularly in the Old Tuberculin preparations, were attributed by the author to faulty manufacture. Obviously, very careful production and standardisation of tuberculin is essential. Although it is probably impossible to produce batches of Old Tuberculin completely identical with each other, preparation in this country is extremely efficient, and it is now unusual for much variation to be found in standard Old Tuberculin, although the method of standardisation has its critics.

Most of the investigators of the patch tests use young subjects, whose positive reactions are due to past or present tuberculous infections. Neiman and co.workers decided in 1941 that children vaccinated with "B.C.G." whose tuberculin sensitivity is of a <u>low</u> order, would provide a more severe trial of the

test. It was found however, that reasonable agreement, (nearly 90 per cent.) occurred in these subjects between the patch and Mantoux tests.

False Patch Reactions.

Cases of disagreement between the Mantoux and patch tests are termed by many, "false patch positive", or "false patch negative" reactions. Studying this question, Kerezturi (1941) found in the literature nine reliable investigations with 4,162 tests, in which the Mantoux test was performed with 1 mg. O.T. or its equivalent amount of P.P.D. These he analysed as follows :-

> Of 1,856 positive to the Mantoux test, 270 (15 per cent.) were negative to the patch test.
>
> Of 2,306 negative to the Mantoux test, 78 (3 per cent.) were positive to the patch test.

Of the 270 false patch negative tests, 225 were observed in one study, (Peck,1939), and of the 78 false patch positive reactions, 67 were reported in one communication (Pearse,1940). If their figures, out of keeping with the others, are withdrawn, the error, or discrepancy, changes from 15 per cent. and 3 per cent. to 3 per cent. and 0.6 per cent.respectively. (Pearse did not think that his reactions were false patch positive reactions, but considered them as indicating the patch test more sensitive than the Mantoux test).

Kereszturi himself tested two groups of school children in 1938 and 1940. His results appear in the following table :-

	1938.	1940.	1938 & 1940.
Total	177	202	379
Mantoux Neg. Patch Neg.	125	112	237
Mantoux Pos. Patch Pos.	31	52	83
Mantoux Pos. Patch Neg.	14	17	31
Mantoux Neg. Patch Pos.	7	21	28
False Neg. Patch Test.	35%	25%	27%
False Pos. Patch Test.	5%	16%	11%

There were therefore wide divergencies between the two tests, and also between the two series. In addition, in 30 cases with positive Mantoux and negative patch test reactions, a second patch test gave positive reactions.

These conflicting results were attributed to feeble reactors i.e. low sensitivity of the patient, errors and changes in criteria and technique, use of different tuberculins, variations in the weather, and in amount of patients' perspiration.

A second patch test was useful in feeble reactors, who were borderline cases, and might produce discrepancies.

On the basis of his own results, which, it may be pointed out, are not convincing, and do not correspond with the average figures of variations between the tests that he himself describes, Kereszturi suggests that the Mantoux test is not yet replaceable by the patch test.

This review of work performed in the United States will now be succeeded by a survey of comparable investigations, much fewer in number, carried out in Great Britain, Canada, South Africa and Australia.

Palin (1939) in England, considered the patch test, if properly used, as reliable as the Mantoux test.

Court (1939), looking for a test simpler than the Mantoux, tested 110 children under 12 years, with the Vollmer patch test and the Mantoux test (0.1 mg. O.T.). No discrepancy was found. All the 79 negative patch tests were repeated but only one gave a positive reaction.

Secondly, 100 children reacting to the Mantoux test (0.1 mg. O.T.) were patch tested; 98 were patch positive. Of the two negative to the patch test, one was a case of generalised tuberculosis with depressed skin sensitivity.

Court concluded that the patch test was reliable to the extent of 95 to 98 per cent.

In another English investigation, Dudley Hart (1941) compared the Vollmer patch test, and the Tuberculin Salve Test (Old Tuberculin and purified tuberculin in paste, squeezed on to adhesive tape (Monrad, 1936)).

700 children under ten years were tested. 587 were negative to all tests. Of 113 Mantoux positive reactors, four were negative to the Salve test, and three were negative to the patch test.

A further 247 children negative to the patch test were tested with the Mantoux test (1 mg. O.T.). Of these, four were positive reactors.

The patch tests therefore agreed well with the Mantoux test. Disagreement, where it existed, was usually due to the use of high concentrations of Old Tuberculin (1 mg.) Some of these positive Mantoux reactions were unreliable, as a further injection of 1 mg. occasionally failed to reproduce the reaction. If the patch tests produced too few reactors, the Mantoux test might be producing too many.

In a more recent survey on 116 children under 12 years admitted to an English base hospital, Mary Crago (1943) compared the Mantoux test (0.1 mg. O.T.) with the patch test (Evans Sons, Lescher & Webb).

Of the 42 Mantoux reactors, eight were negative to the patch test. No mention is made in this survey of late patch positive reactions, which may be fairly common. The results of this small series are unfavourable to the patch test when used alone, and are rather similar to the author's findings with the same patch preparation.

Bell and Jerram (1945) compared the Vollmer patch and Mantoux tests (1:10,000 - 1:1,000 O.T.) in 380 children who were cases of tuberculosis, suspect cases, or contacts with "open tuberculosis". 180 children were Mantoux positive, of whom only 62 were patch positive.

These authors concluded that the patch test was unreliable to the point of being valueless.

These results, very unfavourable to the patch test, are so much out of keeping with most reports, that they suggest that the patches were faulty or that criteria of positive reactions were too exacting.

Pedley (1943) observing that tuberculin testing was becoming increasingly useful and important in young adults in Canada, compared the patch and Mantoux tests. 486 students at McGill University were tested between 1938 and 1941. Ages were between 20 and 30. The Mantoux test was repeated if negative (0.1 mg. and 1.0 mg. O.T.).

The results are tabulated overleaf.

Neg. to M.T. (0.1 mg.) and Patch Test Pos. to M.T. (0.1 mg.) and Patch Test	285 172	59% 35%
Agreement between M.T. (0.1 mg.) and Patch Test	457	94%
Pos. to M.T. (0.1 mg.) but Neg. to Patch Test	21	4%
Neg. to M.T. (0.1 mg.) but Pos. to Patch Test	8	2%
Pos. to M.T. (1.0 mg.) but Neg. to Patch Test	22	

Of the negative reactors to the Patch test, the Mantoux test (0.1 mg. and 1.0 mg.) proved 43 (14%) to be tuberculin sensitised.

Of the negative reactors to the Mantoux test (0.1 mg.), the Patch test, or Mantoux test (1 mg.) proved 30 (10%) to be tuberculin sensitised.

If the Patch test had been used alone, 43 (8.8%) would have been classified wrongly as tuberculin negative.

If the Mantoux test (0.1 mg.) had been used alone, 30 (6.2%) would have been classified wrongly as tuberculin negative.

In adults, therefore, the Patch test was nearly as reliable as the Mantoux test (0.1 mg. O.T.). In mass testing, if an error not over ten, and nearer five per cent. be accepted, the Patch test can be used in young adults. In clinical diagnosis, a negative Patch test should be followed by the Mantoux test (1 mg. O.T.).

In an investigation in 1941 of Vollmer patch tests in African children, Dormer and Friedlander found high correlation between the patch and intradermal tests. In a later communication (1943), the reactions of 1,433 subjects of African and Asiatic origin, were described. A positive patch test had to show follicles and induration with erythema. The discrepancy between the tests was variable, false negative patch reactions

being, for three different schools, 2.4, 6.5, and 17.9 per cent. In adults, and Army recruits, the patch test gave a false negative reaction in 22.2 and 27.3 per cent. False positive patch tests were also frequent, reaching 4.6 per cent.

In 60 tuberculous patients, patches were applied simultaneously to forearm, sternum and back. In ten, the patch on the forearm failed to produce a reaction, while the other patches were positive. The skin of the back gave the most definite reactions, especially where the forearm and chest were habitually exposed to the sun.

Attempting to explain the large and varying discrepancies, the authors questioned errors in the manufacture of the patches, or in the technique. The present writer puts forward the following additional points as possible factors. First, the criteria may have been too exacting. Secondly, two of the groups were adult in character, in whom patch tests may not be reliable. Thirdly, the patches may have dried or deteriorated owing to the heat (Schwartzman et al.,1942). Fourthly, patch tests are known to be unreliable on sunburned skin, possibly due to interference with the absorption of tuberculin. It has indeed been shown that exposure to ultra violet light hinders the response to the von Pirquet test (Morabito, 1926). It may be, of course, that patch tests are unsuitable for use on coloured skin, although some authors seem to have found them satisfactory in this connection.

Colebatch in Australia in 1941 found almost complete correlation between the patch test and the Mantoux test (0.1 mg. O.T.). The exceptions, in his series, were all orthopaedic cases, exposed to the sun.

Another Australian worker, D.Anderson (1941), also compared the two tests in adults. He found that the patch test missed 15 per cent. of the reactors found by the Mantoux test. He was unable to explain this failure by reference to the texture or dryness of the skin, or to the degree of sensitivity to the intradermal test.

The present writer compared the patch test (Evans Sons, Lescher and Webb) with the Mantoux test in

children. The method used was as follows. The patch test was applied, removed after 48 hours by the patient, read in a further 24 hours, and if negative, seen again two days later to make sure that no delayed reaction was missed. At the first or second visit, the Mantoux test was performed, those negative to 0.1 mg. Old Tuberculin being retested usually with 1 mg. Owing to the distances which patients sometimes had to travel, particularly in Cambridgeshire, it was not practicable in every case to perform two injections and many patients merely had the patch test and the injection of 1 mg. Old Tuberculin. A few patients had the comparison made between the patch test and 0.01 mg. Old Tuberculin.

Neg.to M.T.(0.01 mg.) & Patch T.	2
Neg.to M.T.(0.1 mg.) & Patch T.	16
Neg.to M.T.(1.0 mg.) & Patch T.	100
Neg.to M.T.(0.01-1.0 mg.) & Patch T.	118

Pos.to M.T.(0.01 mg.) & Patch T.	10
Pos.to M.T.(0.1 mg.) & Patch T.	32
Pos.to M.T.(1.0 mg.) & Patch T.	40
Pos.to M.T.(0.01-1.0 mg.) & Patch T.	82

Pos.to M.T.(0.01 mg.) but Neg.to Patch T.	0
Pos.to M.T.(0.1 mg.) but Neg.to Patch T.	6
Pos.to M.T.(1.0 mg.) but Neg.to Patch T.	18
Pos.to M.T.(0.01-1.0 mg.) but Neg.to Patch T.	24

Of the total 224 tested, there was complete correlation in 200, and disagreement in 24, i.e. 10.7 per cent. In other words, of the 106 positive to the Mantoux test, 24 (22.6 per cent.) failed to show a positive patch reaction. This large discrepancy is due mainly to the use of 1 mg. Old Tuberculin. If the patch be compared with the Mantoux test, using 0.01 and 0.1 mg. Old Tuberculin, then it is found that the 48 positive Mantoux reactors gave only 6, or 12.5 per cent. of false patch negative reactions. The small number tested with 0.01 mg. Old Tuberculin showed no discrepancy. One patient who was Mantoux negative (1 mg. O.T.) was patch positive. This may have been an example of the false

patch positive reaction, or possibly an instance where the patch test was better than the intradermal.

The above numbers are too small to permit of definite conclusions, but they are suggestive that although a positive patch reaction may be trusted, a negative reaction is unreliable, and should be verified by an intradermal test. In tuberculin survey work, if the patch test be used, allowance should be made for the margin of error. This should be worked out for each particular type of patch test, for there seems no doubt that the Vollmer patch test made by Lederle in the United States is superior to the preparation used by the writer.

Several cases of clinical tuberculosis were included in the subjects tested. It is reassuring to note that the patch test did not fail, in any of these, to produce a positive reaction.

Conclusion.

The patch test (Evans Sons, Lescher & Webb) fails to detect an appreciable proportion of Mantoux positive reactors. It does not usually fail in cases of clinical tuberculosis. This patch test does not produce a significant number of false positive reactions.

Fallibility of the Mantoux Test.

It has been pointed out by many that no test is infallible, although for purposes of comparison between the various tests, the Mantoux test is treated by some writers as always correct. Furculow and Robinson (1941), in an interesting experiment, found a large error in the Mantoux test itself, when P.P.D. (0.00001 mg.) was injected into both arms of an individual, there being a difference between the arms of 3.3 per cent. in the incidence of reactions. When a larger amount of tuberculin was used, a greater variation in the results was observed (Paretsky, 1938).

The whole question of "non-specific" or pseudo-reactions is discussed elsewhere, but it can be suggested here that some of the reported "false" patch reactions are so described merely because of the failure

of the Mantoux test to act as a perfect control. In other words, when the patch test gives a positive reaction, and the Mantoux test is negative, this may be due to the fact that the former is occasionally more sensitive than the latter. Only one possible case of this type occurred in the author's own experience.

The Tuberculin Jelly Test.

This variation in percutaneous tests was introduced by Paterson in 1944, mainly because of the tendency of the Vollmer patches to become dry and less reliable. A jelly was therefore prepared containing Old Tuberculin (95%) and Inert Adhesive (5%) and put up in small tubes. After the skin has been cleansed with ether or acetone, a small portion of jelly is pressed on to the area, which is then covered by adhesive plaster. The test is read, as in the ordinary patch test, in 48 or 72 hours, and a positive reaction is shown by erythema or a follicular rash. A control jelly may be used but is not essential.

This test, because of convenience, good keeping qualities, and cheapness, has become increasingly popular since its introduction. Published reports on its reliability are few as yet. Paterson in a series of 100 children, found the jelly test detected as many reactors as did the Mantoux test (1 mg.O.T.), the ordinary Vollmer patch being about 8 per cent. less sensitive.

This series was encouraging, but the numbers were too small to be authoritative. Bell and Jerram (1945), already quoted in part, compared the Mantoux, Vollmer patch, and jelly tests, in 58 children, cases of active tuberculosis, and 122 children, suspect cases, and contacts. Their results are tabulated below :-

	No. tested.	Mantoux Positive. (0.01 mg.)	Patch Positive.	Jelly Positive.
Active cases.	58	58	31	55 (94.8%)
Suspect cases and contacts.	102	101	31	48 (47%)

21 children, negative to 0.01 mg. Old Tuberculin, were retested with 0.1 mg. Old Tuberculin:-

No. tested.	Mantoux Positive. (0.1 mg. O.T.)	Patch Positive.	Jelly Positive.
21	21	0	1 (4.8%)

In view of these findings the authors dismissed the Vollmer patches as useless. The jelly test, although more sensitive, detected only cases with a high degree of allergy, such as clinical cases, and failed in the other group, thought to be less highly allergic.

Two points are worth noticing about this report. First, the fact that the Vollmer patch test detected only 31 of 101 reactors shown by 0.01 mg. Old Tuberculin in the Mantoux test. In the present writer's opinion, this is so much at variance with previous reports, as to cast doubt on the accuracy and validity of the findings. Secondly, the variation in the efficiency of the jelly tests in the first two series, suggests that technique, or criteria of positive reactions may have been faulty. The evidence of a positive reaction may be scanty, perhaps only two or three scattered papules, and slight reactions must not be ignored.

A similar investigation to the above was performed by Climie (1945) who tested 100 subjects, mainly contact children and young adults, on a hospital staff. Three tests were used, the jelly test, liquid Old Tuberculin covered

by plaster, and the Mantoux test (P.P.D.first strength). Those negative to the Mantoux test were re-tested with P.P.D. second strength.

The results are tabulated below :-

Results	Jelly test.	Liquid O.T.	Mantoux test. 1st.strength P.P.D.	Mantoux test. 2nd.strength P.P.D.
Positive	41	42	54	70
Negative	59	58	46	30
	100	100	100	100

The author concluded that the two percutaneous tests were equal in sensitivity, but were slightly inferior to the Mantoux test, using first strength P.P.D. (It will be remembered that this strength is usually regarded as approximately equal to 0.1 cc. of 1:25,000 Old Tuberculin).

It must be said, however, that this report is rather in contradiction to the optimistic statement by Paterson, that the jelly test is equivalent to the Mantoux test with 1 mg. Old Tuberculin. A possible source of error in Climie's work is that a number of young adults were used, although it has been fairly commonly accepted that percutaneous tests do not give satisfactory results in adults.

Both the papers by Paterson and Bell suggest that the jelly test is rather more sensitive than the Vollmer patch test. If substantiated, this would give the jelly test a very important part to play in tuberculosis work. Some further evidence supporting the claim that the jelly is more sensitive than the patch test is given by Deane (1946) who found in comparing the Vollmer patch and jelly tests in children sensitive to the Mantoux test (0.1 mg.O.T.), that the patch detected 80 per cent. and the jelly 87.5 per cent. respectively of the positive reactors. If the skin were slightly abraded with fine sandpaper, the jelly did not miss any sensitised child.

In personal comparison of the jelly and patch tests, the writer has found that the former gives a more definite

reaction, easier to read than the latter.

A certain number of comparisons were made between the jelly and the Mantoux tests, in the course of dispensary work. Of 30 children positive to the Mantoux test with 0.1 mg. Old Tuberculin, 29 gave a definite positive jelly reaction. One child showed an indefinite jelly reaction and a very marked Mantoux reaction. 54 children, negative to the jelly test, were also negative to the Mantoux test (0.1 mg.O.T.). A small number of children, negative reactors to the jelly test, injected with 1 mg. Old Tuberculin, also showed complete agreement. All cases of tuberculosis gave positive jelly reactions.

These results, although limited in number as regards the positive reactors, are very satisfactory. They show that the jelly test conforms closely in sensitivity to the Mantoux test with 0.1 mg. Old Tuberculin, the error in this series being only 3 per cent.

When slight, doubtful, or delayed jelly reactions occur, it is always wise to perform an intracutaneous test, using a dosage of 0.1 mg. Old Tuberculin. If it be desired to confirm a negative jelly test - as will always be the case in clinical investigations - then 1 mg. Old Tuberculin may safely be used.

The jelly test seems likely to supersede the patch test, by virtue of greater accuracy, better keeping qualities and smaller cost. The only drawback at present is the inaccuracy of dosage. With experience, approximately equal amounts of jelly are used on each occasion, but the amount varies inevitably with the person applying the test.

Conclusion.

There seems to be no doubt that the Mantoux test is a more dependable and sensitive test than any of the percutaneous tests. In surveys and contact work, the patch or jelly test is probably sufficiently accurate, and is much easier to use. It is probable that if it

it were available it would be undesirable to employ, as a first procedure, a percutaneous test as sensitive as the Mantoux test, with 1 mg. Old Tuberculin, since excessive reactions would be frequent. Its absence , therefore,is not serious.

There is a definite place for the percutaneous tests, particularly if supplemented, in clinical work, by the intradermal method.

CHAPTER 3.

Nonspecific Reactions.

The interpretation of the tuberculin test has been complicated by the occurrence of nonspecific reactions. It is because of their existence that definite minimal limits have to be set for the acceptance of positive tuberculin reactions.

Many substances have been found capable of producing reactions resembling the true tuberculin reaction. Indeed the specific character itself of the test has been questioned. These other substances include various bacterial emulsions and toxins, certain proteins, and glycerol broth. It is probable that these substances contain antigens also present in tuberculin, which is not surprising in view of the latter's complicated chemical character.

A relationship exists between many of the various types of acid-fast bacilli. A serological group-specificity probably exists, due to the polysaccharides, while the various proteins produce a type-specificity (Seibert, 1930). The group-specificity may produce puzzling reactions, but in this country reactions due to "paratubercle" bacilli have not been important in man.

Bacteria not belonging to the acid-fast group may also be capable of nonspecific reactions. For example, B.Coli communis, may, on injection, produce a reaction somewhat resembling the tuberculin reaction, in tuberculous animals.

Of the various non-bacterial substances that may produce confusing results, glycerol broth is the most important, and it has been shown that many subjects give a reaction following upon its injection. Ekberg (1934) found that new-born babies injected with 1 mg. of tuberculin, occasionally showed small reactions. These were never more than 3 mm. in diameter and were presumably due to the glycerol, peptone or other chemical constituent of the tuberculin, or to the trauma. Trauma is an unlikely cause, the reaction surrounding a simple needle prick being very small in the present writer's

experience. Freund and Hart (1935) thought that glycerol broth reactors were common and that they occurred usually in tuberculised subjects. Tuberculin negative reactors were usually glycerol broth negative also, but exceptions occurred. The glycerol broth reaction was usually smaller than the true tuberculin reaction, oedema was sometimes absent, and fading occurred earlier.

An important point about the nonspecific agents capable of eliciting pseudo-reactions, is that injection of large amounts of bacterial suspensions or glycerol broth is necessary, while the specific reaction occurs after injection of minute amounts of tuberculin, a clear filtrate cnntaining few bacilli, if any. The nonspecific reactions are of various kinds, but most of them are feeble, atypical in appearance and transient; only a small proportion persist two or three days after the injection. Many of them lack oedema and consist merely of a flat erythematous area. Nonspecific reactions are particularly frequent after the injection of the larger doses of tuberculin, prepared from glycerol veal-peptone broth media (Hart,1932; Smith,1941).

In the ordinary well marked result, the possibility of a nonspecific reaction can usually be dismissed, but when feeble allergy is encountered, small reactions are seen which may be difficult to distinguish.

When glycerol veal-peptone broth was used in the preparation of Old Tuberculin, it was customary, with high test doses, to inject also 0.1 cc. of the broth in the other arm, as a control. This was not regarded as completely satisfactory, however, and a change was made in the preparation of tuberculin, synthetic culture media being introduced which contained no protein. Although containing glycerol, which had been suspect, these synthetic media produced tuberculin giving much fewer nonspecific reactions than tuberculin derived by the older method. The use of a control has therefore become unnecessary, except possibly as a safeguard when high concentrations are being used.

On the introduction of Purified Protein Derivative, one claim was that because of its high degree of purity and the removal of extraneous proteins, there was little

likelihood of nonspecific contaminants being present and causing false reactions. This claim has not entirely been substantiated. Although, with ordinary doses, nonspecific reactions are rare, and even very small reactions to the first test dose can usually be proved to be specific in character, (Climie,1945), it has been shown that the use of large amounts of Purified Protein Derivative produce increasing numbers of false reactions, until ultimately almost all subjects tested give some response. For example, all non-contact children under three years of age tested by Furculow (1941) with 1 mg. Purified Protein Derivative gave a reaction. These reactions were atypical in character and quickly faded.

In a similar investigation, E.Bogen (1942) showed that large doses of Purified Protein Derivative produced nonspecific reactions in uninfected guinea pigs. Sensitisation by previous injections was a possible factor in this experiment.

In the Cambridge investigation, almost 500 subjects were tested with synthetic medium Old Tuberculin, in a dosage of 0.01 mg., 0.1 mg., and 1.0 mg. A control was used in the early stages of the work, but discarded later as unnecessary.

Certain conclusions were drawn from this work, concerning nonspecific reactions and the criteria of true positive reactions.

It was found that negative reactions to the weaker dilutions, were followed often by large reactions to a stronger dose with considerable erythema and oedema. The reaction to the final dose might however be quite small, and occasionally was so small, that its nature was doubtful. It was impossible to foretell the reaction to a stronger dose, except that if a reaction of 5 mm. diameter with erythema and oedema were verified by a further test, it was always followed by a definitely positive reaction to the stronger dilution.

The presence of oedema in a doubtful test was very suggestive of a true positive reaction. Many reactions which showed a small area of erythema on the second or third day proved to be nonspecific, on injection of a stronger dose. These pseudoreactions were usually very

small, and only two subjects showed a nonspecific reaction reaching 5 mm.in size. On the other hand, many reactions showing 5 mm. erythema and no oedema proved by further testing to be true positive reactions.

Conclusion.

Nonspecific reactions are not a source of confusion if the criteria of 10 mm. oedema and erythema are adopted, for a positive reaction. If 5 mm. oedema and erythema are thought to be sufficient it will usually be easy to distinguish the true reaction, but occasionally a nonspecific reaction may cause some doubt. If oedema is present, the reaction is likely to be specific, but the absence of oedema in an erythematous area measuring 5 mm. or more does not necessarily indicate a nonspecific reaction. Most false reactions are less than 5 mm. in diameter when read. Certain reactions occur, which can only be classed as "doubtful", and are probably due to feeble allergy. Nonspecific reactions have not been a major problem since synthetic medium Old Tuberculin became widely used.

CHAPTER 4.

Tuberculin Surveys.

Tuberculin surveys play an important part in the attack on the tuberculosis problem. Although main attention has to be devoted to those very important sources of information, the tuberculosis mortality and morbidity rates, nevertheless tuberculin surveys are able to provide valuable additional information, not otherwise available, concerning the frequency of tuberculous infection.

Tuberculin surveys usually attempt to assess the incidence of tuberculisation of a group. The nation as a whole may be investigated, to obtain a broad picture of the national tuberculosis problem, and to ascertain whether there has been any change in the incidence of infection with changing social and economic conditions. For this purpose fully representative groups have to be selected. It may be desired, however, to examine a particular group of people, e.g. an urban or rural community, or a particular age or occupational group of the population. Similar or dissimilar groups of people may be tested and compared. Particular groups may be retested after a period to assess the effects of changing conditions, passage of time, improved public health services, prolonged association with cases of tuberculosis, or any other factor which may have a bearing on the tuberculosis problem.

In practice, in this country, it has been found difficult to select reliable samples of the general population, and most published surveys describe the reactions of special groups, selected in various ways and not fully representative of the nation as a whole. It is obvious, of course, that some national populations live under such varying circumstances that national surveys will only have a limited value. The isolated shepherd or fisherman of North Wales, has very different opportunities of contact with tuberculous infection, compared with those of the average inhabitant of one of our large cities.

Although selection of subjects may not have been without bias in some particular direction, if enough

surveys are done a reasonable estimate can be made of the national state of affairs. This has been the case in the United States, particularly for the younger age groups. Most British surveys are concerned with "hospital populations" or tuberculosis contacts. In Denmark however, all the school children have been tested, and in Norway and Sweden small districts have been completely examined.

Tuberculin surveys have been made, using all the various tuberculin tests. The accuracy of the results varies with the test used, and with the potency of the preparation of tuberculin. In the case of the Mantoux test, the dilution used is, of course, of great importance. It will be seen therefore that each survey has to be judged on its own merits, and in fact, it is found that many surveys are unreliable, or give incomplete information.

In a large number of reported surveys, radiographic examination of the lungs has also been made of each subject tested, or occasionally, of each person found to be tuberculin sensitive. These examinations are of great value, particularly in case-finding programmes, but are not really essential to the main purpose of a tuberculin survey. Only a proportion of those sensitised to tuberculin, show any typical radiographic changes, and the frequency of tuberculous infection cannot be accurately estimated in this way. This subject will be referred to in later pages.

Tuberculin surveys have of course been made for many years. One of the first was carried out by Metchnikoff in 1911 among the Kalmuck people of South Russia. He was followed by very many investigators, in most parts of the world, particularly in Europe.

These surveys tended to show that among the poorer classes of many industrial cities of Europe, extensive tuberculisation occurred at early ages, and that by puberty most children were positive reactors. For instance, by 12 years, almost all children in a Viennese survey were sensitised (Hamburger,1909), as were three-quarters of the children in a Prague hospital (Ganghofner,1908).

It was obvious therefore that living conditions were such as to expose the population, particularly the young, to frequent contact with the tubercle bacillus, with the resultant possibility of much tuberculous disease.

In clinical diagnosis, except for infants and very young children, the tuberculin test was not likely to be helpful, since most patients of the hospital class were positive reactors, whether suffering from clinical tuberculosis, or other conditions.

These findings were not necessarily applicable in all towns, (although some low figures in various surveys were probably due to faulty technique), and certainly did not always apply to rural communities, which sometimes had a much smaller incidence of reactors. For instance, Hillenberg, investigating a prosperous rural area in Germany in 1911, using the von Pirquet test, found only about 35 per cent. reactors in children aged 14 years. Where the von Pirquet test produced small numbers of positive reactors, there should always be caution before accepting the results as accurate, but it is likely that many isolated rural communities did not have much opportunity of contact with "open" cases of phthisis. On the other hand the country people had probably more chance of being infected by milk. Overcrowding and lack of ventilation were probably as bad in country as in town.

It is possible that some investigations (e.g. Méroz in 1911 in Geneva) showing low figures of tuberculisation in clinics in certain towns at that period, were affected by patients from the countryside coming to the city for medical treatment. As evidence against this idea, it can be shown (Hart,1932) that some of these towns, e.g. Charlottenberg, Rostock, Oslo, had comparatively favourable tuberculosis death rates as compared for instance with Prague, Paris or Vienna :-

Pulmonary Tuberculosis:
Death Rate per 10,000 persons in 1905 :-

Prague	42
Paris	38
Vienna	33
Geneva	29
Oslo	28
London	14.5
Rostock	14
Charlottenberg	13

This is suggestive that the low figures for tuberculin reactors had some basis in fact.

The early surveys showing high frequency of tuberculisation were strikingly confirmed by much clinical and pathological experience. Naegeli (1900) in a very well known contribution, showed that post-mortem examination of subjects over 18 years of age revealed tuberculous lesions in over 90 per cent. of cases. Naegeli's conclusions were supported by many others, although, of course, there was an opposing school of thought which contested his findings. In his work, Naegeli made it clear that tuberculous infection occurred post-natally, and that many subjects who had been infected never had clinical tuberculosis and did not die of tuberculosis. It was fairly well accepted in the first years of this century that adults who came to autopsy would in the great majority of cases, show healed lesions, mainly in the lungs. This was still the case in 1917 when Opie reported finding tuberculous lesions in all of 50 adult subjects which he had examined. About 20 per cent. of young subjects proved to have been infected with tuberculosis.

In 1922 Wason found evidence of tuberculosis in 82 per cent. of her post-mortem examinations, but Todd, of Edinburgh, in 1927, found disease in only 69 per cent. of his cases.

Uehlinger and Blangey in 1937 carried out a large survey - over 1,000 necropsies - in the same Zurich hospital where Naegeli had worked thirty years previously.

Of 141 persons under 18 years, 22 per cent. were infected, of whom nearly half had died of tuberculosis, only a third having inactive lesions. Of the 870 adults, 80 per cent. were infected, of whom 1.4 per cent. died of tuberculosis, and 65 per cent. had "latent-inactive" lesions.

Uehlinger's figures (see below) are nearly as high as Naegeli's for adults, but with this important difference. By the 18th year, nearly all the latter's subjects had shown evidence of infection, while it was not until the 70th year that the former's figures reached this level.

Uehlinger and Blangey.

10-15 yrs.	44% show evidence of infection at autopsy
45 "	75% " " " " " "
65 "	83% " " " " " "
65+ "	91-95%" " " " " "

These figures showing considerable delay in the tuberculisation of the population, received some confirmation by workers in Oslo who found in 1900, that 78 per cent. at the age of 20, showed lesions of primary infection (Harbitz,1904), while in 1936, this level of infection was not reached till the age of 40 (Frimann-Dahl and Waaler,1936).

These investigations were usually restricted to patients of the hospital class - the poorer section of urban communities - and did not necessarily indicate conditions obtaining in the more affluent groups of townspeople, or in rural populations. Indeed, Landé and Wolff, in a rural part of Washington County in 1941, found tuberculous lesions rare in children and present in only one-half of the adults examined.

Pathologists use very intensive methods of search nowadays when they wish to investigate the frequency of tuberculous lesions. Recent post-mortem surveys are therefore probably much more accurate than the reports of thirty or forty years ago, which usually relied on macroscopic examination.

Tuberculosis continued to be extremely widespread, particularly during and following the first World War,

when a phase of improvement in the West European countries was seriously interrupted. With the gradual passing of the hardships following the war, with improving food and housing, and better knowledge of the prevention of disease, the numbers of new cases and of deaths began again to fall.

In Britain, as in many other countries, the decrease in the death rate from tuberculosis began about 1925, and the figures showed progressive improvement until the outbreak of war in 1939.

It seems likely that where national statistics show the numbers of new cases and of deaths to be decreasing each year, the opportunities for tuberculisation become less frequent, particularly in those households where no member of the family is excreting tubercle bacilli. Tuberculin reactions might therefore be expected to become less frequently positive, with possibly a change in the rate at which the young become tuberculised (see autopsy reports above).

It is impossible to say whether improved social hygiene has had any effect on the infection of young contacts which is so frequent in households where a member of the family has pulmonary tuberculosis. Experience at Papworth Village Settlement has shown that even in good surroundings the children are infected and become tuberculin sensitive as frequently as contact children elsewhere. They do not, however, in this favourable environment, develop clinical disease.

In this country, of course, the recent war reversed the downward trend of the tuberculosis figures. The anxiety, intense overcrowding, lack of ventilation due to the "blackout", excessive hours of work, and restrictions in the food supply have all played their part, coupled with the dispersal of tuberculosis patients in the early years of the war, and the increasing shortage of hospital and sanatorium accommodation.

The situation has therefore deteriorated since 1939, particularly as regards tuberculosis in children, but not to such an extent as to take us back to the state of affairs in 1932 when the most authoritative English tuberculin survey was published by P.D'Arcy Hart. The

death rate in 1930 had been 87.2 per 100,000 for all forms of tuberculosis as compared with 61.6 in 1942, and new cases fell from 73,001 to 60,732 in that period.

An important factor in this country in maintaining the incidence of positive reactors and, of course, of tuberculous disease, must be the frequently contaminated milk supply. This danger has become particularly pressing, since school children are encouraged to drink increased quantities of milk, often, in the early war years, neither pasteurised nor boiled. It has been thought by some American writers that the very low but persistent amount of tuberculisation (circa 10 per cent.) found in some surveys of rural American children was due to bovine infection.

CHAPTER 5.

It is proposed now to describe in detail some of the more important and representative tuberculin surveys performed in recent years, with particular reference to work carried out in this country, and the United States.

Great Britain and Eire.

The first survey to be recalled, and one of the most important, was that performed by Hart.

In the course of his investigations on the value of the tuberculin test, P.D'Arcy Hart (1932) tested 751 members of the hospital class in London. Old Tuberculin was used (0.01 mg. - 100 mg.). Random samples of those negative to each dilution were tested further, and the figures adjusted for the whole group on the assumption that those not tested by higher concentrations of tuberculin would have reacted in the same way as those who were. In the present writer's view this is rather a dangerous procedure to follow, as experience has shown wide variations in the percentages of non-reactors to a given dilution, who will give positive reactions to the next stronger dilution. In a recent publication (Standing Advisory Committee on Tuberculosis,1945) it was stated that the injection of 1 mg. Old Tuberculin would detect from 4 to 20 per cent. more reactors than would 0.1 mg. Old Tuberculin. In the writer's work, about 40 per cent. of those tested with 1 mg. Old Tuberculin gave positive reactions, adding approximately 10 per cent. to the total detected by the use of 0.1 mg. Old Tuberculin

It is obvious therefore that if the method of testing samples be used, great care must be taken to secure that the samples are sufficient in number and truly representative.

Hart's findings are tabulated below. The group tested was not quite typical of the general population as all cases of tuberculosis had been excluded :-

Age.	No. tested.	(Adjusted) Percentage of series positive to Mantoux test.
0 - 2 years.	121	6. 5
3 - 5 "	124	18
6 -10 "	245	38
11 -20 "	127	70
21+ "	134	95

Hart thus showed that most children in the particular section of the London population which he tested, were non-reactors. However, by puberty, a majority of the children had been tuberculised (61 per cent. by 14 years) and nearly all by the age of 21.

These findings were of great epidemiological importance, indicating that the infection of the young was taking place over a long period of years, with the occurrence of late primary infections. The tuberculin test was also shown to be of use in clinical diagnosis in the young.

Testing 397 non-tuberculous L.C.C.patients, using the Mantoux test (0.01 mg. - 1.0 mg. O.T.) Kayne in 1934 found the following :-

Age.	Positive Reactions.
0 - 14 years	51%
15 - 29 "	82%
30 - 44 "	93%
45 - 59 "	84%
60 + "	86%

High figures in childhood, rising to a peak in adult life, and tending to fall in old age, were therefore encountered. It is important to notice that in the 15 - 29 years group, 82 per cent. had become positive reactors.

In 1934 Cory tested a group of children seen in

orthopaedic practice in London and the Home Counties. Of 136 children under 12 years, not being treated for tuberculosis, only 12.5 per cent. were Mantoux positive. Negative reactors were retested with 1 mg. Old Tuberculin. The detailed figures are given in the table, and are surprisingly low.

Age.	Positive Reactions.
0 - 6 years. 7 -12 "	7.4% 24.4%
0 -12 "	12.5%

In a study of 452 children examined at Leeds Tuberculosis Dispensaries, using the Mantoux test (0.1 mg. O.T.) Tattersall (1935) obtained the following figures :-

452 children, under 14 years were tested, 61 requiring to be notified as cases of tuberculosis.

Contacts with sputum pos.cases	88% pos.reactors.
" " " neg. "	51% " "
Non-contacts	51% " "

Analysis of those in contact with "open" cases of phthisis showed that in the age group 0 - 5 years, 90 per cent. of the children tested were already tuberculin sensitised. There was, in this area, a very marked difference in the tuberculisation of contact and non-contact children.

Critchley in Bath (1935) tested 200 contact and 100 "delicate children", using the Mantoux test (0.1 mg. - 10.0 mg. O.T.).

His results are given in the following figures :-

Age.	Positive Reactions.	
	Contacts.	Delicate Children.
0 - 5 years	65%	54%
5 - 10 "	85%	67%
10 - 15 "	85%	84%
0 - 15 "	79%	69%

These figures are very high for both groups. The second group may have contained tuberculous children, and not been representative of the general population.

Bradshaw (1939) tested 3,000 children in the Hospital for Sick Children, Great Ormond Street, London, with the Mantoux test, using 0.1 cc. of Tuberculin T. or 0.15 cc. of Tuberculin P.T. (Burroughs, Welcome). The few doubtful reactors were retested with a dilution of 1:100. There was some inconclusive evidence that the percentage of positive reactors had fallen between 1934 and 1938. The series as a whole gave 24.8 per cent. positive reactors :-

Age.	Positive Reactions.
0 - 4 years.	16.2%
4 -10 "	25.0%
10 -12 "	47.2%

As some readings were not made till the seventh day, quickly fading reactions may have been missed. On the whole, the findings were fairly satisfactory.

Price (1939) reported on the results of examining 1,500 children and young adults, mainly out-patients attending Dublin hospitals. Hamburger's ointment was used.

Her results, tabulated below, show low figures of tuberculisation, particularly in children from rural areas :-

Age.	Positive Reactions.
1 year.	4%
5 years.	16%
14 "	30% (urban children)
14 "	11% (rural children)
18 "	18% " "

Children under 14 years showed an average figure of 30 per cent. tuberculisation.

These figures are lower, and probably much nearer the general position, than those given by Crowe in his tests on a group of dispensary patients. It will be seen that infection in the section tested by Price was in the majority of cases delayed till after the school leaving age.

Crowe (1942) in an Irish rural area, used Hamburger's ointment, followed, if negative, by the Mantoux test (1 mg. O.T.), on 181 dispensary patients, suspected of tuberculosis.

The figures are set out below. Although higher than those of Price it is noticeable that tuberculisation had been avoided by one-third of the adults tested.

Age.	Positive Reactions.
0 - 5 years.	17%
5 -10 "	30%
10 -15 "	49%
15 -20 "	44%
Over 20 "	67%

Of the total number tested, 45 per cent.were positive.

Examining 437 Air Training Cadets, aged 15 to 18 years, in South Wales, and using a patch test"that gave less marked reactions than the Vollmer patch test", it was found by Gilchrist and co-workers (1942), that 37 per cent. were positive reactors, 54 per cent.negative and the remainder doubtful. 37, or even 46 per cent.

positive reactors seems rather low for an urban area, and may be due to faulty patch tests, but the result is rather encouraging, and the group should be tested again.

The Prophit Survey (Ridehalgh,1942) began in 1934, an ambitious scheme of investigation of various selected groups of the population by means of annual tuberculin tests and chest radiographs. Synthetic medium Old Tuberculin was used (0.01 mg. - 1 mg.). The minimum positive reaction accepted was "2mm. of definite oedema with surrounding erythema".

Among the controls aged 15 - 30 years only 7.5 per cent. were tuberculin negative; among the hospital nurses, 11.5 per cent.(voluntary) and 17.8 per cent. (municipal), and among boys aged 15 to 16 years, in naval training, 34 per cent. and 21.3 per cent., the rate depending on the proportion coming from rural districts. Since the production of a 2mm. area of oedema was regarded as a positive reaction, some of the positive reactions were really pseudo-reactions. It is certain that a larger percentage were really tuberculin negative, and that the figures quoted are too low. The findings are summarised below :-

Group.	No.	Positive Reactions.
Controls.	1543	91.2%
Contacts.	784	95.9%
Hospital Nurses		
(a) voluntary	953	84.8%
(b) municipal	523	76.3%
Medical Students (Preclinical)	1106	85.4%
Boys in Naval Training.	796 122	62.4% 73.0%

In a later report on the Prophit Survey, Daniels (1944) stated that further experience had shown that a standard of oedema of 2 mm. diameter was too low. The new standard adopted was 5 mm. erythema and oedema.

He gives some figures showing the reactions of nurses on entry to hospital, 3,764 nurses being tested between 1935 and 1943.

Age.	17	18	19	20-21	22-25	26-29	30+
No.tested	121	683	951	978	656	238	137
Positive Reactions(%)	72.7	78.0	80.3	79.6	63.5	87.8	89.8

These latter figures are more reliable and show that complete tuberculisation is not reached, even in the group over 30 years. About 10 per cent. of the nurses were tuberculised between the ages of 19 and 30 years.

In order to determine the real level of tuberculous infection in rural Wales, which had popularly been thought to be very high, T.E.Jones Davis (1943) performed a Jelly Test on the children at school in the County of Radnor.

2,176 children, equal to 88 per cent. of the number on the school register, were found to give only 141 (or 6.5%)positive reactions. The urban areas gave 10.8 per cent. reactors, as compared with 3.8 per cent. in the rural areas. The figures for the various age groups were very low.

Age.	Positive Reactions.
5 - 7 years.	3.8%
8 -10 "	7.2%
11 -13 "	7.5%

Jones Davies believes that these low figures are due to the comparatively favourable position as regards tuberculosis in Radnorshire, to the isolation of the various communities, and to the very low level of bovine infection in the area. A very interesting feature was that 76 per cent. of the positive reactors had a definite history of contact with persons treated for pulmonary tuberculosis.

This survey is apparently the first in which a complete picture of the tuberculisation of all the children in a given area, has been achieved. The results would perhaps have been easier to assess if the Mantoux test had been used, but the jelly test is probably sufficiently reliable to enable us to conclude that only a small minority of children in this area are tuberculised. A survey of the adults in this area would be invaluable.

In 1941, it was decided by E.J.Simpson (1944) at the James Mackenzie Institute for Clinical Research in St.Andrews, to add the Vollmer Patch test to the routine examination of children. The attendance at the Institute included more than half of all the children in the town. The results therefore, gave, almost certainly, a reasonable picture of the position in the entire child population of St.Andrews. 491 children were tested, just under one-third of the entire group being reactors.

Age.	Positive Reactions.
2 - 5 years.	21%
6 -10 "	32%
10+ "	45%

The addition of a tuberculin test to routine examinations at Infant Welfare and School Clinics would add greatly to our knowledge, besides improving the value of the examination. In Simpson's survey, 131 of the positive reactors were radiographed. Five cases of tuberculosis were discovered, with 14 children requiring observation. In this way, the patch test acted as a useful screening test for tuberculosis case finding, as well as giving a picture of the state of tuberculisation of the children of St.Andrews. The figures are similar to previous findings in this country. They indicate that approximately one-half of the children by the age of ten have already been tuberculised. This would have been considered satisfactory in past years but compares unfavourably with many United States surveys. Indeed, the figures are very similar to those of D'Arcy Hart, nearly fifteen years earlier.

Wishing to investigate the incidence of tuberculous infection in apparently healthy children in Bournemouth, Heimann and Paterson (1945) applied the jelly test to 800 children and adolescents seen at infant welfare centres and school medical inspections.

The figures obtained showed very low levels of tuberculisation (see below) reaching their highest incidence in children aged 5 - 10 years. After the 8th or 9th year had been reached, there was little increase in the frequency of infection. As a result of the test, six children were found to be cases of active tuberculosis. The authors were unable to explain why the increased frequency of tuberculosis in children since 1939 should have been accompanied by a decrease in the frequency of tuberculin sensitisation.

Age.	Positive Reactions.
0 - 5 years.	10.7%
5 -10 "	25.5%
10--15 "	23.0%

The following reports by Professors Blacklock and Fleming have been taken last because of their local interest.

In 1936 the former published the results of testing 2,000 children at the Royal Hospital for Sick Children, Glasgow, between 1932 and 1934. Old Tuberculin was used, to a dosage of 10 mg.

Age.	-1	1-2	2-3	3-6	6-9	9-13
Positive Reactions (%)	3.5	13.6	28	30.9	47.8	63.8

The high percentages of positive reactors may have been due in part to the inclusion of cases of tuberculosis- about 14 per cent. -and to the use of the larger doses of tuberculin.

The reactions of a further 4,000 children admitted

to the same hospital between 1938 and 1942 were described by Fleming (1943). In this series, 0.1 mg. Old Tuberculin was used.

Age	0-4	4-7	7-10	10-13
Positive Reactions(%)	9.3	26.3	38.1	44.8

Although living in an area where the tuberculosis problem is more acute than in England generally, these latter children showed an incidence of sensitisation very similar to that reported by other observers. The two Glasgow surveys are not strictly comparable, because of the difference in the dosage of tuberculin, but it seems likely that some decrease in tuberculisation had occurred in the intervening years, particularly in the older children.

United States.

In recent years, many writers have reported large scale surveys in the United States. A few have been here selected, to give some idea of the position in that country. It will be seen from the figures in the various tables that tuberculisation, in many areas, is infrequent in the young, and not complete in the adult.

In a study in 1935 Long,Seibert,and Aronson, using 0.0002 - 0.005 mg. P.P.D. found that 8,000 students at college in Eastern,Mid-Western, and Western parts of the United States gave respectively 50, 25-30, and 50 per cent. positive reactions. The unexpectedly high Western figures may have been due to the tendency of American tuberculous patients to migrate to that area. The more urbanised Eastern states gave higher figures than the Middle West. Another study of 100 freshmen in an Eastern college showed 60 per cent. reactors.

600 white and coloured children, under 14 years, who were general hospital patients, and tuberculosis contacts in Philadelphia, showed the following percentages of reactors :-

Age	Positive Reactions.
0 - 4 years.	18.5%
5 - 9 "	26.7%
10 -14 "	44.3%

These last figures are probably higher than the average since they are derived from a selected group of the population, but they are remarkably similar to many English reports for the normal population.

W.P.Shields (1941) tested over 4,000 subjects in Rhode Island Schools with the Mantoux test (first and second strengths of P.P.D. were again used), and compared his results with those obtained in a large scale survey in the United States in 1937 (Whitney and McCaffrey), in which 57,000 persons were tested.

Age.	Positive Reactions. (Per Cent.)	
	Rhode Island.	U.S.A.
0 - 5 years.	21	24.6
5 - 9 "	22	23
10 -14 "	45	33
15 -19 "	50	36
20+	69	58
All ages.	47.5	36.4

Shields' figures are generally higher than those for the larger survey perhaps again because Eastern States populations are more urbanised.

Many surveys of high school and university students have been made, showing rates of positive reactors varying between 20 and 60 per cent. It is obvious therefore that the state of tuberculisation of the adolescent and young adult must vary greatly in different parts of the country. Even the highest rates however in recent surveys are able to compare favourably with figures obtained in Britain.

Very low rates have been obtained in some studies of young school children. The following table is derived from B.H.Douglas (1939) describing a case-finding campaign in Detroit, 1937 to 1939, over 100,000 persons being tested :-

Age.	Positive Reactions.
0 - 9 years.	6.1%
10 -19 "	18.6%
20 -29 "	38%
30+ "	44%

The above figures are sufficient to indicate that even in large and notoriously overcrowded industrial towns, like Detroit, American conditions are such as to produce, at times, very low rates of tuberculisation.

In another exhaustive tuberculin survey, (reported in N.Eng.J.Med., 1941,225,428), in Chicago on this occasion, 167,000 school children were tested, (one-fifth of the second strength P.P.D.being used). It was found that the incidence of positive reactors had declined as compared with previous years, that coloured children had much higher rates than white children, that Mexican children were most often tuberculised, and that each district had its own "Mantoux rate". The complete figures are seen in the table below :-

Kindergarten & 1st grade school children gave 7% reactors
Eighth grade school children gave .... 20% "
High school children gave .... 21% "

Of 167,000 children tested, 27,401 (16.4%) gave positive reactions. These figures are similar to those of Detroit. Obviously most United States adolescents do not acquire a positive reaction until they leave school.

High figures are still obtained in certain selected groups of the American population. For example, inmates of mental institutions in Minnesota showed 82 per cent. reactors (Burns,1936). First strength and one-half

of second strength P.P.D. were used.

Many American writers have been able to show quite considerable decreases in the "Mantoux rate" in particular communities over a period of a few years. For instance, it was shown by F.Pascher (1934) that in New York City, the rates for 1934 had fallen in various age groups of the child population by 5 to 10 per cent. as compared with 1921-8. On the other hand, this is not always the case. A San Francisco report (Piscitelli,1939), showed no change between the years 1925-8 and 1937.

In view of the possible changes in the incidence of tuberculisation over a period of years, it is advisable, when discussing the results of surveys, and the data obtained on the incidence of infection, to mention the date of the survey.

Rich (1944) has made a rough survey of the present situation in the United States regarding primary infection. His figures, quoted by Pagel (1945), may be taken as a fair approximation :-

Age	4	9	14	19	24	29	34	35	44	49-75
Primarily infected (%)	10	25	35	45	55	65	75	85	90	95

Many more articles on tuberculin surveys in the United States could be quoted, but sufficient facts have been produced to show conclusively that although the situation varies greatly from place to place, in many communities in the United States very low rates of tuberculisation are encountered in the young. In adult life, higher rates obtain, and by the age of 30 years the majority of urban dwellers react to tuberculin. Even in adults, however, some surveys show figures far below comparable British figures. (W.P.Dearing in 1939 found that only 60 per cent. of adults, aged 40 to 49 years were positive reactors, in an area of Tennessee, and Douglas in Detroit in 1939 obtained positive reactions in less than 50 per cent. of adults over 25 years).

Other American Countries.

In Canada, the rate and degree of tuberculisation have also fallen, according to some reports. In a review of the children attending a contact clinic, in the Prince Edward Institute, H. Wright (1941) found a steady fall from 1933 onwards, in the percentage of positive reactors. His figures showed 57 per cent. reactors in 1933 as compared with 35 per cent. reactors in 1939 (0.1 - 1.0 mg. O.T. was used).

As these children were contacts, it is difficult to say with assurance what factor was responsible for the decrease in incidence of tuberculous infection.

Again, in Vancouver, E.S. James (1939) found that from 1934 to 1937 the percentage of reactors in children attending primary school had changed from 20 to 13. First and second strengths P.P.D. were used. The author cites as a factor in this change the absence of bovine infection.

In a survey in London, Ontario, J.R. Wilkey (1943) found low percentages of positive reactions in 4,000 subjects aged 12 to 20. The 12 years old group gave 10 per cent. positive reactors, which had changed to 23 per cent. in the 19 years old group.

Wilkey used 0.1 cc. of O.T. 1:2,000 as the single test dose and his figures are therefore certainly too low. However, if there were even a 20 per cent. error, the degree of tuberculisation would still be low.

F.G. Pedley (1943) sums up the Canadian position by saying that many young adults are tuberculin negative, the percentage varying from 30 to 80 in different places. It is common in Canada to find more than one-half of the young adults tuberculin negative, and the test is not only of epidemiological value, but is of great use in clinical diagnosis in children and adults.

This position is also present in certain other American countries. For example, a survey (Francis, 1941) of school children, nurses, suspect tuberculosis cases, and contacts, in Georgetown, British Guiana, showed only 66 per cent. positive reactors, for the age group 30 to 39 years. Of 1,826 non-contact subjects,

only 36 per cent. were positive reactors. Europeans had high rates of tuberculisation. This rather unexpected fact was thought to be due to their stay in England, Europeans who had never been to England being much more frequently tuberculin negative. Francis used the Mantoux test with 0.1 mg. Old Tuberculin.

Not all American surveys give so favourable a picture. The Cuban National Case finding campaign (Mencia et al., 1939) showed high figures, in marked contrast to those in the United States. Full dosage of P.P.D. was employed, except in children under ten years, where smaller amounts were used.

Age.	Positive Reactions.
0 - 1 years.	16%
1 - 4 "	19%
5 - 9 "	57%
10 -14 "	71%
15 -19 "	80%
20 -34 "	92%
35 -39 "	94%
60+ "	94%

The Cuban figures are an alarming contrast to those quoted previously. They are probably a reflection of the difference in standards of living, and adequacy in public health measures, between the other countries and Cuba.

Europe.

Many investigations have been made on the European Continent. These, as expected, showed varying degrees of tuberculisation, but there had, by 1939, been a general improvement on the figures of the earlier writers. Since then, the tuberculosis problem has of course altered, and many countries have had greatly increased mortality rates. This was not always accompanied by a corresponding increase in the tuberculisation of the general community. In fact, in France, the incidence appeared to be lower in 1943 than

it had been in 1938, approximately 38 per cent, of persons aged 21 years, being Pirquet negative (Rist, 1946).

This discrepancy was apparently due to the fact that the course of disease during the war was so rapid that death intervened before the patient had had time to infect many others. As a result, there was no increase in the numbers of new cases, and an apparent fall in the incidence of tuberculisation.

A somewhat similar state of affairs existed in Holland. Here Van Den Berg (1945) reports a large increase in the numbers of new cases and of deaths in the war years, accompanied by a definite decrease in the incidence of tuberculisation of subjects under 30 years of age (Pirquet test). The impression was obtained that many of the new cases were not due to recent exogenous infections, but were rather due to "flaring" of latent tuberculous lesions, that is, to endogenous reinfection.

Age.	Positive Reactions.
0 - 1 years	15.1%
1 - 2 "	13.9%
5 - 6 "	15.0%
11 -14 "	35.1%
15 -19 "	46.3%
20 -29 "	70.3%

In Scandinavia the incidence of infection has been falling steadily. In Sweden, comparatively untouched by the war, Törnell (1943) states that only 28 per cent. of children leaving school in his area, an industrial one, were tuberculised. Other writers have shown similar findings.

It is difficult to arrive at any conclusions concerning the other European countries involved in the war. It was known in Germany that approximately one-half of the children at puberty were tuberculin sensitive (Geberding,1940), but the present conditions may be different. This applies with even more force to

countries like Poland and Soviet Russia where the tuberculosis problem was very acute before the war.

Asia.

In many backward communities the conditions as regards tuberculosis are at least as bad as was Central Europe forty years ago. This applies particularly to many urban populations in Asia, where adverse factors - war, poverty, overcrowding, and poor nutrition - play an important part.

Tuberculosis is particularly prevalent in China. Investigators have shown high rates of tuberculisation, especially noticeable in the younger age groups in urban populations. Nearly 90 per cent. of students tested by Anderson (1934), proved to be positive reactors. In Peiping, 17 per cent. of children under one year, tested by Woo (1940), were tuberculin sensitive. Other reports show similar high degrees of tuberculisation.

Not all Asiatic towns, however, show such high incidence of infection. There must, of course, in so large a field, be great variations, as is shewn in some reports on Indian conditions.

In Sialkot, a congested industrial town in North India, Sahni (1942) found only 36 per cent. of the adolescents to be tuberculin positive by the age of 18 years. Old Tuberculin was used in dosage up to 1 mg. Even lower figures have been encountered in surveys of rural Indian communities. But tuberculosis is extremely widespread in India and a survey, with the same dosage as above, in Serampore (Lal,1943), is probably more representative of general conditions. The figures are tabulated below. The total number tested was 1,400.

Age	-1	4-5	5-10	10-15	15-20	30-35	45-50
Positive Reactions(%)	59	69	73	87	84	89	97

These very high figures, 69 per cent. being positive by the age of five years, were obtained from unselected

subjects, representative of the city as a whole.

An obvious need exists for further survey work in India, as part of a scheme to direct anti-tuberculosis work to the areas most in need of help.

CHAPTER 6.

Tuberculin tests in Cambridgeshire and Hertfordshire.

In 1942, the present writer began a tuberculin survey of the children and young adults in the town and county of Cambridge. In this region, the tuberculosis problem had never been very severe. This was perhaps due to the scattered and isolated nature of the rural communities, many of them in the Fenland, and to the fact that the only town in the county, Cambridge, had never suffered from the effects of industrialisation or from the severe unemployment which was so prominent a feature of our social life before the war, and which aggravated the tuberculosis problem.

Cambridgeshire therefore had been a fortunate area. In addition, the tuberculosis department had been very active since 1918, the presence of Papworth Sanatorium and Village Settlement making possible the segregation, often for many years, of infectious cases.

The subjects tested consisted of two groups. The first one, of approximately 350 persons, included all patients under the age of 30 years, examined at the Cambridge Chest Clinic. These consisted largely of suspect cases of tuberculosis, 24 cases of active tuberculosis, mainly children with glandular disease, and many contacts of tuberculous patients. A large proportion of the group were referred because of non-tuberculous conditions, such as bronchitis, bronchiectasis and pulmonary collapse, as the clinical practice is not confined to tuberculosis. The patients belonged largely to the hospital class but a considerable proportion belonged to groups more usually seen in private practice.

The second group was made up of 150 factory workers, mainly women, who were examined as part of the anti-tuberculosis programme of the Chest Clinic. These included three cases of tuberculous disease, one showing signs of activity.

As both of these groups consisted mainly of persons living in the county and borough of Cambridge, it was felt that a reasonable estimate of the position in the area

could be obtained.

In 1943 it became possible to compare the findings in Cambridgeshire with results obtained in the course of duties at Tuberculosis Dispensaries in the county of Hertfordshire. This latter county, although neighbouring Cambridgeshire, is of a different character, being less isolated, including in itself rural and urban areas, and being fairly close to London. Its population is about four times that of Cambridgeshire, and the conditions of life are typical of the Home Counties. In the case of Hertfordshire the reactions of 700 children under 15 years were considered, who had attended dispensaries as possible patients or as contacts.

The method of testing varied in the two areas. In Cambridgeshire, most subjects were tested with the Mantoux test, using 0.01 to 1 mg. synthetic medium Old Tuberculin. In many young children, and in order to test its reliability, the patch test was also used. In Hertfordshire, the Mantoux test was employed usually in a dosage of 0.1 mg. synthetic medium Old Tuberculin. Unless there were some clinical indication, 1 mg. Old Tuberculin was not used. About 300 children were tested by the Jelly test, either alone, or in combination with the Mantoux test.

During the war, both counties were reception areas, in which many tuberculous patients found refuge.

Tuberculosis statistics after 1939 were not published in full detail, for reasons of security. However, in tables Ia and Ib, the figures are given, for England and Wales, Cambridgeshire and Hertfordshire, of the numbers of new cases of tuberculosis, and of the death rates, for the years 1938 to 1944.

	New Cases					
	England and Wales		Cambridge-shire		Hertford-shire	
1938	50,689	100.0	137	100.0	375	100.0
1939	46,206	91.2	112	81.8	587	156.5
1940	46,572	91.8	168	122.6	609	162.4
1941	50,964	100.3	203	148.2	691	184.3
1942	52,619	103.8	185	135.0	630	168.0
1943	54,342	107.2	172	125.5	725	193.3
1944	54,313	107.2			742	197.9

Table Ia.

Comparison of numbers of new cases of all forms of tuberculosis from 1938 to 1944 for England and Wales, Cambridgeshire and Hertfordshire. The annual returns have been compared, 1938 being taken as 100.

	Death Rates per 1,000 living.		
	England and Wales	Cambridge-shire	Hertford-shire
1938	.591	.41	.48
1939	.583	.42	.44
1940	.673	.38	.47
1941	.735	.50	.54
1942	.668	.39	.48
1943	.619	.51	.44
1944	.593		.45

Table Ib.

Comparison of the death rates for all forms of tuberculosis from 1938 to 1944 for England and Wales, Cambridgeshire and Hertfordshire.

Table Ia shows that the wartime increase in new cases affected both counties more than the country as a

whole, and Hertfordshire far more than Cambridgeshire. The national death rate for the years 1938 to 1944 (Table Ib) shows a gradual increase, at its greatest in 1941. The Cambridgeshire figures reveal a parallel increase, but Hertfordshire was fortunate in having, apart from the year 1941, a small decline in its death rate.

It is difficult to draw conclusions from these tables, but it seems that the large increase in new cases in Hertfordshire was without effect on its death rate, except in 1941.

It is certain that with the increase in the numbers of tuberculous patients during the war, the chances of infection and sensitisation to tuberculin were greater than in pre-war years, especially in Hertfordshire.

The main aims of the investigations were to gain some idea of the frequency of tuberculisation in normal groups of the population, and to ascertain whether tuberculin tests were likely to be of value in adults.

The Cambridgeshire Survey.

In table II the figures are given of the results of testing 485 persons under 30 years, seen at the Cambridge clinic. These included cases of tuberculosis and contact persons, and the results therefore cannot be taken as typical of the general population. The table does indicate, however, what routine testing in tuberculosis dispensaries may be expected to show, that even in this selected population, only 55 per cent. of the children aged 10-14 years are tuberculin positive, and that over 10 per cent. of the adults are non-reactors.

From the total number examined were extracted all those who were clinical cases of tuberculosis or who had been in contact with such cases (Table III). The remainder, 270 in all, of whom more than one-half had been tested as part of a routine medical examination, were considered as fairly representative of the population of the area. Indeed, by the exclusion of cases and contacts, they might well have been less tuberculised than the general population.

For children under 15 years, the numbers are small and too much reliance cannot be placed on them. It is, however, likely that the figures of 22 per cent. positive reactors for all children under 15 years, and 42 per cent. for children between 10 and 15 years, are fairly accurate. Less than one-half of the children of the latter group are tuberculin positive, and testing is therefore a very useful procedure.

As regards the older subjects tested, it is seen that one-third of those between 15 and 20 years were still tuberculin negative, and, of those between 20 and 30 years, nearly one-fifth had escaped infection. This is quite a substantial proportion of the total, and shows that the theory that tuberculisation is inevitable and universal, is not entirely true. In clinical cases where the diagnosis is in doubt, it will be worth while in the Cambridge area, to test with tuberculin all adults up to 30 years, there being, in persons free from tuberculosis, and not in contact with a case of tuberculosis, a 20 per cent. chance of a negative reaction.

Examination of the figures for the persons in contact with cases of tuberculosis showed a familiar picture (Table IV). Those in contact with sputum-negative cases, although few in number in this series, gave figures higher than those obtained from the "non-tuberculous non-contact" group, but much lower than those given by the subjects in contact with sputum-positive cases. These last persons showed a high incidence of positive reactors, over 60 per cent. for children more than five years old, rising to over 80 per cent. in adult life. The latter figure was identical with that obtained from the same age-group in the "non-tuberculous non-contact" series.

In view of the discussions in the past on the difference in tuberculisation between town and country-side, it was considered that Cambridgeshire, with its very marked contrast in living conditions between the busy overcrowded town and the sparsely inhabited, isolated rural areas surrounding it, might give information of interest. Subjects were therefore divided into the three categories of those living in Cambridge, those living in the rural area, and those

who had lived mainly outside the County (Table V).

Although the figures for the complete age-groups showed almost identical results in all the categories, consideration of the results of the tests in childhood and adult life revealed three important findings.

First, the surprising fact emerged that under 15 years of age, the level of infection was more than 20 per cent. higher in the rural areas than in Cambridge itself. It is probable that bovine infection was responsible for this high level of tuberculisation in the rural children, and indeed it was seen at the Clinic that many of the cases of glandular tuberculosis were in children from the countryside.

Secondly, in the age group 15-29 years, the frequency of infection was 27 per cent. lower in the rural areas than in Cambridge. This was in conformity with the suggestion that rural life in Cambridgeshire offered less opportunity for infection.

Thirdly, the results of the tests in those persons who had lived mainly outside the County, showed a remarkable similarity to the findings for the town of Cambridge. It is likely, therefore, that in spite of its many advantages, Cambridge does not show a lower level of tuberculisation than other areas, mainly in Southern England, from which the persons tested were drawn.

Age	No.	Positive Reactors	Negative Reactors
0-4	33	13 (39.4%)	20 (60.6%)
5-9	67	26 (38.8%)	41 (61.2%)
10-14	82	45 (54.9%)	37 (45.1%)
15-19	97	72 (74.2%)	25 (25.8%)
20-24	138	114 (82.6%)	24 (17.4%)
25-29	68	58 (85.3%)	10 (14.7%)
0-14	182	84 (46.2%)	98 (53.8%)
15-29	303	244 (80.5%)	59 (19.5%)
0-29	485	328 (67.6%)	157 (32.4%)

Table II.
Tuberculin reactions of total number tested (Cambridgeshire).

Age	No.	Positive Reactors (%)	Negative Reactors (%)	Probable Error ⁜	Positive Reactors. Actual Increase (%)	Positive Reactors. Relative Increase (%)
0-4	8	0	100		9	-
5-9	33	9	91	±3.4	33	36.3
10-14	33	42	58	±6.8	22	38.2
15-19	64	64.1	35.9	±4.0	17.8	47.6
20-24	76	82.9	17.1	±2.9		
25-29	56	82.1	17.9	±3.5		
0-14	74	22.1	77.9	±3.3	54.4	
15-29	196	76.5	23.5	±2.0		
0-29	270	61.8	38.2	±2.0		

Table III.

Tuberculin reactions in 270 "non-contact non-tuberculous" persons (Cambridgeshire).

⁜ Probable Error. Differences in the incidence of positive or negative reactions are not regarded as significant unless they are at least equal to the Probable Error x3.

Age	Contacts of sputum positive cases		Contacts of sputum negative cases		Non-contacts	
	No.	Positive Reactors	No.	Positive Reactors	No.	Positive Reactors
0-4	12	5 (41.7%)			12	4 (33.3%)
5-9	15	11 (73.3%)			41	11 (26.8%)
10-14	28	18 (64.3%)			40	21 (52.5%)
15-19	26	24 (92.4%)			68	45 (66.2%)
20-24	44	37 (84.2%)			82	69 (84.1%)
25-29	7	7			58	48 (82.8%)
0-14	55	34 (61.8%)	19	7 (37%)	93	36 (38.7%)
15-29	77	68 (88.4%)	18	15 (83.3%)	208	162 (77.9%)
0 -29	132	102 (77.3%)	37	22 (59.5%)	301	198 (66%)

Table IV.

Comparison of frequency of positive reactions in 470 contact and non-contact persons in Cambridgeshire.

Age	Cambridge (Borough)		Cambridgeshire (Rural)		Outside Cambridgeshire	
	No.	Positive Reactors	No.	Positive Reactors	No.	Positive Reactors
0-14	90	35 (39%)	56	36 (62.5%)	36	13 (36.1%)
15-29	143	120 (83.9%)	61	41 (67.2%)	99	83 (83.9%)
0-29	233	155 (66.5%)	117	77 (65.8%)	135	96 (71.1%)

Table V.

Comparison of frequency of positive reactions in persons living mainly in Cambridge, Cambridgeshire and outside Cambridgeshire.

The Hertfordshire Survey.

In the part of the work performed in Hertfordshire, all examinations were made, as previously stated, in the course of ordinary dispensary work. As in the previous part, the results were collected of the tuberculin tests of those persons free from tuberculosis and not in contact with cases of the disease (Table VI). This again is a selected group with the bias towards producing a favourable impression of the degree of tuberculisation.

For the children under 15 years, of this group, the percentage of positive reactors was 25.5, while for children between 10 and 15 years the percentage was 45.3.

In the case of 200 children, in contact with sputum-positive cases, the corresponding figures were 64.3, and 78.6 respectively. Indeed the youngest children, under five years, showed a percentage of 52.6 positive reactors (Table VII).

Difference in Reactions according to Sex.

Analysis of the incidence of reactions showed a lesser frequency, not statistically significant, among the female subjects tested.

Age	No.	Positive Reactors (%)	Negative Reactors (%)	Probable Error *	Positive Reactors. Actual Increase (%)	Positive Reactors. Relative Increase (%)
-1	5	0	100			
1	11	0	100			
2	25	8	92	±3.7	4.5	4.9
3	40	12.5	87.5	±3.5	5.0	5.7
4	40	17.5	82.5	±4.1	1.5	1.8
5	74	19	81	±3.1	1.4	1.7
6	54	20.4	79.6	±3.7	2.7	3.4
7	52	23.1	76.9	±3.9	(-4.9)	(-6.4)
8	33	18.2	81.8	±4.5	19.8	24.2
9	29	38	62	±6.1	6.4	10.2
10	27	44.4	55.6	±6.4	(-7.7)	(-13.8)
11	30	36.7	63.6	±5.8	2.0	3.2
12	31	38.7	61.3	±5.9	15.5	25.3
13	24	54.2	45.8	±6.7	1.8	3.9
14	25	56	44	±6.7		
0-4	131	10.7	89.3	±1.8	11.6	
5-9	242	22.3	77.7	±1.8	23.0	
10-14	137	45.3	54.7	±2.8		
0-14	510	25.5	74.5	±1.3		

Table VI.

Tuberculin reactions in 510 "noncontact, nontuberculous" children (Hertfordshire).

Age.	No.	Positive Reactors. (%)	Negative Reactors. (%)
0-4	74	52.6	47.4
5-9	66	63.6	36.4
10-14	56	78.6	21.4
0-14	196	64.3	35.7

Table VII

Tuberculin reactions in 196 children, contacts of sputum positive cases (Hertfordshire).

Comparison of results in Cambridgeshire & Hertfordshire.

Comparison of the surveys is complicated by the fact that, as already mentioned, the method of testing varied in the two areas. The use of the intradermal test with 1 mg. Old Tuberculin in Cambridgeshire showed a certain number of reactors missed by a less intensive search, such as occurred in Hertfordshire. In spite of this, the results show lower figures in the former area in several of the groups tested, and it is probable that tuberculisation occurs less often in early childhood in Cambridgeshire than in Hertfordshire.

It is possible to compare two classes in the two counties. In the case of the "nontuberculous noncontact" groups (Table VIII), Cambridgeshire numbers are very few, but do suggest that the incidence of infection is lower in that county in the children under ten years, than in Hertfordshire. The figures for children between 10 and 15 years, and for the whole group, are similar in the two surveys. It is probable that these findings, that approximately 25 per cent. of all children under 15 years of age, and approximately 45 per cent. of children between 10 and 15 years, are positive reactors, are valid for areas other than the two counties, since other surveys have shown similar findings.

Comparison of the results of testing children in contact with "open" cases of phthisis show high figures in both areas, over 60 per cent. being reactors in both surveys (Table IX).

Age.	Cambridgeshire.		Hertfordshire.	
	No.	Positive Reactors (%)	No.	Positive Reactors (%)
0-4	8	0	131	10.7
5-9	33	9	242	22.3
10-14	33	42	137	45.3
0-14	74	17	510	25.5

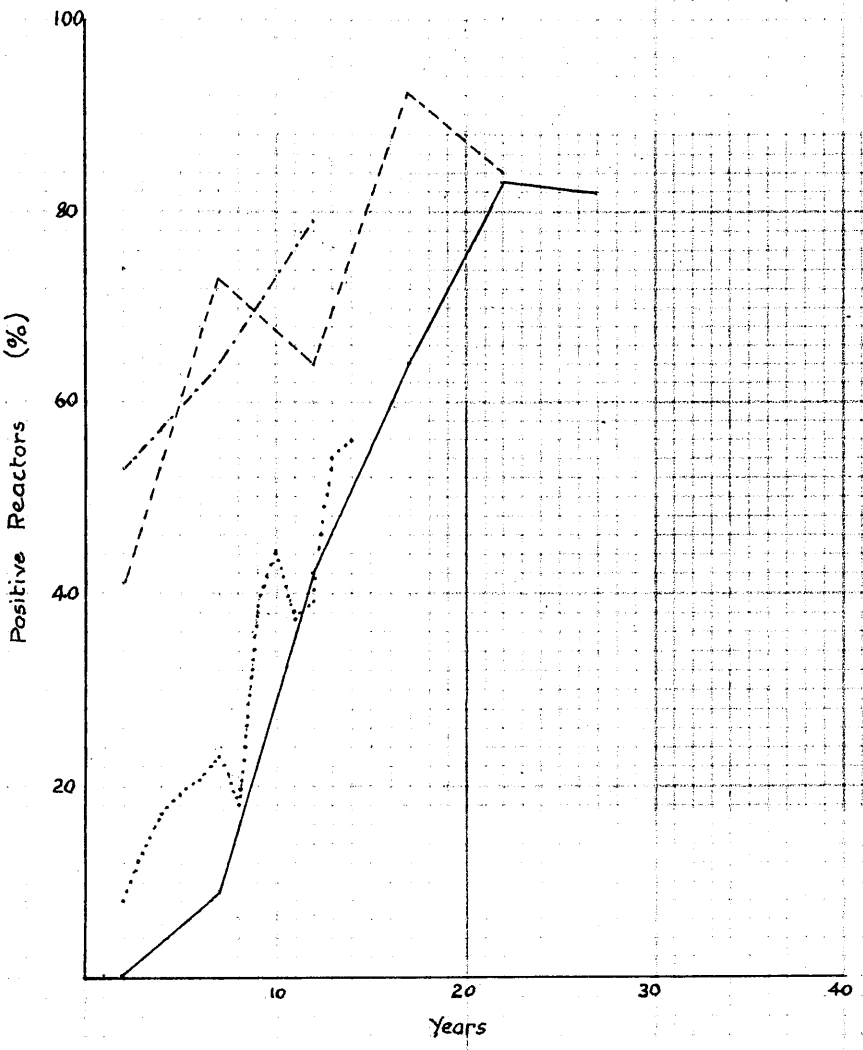
Table VIII

Comparison of incidence of positive tuberculin reactions among "noncontact, nontuberculous" children in Cambridgeshire and Hertfordshire.

Age.	Cambridgeshire.		Hertfordshire.	
	No.	Positive Reactors. (%)	No.	Positive Reactors. (%)
0- 4	12	41.7	74	52.6
5- 9	15	73.3	66	63.6
10-14	28	64.3	56	78.6
0-14	55	61.8	196	64.3

Table IX.

Comparison of incidence of positive tuberculin reactions among children, contacts of sputum positive cases, in Cambridgeshire and Hertfordshire.



——— Non-contact non-tuberculous persons (Cambridgeshire). 1 mg. O.T.

..... Non-contact non-tuberculous persons (Hertfordshire). 0.1 mg. O.T.

------ Contacts (Sputum Positive cases) Cambridgeshire. 1 mg. O.T.

-.-.-.- Contacts (Sputum Positive cases) Hertfordshire. 0.1 mg. O.T.

Comparison with other tuberculin surveys.

It is instructive to compare the results obtained with the findings of other writers, already described in previous pages. It will be seen that the incidence of positive reactors was much higher in the surveys performed by D'Arcy Hart (1932), Kayne (1934), Tattersall (1935), and Blocklock (1936). Cory's figures obtained from children in orthopaedic hospitals in 1934 tended to be lower, while Bradshaw's results (1939) were similar to those of the present writer. Both Price (1939) and Jones Davies (1943), working with children with rural backgrounds, found much lower levels of infection. The results of tests in Glasgow in 1943 by Fleming showed a striking similarity to the writer's findings, although tuberculous children were included. In the work of Simpson (1944), the percentages were higher for the children under ten years, but similar for children over this age. The Bournemouth survey by Heimann and Paterson (1945) showed results very like those of this writer, in the younger groups, although for older persons, their figures were much lower.

In his study of the Papworth children Brieger (1944) reports a higher frequency of tuberculisation, inevitable in a Tuberculosis Settlement.

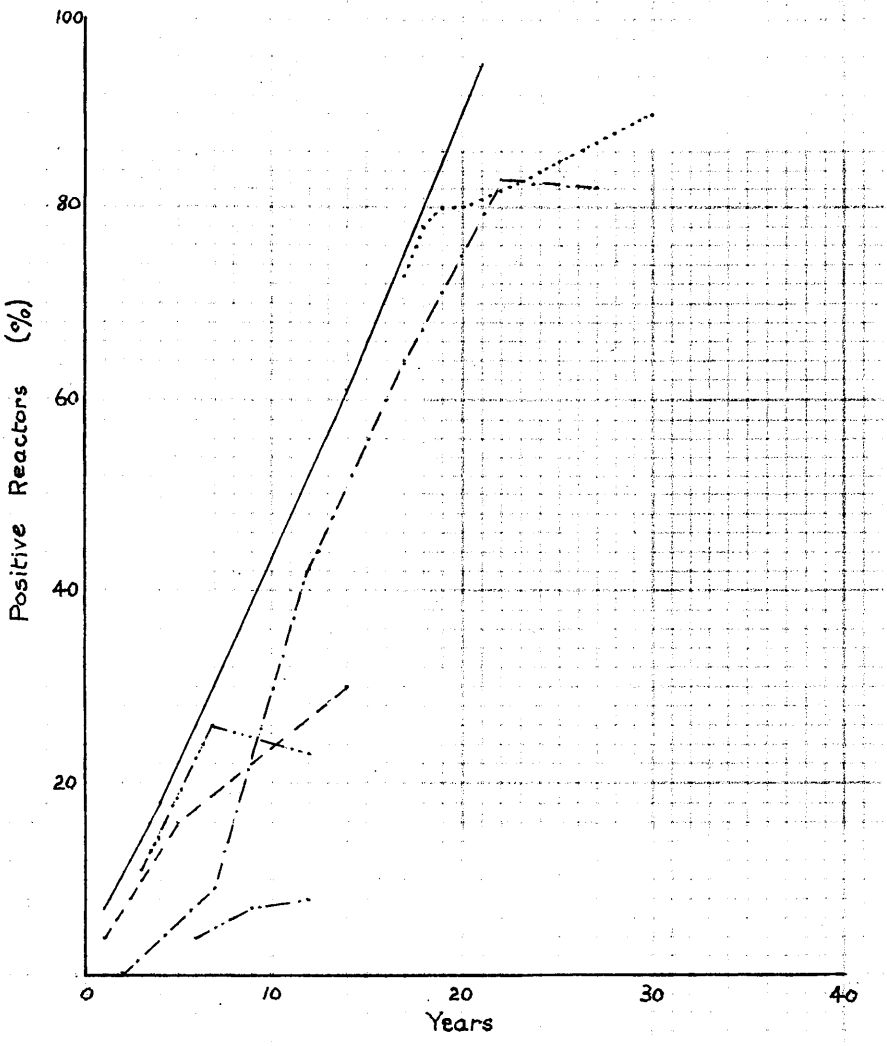
It may be concluded then that there has been a definite decrease in the amount of tuberculisation over the last 15 years, particularly in the younger children.

Turning to foreign countries, the picture is more varied. Many surveys, particularly those performed about ten years ago, on the Continent and in the United States, show a state of affairs similar to that revealed by the present work (Söderström,1931; Groth-Petersen,1936). More recent investigations however, particularly in Scandinavia, the United States and Canada, reveal lower levels of tuberculisation, especially marked in the older children and young adults. (See Törnell,1943; Rich,1944; Pedley,1943). Some areas still show a high level of tuberculisation, and this is usually an indication of a backward community (Mencia, 1939; Lal,1943).

It may be deduced therefore that we are, in this country, in an intermediate position as regards tuberculisation, that we have progressed in the last 15 years, but have not reached the low levels found in certain other countries. This finding is in keeping with the changes in tuberculous mortality and morbidity rates observed in recent years.

The tendency for tuberculisation to become less frequent in the younger members of the community means that primary infection is being postponed until adolescence or adult life. This tendency is even more marked in many other countries. The decline in the incidence of infection is not always striking from a mathematical point of view, especially when compared with the corresponding decline in tuberculous mortality and morbidity rates. On analysis, however, it is unreasonable to expect the figures of sensitisation to show the same decrease as have, for instance, the mortality rates in the last forty years. Since infection may be the result of random and even single encounter with an infectious case, and the resultant sensitisation, in the vast majority of cases, lasts for many years, it will be seen that the tendency for positive tuberculin reactors to become fewer in number will not be marked over short periods of time, unless a striking diminution in the opportunities of infection has occurred.

In some measure then, the tuberculin survey, with its information concerning the tuberculisation of the community, is a better indication of the widespread danger of tuberculous infection than the mortality and morbidity rates, and is a useful corrective to over-optimistic views. It is probably true to say that only when the majority of the community pass through life without a primary infection, will the tuberculosis problem really have been overcome.



——— Hart (1932). 100 mg. O.T.

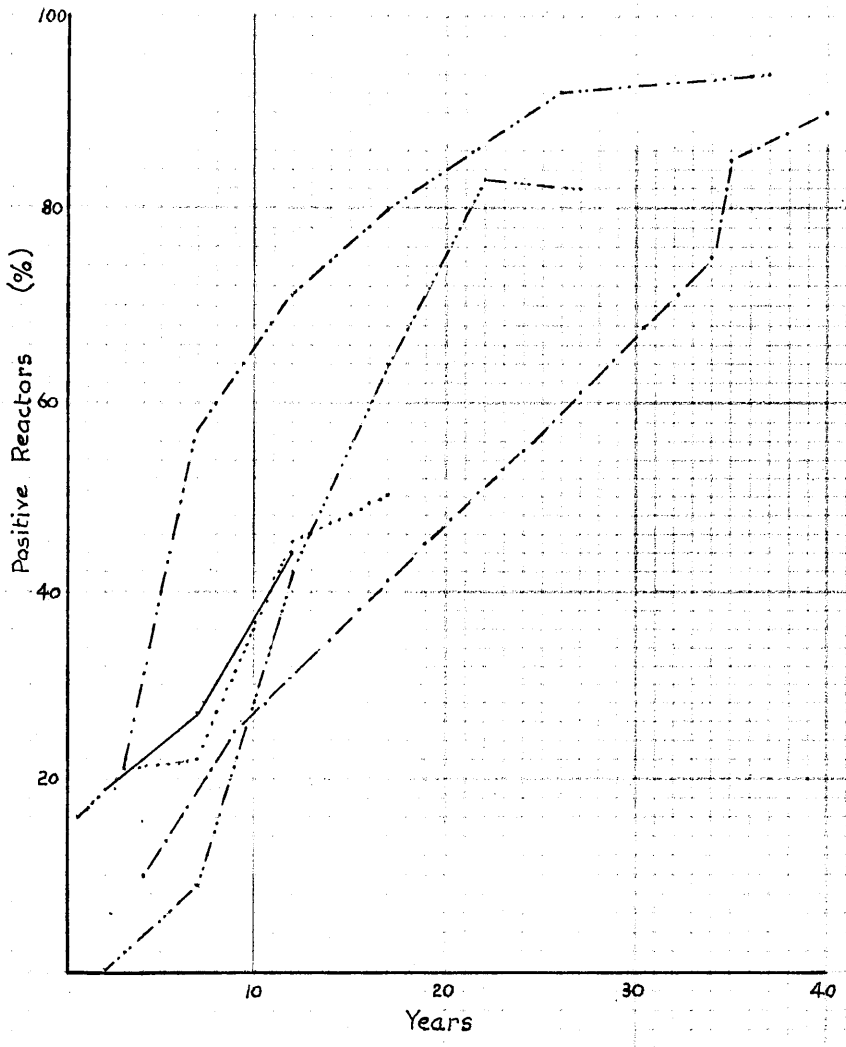
------ Price (1939). Hamburgers Ointment.

-·-·-·- Jones Davies (1943). Jelly Test.

-··-··- Heimann (1945). Jelly Test.

····· Daniels (1943). 1 mg. O.T.

-·-·-·- Non-contact non-tuberculous group (Cambridgeshire). 1 mg. O.T.



——— Seibert (1935). 1st & 2nd Strength P.P.D.

..... Shields (1941). " " " " "

-.-.-.- Rich (1944).

—.—.— Mencia (1939). 1st & 2nd Strength P.P.D.

—..—..— Non-contact non-tuberculous group (Cambridgeshire). 1 mg. O.T.

CHAPTER 7.

Comparative Value of Tuberculin & Radiological Surveys.

A heated controversy, particularly in the United States, has taken place on the relative merits of tuberculin and radiological surveys, these methods being often regarded as excluding each other. Tuberculin surveys have this virtue, that they are inexpensive, and easy to perform, and demonstrate, with a high degree of accuracy, the incidence of sensitisation in a given population. Radiological surveys, on the other hand, are expensive and difficult to perform, and do not give any real estimate of the numbers of persons who have been infected. They fail in this because many pulmonary lesions are too small to be recognised or are hidden by other structures, and because many primary lesions are extrathoracic (12 per cent. -Myers,1939). In the Royal Air Force, only 1.6 per cent. of personnel showed radiological evidence of healed or active tuberculous infection (Trail et al. 1944). It is therefore frequently the case that a subject who is tuberculin sensitive may present a completely normal radiograph of the chest. Radiological surveys have this great advantage, however, that they lead directly to the diagnosis of cases of tuberculosis. Of lesser importance is the fact, discussed more fully in a later chapter, that radiographic examination may occasionally reveal evidence of tuberculous infection in tuberculin-negative persons.

The two methods then seem to be complementary. In epidemiological surveys, the tuberculin test gives more accurate information on whether previous infection by the tubercle bacillus has occurred. In case-finding campaigns, the radiograph is much the more useful.

Occasionally, where the sensitisation incidence is low, it will be possible, usefully, to combine the two methods. In these circumstances, all the persons to be investigated will be tuberculin tested first, and only the positive reactors radiographed. From the point of view of "case-finding" this combined procedure will only be worth while where the percentage of

positive reactors is low, e.g. less than 33 per cent. This combined method is suitable, at the present, most often in children, and in this group is economical. It is usual, nowadays, in tuberculin surveys to radiograph all positive reactors.

It is to be hoped that the increasing use of mass radiography in this country, will not lead to a continuation of the neglect of the tuberculin survey. Both methods have their value whether they are used singly or together. The dramatic results of radiological surveys should not be allowed to overshadow the important, although different, information obtained from tuberculin surveys.

CHAPTER 8.

Clinical Significance of the Positive Tuberculin Reaction.

In this, and the following two chapters, main attention will be paid to the clinical, rather than epidemiological, importance of the tuberculin test.

A positive reaction is, as stated previously, usually the result of tuberculous infection. Reactors may on investigation prove to have a primary infection, or occasionally show "adult type" disease. In the great majority of positive reactors, no clinical evidence of active tuberculosis can be found. What then is the clinical significance of a positive skin test ?

In adult life, a positive reaction means little of clinical importance. This was not recognised at first, and for a time, patients were sent to sanatoria on the basis of positive skin tests, since these were thought to indicate the presence of active disease. When it was shown that most reactors to tuberculin were not suffering from active tuberculosis, but had merely a healed primary infection, this practice ceased.

The position of the test then changed. Since it was believed that most persons were tuberculised, the test was thought of little value. This conception has now altered, of course, and the test has an accepted place, particularly in the examination of children and adolescents, when it must be performed in every case where tuberculosis is suspected.

In infancy, positive reactions are of the greatest significance, and are often the only indication that tuberculous infection has occurred. Under the age of two years, it is generally recommended that a child with suspicious clinical symptoms or signs, who is a positive reactor, should be considered and treated as a case of active primary tuberculosis. In the absence of other indication of active disease, the child with a positive reaction should remain under observation as a suspect case.

Although children are notoriously susceptible to

tuberculous disease, observation of many young contact children tuberculised before the age of two years, has shown that the prognosis is by no means as unfavourable as was sometimes thought some years ago (Calmette,1928). These children often appear quite normal in health, and the majority remain well (Lloyd and MacPherson, 1933).

The prognosis in children under two years, who have positive reactions and are suffering from clinical tuberculosis is, of course, very different and the disease often pursues an unfavourable course. The possibility of generalisation, or development of bony or glandular disease is especially present in this age group. Despite this, recovery often occurs, and it is not unusual, in the case of pulmonary disease, to see considerable radiological opacities gradually disappear, while the child maintains reasonable health.

In the investigation of possible activity of primary tuberculosis in a child, attention must be paid to the opportunities for infection which have existed. A child always in contact with a tuberculous parent may well have a healed lesion by the age of two, or even less, while if the child has been in contact only a short time previously, a sufficient period may not have elapsed to permit of the healing of the disease. In the latter case, the positive reaction indicates an unhealed primary infection.

Between the ages of two and five years, the presence of a positive skin reaction is not as strong evidence of active disease as in the younger child. The positive reaction has to be considered with the presence or absence of clinical findings, and the opportunities for recent infection. The younger the child, and more recent the infection, the more likely is the infection to be still active. The distinction must always be made, of course, between active disease, and progressive disease. As stated previously, many active lesions heal satisfactorily.

Over five years, a positive reaction in itself is even less conclusive evidence of active disease, and often is only an indication of a previous primary infection which has healed in a satisfactory manner.

As routine testing becomes more frequent, it will sometimes happen that a positive reactor is known to have been a negative reactor at a previous investigation. This position often occurs in the supervision of nurses and medical students in hospitals and sanatoria, and of contact children in tuberculosis dispensaries.

When a nurse, or child, shows conversion from the noninfected to the infected state by the change to a positive tuberculin reaction, the further investigation indicated may reveal clinical disease requiring treatment. Again, if in any doubtful clinical case, it can be shown that the patient has recently become a positive reactor, the diagnosis of active tuberculosis is made easier. The information given by routine testing is therefore of great value.

Occasionally, the clinical problem will occur, of the child with an illness of doubtful origin, who is known to have been a positive reactor in the past. The knowledge of the skin test will not prove very helpful in most of these cases, except in so far as tuberculosis must be considered as a possible cause of the illness. This would apply particularly to infants. The possession of a positive reaction in childhood is far from being an index of immunity, although an healed primary infection is some indication of good resistance.

Where routine tests are performed, many symptomless primary infections will be detected. The question of treatment of these conditions then arises. Opinion has varied greatly on this point. Many writers, in the absence of clinical signs or symptoms, would merely maintain observation of the patient, while others recommend prolonged rest and subsequent convalescence. D.Price of Dublin is probably the main exponent of the latter point of view.

The opponents of this conception of primary tuberculosis suggest that there is no definite evidence that rest influences the course of healing of these symptomless primary infections, and that the policy would mean treating a large proportion of the child population as possible cases of tuberculosis.

The implication of this discussion as regards the tuberculin tests are obvious. If it were proved that active treatment, such as bed rest, were helpful in inducing primary infections to heal more quickly, or more surely, then the value of the tests would be enormously enhanced.

The present writer is convinced of the value of knowing when a primary infection has occurred, and is therefore in favour of the routine testing of children. He is not convinced that the positive reactor free from any symptoms or signs of active disease requires prolonged bed rest, or that this treatment would be practicable, if attempts were made to carry it out on a large scale. Advice on proper nutrition and rest, with avoidance of fatigue and strain, and medical supervision is all that is required usually. The provision of "preventoria" and summer camps would be useful, particularly for children from poor homes.

Conclusion.

The positive tuberculin reaction has its greatest value in infancy and early childhood, or where the subject is known previously to have been a negative reactor. The diagnosis of "childhood" or primary tuberculosis cannot be made with any degree of accuracy without the use of the tuberculin test.

CHAPTER 9.

The Significance of the Negative Tuberculin Reaction.

In discussions in the past on the tuberculin test, doubt was sometimes expressed about the significance and value of the negative reaction. In theory, all tuberculised persons, including of course, all cases of clinical tuberculosis, gave positive reactions, and the uninfected, and non-tuberculised, correspondingly gave negative reactions. This simple state of affairs was complicated by the disturbing fact that many writers had reported cases of clinical tuberculosis with negative tuberculin reactions.

The problem can be presented under three headings. First, is it true that all infected persons are positive reactors to tuberculin; secondly, do positive reactors ever lose skin sensitivity and become negative reactors; thirdly, are negative reactors, for example, in adult life, sufficiently numerous to make tuberculin testing worth while?

The Negative Reaction in Clinical Tuberculosis.

Most of the writers reporting negative reactions in clinical cases, used either the von Pirquet test (von Ruck,1909), or the Mantoux test with 0.1 mg. Old Tuberculin (Maxwell,1930; Moncrieff,1931).

These tests are probably approximately equal in sensitivity, and produce reactions in most cases of clinical tuberculosis. There is no doubt, however, that a certain number of patients do fail to react, and that, as a result, absolute reliance cannot be placed on these tests, so far as negative reactions are concerned.

This state of affairs was altered when higher doses of tuberculin began to be used more frequently in the Mantoux test. With the injection of 1 mg., 10 mg., or even 100 mg. i.e. undiluted Old Tuberculin, almost all cases of tuberculosis could be made to react. There were, however, a small number of cases which failed to react to even the highest doses of tuberculin. These

were often meningeal or miliary in type, or moribund cases of phthisis. This group did not number usually more than about 2 per cent., and in some series was almost non-existent.

In his investigation, D'Arcy Hart (1932) found that only 2.2 per cent. of his cases were negative reactors to undiluted Old Tuberculin. This was only 0.5 per cent. less than the number failing to respond to 1 mg. Old Tuberculin which successfully detected 97.3 per cent. of the cases.

Again, using the comparatively small dose of 0.2 mg. Old Tuberculin (1:500) Lyle Cummins (1933) was able to produce reactions in 95 per cent. of a series of cases. Long et al., (1935), testing 45 cases, obtained positive reactions in all of them. In a series of 169 tuberculous children, Vollmer (1938) obtained a positive response to Purified Protein Derivative and the patch test, in 98 per cent. of the children.

Many other reports could be quoted, but it may be accepted now that almost all clinical cases of tuberculosis will respond to tuberculin, a small percentage requiring large doses to evoke a reaction. A further very small percentage will fail to produce a reaction even to undiluted tuberculin. From the statistical point of view, this group is so small as to be of little significance. From the clinical point of view, the group should be remembered. This applies particularly in children.

Even when these exceptional cases have been considered, it remains that a definite negative tuberculin test, adequate dosage having been used, is a very strong indication of the absence of clinical tuberculosis.

The Negative Reaction in Tuberculised Persons.

The next question is whether all infected persons react positively to tuberculin. It is often impossible to answer this question, since in the absence of clinical tuberculosis or radiological evidence of disease, only the test can furnish the required information.

It may be that, as in the case of clinical tuberculosis, occasional tuberculin tests, even where full dosage has been employed, give misleading results. Tuberculised subjects' skin sensitivity varies within wide limits, and it is necessary to use a dosage of 1 mg. Old Tuberculin, before a negative reaction can be trusted. (Since stronger dilutions do not produce many more reactions, and there is always the danger of an excessive reaction with oedema and vesiculation, it is not worth while, in ordinary work, using a larger dose than 1 mg.). Many surveys in the past have shown that nearly all adults - not cases of tuberculosis - were positive reactors (e.g. Opie and McPhedran,1926; Heimbeck,1929; Lyle Cummins,1933). Since all, or nearly all, (95 per cent. or more) of these adults tested, reacted positively, it seems reasonable to assume that for practical purposes, tuberculised, but not actively ill persons, usually react positively to the tuberculin test, the percentage of reactors increasing with the use of larger doses of tuberculin, until, with the injection of 1 mg. Old Tuberculin, almost all reactors are discovered.

The Latent Period following infection.

A special class of negative reactor requires mention here. This is the subject who has been recently infected, but has not yet acquired skin sensitivity. It is stated (Wallgren,1941) that about four to seven weeks elapse between first infection and development of skin allergy. This is an important point in clinical work among the young. In suspicious cases with negative skin tests, it is often worth while repeating the test after an interval of a few weeks.

Desensitisation by Tuberculin.

Another, and less important source of false negative reactions, is the subject who has been desensitised by repeated doses of tuberculin. It is possible, by injecting large doses, to desensitise, and produce a state of skin "anergy". This, it is well known, is sometimes done by farmers wishing to pass an

animal as tuberculin negative. The usual doses employed in the tuberculin test in man are not likely to desensitise. They are, indeed, found to increase the reaction to subsequent injections of tuberculin (Forbes,1938).

Other Factors influencing the Reaction.

Most tuberculous skin diseases are associated with high sensitivity to tuberculin, particularly the tuberculides, which are an expression of the body's allergic response to infection. A group of skin diseases does exist, however, believed by some to be tuberculous in origin, in which the majority of subjects show definite tuberculin "anergy". Of these, Sarcoidiosis is the best known, and a negative tuberculin reaction is a suspect case, in an adult, is helpful confirmatory evidence. There is also some evidence that the presence of acne tends to lessen the frequency of positive reactions to tuberculin, as to other bacterial products (Lynch,1944). In common with cases of clinical tuberculosis sensitised subjects may show depressed reactivity when suffering from advanced disease or toxic conditions, of a non-tuberculous character. Measles and Scarlet Fever are particularly known to cause this in childhood (Westwater,1935). The rash in these specific fevers may alter skin sensitivity for a period. The tuberculin response has also been reported, probably erroneously, to be affected by pregnancy, menstruation, senility, debility, etc. etc.

The Persistence of Positive Reactions.

The question of the permanence of positive reactions may now be discussed. This is an important and rather controversial point, and is bound up with the interpretation of minor abnormalities seen in chest radiographs.

It was at first generally thought that positive reactors remained so throughout their lives. This was due either to the original stimulus of the primary

infection, or to the continued presence of living tubercle bacilli in the primary complex, particularly in the hilar glands, or to the "boosting" effect of repeated reinfections through the course of the years.

In view of the persistence of the positive reactions the sensitisation incidence could be regarded as equivalent to the attack-incidence of infection, i.e. to the number of persons who had ever been infected.

Towards the end of life, in the latter years, the reaction occasionally became negative. This "senile anergy" was due either to the fading of the allergic response after complete healing of the lesion, or to the failing powers of the body, with resultant loss of skin sensitivity. Whichever the case, the elderly often showed some decline in the incidence of positive reactions (Pascher et al., 1941; Amazon,1943). Apart from the aged, who constituted a special group, the persistence of reactions in the child and adult was of importance to the epidemiologist as well as to the clinician. If positive reactions frequently became negative, then tuberculin surveys revealed only a part of the population which had been infected and the sensitisation incidence was not equivalent to the attack-incidence of infection. On the other hand, if after the healing of lesions, the tuberculin test usually became negative, then the sensitisation incidence was rather equivalent to the incidence of unhealed, i.e. active, infections in the community tested.

If the first supposition were true, the value of the test considerably lessened. If the second, the standing of the test changed, and a new value appeared.

Animal experiments in the past, have shewn that, with the healing of a tuberculous process, tuberculin sensitivity often gradually wanes (Krause,1916,1927; Willis,1928). The allergy is not completely lost, however, for larger doses of tuberculin than usually employed, succeed in producing a response (Willis,1928). Many clinical observations were also made (Heimbeck, 1927,1928; Opie,1930) describing the loss of skin sensitivity in man following the healing of tuberculous disease, but in those cases, the Mantoux test was not

employed with the largest doses, and there is therefore the possibility that the skin sensitivity had merely lessened, and not completely disappeared.

When routine testing of contacts and of children became frequent, more information became available. When Lloyd and MacPherson in 1933 retested 1,200 children who had been examined at the Brompton Hospital in 1931, they found that 96 per cent. of the positive reactors were still positive, but that 4 per cent. had become negative. If only those were considered who were fully tested (1 mg. O.T.) then merely six cases (2 per cent.) had lost their sensitivity. Of the positive reactors, very few showed lessened allergy, but one-half of the total number showed increase in their skin sensitivity.

A similar review by D.Zacks (1942) of more than 1,000 feeble-minded subjects in an institution in the United States, who had been tested ten years previously, showed that an average of 3 per cent. changed from positive to negative reactions. The greatest change, 12.7 per cent., occurred in children aged 5-14 years, while the smallest change, 1 per cent., occurred in those over 20 years. Similar findings were reported by Dahlstrom (1940) from the Henry Phipps Institute, when contacts were examined over a period of ten years. In the Prophit Survey of young adults F.Ridehalgh (1942) also found 1 to 2 per cent. of the positive reactors becoming negative each year. Some of these may never have been definitely positive reactors, as Ridehalgh accepted very small reactions. In a careful investigation, Törnell (1943) calculated that only 0.1 per cent. of the positive reactions changed, annually, to negative reactions.

It was commonly observed that many of those who became negative reactors had originally given rather feeble reactions. Further tests with full doses of tuberculin might possibly have succeeded in procuring positive reactions. It was the case that the skin allergy tended to decrease less frequently, as contact was maintained with a case of tuberculosis. In Dahlstrom's series, only 1½ per cent. of his positive reactors, who were in continuous contact with sputum positive cases, became negative reactors. (It is

possible that in Dahlstrom's cases many of the reactions which failed to be repeated, had originally been only pseudo-reactions to large doses of Purified Protein Derivative).

Radiographic examination of the chest has tended to confirm the view that some infected subjects have negative reactions. Very many observers (Amazon, 1943; Ridehalgh, 1942; Savage, 1941; Lumsden et al., 1939; Crimm and Short, 1939) have reported the finding in tuberculin-negative persons of lesions thought to be tuberculous in nature. These lesions are of the "primary complex" type, or more often consist of hilar glands without a visible primary focus, are usually calcified, and apparently healed. The incidence reported has varied widely.

The recognition of abnormalities in the pulmonary hilar shadows is often difficult, and opinions may vary. Amazon (1943) submitting a series of routine radiographs to several observers, found their estimates of evidence of tuberculous infection to range from 22 to 62 per cent!

In addition to the difficulty in deciding when a hilar shadow is abnormal, there is the further complication that not all enlarged hilar shadows or calcified hilar or pulmonary lesions are necessarily due to tuberculous infection, although the great majority are. Some caution is therefore required in accepting the figures of the writers mentioned previously. There do however undoubtedly exist a number of persons with radiological evidence of, usually healed, primary infection, with negative tuberculin reactions. This group, a small proportion of those giving negative tuberculin reactions, confirms the reports that a certain number of positive reactors change to negative reactors in the course of time. It is possible that some of these may never have been positive. It is probably untrue to say, as Allen (1932) maintains, that skin sensitivity can be lost, in short periods of time. The evidence rather suggests that the change takes place gradually, over a period of several months, if not years. Again the statement by Pottenger and Pottenger (1943), that children with hay fever, asthma, etc., treated with a special diet and adrenal cortex,

become less "allergic" generally, and often lose their tuberculin sensitivity, requires further confirmation.

The position then, of the tuberculin test, is as follows. As far as is known, most reactors remain positive throughout life. A very small proportion become negative in the passage of time, presumably with the healing of slight, usually primary, infections; a larger proportion become negative in old age, possibly for the same reason.

A tuberculin survey reveals nearly, but not quite, all those who have been infected, at any time. A small proportion of persons with healed and obsolete infections is missed. The sensitisation-incidence is therefore nearly equal to the attack-incidence of tuberculous infection. This is probably the position obtaining in this country, and it gives the tuberculin test a place of importance in the estimation of the tuberculosis problem.

Frequency of Negative Reactions.

The frequency of negative reactions is a crucial point in tuberculin testing. Only where there is a reasonable chance of obtaining a negative reaction does the tuberculin test become worth while from a clinical point of view. As Mantoux said, in 1910, "contrary to most clinical methods, the value of the intracutaneous test lies in negative results". Apart from clinical work, if sufficient persons are tuberculin negative, the test can be used in case finding campaigns to eliminate the noninfected subjects, and concentrate attention on those sensitive to tuberculin.

Until ten or fifteen years ago, it was generally believed by clinicians in this country that negative reactors were so rare as to make the tuberculin test not worth performing, since almost all patients were positive reactors. As a result the test was largely neglected. It then began to be shewn that a large proportion of children of school age were non-reactors, particularly children who had not been in contact with "open" cases of pulmonary tuberculosis. The detailed figures are given in the chapter on tuberculin surveys.

The tuberculin test thus became extremely useful in

children, particularly those suspect of tuberculosis, for whom a negative reaction usually means an altered diagnosis, and in contact work.

The point now arises as to whether the test can be of use in adolescents and adults, that is, whether improving conditions are causing primary infections to be delayed or even avoided in a reasonable proportion of the population. From a study of the various findings in the reports quoted in Chapter 5 and from the author's work, it appears that the change of encountering negative reactions in young adults not suffering from clinical tuberculosis is substantial, and that it is clinically worth while to perform this test, at least to the age of eighteen years approximately. After this age, when it may be that over three-quarters of the persons tested will produce positive reactions, it is probably not worth while tuberculin testing as a routine measure. In particular or doubtful cases, the test may be useful especially in areas where tuberculisation is of a low order. Thus, in the United States at present, in rural areas, tuberculin tests in adults are a useful procedure. This may well apply also in some of our isolated communities, and is the state to which our population may proceed in the future. Even now, according to the Cambridgeshire figures it is possible to encounter a sample of an adult population which is not completely tuberculised, the figure being between 80 and 90 per cent. In the Prophit Survey, Ridehalgh (1942) found that no less than 25 per cent. of the Irish nurses tested were tuberculin negative. His figures, in this case, are likely to err on the low side. There is then, in clinical work, a place for the tuberculin test in children and young adults.

The questions about the value of a negative test can be answered, with some degree of certainty :-

1) Almost all persons negative to an adequate tuberculin test are free from clinical tuberculosis, and have not been tuberculised. Infrequently a negative reactor may prove to be infected, or rarely, to be a clinical case.

2) A few negative reactions are due to the waning of

skin sensitivity, with the passage of time, in obsolete cases of infection.

3) Negative reactors are sufficiently numerous to make the test worth while performing in children and young adults.

CHAPTER 10.

Value of Tuberculin Test in the Contact Clinic.

In recent years, increasing attention has been devoted to the examination of contacts. This study has been useful as a means of detecting possible sources of infection, and, particularly in children, of diagnosing new cases. It is in the case of the young contact that tuberculin testing becomes of major importance. It is now possible to ascertain whether a child has been infected or not, and in those uninfected, by periodic tests, to learn when infection and sensitisation occur, with all the resultant dangers.

In contradiction to some statements about the inevitability of infection, it is fairly common to find children in contact with an "open" case of phthisis who remain tuberculin negative for considerable periods. This is particularly the case where home conditions are good, and no overcrowding exists.

Contacts do show an increased frequency of tuberculisation at early ages, the frequency varying in different surveys. In this connection the work of Opie (1935) may be quoted. He found in children up to 14 years, 87.5 per cent. of home contacts reacting to tuberculin, while only 53 per cent. of those not in contact were positive. Again, Enid Williams (1938) in Cardiff found in contacts under five years, 66 per cent. positive reactors. These figures are rather higher than those obtained by this writer, namely, 42 and 53 per cent. respectively, in Cambridgeshire and Hertfordshire (see Table VIII), but are nearer to Brieger's figures (1944) for the Papworth children.

A distinction can be drawn between contacts of "sputum positive" and "sputum negative" cases. The contacts of "sputum negative" cases often show lower rates of tuberculisation. Tattersall (1935) found no difference in the frequency of positive reactors among these children and non-contact children - 51 per cent. - while contacts of "sputum positive" cases showed 88 per cent. reactors. Lloyd and MacPherson (1933) also observed that contacts of "sputum negative" cases did not differ greatly from non-contact children in the frequency of tuberculisation. These findings have

again been confirmed, although the numbers of "sputum negative" contacts were small, in the Cambridgeshire work.

It is well known that many so-called "sputum negative" cases, if examined by the modern methods of culture of sputum or gastric contents, can be shown to be excreting tubercle bacilli. The infectivity of these cases has been difficult to ascertain, but since children, in contact with cases considered "sputum negative" after ordinary examination of sputum, do not show high rates of tuberculisation, it is suggestive that these cases are not usually infectious, although some of them can be shown to be excreting tubercle bacilli.

Investigation of Contact children.

Contacts fall into two classes, depending on their reaction to tuberculin.

Positive reactors require full investigation, including a chest radiograph. In the case of the young child, under two years, it is, as stated previously, often justifiable to regard a positive reactor as a suspect case, even in the absence of other findings, and maintain observation for some time. Older children and young adults with no clinical abnormality require examination and chest radiographs at least once per year. This supervision is usually maintained for two years after the last possible occasion on which infection may have occurred.

Negative reactors require slightly different treatment. In the absence of clinical abnormality, it is sufficient to perform a Mantoux test with 0.1 mg. Old Tuberculin, or one of the reliable percutaneous tests. If the clinical findings are at all suggestive of disease, it is essential to ascertain that the child is really tuberculin negative by repeating the test with the Mantoux test, using 1 mg. Old Tuberculin. Where clinical findings are strongly indicative of tuberculous infection, the tests, if negative, should be repeated six weeks later, because of the "incubation period" between infection and development of hypersensitivity. This position is unlikely to occur

frequently, since by the time clinical findings are present, there has usually been a sufficient interval for the development of the characteristic skin changes.

While the possibility of infection continues, the negative reactor should be retested at each examination. If the reaction becomes positive, complete examination is of course required, and careful treatment, with the emphasis on adequate nutrition and rest, if any suggestion exists of active disease. If there is reason to believe that conversion to the tuberculin positive state has been recent, and insufficient time has elapsed to allow of healing of the primary lesion to have taken place, then it will usually be wise to maintain supervision, and modify the patient's activities.

The tuberculin negative subject, no longer in contact with the infecting case, does not require supervision for more than six months after the contact has ceased.

It will be seen from the above that tuberculin testing has an important place in the examination and supervision of contacts. This role will be enlarged in the future if B.C.G. inoculation of persons in contact with cases of tuberculosis becomes a recognised procedure in this country. Since the use of B.C.G. is safe only in tuberculin-negative persons, and since effective immunisation by B.C.G. is demonstrable only by the conversion from the tuberculin-negative to the tuberculin-positive state, it seems that the tuberculin test is destined to play an increasing part in the work of the contact clinic.

General Conclusions.

The positive tuberculin reaction is the result of skin hypersensitivity to tuberculin following upon infection by the tubercle bacillus. The active principle in tuberculin is protein in nature, and bacillary in origin.

Of the many tuberculin tests, the Mantoux test is the most accurate. In contact and survey work, the Vollmer patch and the jelly tests are sufficiently reliable in children, and easier to use.

The use of nonprotein synthetic media has produced tuberculin less likely to evoke nonspecific reactions. These nonspecific reactions are not a source of confusion if no reaction is accepted as a true positive, which shows less than 10 mm. erythema with oedema.

In many countries, tuberculin surveys reveal that a large proportion of the community do not undergo primary infection until adult life. This tendency has been present, to a lesser extent, in this country, and is shown by the results of tuberculin testing 1,200 persons in Cambridgeshire and Hertfordshire.

In these areas, approximately one-half of the children leaving school were still tuberculin-negative. In Cambridgeshire, tuberculisation was not complete even at the age of 30 years. Rural children in Cambridgeshire were more frequently sensitised than urban children, but this position was reversed in the adults, among whom the subjects from rural areas were less tuberculised than those from the town.

Young children were less frequently infected in Cambridgeshire than in Hertfordshire, but in other respects, the results for the two areas were very similar to each other, and to other investigations in the United Kingdon.

Persons in contact with "open" cases of tuberculosis were more frequently tuberculised than those not in contact, but many children remained tuberculin-

negative in spite of prolonged risk of infection.

The clinical significance of the positive tuberculin reaction is greatest in infancy, or where the subject is known to have been a negative reactor. Hypersensitivity to tuberculin usually persists, but, in a small number, may lapse with the passage of time or with the healing of infection.

The negative tuberculin reaction implies, in the great majority of cases, freedom from tuberculous disease, and from tuberculous infection.

The incidence of sensitisation revealed by tuberculin surveys is nearly equal to the attack-incidence of infection.

Tuberculin and radiological surveys have different functions. The former give a more accurate picture of the frequency of tuberculous infection.

APPENDIX.

Risk of Infection.

Attempts have been made to analyse tuberculin surveys, and derive mathematical data from them. Tuberculin surveys do not, however, readily lend themselves to strict mathematical treatment, since so many variable factors are present in the tuberculin reaction and its reading. The results of these studies must therefore be interpreted with some caution.

Tuberculin surveys are able to throw some light on the risk of infection. Infection depends largely on two factors, the receptivity of the subject, and the chances of infection in his environment.

Both of these factors are influenced by the age of the subject. It is well recognised that preschool children are particularly receptive to infection, but, except in a tuberculous milieu, are not frequently exposed to human infection. School children are thought to be much more resistant to infection, but increasingly become exposed to chance infection as their activities take them from home. Young adults appear to be less resistant to infection which they are liable to encounter frequently. These factors influence the infection, morbidity and mortality rates of the various age groups.

Tuberculin surveys have been analysed in order to throw light on this problem of the risk of infection. The simplest method is to consider the increase in the percentage of positive reactors each year. This figure is the absolute risk of infection. Its value is limited since the tuberculin test shows the risk of infection only for the non-reactors, who of course, become fewer during each year. It is therefore useful to calculate the relative risk of infection, that is, the percentage of new positive reactors in relation to the number of negative reactors at the beginning of each year, or age period.

Törnell (1943) has gone into this study in some detail. He believes that the infection risk is fairly constant for each age group, but that it varies between the groups, being smaller during infancy and school life than during working life. Scheel (1933) states that the

greatest change occurs between the ages of 15 and 20 years, a period also of increased stress and activity, and in which a considerable morbidity is found.

Törnell has suggested a formula for the calculation of the risk of infection. If Po and Pn are the percentages of negative reactors at the beginning and end of n years, and k is the constant for infection, then $Pn = Po\ (1-k)^n$.

In surveys, Po and Pn will usually be known, and k can then be calculated. Where this is known for a period of years, the constant for infection for single years may be found by the formula $K_1 = 1 - \sqrt[n]{1 - k_n}$.

This figure is said to correspond well with the annual relative risk of infection.

These findings have been applied to this writer's work, but it was found, possibly because of the smaller numbers used, that the relative infection risk was not a constant figure. Agreement existed with Scheel's statement that the greatest rate of conversion occurred between the ages of 15 and 20 years.

The calculation of the risk of infection is shown in Tables III and VI, pages 66, 69.

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