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TUBERCULIN THERAPY.

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by

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TUBERCULIN THERAPY.

The search for a specific remedy against tuberculosis is almost as ancient as medicine itself.

Preceded by the recognition of the tubercle bacillus by Robert Koch in 1882 as the cause of tuberculosis in all its forms, the introduction in 1889 of tuberculin by the same author was the first attempt to treat the disease on etiological grounds.

Koch's identification of the bacillus as the specific infecting agent, like most discoveries in other branches of knowledge, was preceded by a large amount of speculation as to the cause of the malady.

Regarded as contagious in olden times Villemin,¹ in his communication of December 1865 on the cause of tuberculosis and the inoculation of the same from man to rabbit, was the first to place the infective nature of tuberculosis on a solid experimental basis, and to show that the disease had its origin in an inoculable agent which was readily transmitted from man to some of the lower animals.

Cohnheim² in 1887 showed that guinea-pigs inoculated with tuberculous sputum died from general peritonitis.

Progress was carried a step further by Pasteur's investigations of bacteria, and by some it is even considered possible that had he not been engaged in other directions Koch's great discovery may have been anticipated by some years.

Klebs³ in 1877 was the first to observe actual transference of the virus by artificial culture on egg albumen through several generations before inoculating, although he did not succeed in recognising the bacillus.

He did however find a mobile organism which he presumed to be the cause.

Aufricht⁴ in 1881 and Baumgarten⁵ in 1882 recognised bacilli in the centre of tubercles, but owing to lack of culture and staining methods, were unable to positively identify them as the infecting agent.

To Robert Koch a medical officer of Wollstein, a small town in Polish Prussia, fell the great distinction in 1882 of isolating and making known the distinctive characters of a bacillus, and of establishing its invariable association with tuberculosis.

His previous investigations into anthrax and experimental traumatic fever by perfecting the methods of research paved the way for his brilliant discovery.

His first attempt to demonstrate the bacillus was by staining with methylene blue made faintly alkaline with caustic potash using vesuvin as a counterstain.

He demonstrated the bacilli in all kinds of tissues human and bovine, except where the lesions were caseous or healed.

Further he showed that this organism fulfilled the four conditions which later came to be known as Koch's postulates, viz:-

(1) That the organism should always be found microscopically in the bodies of animals having the disease; that it should be found in that disease and no other, and that it should occur in such numbers and be distributed in such a manner as to explain the lesions of the disease.

(2) That the organism should be obtained from the diseased animal and propagated in pure culture outside the body.

(3) That the inoculation of these germs in pure culture which had been freed by successive transplantations from the smallest particle of matter taken from the original animal, should produce the same disease in a susceptible animal.

(4) That the organism should be found in the lesions thus produced in the animal.

In 1890 Koch was led to his second great discovery of tuberculin; by observing that when a healthy guinea-pig was inoculated with a pure culture of the tubercle bacillus the wound after a few days appeared to heal; but after a further period of from ten to fourteen days, a hard nodule developed which broke down, and remained as an ulcer until the death of the animal.

A totally different result took place when a tubercular, or better still, when a guinea-pig successfully inoculated for four or six weeks previously, was the subject of experiment.

Here the wound healed as before but no nodule appeared and on the second or third day the site of inoculation became hard, assumed a dark colour and spread to a diameter of from 0.1-1 cm.

Finally the indicated area became necrotic, and was cast off, leaving a flat ulcer which quickly and permanently healed, without infection of the regional lymphatic glands, showing that the animal by virtue of the previous infection had acquired such a degree of immunity as to withstand the second inoculation.

He further found that sterilized cultures of tubercle bacilli, when injected in quantity into healthy guinea-pigs did not give rise to general infection, but only to local suppuration, and that in tubercular animals small quantities sufficed to kill within a short time.

If however, very small quantities were given, not only did a fatal result not occur, but improvement followed.

When emulsified bacilli were used, they remained local for a considerable time, were not absorbed, but gave rise to local abscess formation, and at the same time the animal improved, showing that something had been extracted by the fluids of the tissues, from the bodies of the dead bacilli, whilst that giving rise to the abscess was more slowly liberated.

It was the search for this curative agent, evidently liberated from the bodies of the dead bacilli which led to the discovery of tuberculin.

Koch's idea of its mode of action.

As the result of his researches Koch came to the following conclusions:-

(1) That tuberculin did not kill the tubercle bacilli in the tissues.

(2) that it only acted on living tubercular tissue.

(3) that on dead caseous matter it had no action.

(4) that its action was associated with increased vascular and metabolic changes in the living tubercular tissues, causing it to slough or melt away.

This he thought explained why, although an animal may be very susceptible to a small initial dose the quantity could be so rapidly increased, less and less living tubercular tissue being left for responsive action to the tuberculin.

When no further reaction occurred he concluded that all living tubercular tissue was removed and that therefore the animal was cured, but this we now know not to be the case, and that the negative response must be regarded only as immunization against a bacterial toxin.

His recommendation of tuberculin as a therapeutic agent initiated a new era in the treatment of tuberculosis and was based chiefly on his observations on guinea-pigs and its action on lupus.

The remarkable curative effects recorded in many cases of lupus and other forms of tuberculosis led to its extensive use in all stages of the disease without discretion, and in spite of the repeated warnings of Koch himself as to the danger of large doses, and his insistence that man was far more susceptible to its action than guinea-pigs.

He further emphasized the importance of early recognition more especially in the treatment of phthisis, and the danger of its administration in advanced cases.

The result was that many advanced cases were treated wrongly with too large doses which were followed by severe reaction and permanent injury, or dissemination of the liberated bacilli.

In addition to this faulty method of administration, at that time, the part played by mixed infections and influenza was not fully recognised, and so tuberculin as a therapeutic agent fell into disrepute.

But the greatest blow was struck by morbid anatomists, among whom Virchow⁶ was the most prominent, and to whose work is due largely, the discredit of tuberculin.

Their opinions were based chiefly upon examinations of cases which had had a fatal termination, and which had been treated with tuberculin, but post mortem findings have only a relative value in estimating the curative

action of any specific agent, when carefully selected cases are chosen; cases for example which have been under treatment for long periods, and where death has taken place either suddenly or from some intercurrent disease.

No such discrimination was shown in their selection and most of them were advanced cases which proved nothing more than that tuberculin had been ineffectual, or at the most, that in these instances tuberculin for some reason or other appeared to be contra-indicated.

The Reintroduction of Tuberculin.

Although tuberculin had fallen into disrepute with the great body of practitioners, there still remained a small group of workers, notably Goetch, Hager, Krause, Thorne, and especially Carl Spengler, and to whom the credit of re-establishing its recognition is chiefly due.

The severe reaction with destruction of tissue and setting free of the tubercle bacilli which large doses occasioned, and which were the dangerous features insisted upon by morbid anatomists gave the indication for materially reducing the dosage, and thus as far as possible avoiding reaction.

This reactionless method of administration which characterizes our modern treatment dates from the year 1891, and is attributable to the afore mentioned pioneers, although Ehrlich, Guttman, and Petruschky at the same time, and apparently independently used it in the outpatient department of Koch's Institute.

In 1901 Goetch⁷ brought the subject prominently before the profession, basing his assertions on the number of permanent arrests obtained by its use, and the modern method of administration is usually associated with his name.

In recent years owing largely to the brilliant researches of Wright and his Opsonic Theory, which is essential for the proper understanding of the mechanism of immunity to many infectious diseases and especially to tuberculosis, the importance of vaccine therapy has become more generally acknowledged, and treatment established on a scientific basis.

Metschnikoff had already observed that many infecting agents called forth little or no phagocytic response in healthy animals, but that in artificially immunized ones an active response occurred and this he attributed to substances formed in the serum during immunization which stimulated phagocytosis.

The important part played in immunity by the cells by taking up bacteria under the influence of a substance, called by Wright "Opsonin" has now become more fully recognised.

Wright formulated a method of enabling the opsonic power of a serum being determined and thus gave a guide to more accurate therapeutic dosage.

This important branch of blood work appeared destined in future to play a great part in the prevention and cure of many diseases.

Bacteria are so altered by the opsonins that they can easily be taken up by the leucocytes and digested.

As shown by Metschnikoff the leucocytes unaided have no power of taking up bacteria.

Opsonins vary in amount in different individuals, and in the same individual at different times, and under different conditions. Hence a varying degree of immunity.

Further these opsonins appear to be specific, that is, each organism has its own; thus the opsonin for the staphylococcus has no action on the tubercle bacillus and vice versa.

It therefore follows that where we can measure the amount of opsonin present, we can estimate the resisting power of the patient to the causative organism.

Wright's method of estimating the opsonic index is a relative one, and is available for almost any organism, the only difference being in the preparation of the emulsion of micro-organisms.

Two tests are made, one with the serum of a healthy person, and one with that of the patient, and the number of ingested organisms in a given number of leucocytes counted in that belonging to the patient, and that of the healthy person.

The ratio between the two gives the Opsonic Index, Thus if 60 organisms were counted in a certain number of polynuclear leucocytes of the patient's serum, and

120 in that of the control "healthy serum" the opsonic index would be $\frac{60}{120} = .5$ indicating that the patient had only half the normal amount of opsonin, and therefore only half the resisting power to the particular bacterium in question.

Mode of action and preparation
of the various Tuberculin.

The three chief tuberculins which we owe to Koch and which may be taken as a basis upon which all other tuberculins have their origin, are Old Tuberculin, (O.T.) New Tuberculin (T.R.) and New Tuberculin Bacillary Emulsion.

In order to understand their action it is necessary to keep in mind their respective aims either in producing an active or a passive immunity.

By active immunity is meant a change in the organism which results from the action of the bacteria or their products and which leads to the development of protective bodies "ante bodies" in the serum.

By passive immunity on the other hand we mean the production of immunity by a specific serum; the organism receives ready made ante bodies from another animal without any exertion on its own behalf.

Old Tuberculin.

Its preparation and action.

Koch's original animal experiments, which however were never published, were made with a tuberculin which

he named "Original Tuberculin" (T.O.) and differs from the old tuberculin as now understood, only in that it was not concentrated by boiling.

It was made in the following manner: pure cultures of the tubercle bacillus which had grown for 4 to 6 weeks on a 5% glycerine broth, were filtered, and the filtrate concentrated to one tenth its volume thus obtaining in a fifty per cent glycerine medium the soluble bodies secreted by the tubercle bacilli.

Immunity against Bacterial toxin and Bacteria.

With old tuberculin the aim is immunity against a bacterial toxin not against the bacteria themselves, they contrive to live as in the similar case of tetanus and when the toxic immunity has passed off many survive and kill the animal.

With cholera and typhoid the case is different; here it is a pure bacterial immunity; animals treated with fresh agar cultures are protected against the bacteria, but not against the toxins secreted by them.

Living bacteria are destroyed in the bodies of the immunized animal.

Koch's desire was to combine these two forms of immunity in the treatment of tuberculosis, and he thought he recognised a tendency towards this in the acute miliary tuberculosis of man, and the experimental tuberculosis of the guinea-pig, for in both at one stage very few bacilli are to be found, which appears

to be in reality a process of immunization against the bacilli, but at too late a period.

His object was to get the action earlier, but a necessary condition seemed to be to have the bacteria scattered in the tissues, as in some infectious diseases, when the infecting agent not only attacks one organ in particular but by means of the circulation affects the whole body, and where one attack usually confers natural immunity; he therefore aimed at ensuring absorption of as many bacilli living or dead as possible.

He attributed failure to acquire immunity against the bacilli, to their slow growth and stationary character which in the ordinary chronic forms of tuberculosis amounted to little more than a local infection.

His first attempts with this new method failed because the unaltered bacilli were not absorbed and only gave rise to local suppuration.

He then tried by extraction with decinormal soda to obtain as far as possible all the substances contained in the bacilli.

This gave better results, but contained some bacilli which although dead gave rise to local abscess formation.

Finally by grinding a well dried culture without any addition in an agate mortar he accomplished a complete breaking up of the bacilli.

The powdered mass was then stirred up in normal salt solution and separated by centrifuging with two layers, an upper one which contained the glycerine soluble substances and which he called T.O., and a lower layer containing chiefly the substances left behind after extraction with glycerine. The latter was again pounded with water, centrifuged and the supernatant fluid decanted. The process was repeated until no more residue remained. The admixture of the various fluids constituted the T.R.

Koch demonstrated on animals and man that T.R. possessed immunizing properties and this quite independent of reaction, in fact he sought to avoid any, which contrasts strongly with the opinion he formerly held of the necessity of reaction in order to cure with old tuberculin.

An animal immunized against T.R. does not react to larger doses of old tuberculin, and is therefore immunized against all the constituents of the tubercle bacillus.

New Tuberculin (Bacillary Emulsion).

Instead of centrifuging the comminuted bacilli after being suspended in normal saline solution, they were merely allowed to settle and 50% of glycerine added for greater permanence.

Bacillary emulsion is a suspension of one part

of pulverized tubercle bacilli in 100 parts of distilled water to which equal parts of glycerine are added to ensure stability.

The further modification of tuberculin by Koch was the result of his agglutination experiment.

During his treatment of animals with bacillary emulsion, agglutination appeared at the same time as the immunizing properties in the blood, and he inclined to the belief that agglutination was in some way related to, and part of, the complex machinery of immunity.

These experiments led to the opinion that it was better to employ the ground up bacillary mass without separating into layers, and that high agglutinating values could be reached, but with the greatest certainty and speed when the dose was rapidly increased, and severe reactions occurred.

High agglutination values have, however, been obtained without severe reaction, and even in its absence with small doses by Doctors Bandelier and Roepke and with the complete approval of Koch.

Whereas Koch's highest agglutination values were 1-200 and 1-300 these observers obtained by this mild method of administration values up to 1-1000 even with patients in the third stage.

As the result of their researches the following propositions have been laid down by them.

(1) By treatment with the bacillary emulsion, the agglutinating power may always be raised.

(2) The better the prospect of improvement or recovery the more rapidly the agglutinating power rises, and the greater the extent and duration of this rise.

(3) The more unfavourable the outlook the more difficult to raise the agglutinating power at all and the more rapidly it is lost.

(4) Persistence of a very low agglutinating value denotes in general progressive disease.

(5) Determination of the agglutinating power although of great value and interest, is not to be regarded as an essential factor in the technique of tuberculin treatment.

The Diagnostic Value of Tuberculin.

The specific reaction to tuberculin is an acquired peculiarity.

It is not manifested at birth, and increased with age in proportion to the known frequency of tuberculosis.

A positive reaction implies infection by the tubercle bacillus at some time or other.

For purposes of diagnosis four methods or tests are now in use.

- (1) The Cutaneous.
- (2) The Percutaneous.
- (3) The Conjunctival.
- (4) The Subcutaneous.

Von Pirquet has the credit of first explaining not only the theory, but the practical application for diagnostic purposes of tuberculin vaccination.

His observations with ordinary lymph vaccine led him to the conclusion that reaction within 24 hours only occurred in a previously vaccinated subject, and that it was brought about by the union of toxin 'Vaccine' and reaction products which he termed 'anti-bodies', and that the presence of these anti-bodies as shown by the reaction to the vaccine is proof of previous infection.

An analogous reaction occurs when a tuberculous subject is inoculated with tuberculin, and the characteristic local reaction is due to a rapid local formation of anti-bodies as the result of the tuberculin stimulus.

The formation of anti-bodies does not appear to be peculiar to vaccinia and tuberculosis, but applies to many other diseases, and probably to all those of micro organismal origin.

In the cutaneous method of Von Pirquet old tuberculin is used, and in 2 strengths one undiluted, and the other a 25% solution with $\frac{1}{2}$ % phenol for preservation.

The undiluted solution has the advantage of being more reliable, one application being usually sufficient, whereas with the diluted, several inoculations may be necessary before feeling justified in accepting the conclusion.

Some authorities maintain that the stronger solution is too delicate, that cases are met with which give a negative reaction not only to the dilute solution, and the conjunctival test, but also to the subcutaneous method of administration, and yet show a positive reaction to it, "the stronger solution". The same authorities assert that when in doubt the subcutaneous method must decide.

Now ~~this~~ seems to me to be a peculiar and weak suggestion and in the absence of reasons, which at any rate I have not been able to find, and if we recognise the difference between clinical and anatomical tuberculosis; for if the cutaneous test is of any value at all as a diagnostic method, then the more delicate it is, the more valuable should be its service. I have not had occasion to try the subcutaneous method as a confirmatory test, but have seen a case of intractable ulcer of the leg; evidently tubercular in nature, where a negative response occurred with repeated ocular instillations and diluted tuberculin after Von Pirquet, but with a positive reaction with the undiluted solution, and where rapid healing followed the use of tuberculin emulsion.

Here the response to the undiluted tuberculin suggested the advisability of trying tuberculin treatment.

With children the dilute solution seems always sufficient as negative reactions are always followed by

the same result when the stronger solution is used.

When a positive reaction occurs it is said to be usually first seen at the end of 24 hours, but in my cases, about 40 in number, the reaction was not visible in more than half. Until after that period, usually on the second day's visit, 36-48 hours after the inoculation.

Late reactions sometimes occur as late as the 3rd or 4th day, and in all the cases of this class which have come under my own observation, the clinical evidences of tuberculosis have been absent.

Where evident tubercular disease was present except in advanced cases the reaction has always been early and distinct though varying in intensity.

Occasionally a negative reaction takes place in spite of the actual presence of tuberculosis.

This seems to be explained in some cases by the immunity of the subject from previous specific treatment, or as in the advanced and late stages of the disease by a failure of physiological response to the stimulant "tuberculin".

In the late stages of tuberculosis it regularly fails and in mixed infections it may fail, or the response be delayed until after the second inoculation, and even then its appearance may be tardy.

In the final stages of miliary tuberculosis and in tubercular meningitis it is usually negative.

No general, but only local symptoms follow the application of the cutaneous test, but where deep scarification has been practiced, the regional lymphatic glands are apt to enlarge and become tender. Deep scarification is unnecessary and should not be made for another reason, viz. it is apt to cause a severe traumatic reaction which makes comparison with the controls more difficult, and hence minimizes the delicacy of the test, especially in those cases where the reaction is not very pronounced.

The positive cutaneous reaction is a specific anatomical tubercular lesion, as shown by Daels who in microscopic sections of the papules found central giant cells of the typical Langhous form, with epithelioid and round cells at the periphery.

This has opened up the question of the possibility of general infection, but so far no evidence is forthcoming in support of it.

Prognostic and Localizing Value.

A positive reaction to the tuberculin cutaneous inoculation gives no indication of the site or activity of the tubercular process, neither does it prove that the disease the person is suffering from is tubercular. It simply indicates that at some time the subject has come in hostile contact with the tubercle bacillus. A

negative reaction in general indicates absence of tuberculosis except in advanced cases, in miliary tuberculosis, tubercular meningitis and in artificially immunized persons. A negative response in undoubted tuberculosis has no prognostic significance.

Von Pirquet's method is an extremely valuable and reliable means of detecting latent and active tuberculosis as shown by the fact that 97-98 p.c. of known cases of tuberculosis both in adults and children react, and if we exclude those in the last stages etc., its action may be said to be constant.

On account of its simplicity and harmlessness its prophylactic value, more especially in investigation and hygienic treatment of school children cannot be overestimated, and no doubt in the near future will be taken advantage of.

The Percutaneous Method of Moro .

Moro, whose method followed that of Von Pirquet rubbed into the skin of the epigastrium, or that in the region of the marmer equal parts of old tuberculin and anhydrous lanoline.

Various degrees of reaction occur from isolated scarcely visible red spots, to confluent patches of many papules. The reaction appears usually within 48 hours, sometimes within 24 hours, not uncommonly hpwever, in my experience, not until the third or fourth day.

The spots or papules remain for a few days, then gradually subside, with slight desquamation in the more severe reactions and often with a little pigmentation.

A more certain reaction occurs if the natural fat of the skin is previously removed with ether so as to allow more ready absorption, and the inner side of the forearm is perhaps the most accessible and convenient part on which to apply it.

Its diagnostic value is as one might almost have expected considerably inferior to the cutaneous test for not only is the tuberculin diluted, but the intact skin, the permeability of whose epithelium is very variable, is used as the medium of absorption. The only advantage seems to be that it may be used in those who object to vaccination.

It is further said to be the most harmless of all diagnostic methods.

The Conjunctival Tuberculin Test.

Although this method is often associated with the name of Calmette alone, who certainly was the first to draw attention to the diagnostic significance of the local conjunctival reaction in tuberculosis, Wolff Eisner at an earlier period showed the possibility of a local conjunctival reaction in that disease, so that many feel that justice is only done by coupling each name with its origin.

It is also interesting to note that although in point of time, the cutaneous test of Von Pirquet was first in the field, Wolff Eisner at the discussion of Von Pirquet's paper on Cutaneous Diagnosis on May 15th, 1907, mentioned his observation.

Calmette employed a 1 p.c. glycerine free dry tuberculin for adults and $\frac{1}{2}$ p.c. for children, and called the reaction "The Ophthalmo-Reaction".

Wolff Eisner designated the reaction "The Conjunctival Reaction" which is the more correct as the appearances are almost always exclusively limited to that membrane.

Method of Preparation of the Tuberculin.

According to Calmette this was of the greatest importance in order to avoid undue irritation.

He recommended a tuberculin precipitated by 95 p.c. alcohol, obtained from bovine tubercle bacilli in the Pasteur Institute at Lille, and freed by a complicated process from glycerine resin and wax.

This whilst free from irritating matters, still retains the potent bacillary bodies.

His claim that he has used this test in 10000 cases without harmful effects does not appear to have been shared by other and subsequent observers. The preparation in use today and which is considered the best is Koch's old tuberculin in glycerine solution with $\frac{1}{2}$ p.c. phenol.

This produces no appreciable irritation or harmful effects when used in the above percentage, or even when increased to twice the strength where initial failure to excite a reaction has occurred. It is necessary, however, before instillation, to be quite sure that the conjunctiva and especially the cornea are quite healthy, and that there are no evidences in the form of opacities of past injury or disease.

It has been stated that in perfectly normal eyes harmful results have occurred; this has not been my experience, and I should think that where sufficient care has been exercised in the selection and strength of solution, such cases must be so small that for all practical purposes they may be regarded as a negligible quantity.

None the less these reports have had the effect of causing a large body of practitioners to discard the use of Calmette's reaction altogether, they preferring to use the safer and more certain method of Von Pirquet. In very young children for reasons of convenience and ease of application, the cutaneous test is certainly preferable to the conjunctival and should always be adopted.

The method of instillation is of considerable importance. The lower eyelid should be slightly retracted whilst the eyeball is elevated by the patient, and the drop of tuberculin gently placed without touching

the conjunctiva near the inner canthus, if the process is roughly done or the reagent dropped from some distance on to the globe of the eye, undue irritation and lachrymation is apt to occur, and the tuberculin in part, or wholly washed away.

It increases the certainty of reaction if the patient for a short time remains looking upwards and as far as possible avoids blinking.

The reaction when positive is usually seen in from 4-36 hours; generally best at the end of 24 hours, and varies from a faint redness limited to the inner canthus and semilunar fold to a more intense injection with a serous, or more rarely a purulent secretion of the whole palpebral, and ocular conjunctiva.

Slight reactions have a tendency to appear late, and are often best seen after 48 hours.

Unless one is prepared for the extreme delicacy of this test, many cases will be regarded as negative, which are undoubtedly positive.

A very careful comparison of the two inner canthi and semilunar folds with the eyes alternately directed outwards will show any difference in tint of these parts, and the slightest appreciable injection of the eye, in which the reagent has been placed must be regarded as positive.

The weaker solutions of Calmette's tuberculin not unfrequently fail to excite a reaction, even when

tuberculosis is undoubtedly present, so that it may be necessary not only to repeat the instillation, but also to increase its strength, before accepting the conclusion.

When a repetition is called for either the same or the opposite eye may be selected.

It has been asserted that to repeat the instillation in the same eye, or even in the other is liable to lead to a false result, and therefore an incorrect diagnosis on the ground that after the first instillation, the patient formerly perhaps free from tuberculosis now possibly becomes an infected subject, and thus reacts to the second application.

The chief disadvantage of using the opposite eye is that the one already used cannot so safely be used as a control.

Some physicians maintain that repeated instillations are not unattended with danger to the eye; this has not been my experience.

After a positive conjunctival reaction no matter however slightly marked, no further instillations should be made, nor should the subcutaneous method be used as a confirmatory test, at any rate for several days after complete subsidence of all redness, as severe recrudescences have been known to follow the hypodermic method, and in a few cases this has repeated itself after each injection of tuberculin for therapeutic purposes, with the result that specific treatment has had to be abandoned.

For the same reason it is advisable not to use the conjunctival test after the subcutaneous.

Calmette's reaction should not be used in sucklings, or in scrofulous children under 12 months old, but in older ones the reaction is much the same as in adults. It is more convenient, however, as has already been stated to employ Von Pirquet's test in all young subjects. Positive reactions have been recorded where there was no evidence, certainly no clinical evidence of tuberculosis as in carcinoma, scarlet fever, rheumatoid arthritis, acute rheumatism, secondary syphilis, acute bronchitis, enteritis, etc. and from this the non-specificity of the reaction has been deduced, but the regularity of the appearance of the conjunctival with the other diagnostic methods must be regarded as something more than a mere coincidence.

Further absence of clinical evidence must not be taken as synonymous with anatomical freedom from disease.

A positive reaction implies the presence of specific reacting antibodies, which indicate active or latent tuberculosis.

In advanced disease Calmette's reaction may fail as may all other diagnostic tests and for the same reasons, viz. failure of physiological response, anti-tuberculosis in the serum of the patient's blood etc.

The disadvantages of Calmette's test are firstly - That several instillations of increasing strengths may be required before a reaction is elicited, or before one can feel justified in accepting the result, and according to some authorities this is not unattended with danger to the eye. Secondly - That occasionally after its use, treatment by tuberculin has to be suspended on account of conjunctival congestion and inflammation following each injection.

Bandelier and Roepke give the following instructions regarding frequency of instillations and strengths of solutions.

Four instillations varying in strength from $\frac{1}{2}$ -1 p.c. in children, and 1-4 p.c. in adults, at intervals of two days.

Should no reaction follow one may infer the absence of tuberculosis.

Although cases which require repeated instillations usually belong to the quiescent order, this is by no means constant; an active tubercular focus, especially in the earliest stage may require repetitions, whilst an old dormant one may respond to the first. Calmette's test must be regarded as a useful and reliable diagnostic method, and provided suitable cases are selected, and the contra-indications known it is practically free from any harmful effects.

The Subcutaneous Tuberculin Test.

This, the oldest diagnostic method is performed with Koch's old tuberculin obtained from cultures of human tubercle bacilli.

Another tuberculin prepared by an analogous process from bovine tubercle bacilli is also occasionally used, but as it is less certain in its action, and the reaction occurs later, it is not frequently employed.

Two dilutions are employed 1-100 and 1-1000 with the usual $\frac{1}{2}$ p.c. phenol for preservation purposes. Accuracy of dosage is one of the great advantages of this test, and when it is remembered that tuberculin is the most powerful therapeutic agent we possess, the importance of this is at once apparent. In all other diagnostic methods the dose per individual is incalculable, depending as it does upon the medium through which it is carried.

Tuberculin has been given intravenously, and in this way. The reaction time is shortened, but in addition to the inconvenience and skill required in its administration, more especially in young children and stout persons, the risk of exciting a severe reaction makes it a less desirable method than the subcutaneous.

Koch's dictum conveyed in his first communication, that "To attain a reliable result tuberculin must be given subcutaneously" is as true today as when it was uttered, for the subcutaneous method stands preeminently the most trustworthy of all diagnostic tests.

Dosage.

Great differences of opinion have prevailed as to the size of the initial dose and also as to frequency and rate of increase of subsequent doses, before the presence of tuberculosis can be excluded. Koch's first instructions were: Begin with 1 milligramme, increase to 5, and finally to 10 milligrammes. This initial dose has been found too large, especially in delicate and nervous subjects, and in cases of recent infection.

It is now universally agreed that the following sequence of dosage should be adopted for adults, and half the quantities for children.

Initial dose $\frac{2}{10}$ milligramme.

Second dose 1 milligramme.

Third dose 5 milligrammes.

Final dose 10 milligrammes.

Should there be no response to the initial dose, it is absolutely essential for the production of a reaction to increase the succeeding doses suddenly, for with a too gradual increase a tuberculin tolerance occurs even in tubercular subjects, at the same time this increase must not be too abrupt lest a severe reaction supervene.

A rise of temperature however slight is a contra-indication to any further increase of dosage, but the same dose may be repeated.

In delicate and nervous persons it is better to repeat the same dose a third time before proceeding to the higher quantities.

A feature especially characteristic of tuberculin and insisted upon by Koch, is that a second dose even of the same magnitude not infrequently calls forth a reaction in a tuberculous subject who did not respond, or whose response was doubtful to the initial dose.

Another feature, and one of great interest and practical importance is, that should the slight response invoked by the initial dose subside on giving a second of the same size, and more especially with a larger dose, the opinion may safely be held that tuberculosis is absent.

From this it follows that we should only increase the dose when no reaction follows, otherwise repeat the initial dose.

Of late years a condition of hypersensitiveness to solutions containing albumen when given hypodermically and called anaphylaxis, has been said to occur with tuberculin injections, and that as the result of the assimilation of the proteins contained in tuberculin a repetition is not unattended with danger.

The same objection has been raised and on the same grounds to the repetition of diphtheritic serum in diphtheria, and several sudden deaths have been recorded which were thought to be due to this cause,

and not as previously assumed to the diphtheritic toxin. On theoretical grounds the phenomena of anaphylaxis seem pretty well founded but are so variable and inconstant, that as yet for all practical purpose, we must admit we know little of real value, certainly as far as I know, no untoward effect which could be attributed to it has occurred after injections of tuberculin in tubercular subjects, and anaphylaxis is unknown in the healthy and in doubtful tuberculosis even after large and repeated doses of tuberculin.

The Maximum Dose.

A great deal of controversy has centred round this question.

Koch stated and others have agreed with him that the maximum dose should not exceed 10 milligrammes, but he was in the habit of repeating this dose before assuming the absence of tuberculosis, and undoubtedly cases of tuberculosis do occur, usually old and latent, especially in glands, which only respond to a repetition of the maximum dose; as the object however of any diagnostic method is not to stir up lesions which for all practical purposes are cured, it is now generally agreed that a negative response to a single maximum dose excludes tuberculosis.

Mode of Action of Tuberculin.

Many theories have been put forward to explain the action of tuberculin.

Koch himself explained the reaction by the increased histological and metabolic changes in the tubercular foci.

Ehrlich regarded the middle of the three layers of cells which surround a tubercular focus as the seat of reaction.

In it the cells which are still capable of response to the toxins of the bacilli produce the antibodies which are the essential characteristic of the tuberculin reaction.

The Albumose theory, advanced by ["]Kühne, Matther, and Krehl which denies the specificity of the tuberculin reaction, explains the reaction by assuming that the albumoses in the tuberculin are attracted to the albumoses in the diseased areas which causes the local reaction, and at the same time, and by the same means the albumoses previously present in the diseased foci are thrown into the circulation resulting in a general reaction.

This principle argument against this theory is that tuberculin freed from albumose causes both a local and a general reaction, and further much larger doses of albumose than are contained in tuberculin is required to produce a toxic albumose effect. The theory of Carl Spengler is very ingenious. He put forward the suggestion that uncombined toxins are present in the organs or their cells, and that antibodies in the blood

keep them in check, but when the tuberculin toxins are injected, some of the antibodies are drawn off from the blood, and the balance is upset with the result that the toxins from the tissues flood the circulation.

The Tuberculin Reaction.

This manifests itself in a two-fold manner,

1st, Local or specific.

2nd, General.

The local reaction shows itself principally in increased evidence of disease in the tubercular areas. This accentuation of physical signs is now regarded as of almost equal testimony of the presence of the disease, as the finding of the bacillus itself. The localizing action of the subcutaneous method is one of the great advantages of this as compared with the diagnostic tests.

The augmented physical signs and symptoms vary of course with the tissue involved in the morbid process. Glands become tender and swollen; the cutaneous tissues red and oedematous; bones and joints indicate its presence by pain and swelling; increased expectoration, pain and crepitation manifest themselves in the respiratory organs, and tubercular foci in the nervous system give their corresponding indications.

The general reaction is characterised by those of fever in general.

A rise of temperature to various degrees according to the severity of the reaction with rapid pulse and increased respiratory action, headache, thirst and malaise. This reaction is generally abrupt in its onset, and as equally rapid in its subsidence, leaving for a short time a feeling of well-being, and an absence or amelioration of many of the former troublesome symptoms.

Contraindications to the use of tuberculin subcutaneously

For diagnostic purposes.

It is necessary at the outset to emphasise the fact that tuberculin for diagnostic purposes should not be used as an alternative method; that where the ordinary methods are sufficient to establish a diagnosis, the subcutaneous test is not only superfluous, but under certain circumstances may be attended with positive harm.

In advanced cases of tuberculosis the tissue capable of reacting may be small, and antituberculin present in such quantities in the blood, that toxic doses may be required before a reaction can be elicited.

A temperature above normal, 98.6 in the axilla is also a contraindication, on account of the difficulty in correctly estimating the reaction fever, and besides this the reaction processes which cause the fever interfere with the action of tuberculin.

In some nervous subjects the temperature is very unstable, and in these cases provided the temperature

can be referred to the temperament and not to a local focus of disease tuberculin may be used; slight reactions, and occasionally even more severe ones are however sometimes difficult to estimate at their proper value.

The subcutaneous test should not be used in cases with recent haemoptysis, for not only are the cough and expectoration increased during reaction, but on account of the destruction of tubercular tissue the tendency to haemorrhage is increased.

Advanced and serious heart disease is also a contraindication more especially those forms in which the myocardium is involved.

The urine in all cases should be examined prior to its administration, for kidney disease even of a non-tubercular character may be seriously aggravated. Epilepsy which may have been quiescent for years, has been reanimated and thus is held a contraindication.

In hysteria the temperature from slight causes may oscillate, hence this method in such cases may have a qualified value, but where the local tests are negative and the tubercular suspicion still exists, its use may decide the question.

In miliary tuberculosis, the intestinal ulceration with peritonitis, and during convalescence from severe diseases such as typhoid fever, pneumonia, pleurisy, etc., it is advisable to withhold its use for fear of aggravating and disseminating the disease.

In cases with a tendency to cerebral haemorrhage, and in severe diabetes it should not be used.

Keeping in view these contraindications and remembering that the object of the subcutaneous test is to establish an early diagnosis, and to locate the disease in those cases in which the usual clinical and bacteriological methods fail, it must be regarded as a valuable and safe diagnostic agent. Before leaving the diagnostic methods the needle track reaction of Escherich may be mentioned. It is really a modification of Von Pirquet's, and an attenuated subcutaneous test with a local, and generally no constitutional reaction.

Half a milligramme of old tuberculin in 1 c.cm. of normal saline solution is prepared, and an initial dose of $\frac{2}{10}$ milligramme injected into the inner side of the forearm.

With a positive reaction inflammation arises in the subcutaneous tissue, and shows itself usually within 24 hours as a sharply circumscribed red spot, oedematous at its margin and somewhat tender.

The characteristic reaction is not at the site of puncture but at some distance from it.

A maximum is reached in 48 hours and passes off in the course of from 4-10 days.

The needle track reaction is said to be of especial service in estimating the significance of fever and temperature oscillations; thus fever without a local reaction would indicate the non-tubercular

character of the lesion, but even when the greatest care is taken occasionally a febrile reaction occurs and as fever under practically all circumstances must be regarded as an absolute bar to the subcutaneous administration of tuberculin for diagnostic purposes, its indications and contraindications are practically synonymous with the ordinary subcutaneous test.

Tuberculin in the Treatment of Tuberculosis.

In a disease like tuberculosis with its varied manifestations, its acuteness and chronicity, it is no easy matter to estimate the real value of any specific system of treatment, and in many cases years must elapse before its true position can be stated.

Especially is this true in relation to tuberculosis of the lungs; where temporary improvement takes place often under different methods of treatment but there are cases and not a few where the results of tuberculin treatment are so rapid, striking and apparently permanent, that in all fairness, in this its second advent should be recorded.

Like all other remedies of a specific character it has its failures, and when used indiscriminately its disasters, but applied with care and caution I am convinced that in tuberculin we have an agent of undoubted merit, not only in one form of tuberculosis but practically in all cases where any reasonable hope of amelioration or cure can be entertained.

Of late years we have heard a good deal of the value of the opsonic index as a guide to the administration of tuberculin and of vaccines in general.

This may be true in the hands of experts and those who have ample time and leisure at their disposal, but until its technique is simplified and its results more reliable, it will remain practically worthless to the general practitioner.

He must rely upon clinical indications as his guide and in my experience these are all sufficient.

Some tuberculin enthusiasts have of recent years sought to minimize the importance of sanatorium treatment, and held out tuberculin as almost a panacea for all tubercular ills, a course which is again likely to place the remedy in a false position.

The two must be regarded as interdependent if the best results are to be attained, and all my cases as far as was possible have had the advantage of both methods of treatment. At the same time if I were given the choice between sanatorium treatment and no tuberculin, and tuberculin treatment with ordinary healthy surroundings I should prefer the latter as more likely to be immediately and permanently beneficial. Although tuberculosis of the lungs is the most frequent form met with by the general practitioner, manifestations of the disease in other organs and situations are by

no means infrequent, and my experience is that tuberculin is equally if not more efficacious in these cases than in those of the pulmonary organs. Today, open air, good feeding, appropriate exercise and tuberculin should be regarded as the basis of treatment in all cases of tuberculosis, and in a large proportion, especially of early cases these measures are successful.

Where the disease attacks the extremities Bier's passive congestion method ought in addition on all occasions to be given a long and fair trial, as I have seen the most unlikely and apparently hopeless cases recover under its use.

The great cardinal principle to be observed in the administration of tuberculin is the "avoidance of reaction", and this in the vast majority of cases is possible provided a minimal dose of $\frac{1}{5000}$ mgm. is commenced with, and this is repeated once or even twice should the slightest reaction occur. The frequency and dosage vary with each patient but no attempt should be made to hurry the treatment in the false hope of obtaining a rapid cure.

An interval of a fortnight between each injection is a good working rule, but in some cases it is in the interests of the patient to give them earlier, whilst in others three or four weeks interval should intervene.

As long as any induration exists at the site of inoculation, a second injection should not be given,

and when repeated it is better to be content with the same dose. It is evident from the above assertions which I believe to be true that each case must be treated on its own merits, and the general condition of the subject, the pulse, temperature, and the local condition at the site of injection serve as guide for future treatment. As to the site of inoculation, I have found as the result of trying various localities that between the scapulae the most suitable. The forearm is a very convenient place but unless rest of the part is enjoined, an inconvenience to many, local irritation and abscess formation are apt to occur.

In only one case and this was where the injection was given in the forearm has abscess formation occurred.

This did not appear to be due to any fault in the preparation or technique as subsequent injections were followed by induration and softened, and then by rapid absorption without rupture or incision. I was much impressed by the peculiar local reaction of this patient, a girl of 17 years, with tubercular glands on both sides of the neck, one of which had suppurated and which was incised and scraped.

The first injection was in the right forearm, dose $\frac{1}{5000}$ mgm. tuberculin T.R. Bacillary Emulsion.

Four days later a hard, somewhat tender swelling occurred close to the site of puncture.

This somewhat rapidly softened and on the seventh day ruptured.

No treatment was adopted beyond a clean dressing and the part rapidly healed leaving some pigmentation of the skin.

During this time there were no constitutional symptoms, no rise in temperature or altered pulse rate.

At the end of three weeks all induration had disappeared at the site of inoculation, and a second dose of $\frac{1}{5000}$ mgm. was given into the left arm.

On the seventh day a local hard swelling of slightly larger extent than that which had occurred on the right arm formed, then softened, but now instead of emptying itself through the skin was quickly absorbed and in 10 days nothing was to be felt at the site of injection. A third injection was given at the end of another three weeks into the right arm, dose $\frac{1}{5000}$ mgm. ten days elapsed and then a much slighter induration without softening took place at the site of inoculation and in a week no trace of thickening could be felt. Subsequent injections have not been followed by any induration.

Now it has been suggested that local abscess formation may be due to living bacilli in the emulsion, but the evidence in this case seems to my mind entirely opposed to such a view, as it is not likely that the abscess would have healed so rapidly under such conditions, and Koch himself in his earlier communications pointed out that whilst constitutional immunity was produced, local abscess formation due to some irritant generated by the bodies of the "dead" bacilli was not uncommon.

Contraindications.

Many associated diseases and conditions most of which have already been mentioned, are held to contraindicate the therapeutic use of tuberculin, but in actual practice the number of cases where it would be dangerous or unwise to use it is comparatively small.

Mixed infections with higher temperatures are perhaps the most frequent and important contraindications, but here the associated microorganism is the bar to treatment, and provided its influence can be overcome by suitable vaccine etc. treatment, tuberculin in many cases may be used with advantage.

Again my experience is that these mixed infections are far more frequent in the late stages of tuberculosis, when treatment of any kind is least effective.

In the early and most curable stage mixed infections are much less common.

Early diagnosis is therefore the best way of avoiding mixed infections and most other contraindications.

Heart disease and disorders of the nervous system do not in my opinion contraindicate the use of tuberculin, provided the patient is otherwise suitable, and on more than one occasion, probably as the result of the confidence placed in the new remedy, I have known tuberculin to have a distinct sedative action and annoying slight variations in temperature subside. In phthisis with severe haemoptysis it is better to withhold its

use; but small haemorrhages are not uncommonly arrested during its administration.

In tuberculosis complicated with chronic kidney disease, tuberculin is not likely to be of much value and may possibly irritate the diseased organs, although I have never seen any indications in the urine where the kidneys were healthy suggestive of irritation.

Where the disease of the renal tissue is tubercular tuberculin gives the best chance of recovery.

Form of Tuberculin used.

In my earlier cases tuberculin T.R. was used, later tuberculin T.R. Bacillary Emulsion and I think it a more effective agent.

The initial dose in all cases has been $\frac{1}{5000}$ mgm. both for adults and young children.

In the very young $\frac{1}{10000}$ mgm. has been the minimum initial quantity administered.

In no case have I found it necessary to exceed $\frac{1}{500}$ mgm. as a maximum dose.

The patients have been drawn from all classes, many of whom were compelled to continue their work and all who were able and free from fever were allowed to go about, but advised to rest for the first few days.

In hospital the temperature and pulse are taken every four hours for the first three days, after this when there is no deviation from normal the usual morning and evening observations are made. Every case is weighed prior to treatment and this is repeated each week.

Case I.

A girl 17 years of age whose case has already been partially recorded, who had bilateral enlargement of the cervical glands, one of which softened, was incised and scraped. In this patient the result of treatment which beyond the operative measures adopted was by tuberculin, was most satisfactory; the wound healed rapidly and in three months time no gland could be felt in the neck.

Constitutionally she seemed to derive even more benefit, for, from being an anaemic badly nourished individual in a very short time she gained colour and put on weight, and in every way expressed herself as being much better.

The injection which formerly caused local irritation and induration and on one occasion suppuration, now are given without the slightest local change.

Case II.

This was a middle-aged female who at 15 years of age had had the right foot amputated for tubercular disease of the tarsus. She came into hospital with Pott's disease of the spine and paraplegia, also with tubercular disease of the left tarsus and the right elbow. Tubercular with Bier's treatment and rest have resulted after 18 months in all these lesions being healed, and she is now a stout ruddy woman, able to go about in her former manner.

The patient is convinced that the tuberculin has played a most important part in her restoration, as prior to its administration she had practically had the same treatment for many months with little or no improvement.

Case III.

This was a young girl of 19 years of good family history, and who had always enjoyed good health up to 9 months prior to admission to hospital, when she began to complain of frequent and painful micturition especially at night. Tubercle bacilli were found in the urine, she had no temperature and she seemed a favourable case for tuberculin. Tuberculin was given and gradually increased but no improvement followed.

A suprapubic operation was performed with the object of draining the bladder and seeing if anything further could be done but the whole interior of the organ was found infiltrated with tubercular granulations. The patient died exhausted 3 months after the operation, tuberculin having had apparently no effect.

Case IV.

This was an intractable ulcer of the leg which had repeatedly healed and broken down during the previous 18 months. She presented the facies of congenital syphilis and another sister's appearance corroborated this view, but the usual antisyphilitic remedies had no effect. Several members of the family had died of

phthisis, and Von Pirquet's reaction was positive. Tuberculin was given every 14 days and the ulcer was healed in 6 weeks.

Case V.

A young man 20 years of age with tubercular glands of the neck on both sides. Those on the right suppurating which were incised and scraped, tuberculin was given in increasing doses every 14 days without reaction. The wound practically healed by first intention the glands slowly decreased in size and after 3 months treatment could scarcely be felt, he gained in weight and colour, and now after 4 months treatment is quite well.

Case VI.

A female 28 years of age with fairly advanced tubercular disease of the left apex of the lungs, tubercle bacilli were found in the sputum.

Tuberculin was commenced in June 1910 and now after 4 months treatment, although she has continued her household duties she looks and feels decidedly better. The dullness has diminished, the cough and expectoration has decreased and she has gained 7 lbs. in weight. T.B. are however, still present in the sputum.

Case VII.

Boy aged 6 years admitted into hospital with early hip disease; Xrays showed blurring outline of

the joint. Rest and tuberculin were followed by rapid improvement in general health and local symptoms. Discharged at the end of six weeks as outpatient, increased in weight, free from pain, and wearing a double Thomas's hip splint.

Nine months have now elapsed and the boy has quite recovered.

Case VIII.

A male dentist aged 31 with cough, wasting, and tubercle bacilli in the sputum.

The physical signs consisted chiefly of Rhonchi and occasional scattered moist sounds through both lungs.

There was no appreciable dullness or local limitations of respiratory expansion.

The first injection of $\frac{1}{5000}$ mgrm. of tuberculin was followed by a feeling of illness and prostration and he retired to bed with a temperature of 100 F. This subsided after 2 days.

The opsonic index prior to the injection was .55 compared with my own blood, 15 days after the opsonic index was .7.

The injections were continued at first with the same dosage without reaction, and now after 3 months treatment he has gained 20 lbs. in weight. His general condition is markedly improved, practically no physical signs are detectable though a few T.B. are still present in the sputum. He has followed a busy professional practice the whole time.

Case IX.

A girl 18 years of age, a cotton weaver by occupation who for 8 years had had a sinus in the foot from caries in the tarsus. Suddenly she was seized with acute abdominal pain, vomiting, and when seen had a temperature of 102.2. She was thought to have a perforation, but on abdominal palpation an ill-defined tumour with partial resonance could be felt in the left loin, evidently matted intestine, the result of peritonitis of tubercular origin; there was no diarrhoea.

The temperature and pain rapidly subsided and at the end of 10 days tuberculin $\frac{1}{5000}$ mgrm. was given; this was repeated after 14 days and at similar intervals with increasing doses without reaction. During 4 months treatment when improvement steadily occurred, both constitutionally and locally she had only two slight attacks of local peritonitis of short duration, the first a week after the first injection, the second much less severe at the end of the fourth week. The tumour which on admission was the size of a child's head, on her discharge was scarcely discernible. The sinus which was scraped was healed.

Case X.

A female housekeeper 42 years of age with disease of the sacrum and discharging sinus and staphylococcic infection; a vaccine from her own cocci was given alternately with tuberculin; sinus healed in 4 months.

Case XI.

A female 38 years, housewife, a tubercular sinus of foot. Bier's treatment and tuberculin effected a cure in three months.

Case XII.

Male 18 years with Haemoptysis but no T.B. in sputum, a family history of tuberculosis.

Local Rhonchi and a few fine crepitations at the right apex. The haemoptysis ceased and no physical signs were heard at the end of 2 months.

Case XIII.

A female 25 years of age who 3 years previous had had left side pleurisy with effusion, advanced disease of the left lung, T.B. in the sputum; after 4 months treatment no improvement in the physical signs could be recognised although she stated she felt better, and had gained 5 lbs. in weight. There was always a slight reaction after each injection in this case, and a minimum dose was never exceeded.

Case XIV.

A female, 27 years, tailoress, with slight dullness above the right clavicle and occasional crepitation, cough and diarrhoea, the last of 18 months duration. The diarrhoea only occurred in the morning, and was attended by colicky pains but there was no abdominal tenderness or induration. T.B. were present in the scanty sputum.

After 4 months treatment with tuberculin and open air, the cough and expectoration had ceased, and beyond slight impairment at the right apex, no physical signs were present.

The diarrhoea was much less troublesome and painful, but had not ceased. Von Pirquet repeated gave negative results.

Case XV.

A female 17 years of age with an obstinate skin affection of 7 years duration involving the face, and which had been diagnosed at a skin hospital as Lupus Erythematosus gave a well marked positive reaction with Von Pirquet.

After the first dose of tuberculin improvement was distinct and in a month one side of the face was free from disease, and the skin was almost normal in texture, the other side although not showing such a rapid change had also improved. After 4 months treatment the skin looked healthy and was apparently free from disease.

Case XVI.

A boy aged 7 years with the facies of congenital syphilis and stunted growth was admitted into hospital for extensive glandular enlargement on both sides of the neck.

There were bilateral corneal opacities with marked

photophobia and conjunctival congestion. Antisyphilitic treatment had been tried without effect.

The spleen was normal and a blood examination revealed the following condition.

Haemoglobin.	75.1.
Red cells.	5,360,000.
Col. Index.	.7.
White cells.	10,980.
Differential Count.	
Polymorphs.	70.6 p.c.
Monomorph.	29.4.
Eosinophiles.	Nil.

Von Pirquet's reaction was positive, and fairly well marked.

Tuberculin B.E. $\frac{1}{5000}$ mgrm. was given.

Three days later the photobia had gone, and the conjunctival congestion was much less. Before the next injection was due at the end of 14 days there was appreciable diminution in the glandular swellings.

In no previous case have I seen such rapid and unmistakable improvement follow a single dose of tuberculin, nor was this change limited to the parts diseased; his whole general condition seemed to be benefitted and at the end of six weeks he was practically well.

Beyond the ordinary hospital diet and the administration of tuberculin nothing was done and as he came from a good home the difference in his condition

may fairly be ascribed to the tuberculin.

Case XVII.

A girl 16 years of age admitted with tubercular peritonitis.

She had recurring attacks of pain with slight fever.

Tuberculin in minimal doses of $\frac{1}{5000}$ mgrm. were given every 14 days in the apyrexial periods but no improvement occurred.

This girl died from acute general tuberculosis 4 months after admission.

The tuberculin injections were not followed on any occasion by reaction, and the acute dissemination occurred just when another injection was due. I cannot say that the injections in no way contributed to the spread but the impression left on my mind was that they did not. The patient always expressed herself better after each injection and looked forward to them.

Case XVIII.

This case is one also in which tuberculin failed to produce any effect.

A girl 18 years of age with tubercular ulceration of the bowel and slight apical affection of one lung with T.B. in the sputum.

She was an almost apyrexial case, the temperature never rising above 99°F.

Tuberculin was given for several months but without any effect.

No reaction followed and the doses were increased.

She was taken home and died 4 months later exhausted.

Case XIX.

A boy aged 5 years with a bad family history of tuberculosis, his father having died of phthisis and a younger brother having tubercular disease of the metatarsal bones, was admitted for tubercular disease of the hip of six months duration.

XRay showed blurring of outline of effusion into the joint.

He was put at rest and tuberculin given. His general and local condition quickly improved and at the end of six weeks he was discharged with a double Thomas's hip splint, looking much better and free from all joint symptoms.

Case XX.

A man 28 years of age admitted with pleural effusion.

Clear fluid was drawn off which showed a great excess of monomorphonuclear leucocytes. No tubercle bacilli were found in the sputum, but Von Pirquet gave a vivid positive reaction, and the tuberculo-opsonic index was .7 pointing to the tubercular nature of his condition.

Tuberculin was given, no fluid reaccumulated and he was discharged in good health at the end of the fourth week.

Summary and Conclusion.

Although during the last fifty years there has been a marked diminution in all forms of tuberculosis in this country, tabes mesenterica excepted, it is doubtful if this decline, which to a large extent is due to improved sanitary conditions and better housing, will continue unless methods other than physical examination are adopted with the object of its earlier recognition, thus allowing preventive and curative measures to be adopted at the most favourable moment.

In fact the modern crusade against tuberculosis stands or falls on this ability to diagnose before the infective stage or at any rate to recognise it at the earliest possible date.

Of late years attempts have been made in this direction and with considerable success.

The discovery of the tubercle bacillus as the causative agent initiated a new era in preventive treatment, and it is now the usual practice for practitioners either to examine morbid products for the organisms themselves or to seek the opinion of the many laboratories private or municipal provided for that purpose.

In the still earlier cases, or where tubercle bacilli cannot be found, the various cutaneous methods give when taken in conjunction with clinical symptoms and signs fairly reliable indications for treatment both of a prophylactic and therapeutic kind.

Of the several local tests, Von Pirquet's reaction must be regarded as the most valuable and reliable. Properly carried out it is free from danger and has rendered Calmette's method with its possible risk to the eyes superfluous.

Moro's test except in those rare cases where patients object to vaccination has no advantage over Von Pirquet's and on account of its having to act through unbroken skin is less trustworthy.

With a positive Von Pirquet's reaction it is unnecessary and unwise to go further and use the subcutaneous method, but there are cases I believe, although none have as yet come under my own personal observation where all local tests have failed and yet a positive response has occurred to the subcutaneous test proving the tubercular nature of the subject, so that the latter test must be regarded as the most delicate and the final court of appeal.

As a therapeutic agent tuberculin is, properly administered and with due regard to contraindication, dosage, etc. unquestionably the most powerful remedy for good which we possess.

An early diagnosis, absence of secondary infections, little or no fever, and strictly local affections are the four conditions which when present together, especially demonstrate its efficacy, although one can not use tuberculin long without being impressed with the

varied effects in apparently the same class and type of cases, due no doubt to the different degrees of resisting and recuperative power.

Many of the cases here recorded possessed few of these advantages and as was almost to be expected the results were disappointing, although in some, not without a measure of amelioration and perhaps prolongation of life.

The cases which improved and recovered invariably showed the first indications in their general health, increase of weight, colour, and appetite, and later in the local diseased area.

In a few cases which seemed otherwise suitable for tuberculin treatment, almost afebrile and disease strictly localized but extensive, the remedy failed to convey any benefit, even though there was no reaction and the tuberculin was pushed.

Probably the fibrosis, for they were cases of chronic fibroid phthisis chiefly, was so extensive as to prevent the action of tuberculin.

Nervous and irritable patients generally make unsatisfactory subjects for tuberculin treatment, yet not invariably so, as some of my most successful cases were of this type.

The knowledge that something unusual and with a reputation for good in some cases, was being tried, gave a more hopeful outlook with its not infrequent sedative effect.

In my experience children usually derive more benefit than adults probably because the diseases from which they suffer are more localized and the lungs are less frequently involved.

The opsonic index was only taken in a few cases. In some it was raised after the tuberculin injection, but the negative phase was very variable.

I am doubtful of its value in tuberculosis. A high index does not necessarily mean improvement, and vice versa, a low index is not incompatible with improvement.

As to the advisability of treating patients with tuberculosis outside a sanatorium or other institution where they are constantly under supervision I cannot agree with those who would debar the many who from lack of opportunity or means are unable to avail themselves of such advantages the use of tuberculin, provided they are suitable cases, their home surroundings are good and they have sufficient intelligence and are willing to cooperate with the doctor and follow his instructions.

In a disease like tuberculosis whose duration often extends over months or years, with varying degrees of improvement and relapses, it is difficult to bring home evidence of the curative value of any remedy, and I am aware that the cases quoted cannot be taken to show anything conclusive.

It is difficult in many cases to say to what

extent the improvement was due to dietetic-hygienic conditions, but there is no doubt in my mind of its curative action in some, and beyond the case of acute dissemination already mentioned, which probably had nothing to do with the tuberculin treatment, no harmful results were ever noticed.

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