An Address

ON

THE PRESENT EVIDENCE FOR AND AGAINST THE USE OF TUBERCULIN AS A SPECIFIC CURE.

DELIVERED AT A COMBINED MEETING OF THE CITY DIVISION OF THE BRITISH MEDICAL ASSOCIATION AND THE FINSBURY MEDICAL SOCIETY.

BY

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It is a fact that no such unanimity exists in the profession as to the specifically curative effects of tuberculin in any of its forms in cases of tuberculosis as exists with regard to the use of diphtheritic antitoxin against infection with the Klebs-Loeffer bacillus. It is also a fact that tuberculin is nevertheless being widely used as a true specific, and observers are to be found—some who are certainly convinced of its efficacy; some who, though they are uncertain, are driven to use it by the force of opinion of those who are certain. There are others who are equally sure that the evidence of its specific value is insufficient, and even that it is a harmful drug, and they will not prescribe it.

With such a chaotic state of affairs it is reasonable to consider the whole subject critically, to take the evidence for and against its use, and to endeavour to arrive at some satisfactory conclusion.

KOCH'S FUNDAMENTAL EXPERIMENT.

It cannot be out of place, with such a programme, to go back to Koch's own experiments and to examine calmly his statements and see whether, after all the years that have elapsed since 1890-91, any support for his contentions has been advanced.

Koch's first public utterance on the use of what was known as tuberculin three months later was made at the first general session of the Tenth International Medical Congress, held in Berlin on August 4th, 1890, and can be found in the reports of the congress in various periodicals—for example, in the *Deutsche medizinische Wochenschrift*¹—and in the *BRITISH MEDICAL JOURNAL* of August 16th, 1890, p. 383. His address was largely a general survey of the accomplishments and the hopes of bacteriological study. After referring to the efforts he had made to discover something which, whilst checking the growth in the body of tubercle bacilli, effected no harm on the body, he said, with a very pointed observation, that his investigations, though carried out for nearly a year, were not complete, and

that guinea-pigs, which, as is well known, are extraordinarily susceptible to tuberculosis, if exposed to the influence of this substance cease to react to the inoculation with tuberculous virus, and that in guinea-pigs suffering from general tuberculosis, even to a high degree, the morbid process can be brought completely to a standstill without the body being in any way injuriously affected.

In the same German periodical² during the month of November, 1890, he published an article on "*Weitere Mittheilungen über ein Heilmittel gegen Tuberkulose*," giving the results of the application of this substance to the cure of human tuberculosis. In 1891 Koch gave further experimental details:

If a healthy guinea-pig is injected with a pure culture of tubercle bacilli, the inoculation puncture as a rule closes and in the beginning appears to heal; in the course of ten to fourteen days a small nodule occurs which soon breaks through the skin, forming an ulcer which lasts until the animal dies. Quite a different result occurs if a guinea-pig which is already tuberculous is inoculated, especially if the inoculations take place four to six weeks after the first one. In such an animal the seat of inoculation at

first closes as in the above animal, but no small nodule forms; on the next or following day a peculiar change takes place at the site of the inoculation. This becomes indurated and darker in colour, and these changes spread over the neighbouring parts until the total area measures about 0.5 to 1.0 cm. across. During the next days necrosis of the skin takes place, and there remains a superficial ulcer which ordinarily heals quickly and permanently without the neighbouring lymphatic glands being infected. The injected tubercle bacilli act quite differently upon the skin of a healthy as compared with that of a tuberculous guinea-pig. This striking change does not belong exclusively to living tubercle bacilli, but occurs just the same with dead tubercle bacilli, whether they have been killed by prolonged low temperatures or by heat or by certain chemicals.³

If you will peruse the works of modern writers (Löwenstein, Cornet,⁴ Römer, Bandelier, and Roepke⁵) who concern themselves with the use of tuberculin, you will find the above paragraph. They all fall back upon it as the original statement published by Koch in support of the use of tuberculin. Löwenstein, who is responsible for the article on the therapeutic application of tuberculin in man, in Kraus and Levaditi's *Handbuch der Technik und Methodik der Immunitätsforschung* (Erste Band, S. 821, 1908), goes on further to say that by means of these fundamental observations of Koch it was established that the animal body after a single injection developed definite resistance against reinfection—a statement which every reader will acknowledge is quite in accordance with the experimental data given by Koch. Löwenstein proceeds to say that the idea of using these agencies which rendered the second injection innocuous as a means of influencing the deposits brought about by the first injection led Koch to the specific treatment of tuberculosis. Koch thought if antecedent tuberculosis profoundly modified subsequent inoculation, it was possible that inoculation also profoundly affected the antecedent tuberculosis. He experimented, and stated the experiments confirmed his speculations.

At this point it is necessary to pause and realize how the modern worker views the fundamental experiment above detailed. What must be noted was that Koch in the first part of his experiments practically performed a von Pirquet test upon his tuberculous guinea-pig. The superficial ulceration which healed and which resulted from the second inoculation was an expression of the phenomenon now known as a von Pirquet test, and is explained, as will later be seen, by the laws which govern anaphylaxis or hypersensitiveness. Now follow Koch's further observations.³ He found that if the second inoculation of a tuberculous guinea-pig with tubercle bacilli was a large one, the animal died. This again is easily understood, thanks to the development of our knowledge of anaphylaxis, as being an example of anaphylactic death. The crucial point now remains, and that is that Koch³ observed that if small frequently repeated doses of tubercle bacilli were injected into a tuberculous guinea-pig, not only was the general condition of the animal improved, but the ulcerating wound, situated where the tubercle bacilli were originally injected and which caused the animal to become tuberculous, also showed favourable retrogressive changes, and the disease was brought to a standstill in the animal.⁶ It was, in fact, cured.

Now, this definite statement of the actual bringing the disease to a standstill, or of the favourable influence upon tuberculous lesions in guinea-pigs, coming from such an authority, ought only to be questioned with the greatest care. There is no need to recall the stir made by subsequent papers, in which marvellous cures in men were announced, because of the many disastrous consequences to life which also were so obvious. It is said now that too great doses were given and the wrong cases were treated. These statements have been repeated all over the world, and it must be admitted the swing of the pendulum has brought tuberculin into use again.

But what has happened with regard to the original experiments? Has any one been able to repeat Koch's experiments, and show that an infected guinea-pig can be cured by the use of tuberculin, whether old tuberculin (T.A.) or the second tuberculin (T.R.), or the third tuberculin (B.E.), or albumen-free tuberculin, or bovine tuberculin, or tuberculin derived from avian or other sources? Has it ever been successfully essayed to cure cattle of

tuberculosis by such means rather than slay them because they have been proved to be tuberculous by the tuberculin test? Is it not a certainty that if bovine tuberculosis could be cured by the use of tuberculin, its use for such purposes would be world-wide? On the contrary, we hear of numbers of cattle being slain in order to stamp out the malady. We even hear of cattle being "doctored" so that they will not give the tuberculin test, and so be saved from destruction. If it were proven that tuberculous cattle could be cured by vaccination by means of tuberculin, we may be quite sure (1) that it would be widespread in veterinary practice, (2) that the whole medical profession would have adopted it with very little hesitation, and they would have been justified. But where are the reports on cattle which should make us at ease on this point? Frankly, they do not exist. There are many reports dealing with the preventive treatment of calves by means of tuberculin, but even that important question cannot be satisfactorily answered because of fallacies which in part beset Koch's own original investigation. Supposing a calf does not give the tuberculin test, and therefore is considered to be free from tuberculosis, and a prophylactic course of tuberculin is given to it, and it neither yields a tuberculin test eventually nor becomes tuberculous, how can any one argue from such data that the apparent freedom from tuberculosis is a reality, when it is known—

- (1) That an animal may cure tuberculosis spontaneously (and yet give a tuberculin test);
- (2) That it may be tuberculous and yet not give a tuberculin test, and
- (3) That the undetected tuberculosis that it may already be burdened with may be (see Koch's experiment) the reason why it cannot be reinfected?

These facts have plagued veterinary surgeons to such an extent that there is not unanimity amongst them as to the value of the evidence for using even prophylactic vaccination in calves, and it also explains why there is no attempt to vaccinate tuberculous cattle in order to cure them. Can it be wondered at that the medical profession is not unanimous in its advocacy of the present fashion for curing human tuberculosis with any form of tuberculin administered in any particular method? Contemporary textbooks and guides to the use of tuberculin do not face these difficulties of comparative therapeutics, and one well known one is a standing example of the troubles caused by Koch's unconfirmed experiments—on one page it makes out that when the tuberculous guinea-pig was injected with subsequent doses of tubercle bacilli the ulcerating wound formed where the *first* injection was made, which caused the guinea-pig to become tuberculous, healed as a result of the second injection, and yet on a later page the author says it was the small superficial necrosis of the *second* site of inoculation which healed.

To sum up the evidence in favour of the allegation that tuberculin can cure a tuberculous animal, whether calf or guinea-pig, there is no evidence but Koch's. Bandelier and Roepke⁷ admit that they must confess that the healing of infected guinea-pigs and rabbits by means of tuberculin preparations has been accomplished by only a few authorities who have been engaged in such extremely tedious studies, and shield themselves from criticism in this direction by saying that rabbits and guinea-pigs are such unsuitable animals to work upon. And yet these two authors, like all others who advocate the use of tuberculin, set out in full the details of Koch's experiments which led to the introduction of tuberculin and say that the basis of its use is these self-same experiments on guinea-pigs. What has been said to be a proof is entirely nullified by the fact, admitted by bacteriologists, that both varieties of animals may be spontaneously tuberculous and may spontaneously cure themselves of the tuberculosis, and yet this cannot be established until after the death and complete dissection of the animal. If this is the case with guinea-pigs and cattle, the lives and deaths of which can be so fully observed and encompassed, it is just as certain with regard to human beings, who, like the animals, may be tuberculous and yet yield no test, chemical or otherwise, that they are.

To many physicians the result of animal experiments is quite enough, or shall we say the difficulty of establishing

or not the fact of tuberculous disease in animals is great enough to make them set their faces against the practice of using tuberculin to cure human tuberculosis? And yet hard things have been said about withholding tuberculin from tuberculous mankind. The pendulum has swung back in favour of using tuberculin again; but it is even more impossible to-day than it was in the years immediately succeeding 1890-91 to quote evidence in support of Koch's experimental results.

The Modern Dosage in the Use of Tuberculin.

Ignoring the unsatisfactory nature of Koch's alleged cures of tuberculosis in animals which have never been confirmed and which will not stand criticism, though such of his experiments which show merely the truth of the principles of anaphylaxis have been fully confirmed, workers abroad have developed the practice of giving the tuberculin in infinitesimal doses compared with the original ones. But in face of the objections already raised in the last section, it really does not matter whether the dosage is large or small so long as the experimental proof of cure by means of tuberculin has never been established. Neither large nor small doses of tuberculin are used to cure the tuberculosis of cattle.

The Experience of Urinary Surgeons of the Value of Tuberculin.

It is pointed out that, despite the abandonment of the use of tuberculin in other affections, certain urinary surgeons have remained loyal to the use of tuberculin in this disease. Marvellous cures of the disease are recorded even during the years immediately succeeding 1890-91.

Later on it will be pointed out that the element of "control," without which no specific cure can be established, forms no part of the demonstration of the extreme usefulness of tuberculin in these cases. It is usually found that some of the number to whom tuberculin is given are "better after receiving it."

The Post-mortem Demonstration of Cured Pulmonary Tuberculosis.

Much capital has been made out of such well-known phenomena. There is no hesitation whatever in admitting that tuberculosis may be completely cured, but to argue that because tuberculin does produce a reaction in a large number of tuberculous animals and in man it must be a means of effecting this cure is illogical. No one questions that the Widal test is a proof of typhoid fever, and yet no one has established that typhoid vaccine is a cure for typhoid fever already contracted. Observations seem to show that it is a prophylactic against typhoid fever for one or two years, and so tuberculin may be a prophylactic against tuberculosis for a period of three months in cattle, but no one has the right to say that a process which is an effective agent in preventing a disease must *ipso facto* be effective when the disease has already begun.

The Encouraging Effect upon the Patient and Doctor of doing something for the Patient instead of leaving him to specifically Cure or Not Cure Himself.

It almost seems out of place to consider such a matter in the discussion of so serious a subject as the adoption of tuberculin to cure tuberculosis. No reference would be made to it were it not that we are in direct contact with patients. Patients ask for tuberculin to be administered, and how can we refuse them when the public press lends its advocacy, when tuberculin is even used in obedience to the permission of the Insurance Act? What every man must feel is that if his convictions are that such and such a remedy cannot cure specifically he must say so and withhold it.

The Antitoxin Treatment of Diphtheria.

So impressive was the great reduction of the mortality after the introduction of diphtheria antitoxin that the hope arose that all infections would yield the same happy issues. It is a fact that there are many who to this day think that tuberculin is an antitoxic serum, and should therefore be successful. The final section of this address will serve to show that such a view is utterly wrong. The use of the serum of a horse which carries in it material which is capable of neutralizing the poisonous effects of diphtheria bacilli, and that

this can be shown to occur in a test tube as well as in the human body, is one thing, but to cure an infection with the tubercle bacillus by means of tuberculin derived by breaking up tubercle bacilli and making an emulsion of them is quite another.

The Variety of the Cures of Tuberculosis.

There are those workers who still maintain that sanatorium methods are the only ones which effect a cure of tuberculosis; there are others, again, who repudiate all such claims, and who advocate treatment with tuberculin alone; and now there is a group of workers who maintain that the combination of tuberculin and sanatorium treatment is necessary. These facts alone point to a difference of opinion which begets the suspicion that perhaps the tests applied to prove the efficacy or not are at fault. A most important paper has recently been published by Messrs. Palin Elderton and Perry.⁸ They show that tuberculin treatment does not contribute any increased length of life to the patient when carried out in conjunction with sanatorium treatment, as judged by the large amount of material for investigation provided by Dr. Lawrason Brown in America and Drs. Prest and Guy in Scotland. The same suspicions are aroused when distinguished Continental workers put forward the idea that the disease is after all to be cured by an antituberculous serum, and when it is said a "cure" is to be found in quite a different direction—namely, by the production of artificial pneumothorax. Of Friedmann's cure we have still to await further details. We have heard of "pneumosan" and "dioradin." With such a varied list of cures, blessed by one school and condemned by another, is it remarkable that the layman should also offer his "remedies" for a cure? Further, is it remarkable that members of our profession are also convinced that the specific cure has yet to be found? Professor Metchnikoff in his recent address⁹ delivered in London has nothing to tell us of a remedy which specifically cures tuberculosis.

The Method Adopted to Test the Value of Tuberculin.

No one can look into the problem of the cure of tuberculosis without becoming aware that the secret which underlies the existence and development of so many vaunted "cures" is to be discovered in our ways of estimating their value. When the layman copies these ways we are angry, and condemn him, and feel justified in doing so (1) because he does not announce his cure through channels which we consider proper, and (2) because we argue that he does not know the nature or course of the disease. We have seen with regard to tuberculin that there is no confirmation that an animal can be cured of tuberculosis by means of it; therefore in advocating it, we put ourselves in a faulty position similar to that of the layman with his "causal" cure. There remains, then, but one way in which we differ from him—we know the nature and course of tuberculosis, and he does not. It seems to me that we have not made enough of our knowledge of the course of tuberculosis if left unaided. Of 1,532 cases of pulmonary tuberculosis (tubercle bacilli being present in the sputum), it was found that one-seventh lived five years and more from the date of the manifestation of tuberculosis, one-thirtieth lived over fifteen years, and in five cases there was documentary proof that they had lived sixteen, eighteen, twenty-four, twenty-five, and forty years. Not one of these cases had been treated in a sanatorium nor had they received tuberculin.¹⁰

The fact is that as a profession we are wrong in our methods of estimating "cures" in the only sense a layman wants to hear of them—real "cures," complete eradication of the cause. We have too long judged of "specific" cures without allowing for the *post hoc, propter hoc* fallacy. We cannot afford to do so any longer, because our statements are being revised by skilled mathematicians; our "impressions" of proof of cure have been put into the scales and they are found wanting. Professor Karl Pearson tells us¹¹ that, taking our own death certificates as supplied to the Registrar-General, it is clear that a fall in the death-rate from tuberculosis of the lungs had begun in 1835 and continued till 1891. Since then it has ceased to fall, despite the help that has come, so it is said, from the use of sana-

toriums and of tuberculin. It has been said that tuberculosis dispensaries have led to a great fall in tuberculosis in a certain town, but the same critic is able to show that the fall was paralleled in two other towns in which the dispensary system had not been introduced. We physicians, therefore, have failed to establish by our own death certificates or by our methods of inquiry any improvement due to sanatoriums, tuberculin, or dispensaries. The improvement was due to a natural process of which we have been unmindful.

It is not without interest that I should have figured as one of the collectors of evidence in favour of the use of tuberculin.¹² In 1905 tuberculin was not used in this country for the cure of pulmonary tuberculosis. I circularized every institution which had to do with this disease and found this out. Following out non-critical methods, I published results such as the following: Of 656 early cases treated with tuberculin, 91 per cent. reached a certain standard of improvement, whereas, of 611 not treated with tuberculin, only 62 per cent. reached the same standard. But when the individual accounts of certain workers whose reputation is world-wide were looked at, the large difference of 29 per cent. disappears. Dr. Turban treated 86 cases with tuberculin, and of these 52.6 per cent. achieved permanent good results; of 241 not treated with tuberculin, only 39.4 per cent. achieved the same result—a difference of 13.2 per cent. Dr. Trudeau was able to find that the use of tuberculin was followed by an increase of cures of 8 per cent.

Now it may be argued that these last figures are quite good enough, and until they are found to be wrong it would be useless to deny the use of tuberculin simply because experiments on animals had failed to establish the same happy results. At the time I wrote that article I thought so too, but subsequent experience has shown that cases reported to be cured too often broke down again later, that "permanent good results" gave place to permanent and final bad ones, and that physicians are not sufficiently skilled in making mathematical deductions. It is obviously difficult to find proof of the efficacy of tuberculin treatment by methods which do not take into consideration the whole of the life, or which cannot be controlled as can those in animals, by slaughter and the examination for active disease. An interested critic of our methods of testing the value of tuberculin propounded to me a method which, if carried out in a large number of cases, would satisfy him. I was to find a group of cases of pulmonary tuberculosis which were recognized by tuberculin advocates as suitable for treatment with a reacting dose of tuberculin; half were to be treated with tuberculin and half without, other conditions being equal. The choice of each half was to be left to chance; I was not to pick out those "specially" favourable ones as suitable for tuberculin. This method of testing the value of tuberculin is opposed entirely in principle to that advocated by modern workers. Bandelier and Roepke¹³ lay it down as an axiom that the cases must be selected ones—individualization is the secret of success—extremely early cases are the only likely ones to give satisfactory results (*sic*); they do not give sufficient prominence to the fact of spontaneous cures in such cases. As a test of the improvement of the lung condition, I chose the method of registration of the advance or retrogression of râles after three months' treatment. Dr. Rigg, the house-physician who bore the burden of the test, has recently published the results.¹⁴ Of the 10 tuberculin treated patients, 1 improved, 4 became worse, and 5 remained *in statu quo*. Of 9 non-tuberculin treated patients, 4 improved, 3 were worse, and 2 remained *in statu quo*. It cannot be said that this is a clear argument against the tuberculin effects on the lung, because it might equally well be maintained that it was an argument against using a remedy which so raised the temperature as to keep the tuberculin treated patients in bed, whilst the others were up and about; but still this method of giving tuberculin is advocated at the present time and is being extensively used. We are now trying a series of cases in which this difficulty will be met.

The Evidence of Individual Cases, or of Series of Cases, Neither Controlled.

No greater fallacy needs exposing than that which underlies the statements of individuals who have been "cured" after this, that, or another treatment. One has

only to ask, as veterinary surgeons have now to ask themselves, How can one be sure when a human being or animal appears to overcome a tuberculous lung affection that such victory has necessarily followed, not from Nature's efforts, but because of the remedy used before the improvement comes? It is certain that if any proprietary article or quack remedy, etc., were applied to cases of pulmonary tuberculosis, some of the individuals would get better after its use. The same may be said of tuberculin. Such evidence is set at naught because patients recover spontaneously just as cattle do. But there have been many series of cases reported in which it is said there is evidence that tuberculin is a specific cure. The criteria have differed in different reports. Bandelier has published results of tuberculin treatment; he found that 100 per cent. of the cases in Turban's first stage lost their tubercle bacilli; 87 per cent. of the cases in Turban's second stage and 44.2 per cent. of the cases in Turban's third stage also lost their tubercle bacilli. The total cases treated numbered 202. We have a right to ask, What would such cases have done without tuberculin? And it is right to object that disappearance of tubercle bacilli from the sputum is too often but a temporary phenomenon.

What Does Tuberculin Do?

Like all vaccine treatment, tuberculin is certainly capable of effecting a change in the aspects of the disease. But it has never been experimentally proved that such changes are curative; the alleged curative changes can be explained on anaphylactic grounds. To explain this requires technical consideration.

We know that when diphtheria bacilli invade the body, they poison the body by means of diphtheria toxin; the patient may resist the effects of this toxin by manufacturing his own antitoxin; nowadays we do not wait to see if he does, we administer antitoxin developed experimentally in the horse. The toxins of tetanus and botulism or sausage poisoning can be met by a similar mechanism. The chemical response of the cells of the body to and against the toxin are figuratively expressed as receptors of the "first" order of Ehrlich. Their interaction is diagrammatically figured in most textbooks of bacteriology. These receptors are certainly of therapeutic value.

When the typhoid organism assails the body, a different group of chemical actions is developed on the part of the body cells; the serum of the body now possesses not anti-toxic but agglutinative properties; no one has demonstrated that this development of what are known as receptors of the second order has any therapeutic significance, though the diagnostic value is of the greatest importance (Widal test for typhoid fever).

It is seen, then, that receptor development following upon bacterial invasion is not necessarily of benign curative purpose. We may expect more complicated receptors than those of the first and second order to be developed, of different properties, and again not necessarily of therapeutic value.

This brings us to the consideration of another group of receptors—the third order—which has particular interest in connexion with this address. It enables us to understand better the meaning of anaphylaxis, of a von Pirquet test, and of a tuberculin test; it also enables us to understand such complicated tests as the "complement fixation" test for tuberculosis, and if recent experiments are confirmed it will enable us to understand how the effects of tuberculin administered as a curative agent can be explained on other grounds than therapeutic ones; finally, it will help us to understand why two cases—one under the care of A. Fraenkel and one under Wolff-Eisner—developed a tuberculous ulcer on the tongue and tuberculosis of the lungs respectively, whilst undergoing a course of tuberculin treatment for lesions located elsewhere in the body.¹⁵

Let us suppose that a tubercle bacillus (A) enters into the body of an animal. It may, and probably does, in countless instances suffer annihilation by agencies which have been transmitted from the animal's parents. No infection occurs, and the animal is none the worse. But supposing there is more than one bacillus, or that the one gaining access is more virulent, or suppose that the animal has inherited from the parent no insusceptibility, something like the following takes place: A cell of the

body (B) in the neighbourhood of the deposit of tubercle bacilli is busy with one of its physiological duties of absorbing nourishment; it includes the tubercle bacilli in this category, and the effect upon the cell is to increase its appetite for more (a popular expression for Weigert's law that an excessive stimulus provokes an increased supply of receptors or chemical affinities). Let us represent this increased appetite by a cell with several receptors attached to it of the pattern c. This is known as an "amboceptor," because it can attach at d a special agent known as complement (x), which is present in all living healthy animals, more in some than in others; at its opposite extremity, e, it can also attach to itself a tubercle bacillus (A) or tuberculin (A'), which also

DIAGRAMMATIC REPRESENTATION OF CELLS, RECEPTORS, ETC.

A, Tubercle bacillus, with its chemical affinity for cells of the body represented by a receptor. A', Tuberculin, with its chemical affinity for cells of the body represented by a receptor. B, A cell of the body showing four fixed or sessile affinities or amboceptors, c, capable of uniting with a tubercle bacillus or tuberculin at e and with complement, x, at d. M, Tuberculin-anaphylatoxin, composed of three elements—complement, amboceptor, and tuberculin. N, Tuberculo-anaphylatoxin, composed of three elements—complement, amboceptor, and tubercle bacillus. P, A ferment present in each amboceptor. The combinations M or N when completed lead to the dissolution of the tuberculin or the tubercle bacillus and the cell B. The liberation of digestion products is accompanied, according to the quantity liberated, by the phenomena of anaphylaxis in slight or extreme degree, anaphylactic death, anaphylactic shock, or "tuberculin reaction," with rise or fall of temperature, etc. R, Tuberculo-anaphylatoxin operating on a "prickle" cell, L, of the skin. The change in the cell, L, contributes to the production of what is known as a "von Pirquet" reaction; if it took place in a conjunctival cell, to a "Calmette" reaction. R Represents "free" tuberculo-anaphylatoxin. Were it possible to demonstrate the existence of "free" tuberculo-amboceptors, then the serum treatment of tuberculosis would be reasonable. Were it possible to demonstrate "free" tuberculin amboceptors, the tuberculin treatment of tuberculosis would be reasonable; but in both cases the undesirable effects of anaphylaxis would have to be met.

have chemical affinities represented figuratively as receptors (x and x'). We must also suppose that resident in the amboceptor is a special ferment (P) which is capable of acting upon protein and breaking it up into much simpler bodies—for example, peptones or albumoses, or amido-acids, and into some substance capable of influencing temperature. We will suppose (at first) that these amboceptors are anchored to the cell B. When to this "sessile" or "fixed" amboceptor complement is attached at d and

antigen (in the shape of tuberculin or tubercle bacilli) at E, it is as if a match had been put to a firework. The ferment resident in the amboceptor can now operate on the cell B and the antigen E, and lead to the above proteolysis of both. If this is complete a liquid residue is all that remains, if incomplete the cell B is swollen and its nucleus obscured; cell death is more or less complete. Presumably when a focus of tuberculosis develops all the cells in the neighbourhood undergo change, and we recognize a "tubercle" by the naked eye—grey, white, or caseating according to the stage of action. But it is possible that cells far removed from the seat of tuberculosis may also have their special receptors developed—for example, in the skin L, subcutaneous tissues, etc. We must suppose, too, that these receptors may be inherited, or they may develop after birth as the result of an infection. They may exist, therefore, although there is no certain tuberculosis present in any part of the body. In other words, these receptors are a sort of hall mark of infection which may be inherited or acquired.

Now let us introduce into such a tuberculous animal a dose of tuberculin as Koch did in his original experiments. This reaches E in numerous cells; complement is fixed and a "reaction" is set going, so thoroughly described by Koch years ago. One thing we now know is that such reaction is a test of the presence of suitable receptors, *not necessarily of active tuberculosis*. The reaction is slight or brisk, and may be fatal, according to the available receptors and the dose of tuberculin. This helps us to understand the catastrophes following on Koch's introduction of tuberculin. The temperature may rise or fall or remain unaltered according to the amount of poisonous material let loose when the reaction takes place. The combination of complement, amboceptors and antigen, for example, tubercle bacilli or tuberculin, is known as "anaphylatoxin," the reaction this brings about as "anaphylaxis." If tuberculin is given repeatedly, it will use up all the tuberculo-amboceptors, until reaction is no longer given. The individual can, as is well known, become completely insensitive to tuberculin; this insensitiveness cannot experimentally be transmitted from one animal to another.¹⁶ We begin to see why it is that the giving of tuberculin is not necessarily followed by cure because there is no reaction, and we see why Fraenkel and Wolff-Eisner's cases, though undergoing treatment with tuberculin, were yet developing fresh tuberculous lesions elsewhere. Koch was able to show the difficulty of reinfecting his tuberculous guinea-pigs when he reinjected them with tubercle bacilli in small amounts; it is easy now to see why; the tubercle bacilli were at once fixed by tuberculo-amboceptors and digested, producing symptoms or not according to the amount of available receptors and tubercle bacilli; these experiments, first announced by Koch, have now been shown by Römer¹⁷ to be true. Whether temperature alterations occur is dependent upon the amount of poison liberated (Thiele and Embleton).¹⁸

Now, the theory thus given says nothing about an attack upon the tubercle bacilli which are responsible for the formation of the amboceptors in the first case. Such organisms may be locked up in some fibrous focus, they may be quite unaffected, they may be busy provoking the formation of fresh amboceptors. Indeed, so far as animal experiments go, no one has ever succeeded since Koch did, *pace* the "few cases" referred to by Bandler and Roepke¹⁹ (no reference given), in showing that the injection of tuberculin does affect the life of these organisms, to the extent of bringing the tuberculous process to a standstill. This part of his original statement has never been confirmed, whereas the rest has been repeated by Römer. Römer gives no statement to the effect that in repeating Koch's experiments he also was able to cause the original tuberculous process to come to an end. Römer's writings show only too well the impossibility, which he fully recognizes, of ruling out spontaneous cures and infection. It is so common to hear that vaccines, including tuberculin, increase the individual resistance, that the increase of the resistance is shown in the diagram, and that the diagram is a perfect support of the contention that just as the amboceptors attach themselves to artificially introduced tuberculin or tubercle bacilli, so they will attach them-

selves to tubercle bacilli naturally occurring and causing the development of amboceptors. The reply must be that the absence of proof of this last happy issue in animals negatives such a view, and it is also understandable that tubercle bacilli ring-fenced in inaccessible fibrotic or caseous foci are not approachable by such a mechanism. There is nothing of a curative nature to be discovered from anaphylaxis; it is a reaction, not necessarily defensive, of the body to any foreign protein introduced from without, whether bacterial or other.

The recent work of Drs. F. H. Thiele and D. Embleton²⁰ on some observations on the production of temperature variations should be read by those who are interested in the problems associated with tuberculin treatment. They show that very probably the poisonous effects produced in the body by bacterial invasion are not the results of poisons developed in and by the living bacteria, but are due to the operations of the invaded organism which, by means of its amboceptors, produces poisons by the digestion of the invading bacteria. Indeed it looks as if the body may tolerate infection well enough, but what it cannot always tolerate is the poisoning which is set agoing when the body cells react against these bacteria. Tuberculin when administered actually helps this poisoning; in 1890 and 1891 such catastrophes were frequently seen because large doses of tuberculin were used; when, since 1905 and 1906, some form of tuberculin has been administered in small doses the poisoning has been whittled down to small injuries as tuberculin reactions and tuberculin cures. This may sound a revolutionary doctrine, but it is one which follows upon the advent of the discovery of anaphylaxis.

The Bearing of the Success of Antityphoid Inoculation.

So far my task has been an easy one; practically all the points in favour of the use of tuberculin to cure disease already existent have been met with counter-explanations, and I sincerely hope my arguments have been fair and have convinced you that the tuberculin cure of human tuberculosis so far is unproven.

But I admit to you I am in a great difficulty when I contemplate the fact announced by Sir William Leishman in this country and by workers abroad in favour of antityphoid inoculation. It has been shown that the prophylactic inoculation with a typhoid vaccine confers on the individual for about two years a lessened risk of contracting typhoid fever; or if contracted, of reducing the case mortality until at the present time, amongst those so inoculated, the number of soldiers in the British army who contract typhoid fever is less than the number who died from it a few years ago. The advocates of the tuberculin treatment of *established* tuberculosis, or for the vaccine treatment of any *established* infection, feel that if typhoid fever can be reduced in case incidence and in case mortality by vaccination before the disease is developed, it should be able to be controlled by vaccination after the disease is developed. I can say at once that figures have yet to be published to establish this speculation. It is not difficult to see that if antityphoid amboceptors are developed in a healthy individual before he contracts typhoid fever, when the infection does occur it finds the cells of the body *ready* to digest the bacilli as they arrive. Every cell to which the typhoid organism gets access is provided with receptors whose life is about two years, which are ready to behave in the manner above described.

If tubercle bacilli, on the other hand, gain access to the body, if they surround themselves with an almost impenetrable ring of fibrous tissue, caseous or calcified material, then any subsequent development at a remote part, say, of the skin or subdermic tissues of "sessile" tuberculin- or tuberculo-amboceptors by means of injections of tuberculin or tubercle bacilli, may be quite unable to reach the tubercle bacilli. Once again, and finally, until animal experiments can be made showing that this difficulty can be overcome, or until a critically controlled application of tuberculin to a large number of tuberculous human beings can be shown to cure the tuberculous lesion, I submit that the case for tuberculin cure is unproven.

There still remains one more point which must be discussed, and it is this: It may be fairly asked whether it is

not possible that some of the alleged cases of cure of tuberculosis by means of tuberculin are, after all, real and explainable on the ground that all the tuberculin-amboceptors figured in the above diagram do not exist in the form of "fixed" receptors—that some are "free," circulating in the blood stream, and are capable in certain "suitable" "early" cases of tuberculosis of gaining access to the tubercle bacilli present in the focus of tuberculous disease before the latter is rendered inaccessible by fibrosis or other processes of caseation, etc. Such a possibility must be admitted, because by the "complement" fixation method it is possible to demonstrate in certain tuberculous subjects the presence of antibodies in the serum. The answer is that, though infection with living tubercle bacilli may be productive of the formation of tuberculo-amboceptors, which will react to living tubercle bacilli introduced at a second injection or to tuberculin, and which may be free in the blood stream and may give a positive complement fixation test, no one has ever succeeded in proving that if a healthy animal is injected with tuberculin, tuberculin-amboceptors are produced, which will react to living tubercle bacilli, causing their death and solution, or that the serum of such an animal gives a complement fixation test, using living tubercle bacilli as antigen. Moreover, it is well known that no one has ever succeeded in demonstrating in a non-tuberculous man a positive von Pirquet reaction, simply dependent upon repeated previous injections with tuberculin.

Though experimentation has shown that previous tuberculosis, by means of tuberculo-amboceptors, certainly "fixed" in character and may be "free," may prevent subsequent infection with tuberculosis, it has not shown that tuberculin-amboceptors, "fixed" or "free," can prevent subsequent tuberculous infection. Römer¹⁷ has supplied some evidence which supports this latter contention, for he has found that cattle immunized by living tubercle bacilli and normal animals both show about the same sensitiveness to tuberculin, while the immunized animals show a high degree of hypersensitiveness to tubercle bacilli as a sign of their immunity, and the control normal animals do not.

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THE *Liverpool Daily Post and Mercury* has succeeded in collecting £2,000 in ten days for the purpose of supplying radium for the treatment of cancer at the Liverpool Royal Infirmary.

AN international congress on the protection of infancy is to be held in Brussels in July. The work of the congress will be divided among two sections: (1) Children morally abandoned, with special reference to the competence of the courts in respect of children, and the organization of supervision, having regard to liberty. (2) Infancy and puericulture, including the establishment of uniformity of the bases of statistics of infant mortality; consideration of the means of popularizing the principles of hygiene and puericulture; measures of protection for the child outside the home, whether of the father, the mother, or the legal guardian. The sections will discuss together the question of the creation of an international bureau for the protection of infancy.

PLEA FOR UNIFORM METHOD OF TREATMENT WITH TUBERCULIN.

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NOTWITHSTANDING much excellent work which has been accomplished during recent years in connexion with the specific treatment of tuberculosis, there still exist much confusion of thought and diversity of practice with regard to the best method of administering tuberculin. There is little or no uniformity of practice in the variety of tuberculin used, in the method and frequency of administration, or in the cases selected for treatment. To the writer it seems that what is urgently required at the present moment is the placing of the treatment of pulmonary tuberculosis with tuberculin on a rational uniform basis which will provide a guide to the general practitioner, who rightly complains against the multiplicity of tuberculins recommended and the difference of opinion regarding treatment which exists among experts. It is not possible, nor in view of the value of comparative studies is it desirable, that a uniform method of treatment with tuberculin should be applied to the whole country. It is certainly desirable, however, that some uniform procedure with regard to the methods and variety of tuberculin used should be applied in each county or district in which the machinery for dealing with tuberculosis is now being established. The aim of tuberculin treatment is to evoke a focal immunizing response *pari passu* with the production of a well-marked degree of tolerance both to the endotoxin and the exotoxin of the tubercle bacillus. The production of a rapid and well-marked tolerance to the exotoxin alone by the inoculation of filtrates of various strengths does not protect the patient sufficiently against the body of the bacillus, and may indeed mask the presence of a slowly progressive lesion. The researches of Koch, Wright, and other observers have demonstrated that it is the body of the bacillus with the contained endotoxins to which we most look for the production of any efficient and permanent immunizing response. Moreover, clinical experience bears this out. Recently I examined a patient who had received over 90 inoculations of exotoxic tuberculins of increasing strengths. There was an entire absence of constitutional symptoms, but crepitations were audible over four lobes, there was a large interarytenoid ulceration, and the urine contained tubercle bacilli. This patient followed his occupation up to a few weeks before death. Clearly in his case the production of tolerance proved a curse in disguise.

It has generally been accepted that the method of treatment with tuberculin is the same at the dispensary as in the sanatorium, but this is not the case. In the sanatorium patients are under constant medical supervision, and the amount of muscular and respiratory activity is regulated according to the requirements of each individual case. In the sanatorium treatment by auto-inoculation takes the place of the preliminary course of treatment with exotoxic tuberculin at the dispensary. I have previously¹ pointed out the excellent results obtained in a sanatorium by a course of tuberculin containing both endotoxin and exotoxin administered when patients have ceased to react to the maximum amount of walking exercise and manual labour; in other words, when a certain degree of tolerance to exotoxin has been secured. At the dispensary, on the other hand, the muscular and respiratory movements of the patients are not under intelligent control. The patient is liable to show sensitiveness to auto-inoculation with the exotoxin of the bacillus, hence a degree of tolerance sufficient to steady the temperature must first of all be produced by a course of treatment with exotoxic tuberculin. The method of administration and frequency of dosage are a source of no little diversity of opinion. In my experience the most efficient and permanently beneficial focal result is obtained by inoculating the patient once a week and by gradually increasing the dose without the production of any marked general or focal reaction, 99° F. being regarded as the danger zone. It is true that if the doses are rapidly increased and reactions are ignored a high degree of toxic tolerance may be obtained, but this is secured at the