PRESENT POSITION OF TUBERCULIN THERAPY.

A THESIS

By

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PRESENT POSITION OF TUBERCULIN THERAPY.

I. Introduction.

Tuberculosis is the commonest and the deadliest of all the diseases that attack the human race. It has a greater mortality than that of any other disease. Koch estimated that 1/7 of all the deaths in the civilised countries was due to tuberculosis and that pulmonary tuberculosis constitutes about 11/12 of all forms of tuberculosis occurring in man. The statistics of Great Britain and of other countries probably understate the prevalence of this disease. It is stated that in Berlin tuberculosis is responsible for 1/3 of all the deaths between the ages of 20 and 50. In England alone there are more than 55000 deaths recorded each year—more than 150 deaths every day. Kayserling stated at the Paris tuberculosis congress that 1/3 of all the deaths and that half of the sickness amongst adults in Germany were due to tuberculosis. Newsholme is of opinion that 1/9 of all the deaths in England and Wales is due to tuberculosis. Pye Smith states that 1/3 of the deaths between 15 and 45 years of age in -
in England is due to phthisis. The United States Census of 1900 showed the mortality from tuberculosis to be $\frac{1}{9}$ of all the deaths.

Tuberculosis has been stated to be not only a disease of all nations but also a very common disease amongst all civilised nations. No race is exempt from the ravages of consumption and no country is exempt. It is prevalent in all latitudes and in all altitudes. It is known to occur in all regions whether dry or moist, high or low, warm or cold. The comparative infrequency at high altitudes is easily explained by the sparseness of the population. Tuberculosis is said to be less common in the tropics than in the temperate regions. The frequency of the disease is determined more by overcrowding, poverty, occupation and neglect of the laws of health than by geographical situation.

The universal distribution and the prevalence of the disease in the various parts of India, the high rate of mortality from it, the easy preventability of the spread of infection in the early stages &c. were all pointed out in recent times by Dr. Turner, Col. Robert, Dr. Bose, Col. Rogers and others. The study of the post-mortem records in the Calcutta Medical College Hospital
Hospital by Col. Rogers brought out the startling fact that 25% of the bodies examined post-mortem showed signs of active or latent tuberculosis. In Madras the disease is fairly common and is distributed over the whole presidency. The percentage of bodies in which tuberculosis lesions were found post-mortem in the General Hospital, Madras, during 5 years, is given below:

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>1907</td>
<td>27.7%</td>
</tr>
<tr>
<td>1908</td>
<td>8.4</td>
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<tr>
<td>1909</td>
<td>11.5</td>
</tr>
<tr>
<td>1910</td>
<td>9.0</td>
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<td>1911</td>
<td>11.2</td>
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</tbody>
</table>

The average for the five years is 13.5%. The returns of the Surgeon General, Madras, for cases treated for tuberculosis in the hospitals and dispensaries of the presidency show an increase year after year. This increase is really due not only to an actual increase in the prevalence of this disease but also due to better diagnosis in recent times. In this country it is very difficult to obtain accurate returns for the deaths from tuberculosis. The figures available must be far below the actual number of deaths owing to inefficient registration. The rate of mortality from tuberculosis alone for the whole of India is
is stated to be 1 in 11 or 9% of all deaths which is not far from the rate for England and Wales, namely, 11%. This is enough to show that the disease is fairly common in this country.

II. Historical Outline.

Consumption has been studied by physicians since the days of Hippocrates and Galen. At the end of the 17th century Sylvius made a scientific study of the pathology of the disease and believed in its contagiousness. In 1891 Laennec made very important additions to our clinical knowledge of the disease. In 1865 Villemin after an elaborate experimental study came to the conclusion that tuberculosis was a specific affection, that it had its origin in an inoculable agent and that it should be classed with specific diseases like small-pox and syphilis. It was, however, reserved for Robert Koch by finding life in the tuberculous masses to solve the mystery that was beyond the range of the eye or the microscope. By his epoch-making labours Koch removed every vestige of doubt and at last convinced even the sceptics by discovering the cause of this widespread
widespread malady and exhibiting it in splendid isolation as a pure culture consisting of millions of tiny little organisms upon the surface of solidified blood serum. Koch thus demonstrated the existence of tubercle bacilli in the tuberculosis tissues and convinced the scientific world that this tiny germ was the one and only cause of tuberculosis. It was first recognised by its property of being deeply stained by certain aniline dyes (methylene blue, gentian violet, fuchsin &c.) and retaining the stain even after the addition of strong acids.

Ever since that memorable gathering of the physiological society of Berlin on 24th March 1882 when Koch announced his brilliant discovery, heralding a new era in the history of medicine, our knowledge has increased by leaps and bounds. The discovery of the specific bacillus of tuberculosis was the first step towards those successful investigations of Behring, Kitasato and Wernicke which terminated in the discovery of a specific remedy for diphtheria and tetanus.

Having discovered the specific cause of tuberculosis Koch next proceeded to search for an agent that would destroy the parasites in the living tissues. Years of unremitting toil, during which he exhausted the vega-
the vegetable and mineral kingdoms in his researches led him to the disappointing conclusion that all disinfectants which would kill the bacillus in the tissues, would kill the tissues also. Proceeding thence on entirely new lines Koch made experiments on guinea-pigs with graduated doses of dead bacilli which have revolutionised our ideas upon infection and immunity. He found that when a healthy guinea-pig is inoculated with a pure culture of tubercle bacilli the wound usually closes up and seems to heal in a few days. But in 10 to 14 days a hard nodule appears at the site which soon breaks down forming an ulcer which persists till the death of the animal. If, on the other hand, an animal already infected with tubercle be inoculated with a culture of the bacilli, the wound, though it would heal up at first, shows no tendency to form any nodule and about the second day becomes hard and assumes a dark colour not limited to the site of inoculation, but spreading to the surrounding tissue for a variable distance. In a few days, again, it becomes clearer and the altered skin shows necrotic changes; it is eventually shed and leads to the formation of a flat ulcer which heals quickly and permanently without infecting the surrounding lymphatics. Buncher who followed
followed Koch came to much the same conclusions. He defined the condition of the organism after recent infection as latent irritation caused by the tubercle bacilli present in the body. This latent irritation is, in its nature, not a passive condition, but an active re-action of the tissue elements which exert an attempt to free themselves from the exciting cause of infection. He also drew attention to the febrile symptoms as a sign of this re-action.

This was followed by Koch's further observation that the same phenomena which appear after the re-injection of living and dead bacteria can be produced with their extracts —— tuberculin. From this he evolved the principle of specific treatment, discovering that the disease can not only be prevented, but cured through the medium of its own cause. It was in November 1890 that Professor Koch gave an account of a substance which, in his own words, was able "to render animals immune against tubercle bacilli and to bring a standstill the tuberculous process in animals." This new remedy for tuberculosis, afterwards named tuberculin, consisted of a
of a glycerin extract of tubercle bacilli evaporated to \( \frac{1}{10} \) of its bulk in a water-bath and then filtered through a porcelain filter.

Tuberculin is the general name for the toxic products of the tubercle bacillus grown upon the artificial media of the laboratory. It is not a serum. Its character and effects vary with the mode of preparation. The toxic products of the bacillus are the soluble, diffusible extractives and the endotoxins of the solid cell-body. The effects of tuberculin were chiefly studied in guinea-pigs. It has been found that man is far more sensitive to tuberculin than guinea-pigs, though there is in man far greater resistance to infection with living tubercle bacilli. In man tuberculous lesions tend to be localised and remain so for months or years. Tuberculin has a selective action on these localised areas of lesions. It has very little effect upon healthy persons or even upon sick persons provided there be no tuberculosis. But if the person be tuberculous it will produce a severe general and local reaction. The General reaction shows itself in the form of fever accompanied with a rigor. It may reach \( 103^\circ \) or even \( 106^\circ \). Other symptoms are
are headache, pains in the limbs, loss of appetite, nausea &c. The local reaction may best be seen in lupus patches in which tuberculin picks out the diseased tissues and spares the healthy and healed parts. It would thus be seen that tuberculin will be an indispensable diagnostic agent. We may thereby be in a position to diagnose doubtful cases of incipient phthisis even when, on account of the absence of tubercle bacilli or elastic fibres in the sputum, or by the absence of physical signs, it is impossible to come to any conclusion regarding the nature of the disease. This reaction, general and local, to tuberculin is specific and occurs only when tuberculous lesions exist in the body. In large enough doses, as Koch proved in his own body, tuberculin, like other bacterial products, is a poison capable of producing fever and other severe symptoms. But besides these ordinary bacterial elements, tuberculin contains a substance which has a selective action upon tuberculous tissue and thereby causes the specific reaction. This action upon the tubercular tissue is essentially inflammatory. Healthy tissue is rigidly respected. Now, while it is easy enough to describe accurately this extraordinary effect of tuberculin upon tuberculous
tuberculous tissue, as yet, its intimate nature is a hidden mystery. It has been shown by Wasserman and Bruck that the tuberculin reaction depends upon the action and interaction of tuberculin as an antigen and its antibody, styled antituberculin existing in the tuberculous focus. This antibody (antituberculin), by virtue of its eagerness for combination with antigen extracts the whole quantity of tuberculin injected from the blood and concentrates it in the tubercular focus. In this combination of antigen (tuberculin) and antibody (antituberculin) complement is fixed and in consequence the tubercular focus shows an increase of leucocytes, ferments, etc., which possess protein-digesting properties, leading to softening of the tubercular tissues. This focal reaction is usually accompanied by fever the result of the absorption of softened tubercular tissue.

Koch's original view of its action. Koch emphasizes that Tuberculin does not kill the bacilli present in the tissues, but that the tissue alone, which encloses the bacilli, is affected by the action of the remedy. In this well-marked circulatory disturbances and great metabolic changes occur, resulting
resulting in some parts necrosis and casting off of a slough, in others, rather in the disappearance,—a kind of melting—of the tissue. The remedy can only influence living tubercular tissue; on dead, caseous, necrotic tissue it has no action.

Koch's original method. In cases of tuberculosis of skin, gland, bone and joints, 10 c.m.m. were given as an initial dose and one or two weeks later, the dose was repeated and persevered with until the reaction ceased. In phthisis the same dose was used at first but later reduced to 1 c.m.m. If fever resulted the same dose (1 c.m.m.) was repeated daily until no reaction followed. Then the dose was raised to 2 c.m.m. But a certain number of more vigorous phthisial persons were also treated with large initial doses or with a rapid rise in the dosage.

Results. Persons in the early stage of phthisis were all entirely relieved of symptoms of the disease in 4 to 6 weeks, so that they could be regarded as cured. From these observations he concluded that early phthisis was curable with certainty by tuberculin. In
In advanced cases notable improvement was attained. Little or no result was achieved in the severer forms with cavity formation. The most essential point was in its earliest possible application when all cases of tuberculosis came to early treatment.

Causes that led to its falling into disrepute.

Since the introduction of tuberculin by Koch for curative treatment of tubercular diseases, there have been marked fluctuations in its popularity in the medical world. It was received with enthusiasm and subjected to extensive clinical trials. The astonishing cures in lupus and other forms of tubercle led to an over-estimate of its curative power. With misguided enthusiasm advanced cases were treated with too large doses, resulting in too severe reaction, and obvious and severe injury resulted from the faulty methods of application. Many observers reported that it was a dangerous remedy and it soon fell into disrepute. The report of the Brompton hospital for consumption in 1892 stated that tuberculin did not favourably influence the course of the disease in the majority of cases. The reaction against it was probably excessive. It proved disappointing for several
several reasons. The doses recommended by Koch were too high and it was used in unsuitable cases. It was therefore practically abandoned as an agent, if not positively harmful, at least incapable of effecting the good claimed for it. It was no longer looked upon as a curative agent but the febrile reaction, which it produced in a tubercular individual, was regarded as of value in diagnosis. In veterinary practice it has found a permanent value as a means of recognising concealed tuberculosis and recently Calmette, Wolff-Eisner and Von Pirquet have utilised it successfully for human diagnosis. Koch had previously warned against this rash use of the tuberculin in all manner of cases. He had stated that it was of no avail except for tuberculous disease and that if other complicating conditions exist—if other microbes are associated with tubercle bacilli in the morbid process—tuberculin may fail absolutely to assist or modify the process; in these it may then do harm and perhaps even hasten a fatal issue. Tuberculin treatment aims at a progressive process of active immunisation, radically different from the passive process in which antitoxic serum is supplied ready-made. Active
Active immunisation makes a large demand upon the energy of the tissue-cells and requires that the cells and tissues should be in a relatively healthy state. In the presence of various microbes, such as streptococci, the energy of the cells may be so depressed that active immunisation by tuberculin cannot be expected. Tuberculin treatment has therefore limits unknown in the antitoxic treatment of diphtheria. The failure of tuberculin in 1891 was due to a disregard of the limitations and restrictions laid down by Koch and to a general ignorance of the role of mixed infection in pulmonary tuberculosis. The key to a successful treatment with tuberculin is a proper selection of cases by means of bacteriological methods or by a judicious use of tuberculin itself as a diagnostic agent. Indispensable to success is a thorough knowledge of the variabae, complex and treacherous condition of mixed infection. As a rule fever is the danger signal and strongly suggests a secondary or mixed infection. On the other hand, fever may be absent and yet mixed infection may be imminent. By a fatal coincidence tuberculin as a remedy for tuberculosis was tried when influenza raged
raged in Europe as a violent epidemic. The fact that it occurred within a few days or weeks of injections of tuberculin in 1891, proves incontestably that tuberculin was used in hopeless and totally unsuitable cases.

The dangers associated with the administration of old tuberculin led Koch and his pupils to continue their researches in order to produce a safer tuberculin. In 1897 Koch announced that he had prepared a new tuberculin which retained the curative and immunising power of the old one but did not produce any dangerous febrile reaction and no ill consequences resulted from its use in tubercular cases. He found from numerous attempts to immune animals with dead bacilli that sub-cutaneous injection of the bacilli produced abscesses and intravenous injection of the bacilli produced lesions in lungs identical with tubercular process. It was therefore necessary to administer the bacilli in such a way that they could be absorbed without producing these effects. Admixture of chemical substances to the bacilli was found impracticable as the immunising action of the
the organisms was thereby destroyed. After many attempts Koch obtained a new form of tuberculin by a mechanical process which contained the curative and immunising substances of the bacilli in a form suitable for injection. The results which Koch obtained showed that no ill effects of any kind were produced by the injection.

III. The Various Kinds of Tuberculin.

1. Old tuberculin (T.O.) The first tuberculin prepared by Koch, called the old tuberculin, is a clear brownish fluid of complex composition. It is prepared from a glycerin-broth culture of tubercle bacilli 6 to 12 months old. The culture is evaporated to 1/10 of its volume and then filtered through a porcelain filter. It is practically a solution, in glycerin, of the extra-cellular toxins produced by the organism.

Preparation of Dilution: The diluting fluid is \( \frac{1}{2} \) per cent phenol solution. 1:10 dilution of the
the original fluid often remains unchanged.

**Initial dose.** 1 c.m.m. may be used in favourable cases in the first and the second stages of the disease as an initial dose. If temperature is above 37°C or if reaction occurs, reduce it to .01 c.m.m. In case severe general reaction occurs, go down to .001 c.m.m. With small doses up to 10 c.m.m. increase of one or more divisions in the pipette may be made at each injection according to susceptibility.

**Interval.** Twice a week is the rule. Above 10 c.m.m. this should not be less than three clear days.

**Maximal dose 1000 c.m.m.**

Old tuberculin is the best for diagnosis. As a therapeutic agent it may be given whenever active focal reaction is desired, as in phthisis, for producing severe reaction in a focus which is uncomplicated, well circumscribed and not too pronounced and also in tuberculosis of skin, joints, bones &c.
2. Koch's original Tuberculin. (T.O.A.)

It is prepared exactly like the above though it has not been concentrated to 1/10 of its volume. It has been extensively used in Belgium, Switzerland and other places owing to its low toxicity. It consists of a filtered culture of tubercle bacilli of human origin, not concentrated by boiling and completely free from the bacillary, bodies themselves. It contains exclusively substances which have been produced by the tubercle bacilli during their growth and abstracted by the culture fluid.

**Dilution.** 1 c.c. of T.O.A. corresponds to 1/10 or .1 c.c. of T.O.

3. Albumose-Free Tuberculin (AF).

This was introduced by Koch to avoid the fever caused by albumoses. It is prepared by the growth of bacilli on media free from albumoses.

**Properties.** It is better tolerated than T.O even by very sensitive persons. Treatment can be carried to the end without trouble. The action is not inferior to T.O.

**Dosage** is the same as for T.O.
Toxic and bacterial immunity. With T.O. the aim was simply the attainment of immunity against the bacterial toxin. On the bacilli themselves the immunity has no influence, like the tetanus anti-serum. With cholera and typhoid it is a question of pure bacterial immunity. Koch's aim was to combine both these forms of immunity in his treatment of tuberculosis. He recognised a tendency towards immunity in the miliary tuberculosis of man. He aimed at obtaining the immunity at an early stage of the infection. He held that immunity did not take place because the tubercle bacilli are present in the tissues in such small numbers and grow so slowly. Therefore the process of immunisation did not occur. It only takes place when bacilli distribute themselves rapidly in the whole body as in miliary tuberculosis. It was therefore necessary to ensure the absorption of as many bacilli as possible whether living or dead. For this purpose Koch obtained a complete breaking up of bacilli by grinding a well-dried culture in an agate mortar. The powdered mass was stirred up in
in normal salt solution and separated by centrifugalising into two layers. The opalescent fluid was decanted off and formed the T 0, possessing the properties of the old tuberculin. The deposit was dried, pounded, treated with distilled water and centrifuged, the supernatant fluid being again decanted. This process was repeated until practically no more residue remained. The various fluids, collected together, constitute the new tuberculin (TR). It is made of such strength that one c.c.m. of TR contains 2 mgms of dry tubercle powder. 20% of glycerin is added to ensure its preservation. The dose recommended by Koch was 1/500 mgm gradually increased to 20 mgms. TR does not require the same precaution in administration as T 0. It is the mildest of Koch's preparations. Hence it may be used as a preliminary to a course of T 0 or of bacillary emulsion.

Properties of T.R. TR possesses immunising properties unquestionably. Considering reactions necessary in the case of T 0 to obtain curative result, with TR Koch sought to avoid them. The important point is, by gradually increasing the dose, to make the individual insensitive to TR. A person immunised against TR does
does not react to large doses of T 0 and is therefore immunised against all constituents of the tubercle bacillus.

**Indications and contra-indications.** In advanced cases of phthisis especially those with severe mixed infection and high fever, T.R should not be employed. But in all others striking improvement far exceeding that which T 0 results.

Cases of extensive physical signs such as haemoptysis, night sweats, great dyspnoea, heart disease, renal disease, epilepsy, hysteria, general glandular involvement, meningitis, intestinal tuberculosis etc., are also contra-indications to the use of tuberculin.

5. **New Tuberculin - Bacillary - Imulsion (B E).**

Koch modified his new tuberculin to the extent of no longer separating T 0 and T R. Instead of centrifugalising, the comminuted bacilli, after being suspended in normal saline, were merely allowed to settle and 50% glycerin added for greater permanence.
Bacillary emulsion is a suspension of one part of bacilli in hundred parts of distilled water to which equal parts of glycerin are added. The stock solution contains in one cc, 5 mgm of solid substance.

Initial dose. 1 cmm may be given in favourable cases of stage one or two with general good health. If reaction occurs begin with .01 cmm. With susceptible patients, only increase the dose by 100 cmm to avoid severe reactions.


Prepared as suggested by F. Meyer with dried human bacilli mixed with fresh tubercular serum and kept in incubators at 37 C for several days. It is then shaken until no whole tubercle bacilli can be found. The crushed bacilli are separated from the serum, washed with saline and made into emulsion with 40% glycerin-water to which ½ % phenol is added.

Dose. Begin with 1 : 1,000,000; end with ½ cc of stock solution.

This contains all substances having immunising properties whether in culture fluid or in bacteria themselves. It is composed of extra-cellular toxins of the broth culture of special formula and of intracellular toxins extracted from the bodies of the bacilli with 1% phosphoric acid at 60° to 70° C. This tuberculin has been warmly recommended by Sahli who prefers it to T 0 and T R.

8. Carl Spangler's Immunising Substances.

A T O  (Original old T)
P T O  (Original Bovine Tuberculin)
P E   (Bovine Bacillary Emulsion)
P V   (Bovine Bacillary Vaccine)

Von Brauns, Fruhwald, Hollos and others have recorded favourable results with these preparations.

Other Tuberculins. These are important modifications of Koch's preparations and include tuberculins of Hirschfelder, Jessen, Jacobs, Bandran, Sciallare and others.
Vacuum tuberculin of Carl Spengler, Landmann's tuberculol, Kleb's antiphthisin, Rothschild's auto-tuberculin, Wolf-Eisner's mixed tuberculin (T & T R), Gabrilowitsch's endotin, Calmette's tuberculin (CL) &c., need only be mentioned.

IV. KOCH AND THE GERMAN SCHOOL.

Tox-immunity. The disappearance of reaction to tuberculin was originally interpreted by Koch as a sign of the complete healing of the tubercular tissue. To-day we know that this is not the case and that tolerance of tuberculin is to be considered an immunisation against the bacterial toxin. The systematic production of toxin-tolerance and finally tox-immunity must offer advantages to the organism in its fight against the disease, as many of the general toxic phenomena of tuberculosis are to be attributed to the absorption of the toxic substances from the tubercle bacilli. Tuberculin treatment quickly removes the general toxic symptoms such as headache, pains in the chest, nervous irritability, loss of appetite &c. It can also immunise a patient against those quantities
quantities of toxin which he may often suddenly produce by unusual exertion (auto-tuberculin).

The experiments of Pickert show that patients whose disease takes a conspicuously favourable course possess a raised natural resistance to tuberculin, which speaks for a high resistance of the organism to the disease. The tuberculin tolerance is evidently advantageous; it is a sign that the disease organism is repelling the toxic action of the tubercle bacilli, that it has acquired a relative tox-immunity.

Lowenstein and Pickert have proved that true anti-toxins occur in the blood of tuberculin-treated patients. The antitoxins play an important part in the healing process of tuberculosis especially when formed at an early stage in the disease. Koch thought that animals artificially raised to high agglutination values possess a certain degree of immunity against infection by tubercule bacilli. We know that the production of agglutinating substances takes place regularly in the process of immunity and hence in the specific treatment of tuberculosis the phenomenon of agglutination is a favourable process for the simultaneous occurrence of immunising processes.
Tuberculin treatment a natural healing method.

Tuberculin treatment and all active immunising procedures are reckoned natural methods of healing. It helps the organism to form the antibodies which cannot be produced in sufficient quantity without such help. By the biological production of the natural means of defence the specific treatment only imitates and assists the spontaneous processes of healing. This is proved by Lowenstein and Pickert's method of testing tuberculin immunity by means of mixtures of tuberculin serum.

The tuberculin method does not set itself up against other methods of treatment. In less severe cases these may suffice but in severer ones tuberculin treatment cannot be dispensed with.

Pioneers of the modern view. The credit of holding fast to the established value of tuberculin and bringing it again to merited recognition is due to Goetsch, Hager, Krause, Thorner, Carl Spengler and Petruschky. What the morbid anatomists had seen to be the dangerous feature in the action of tuberculin was the stormy reaction which, on the one hand, gave rise to dangerous destruction of tubercular tissue and on the other, by setting free the tubercle bacilli, might lead to extension of the tubercular process and
and transference of diseased germs to other organs.
This gave the indication to reduce the therapeutic doses of tuberculin and as far as possible to avoid reaction.

**The mild method of administration.** This method was inaugurated in 1891 by Ehrlich and Guttman, Lichtheim, Aufrrecht, Biedert and by Petruschky who employed it for years in the out-patient department of Koch's institute. In 1901 it was again brought to the front by Goetsch and it is with his name that the method has been generally associated.

**Choice of site for injection.** The most suitable method of administering tuberculin for therapeutic purposes is the subcutaneous. Koch has recommended the skin of the back below the shoulder blades, alternately on each side. For the patient's convenience the fore-arm is generally chosen. Carl Spangler chooses the extensor surface of the fore-arm.

**Other methods of administration.** Of late years there has been an attempt to administer tuberculin otherwise than subcutaneously. These methods have been intravenous, intrapulmonary, by inhalation, by mouth, by rectum, percutaneous and cutaneous.
Intravenous method. This was recommended by Koch, who observed that the agglutinating power of patients treated with tuberculin subcutaneously could be raised yet further by giving the same preparation intravenously. But really there is only a difference of degree and of time between the two methods.

Intrapulmonary method. This was introduced by Jacob. This has no advantage over the preceding.

Tuberculin inhalation. Kapralik and Schroetter employed tuberculin inhalation for producing immunity. The procedure is free from danger but it has several disadvantages.

Oral method. The administration of tuberculin by mouth, first recommended by Freymuth, is also worthless in accordance with the recent investigations of Lowenstein, Jochmann, Hell, Mollers, Heinemann and others; for absorption from the alimentary canal is relatively inert. Thus tuberculin both per orem and per rectum produces no reaction in a tubercular guinea-pig (Laffert, Dieterlen). According to Ransom physical factors are chiefly responsible for this result. -- According to Calmette's investigations effective action
action would be most likely with the internal administration of bacillary emulsion in the form of Keratin-coated gelatine capsules.

Percutaneous application. This has been employed by Carl Spengler in the case of very weak phthisical patients with fever and hyper-susceptibility to tuberculin. Krause has seen no results from it.

Munch's method. Munch and Poepelmann have used Pirquet's cutaneous inoculation with pure tuberculin repeated every four to ten days.

The subcutaneous method seems to be the one which offers the great advantages of sparing the stomach, absorption in absolutely unaltered condition, and the most exact dosage.

Two contrasting methods of dosage. The first tuberculin era was the period of large doses and severe reactions. The endeavour to avoid dangerous reactions led to a gradual reduction of the doses. Goetsch seems to be the first to recommend the avoidance of severe reactions. From that time dates the beginning of the second tuberculin era. It does not appear to be known that the idea of larger doses of tuberculin has no longer anything whatever in common with the idea of severer reactions. The exclusive use of small and the
the smallest doses has not been able to produce any valid reasons to justify its existence. Nourney injects only the smallest doses at long intervals in order to produce and maintain "tuberculin energy". Wright's method, which he built up into a system of his own, rests on the same principle of treatment and is being more and more abandoned. The continuance of the smallest doses is not very effective and easily leads to hypersusceptibility, the production of which in the course of tuberculin treatment has never been of advantage to the patient. On the other hand some recently published statistics of Penzoldt speak in favour of large doses used with caution. With sufficient care it will be then possible in the majority of cases to carry through a course of tuberculin treatment to a finish without appreciable rise of temperature and without damaging the general health. But the susceptibility to tuberculin varies in different individuals and treatment must therefore, strictly individualistic.

Regular observation of temperature during the course of treatment is essential. The fever limit is 37.3°C. As a control the observation of body-weight is of importance, in some cases, of the pulse. Loss of weight and sudden increase in the pulse-rate
pulse-rate are to be construed as the expression of an over-dose of toxin in the absence of other obvious cause. Loss of weight must prevent the increasing of the dose. The slightest rise of temperature must have subsided before the next injection is given. The dose must then be the same as the previous one and only be raised as the temperature curve becomes quite normal.

The maxim to remain as far as possible to the reaction-limit without well marked reactions occurring coincides with the experience that the most evident success has been obtained with slight reactions up to 38°C or a little over.

**Cumulative action and hypersusceptibility.** It may happen that repetition of doses may give rise to accumulation of toxin and rise of temperature. This is the cumulative action of the toxin. More modern is the explanation of the occurrence by a toxic hyper-susceptibility. It assumes an increased susceptibility due to too rapid increase of dosage; in other words, it is due to an over-dose of toxin. In tuberculin treatment the occurrence of hypersusceptibility is altogether unwelcome and the most frequent cause of harm.
**Time of injection.** The morning and not the evening is the best time for injection.

**Maximal dose.** There is an absolute maximum and an individual maximum. It must be the aim to approach the absolute maximal dose as nearly as possible in every individual case. In active immunisation there are no ready made anti-bodies for the patient to assimilate but they must first be produced with the help of the toxins introduced. Rapid increase has on the one hand no curative value; on the other hand the severe reaction may reduce his power of resistance and, by producing hypersusceptibility, may stand in the way of the continuance of the course.

**Serial treatment-Petruschky.** Petruschky has evolved a system of interrupted treatment. In this method the average duration of treatment necessary is two years, periods of two to three months, during which injections are given, alternating with pauses of three to four months. But permanent success increases with the duration of treatment. Jochmann thinks that the disappearance of the cutaneous reaction with favourable clinical conditions may be considered an indication for the cessation of tuberculin treatment and on the other hand
hand the reappearance, in a subsequent test after some months, as indication for the beginning of the after-treatment. We recommend previous treatment with old tuberculin up to 300 to 500 c.m.m. until the skin fails to react to the test made with old tuberculin. At this time there is always a positive cutaneous reaction to bacillary emulsion. So treatment with bacillary emulsion must follow until the skin fails to react to this preparation also.

Lenhartz, Oppenheim, Lowenstein and Pickert have shown that the cutaneous reactivity generally dies away when a relative immunity is reached to the larger dose subcutaneously. The cutaneous reaction to old tuberculin disappears earlier than that to bacillary emulsion, while patients immunised with bacillary emulsion no longer display reaction to old tuberculin.

Schroeder, Ulrici, Krause and Curschmann consider the diagnostic reactions of tuberculin to be of no value (worthless) or even harmful. Junker, Brecke, Penzoldt and F.Kraus state that tuberculin diagnosis is a valuable adjuvant.

Penzoldt thinks that "every physician can learn tuberculin treatment and he must learn it."
F. Meyer says "that tuberculin treatment becomes an important feature in the practice of the family doctor."

The Austrian physicians Sorgo, Suesz and Lamb, consider tuberculin a valuable remedy in pulmonary tuberculosis, which should be used much more than formerly and also in ambulant treatment with careful selection of the cases.

Beninde, Hellenburg and others are in favour of starting tuberculin dispensaries for ambulant practice. Bandelier and Roepke think that tuberculin must be an integral part of the equipment of every physician and that then and then only it will fulfil its destiny to assist in the extirpation of the disease.

V. Wright and the English School.

During the last few years there has been a considerable revival of interest in the tuberculin treatment. This has been due, in England, chiefly to the researches of A.E. Wright on Opsonins, and the application of the
the opsonic index determinations to the treatment, placing it in a line with the treatment by other vaccines. It must not, however, be forgotten that many physicians have continued to use tuberculin, ever since its introduction, quite independently of Wright's work on the subject. The detailed method associated with Wright's name for the determination of the opsonic index is not an essential part of the Therapeutic application of tuberculin. Previously the tuberculin treatment has been regulated by other clinical signs including pulse, temperature, local signs and symptoms, and prolonged experience justifies the statement that these clinical signs will suffice, apart from the opsonic index determinations. The complexity of the technique of Wright's method is also an insurmountable difficulty in many cases and detract greatly from its general utility. The margin of error is such a complicated process must necessarily be considerable and this fact must also be taken into consideration in estimating the practical method. The question of the utility of the method in practice must therefore still remain an open one. Wright's work, however, has given a fresh start to the active immunisation method of the treatment of tuberculosis, and
and what we particularly owe to Wright is the demonstration that small doses of tuberculin are effectual and that large ones are unnecessary. The peculiar action of the tubercle bacillus as shown by the slowness and chronicity of the lesions which it produces, the tendency to spontaneous healing of tubercular foci by caseation and encapsulation, place this organism on a somewhat different footing from the other organisms as regards the process of immunisation, and the dosage of tuberculin may differ from that of the other vaccines. There is little doubt, however, that in certain cases of localized tuberculosis, such as Bupus, tubercular joints, and Genito-Urinary tuberculosis, improvement has followed the use of tuberculin according to Wright's method.

The fundamental facts on which the opsonic theory is based will now be briefly dealt with. The study of the problems of immunity in recent years has shown that the development of the antibodies in the blood or body fluids bear an intimate relationship to the process of immunisation. The phagocytic theory of Metchnikoff has been found insufficient to explain all the phenomena though it is believed that the leucocytes do play a subsidiary part in the protective processes
processes leading to the production of immunity. The evidence for regarding the blood-serum as all-important in this respect may be briefly given. The bactericidal action of the blood-serum outside the body was first established by V. Fodor, Petruschky, Nuttal, Behring and others who showed that typhoid, diphtheria and tetanus bacilli could be destroyed by fresh blood. This action was attributed by Buchner to certain albuminous substances present in the blood serum, which he termed Alexins. Pfeiffer also showed that a bacteriolytic action was present in the serum. He injected cholera vibriones into the peritoneum of artificially immunised guinea-pigs and observed their complete destruction and agglutination into masses, followed by gradual degeneration. He termed this the lysogenic action of the serum. The investigations of Gruber, Durhan and others have shown the existence of another anti-bacterial phenomenon in blood serum, that is, agglutination or clumping. Grunbaum and Widal have utilized this action of the serum for the diagnosis of Typhoid and it has also been applied to other diseases. This action is held to be due to the specific substances present in the serum, called agglutinins. Wright believes that the action of the serum, on bacteria, which prepares them for ingestion by the phagocytes is due to still another bacterio-tropic
bacterio-tropic agent hitherto unrecognised. To this substance he gave the name Opsonin. The presence of a substance in an immune serum which made the corresponding organism sensitive to phagocytosis was first demonstrated by Denys and Leclef in 1895. They also showed that the serum produced this effect by acting on the organism, not on the leucocytes. The relationship of the Opsonin of Wright to the various other anti-bodies i.e. anti-toxins, agglutinins, cystotoxins and precipitins, is not definitely known. Wright believes that Opsonin is a substance distinct from the others and has a specific action of its own, differing from that of any of the previously described bacterio-tropic agents. Wright demonstrated the presence of opsonins in the blood by the following experiment based on a method first devised by Leishman. A little freshly-drawn blood is received into a tube containing 2% solution of sodium citrate to prevent coagulation. The blood corpuscles are then thrown down by rapid centrifuging and the supernatant fluid pipetted off. The cells are then thoroughly washed with a solution of normal saline and again centrifuged. This is repeated until the corpuscles are entirely free from blood plasma. An emulsion of an organism, say the Staphylo-coccus, is obtained and also
also the blood serum from a healthy person. A small quantity of blood cells are then drawn in the capillary tube of a long pipette and then an equal quantity of staphylococcic emulsion and blood serum are added. In a second pipette the same ingredients are drawn up with the exception that normal saline is used instead of blood serum. The contents of the pipettes are well mixed. The pipettes and their contents are incubated for 15 minutes at a temperature of 37°C. A drop from each of the pipettes is stained and examined under the microscope. In the first case active phagocytosis will be found to have taken place and in the second scarcely any at all. It is therefore quite evident that something present in the blood serum has greatly increased phagocytosis. This substance is the opsonin of Wright.

The nature of opsonin is not yet known. It has never been isolated but certain of its properties have been discovered. Thus when the serum is heated to 60°C the opsonins are destroyed and their power of inducing phagocytosis is lost. Lawson has shown that opsonins are also present in some of the secretions such as milk, sweat, and urine. It is supposed to be present in the blood as a precursor of opsonin or pre-opsonin —
pre-opsonin and from this a specific opsonin is produced under appropriate stimulation by different bacteria. Other observers state however that opsonins are not specific. Muir and Martin hold that two kinds of -- opsonins are present in the serum, one is thermo-labile and the other thermo-stable. They proved that the thermo-labile opsonin of normal serum was non-specific and could be removed by other micro-organisms. Dudgeon and Shatlock showed that by adding melanin to the serum of a tuberculous patient the serum was deopsonised and conversely saturation of the serum with the tubercle bacilli largely reduced the phagocytosis of melanin. This, they held, showed that the chief increase of -- opsonin was not of a specific kind.

The opsonic theory attempts to explain the action of vaccines by their stimulation of the immunising machinery of the body to the increased formation of opsonin. Wright holds that the practical application of opsonic theory enables us to follow the successive phases of immunisation, and we can step in and assist the process by injection of vaccines. By estimating the opsonic index in cases of tuberculosis he was able to observe the variations in the amount of opsonin present, as shown by, what he called, the positive and negative phases. From these variations he deduced that in an untreated
untreated tuberculous individual spontaneous auto-inoculations occur from time to time, which follow a certain cyclic periodicity. The negative phase or the period of low opsonic index shows that there has been an outpouring of either the tubercle bacilli or their products of metabolism into the system from the tuberculous focus and this has used up most of the opsonin present. The positive phase which followed the negative was due to the increased production of opsonin owing to the stimulation of the machinery of immunisation by the bacilli and their products. He also showed that these auto-inoculations could be influenced by artificial means; thus, by massage he brought about a negative phase due to the increased outpouring of bacilli and their products. He utilized such artificial auto-inoculations as an aid to diagnosis. He also showed that the administration of tuberculin acted in a similar way to spontaneous or artificial inoculation. A dose of tuberculin was followed by a negative phase. Opsonin was used up for coping with the inoculum. This provoked a fresh production of opsonin in increased amount and was therefore succeeded by a positive phase. The process of immunisation could thus be regulated by appropriate doses of tuberculin at suitable intervals, the aim of the injections being to get the index to oscillate within normal
normal limits as in a healthy individual. Clinically, the negative phases coincided with a feeling of illness, temperature being raised and the pulse accelerated. On the other hand during a positive phase the patient felt better and brighter. Wright showed that the amount of opsonin in the serum also corresponds with the amount of other immunising substances. By estimating the opsonic index, therefore, from time to time we are enabled to gauge the progress of immunisation and to help it on when necessary by inoculation with tuberculin. Although Wright's theory is sound and its application ingenious, its practical value in relation to treatment is still doubtful. In its present form the technique of opsonic index determinations is far too complicated. If we are to carry out the treatment properly very frequent estimations of the index are necessary and the variations due to spontaneous and artificial auto-inoculation must be taken into account or eliminated. As Wright has himself pointed out spontaneous auto-inoculations affecting the opsonic index are of constant occurrence, the result of exercise, excitement and various other factors, and the question may well be asked whether even daily estimations of the opsonic index which is subject to such frequent changes can afford
afford any reliable guide to the progress of immunisation. Some observers have attempted to simplify the technique. The opsonic index thus loses its practical value for a large section of practitioners who can and must take part in the specific treatment of tuberculosis. The present tendency is therefore to seek some other reliable guide to the administration of tuberculin than opsonic index determinations and the researches that are being carried out at the present time have been undertaken with that object, e.g. the works of Doctors Latham and Inman. Wright's method has, however, been of undoubted value in giving a great stimulus to vaccine and tuberculin Therapy and placing this mode of treatment on a scientific basis replacing the former empiricism and uncertainty of dosage by some degree of precision.
VI. Modern Experimental Work.

Recent investigations regarding the nature of the tubercle bacillus have been so numerous and revolutionising and so beset with controversy that it may be useful to briefly review the subject in its more practical aspects.

We may group the recent work under three headings:—

1. The avenues of infection whereby the tubercle bacillus gains entrance into the body.

   I. The avenues of infection. That is to say, do we become infected by inhaling the tubercle bacillus or by swallowing it? The original view, supported by the inhalation experiments of Koch that the lungs always become infected by direct inhalation of bacilli in dust, &c., has been weakened by modern work in several directions.

   (a) by finding (as described below) that fine particles can reach the adult lungs more readily by swallowing than by inhalation.

   (b) That in the disgusting habit of expectorating in the streets, any tubercle bacilli in the sputum are probably killed by the light and air before they are dried
dried into dust.

But we cannot be sure of this, and at any rate one cannot doubt that in dark, stuffy rooms the tubercle bacillus will survive for months in a virulent condition. Neither can the inhalation of fresh germs in fine spray, produced by the coughing of a consumptive patient, be considered free from grave risk (Fluggs).

But the trend of recent experiments favours the bowel as the most fertile channel of infection and especially the bowel of the infant. Indeed, no less an authority than Von Behring has for years advocated the extreme view that the infant's bowel is the chief portal of infection, and that adult tuberculosis is generally due to the lighting up of tubercular foci which have been kept quiescent since infancy. He brings evidence that the bowel wall of the infant is certainly very permeable.

In this connection the following recent experiments by Vansteenberghe and Grysz from Calmette's laboratory are of the greatest interest. They find that in rabbits which have been made to breathe a very smoky atmosphere, the lungs do not become blackened if the gullet is first ligatured. Similar results with charcoal fed to rabbits originated from the St. Thomas's
St. Thomas's Hospital Laboratory.

Also, that in adult guinea-pigs which have been fed with food containing lamp black or Chinese ink the lungs after one or two days show black islands scattered over the upper and along the borders of the lower lobe. If the same experiment is repeated in young guinea-pigs the mesenteric glands are blackened but the lungs show no pigmentation. This is apparently due to the mesh-work of the juvenile mesenteric glands being finer and thus proving a more efficient filter.

These experiments have since been confirmed by Sir W. Whitla and Symmers.

If cultures of tubercle bacilli are fed to goats and kids the same difference in permeability of the adult and juvenile mesenteric glands can be demonstrated.

Naturally, experiments such as these have had great influence in changing opinion in the past year or two from the inhalation theory of infection towards the view that the tubercle bacillus gains entrance generally by the bowel.

Here, especially in the young, it may be
be arrested at the mesenteric glands or it may be passed on (in the adult) into the blood (via Thoracic duct) and be arrested at the first set of blood capillaries which it meets, namely those of the lung.

The tonsils must be considered sometimes to give admission to the tubercle bacillus, for, excised tonsils are tubercular in 8% of cases.

But, of course, in ordinary life the distinction between infection by inhalation and bowel-absorption is apt to be lost, owing to the fact that most of the inhaled bacilli would be arrested in the mouth or upper respiratory passages and subsequently swallowed. Hence in either case we must take the same rigid precautions against tubercular sputum.

In the light of these experiments, the great prevalence in children of non-pulmonary tuberculosis and their comparative immunity from the purely pulmonary form become perfectly intelligible, as also does the converse state of things in the adult. And this accurate correspondence between theory and practice supports, in its turn, the bowel-absorption theory of tubercular infection in human beings.

These conclusions indicate the vast importance
importance of a non-tubercular food-supply, especially where it is uncooked. Tubercular meat, since it is sterilised by cooking, is of subsidiary importance. But milk may contain tubercle bacilli when obtained from a tubercular cow even when the udders are healthy. Butter being a poor culture-medium is a much more sterile material than cream or milk. The analyses are rendered variable and valueless in many cases by including all acid-fast bacilli, but the true tubercle bacillus, pathogenic to guinea-pigs, seems to have been present in over 10% of samples of butter.

Thus the wretched bottle-fed infant has to choose either the unboiled, and hence frequently tubercular, milk or the habitually boiled milk which tends to produce scurvy.

Reformers are faced on the one hand, with a preventable tubercular mortality of 5000 a year (in England) and on the other hand, with an enormous percentage of tubercular cattle. Ten per cent of slaughtered cattle show gross tubercular lesions and 30% of milch cows are shown by the tuberculin test to be tuberculous.
II. Intercommunicability of the human and bovine types of tubercle bacillus. When Koch startled the world a few years ago (1901) by declaring that the tubercle bacillus of man and the tubercle bacillus of the ox were two different organisms, he asserted that all our precautions against tubercular meat and milk were useless and needless. But the anomalous position served to stimulate a vast amount of research from which it has been found that human beings are subject to infection by both types of bacilli. For instance, in sixty cases of human tuberculosis, fourteen had the bovine type of bacillus and in cases in which infection had apparently occurred by the bowel and nearly 50% were bovine in origin. The German figures give only 10% of bovine bacilli in human tuberculosis diseases.

Speaking broadly and tentatively, it has been thought that tuberculosis localised to the respiratory tract, as in adults, is generally due to the human type of bacillus and that tubercular diseases of the abdomen, bones, joints, skin, miliary tuberculosis and tuberculosis of children, are generally bovine in type. (Raw). But this generalisation is probably far too sweeping. Recent experiments from St. Thomas's Hospital have shown that tuberculosis in birds is due to a tubercle bacillus of so distinct a type as not to constitute
constitute a danger to human beings.

The recent Royal Commission on Tuberculosis has shown that calves can be readily infected by injecting tubercle bacilli under the skin and there are undoubted instances where man has accidentally been infected from bovine sources (Osler.)

Monkeys are readily infected by a diet of tubercular cow's milk and goats which have been fed with the milk of cows whose udders had been injected with the two types of bacilli, the bovine type of infection has proved far more virulent than the human.

So that there seems to be already abundant evidence that tubercular cows ought never to be used to supply milk for human food. And yet the present proportion of milch cows, shown by the tuberculin test to be tubercular, is about 30%. On the other hand it is only fair to state that direct evidence of the infection of human beings by tubercular milk is necessarily very scanty and against the animal experiments it may be urged that they are much more susceptible to the bovine bacillus than are human beings.

It is now certain that we do not inherit the
the tubercle bacillus but only the tendency to infection. Whenever therefore there is no strong reason to the contrary, it is obvious that milk must be always sufficiently heated to kill any bacilli which are only too likely to be present; that is to say, to 95 °C. for 1 minute or 70 °C. for 30 minutes. This is the more essential for children and those hereditarily predisposed.

III. Treatment by production of immunity.

Under this heading will be included active and passive immunity in animals and men together with some recent diagnostic methods and opinions upon the Tuberculo-opsonic index.

Active Immunisation is a change in the organism which results from the absorption of bacteria or their products and which leads to the occurrence of specific protective bodies (Anti-bodies) in the serum. This form of immunisation is therefore an indirect one, the organism having to prepare its own protective bodies and hence it has been called by Ehrlich active immunisation.

Passive immunisation means the production of
of immunity by means of a specific serum. The organism appropriates protective bodies ready-formed by another individual. It has no effort to exert of itself, the process being a passive one.

Behring has of late immunised thousands of calves by injecting into their veins a culture of human tubercle bacilli which are but slightly virulent to the calf. This is repeated in six months and the resulting immunity lasts for years and probably for life. Thus by supplying the cow with a vaccine of human origin we have re-paid the debt which we have so long owed the cow for supplying us with a vaccine of a bovine origin against small-pox. These cows will at any rate supply pure milk and in the hope that their milk contains immune bodies it is now being supplied to consumptive patients. Behring also gives by mouth to these patients a [chloral] extract of tubercle bacilli - walled Tulase.

Numerous attempts have been made to produce passive immunity in tubercular patients by injecting them with the blood serum of animals in which attractive immunity - had been produced by the inoculation of tubercle bacilli or their products but all these sera have been
been failures, for example, the attempts made by Trudeau and Baldwin, Auclair, Ferran, Maragliano, Marmorek and others.

Raw is now trying the injection into patients of the serum of tubercular cows, the serum having first been shown, by injection into guinea-pigs, to contain no bacilli.

But at present the chief hope of fighting established tubercular disease seems to be centered in the future of Tuberculin. Koch's original tuberculin (T.O.) and new Tuberculin (T.R.) are the preparations generally used for injection. T.O. has proved invaluable as a diagnostic reagent in cattle. When properly applied this Tuberculin has an error of only 5%.

T.R. is nearly always selected for Therapeutic purposes and there are three methods of using it.

1. The continental, where the patient is educated to tolerate enormous doses of tuberculin which is gradually increased from $\frac{1}{5000}$ mg. up to even 20 m.g.m.s.

2. Wright's method of minute doses ($\frac{1}{5000}$ mg to $\frac{1}{500}$ m.g.) where the dosage and the intervals of the
the dosage and the intervals of the injections are regulated solely by their effect on the Opsonic-index.

3. The same tiny doses regulated by experience and clinical effects without the opsonic-index.

Calmette uses the alcoholic precipitate from tuberculin dropped under the eyelid as a diagnostic test for tuberculosis. If the conjunctiva reddens the patient is considered to have a tubercular focus somewhere, either active or latent. This test is a valuable one and has an accuracy which can only be guessed as being about 90%. Unfortunately the test is scarcely justifiable except when diagnosis is of urgent importance, because the resulting inflammation is sometimes rather persistent and may lead to severe Keratitis or granular conjunctivitis, especially in strumous children. If this opthalmo-reaction falls into disfavour with children, the cutaneous reaction of Von Pirquet may take its place. It is said to be relied upon in children but not in adults.

The subcutaneous Tuberculin Test is probably not much used in England. It is a very trustworthy test but it involves the injection of 1/10 m.gm. of Tuberculin (T. O.) and if temperature does not rise
rise much the dose is raised to 3 or even 10 m.gm. A patient is likely to be considerably upset even by such small doses as 1/1000 m.gm. of T.R. and hence the dosage required for the tuberculin test seems formidable but Möller states that after 20,000 injections he has never seen disseminated tuberculosis as a result.

Other recent methods which are claimed to be diagnostic of tuberculosis are: (a) an opsonic index outside the normal limits (8 to 1.2). (b) the agglutination test of the patient's serum on an emulsion of tubercle bacilli. (c) The valuable but very elaborate method which utilises "the deviation of the complements", well described by Emery.

So much for the modern diagnostic methods.

Now with regard to the vaccine treatment of tuberculosis, the method of minute doses of T.R. at infrequent intervals (one or two weeks) is entirely the outcome of measurements of the opsonic index which Wright found, could be maintained at a high level better by such small doses than by the large doses formerly in Vogue. The opsonists declare that vaccines against a powerful and slow-reacting bacillus, like the tubercle bacillus, should never be employed
employed without the laborious guidance of the opsonic index, lest a dangerous depression of the index should be produced by wrong dosage.

At the present moment a fierce controversy over the whole subject of opsonic indices and their clinical application is being waged and the position is an extraordinary and interesting one. During the past two or three years a large number of workers have tried to follow in the footsteps of the original opsonists. Strangeways and his co-workers tested the method (August 1907) most thoroughly and conscientiously and found that it yielded utterly inconsistent results which were worthless as a clinical guide.

Then Reyn and Petersen (March 1908) tested the method on a large scale at the Finsen Institute in Copenhagen after learning the technique in Wright's laboratory. They concluded that:

1. Lupus patients have not on the average a low index.

2. Injections of T.R. do not on the average increase the index nor did they improve the Lupus.

3. Effect of T.R. injections on the index was so uncertain that the index has been valueless
valueless as a guide to treatment.

New Barnes started as a research scholar (June 1908) to study the opsonic index in Rheumatic fever &c. After practice, he was able to get consistent results with Wright's method but directly he began to work with secretly numbered slides, his indices became discordant and valueless. By an intensive method he obtained consistent results but they were not confirmatory of Wright's positive and negative phases. These discrepancies cannot be entirely due to technique but must be chiefly due to the counting of the ingested bacilli. For the difficulty has been this that slides prepared and stained by an expert may be counted by him and yield consistent results and then be handed over to skilled and conscientious pathologists whose count may give discordant and worthless indices.

Another awkward fact for the opsonic doctrine is that babies do not appear to depend on opsonins for their bacterial defence, but often thrive on an index of .01 (Wells).

But in spite of the brave show which opsonists are still making the opsonic doctrine is assailed by
by an increasing number of investigators whose attacks combined with much practical short-comings have tended to produce wide-spread distrust as to the practical value of the opsonic index. Some go so far as to deny its existence. But, as a method of research in the best hands, it is scarcely possible to mistrust its trustworthiness and the great value of the lessons it has taught us.

**VII. CLINICAL TRIALS.**

The following cases were under my care at the Quilon District Hospital in 1913–1914 when I was in charge of the institution. In all these cases the tuberculin treatment was carried out along with the hygienic dietetic measures. A certain amount of selection was made in the cases. The injection was made in the forearm or the outer aspect of upper arm for the convenience of the patients. In a few cases the injections were given in the flanks with an all-glass syringe and the patients
patients, generally, were kept in bed for 24 hours after the injection. As a rule the first few injections were given by myself or by my senior Assistant but latter on, the injections were given by one of the European nursing sisters, who had some special training in the work.

**Case 1.** A young man of about 30 years. Family history rather bad. Father died of fever and cough lasting for more than a year. Mother alive but not in very good health. No brothers. One sister married but looking thin and anaemic with no children. He had cough, indigestion with one loose motion a day and had fever for three months. There were no definite physical signs in the lungs. He was thin, rather anaemic and said he was losing weight; was in good circumstances. He was put to bed and light nourishment was given. The temperature was 100 in the evenings. In a week his appetite improved. His diarrhoea was better. Temperature came down to 99.1/10,000 m.g. of T.R. was injected. Temperature rose to 101 the next day. In a week a second injection was given. The reaction was less than before. After 6 weeks he was improved so much that he was allowed to go home and return for the injections every week. His weight gradually increased,
increased and he said he felt better. The injections were subsequently given at longer intervals. He was 4 months under treatment and the maximum dose was .01 mg. He has had no relapse for past nearly 18 months.

**Case 2.** A man in affluent circumstances age 43. Family history not very bad. Mother alive and well. One brother died of pneumonia. A sister alive but not well. Father died of fever. Exact cause not known. Two other brothers alive and well. He was often subject to low attacks of fever and ill. There was cough for over a year. Rough respiratory sounds on the apex of right lung. He was put in bed and in three days the first injection was given. There was a severe reaction. Temperature rose to 103 the next day; there was vomiting and headache. These subsided in two or three days. The second injection (dose as before) was given only after a fortnight. Temperature was only 100.5 on the second day. The subsequent doses were gradually raised till .01 mg. was reached. He was discharged from the hospital two months after admission but took up a house next to the hospital where he lived for 6 months. He is now apparently quite well but is still getting the injections monthly.
Case 3. — A young Eurasian woman. Age 18. Had slight dullness and feeble breath sounds just to the inner side and the angle of left scapula. She gave a history of cough and fever lasting for three months and a feeling of great exhaustion on slight exertion. She had brought up a dram or so of blood on coughing the previous day of her admission. She was put in bed and sedatives and astringents were given and light nourishments ordered. In a week the temperature came down to 99.4 in the mornings, the cough was better and appetite improved. A fortnight after the admission the first dose of injection was given. Temperature rose to 101 the next morning. The injection was repeated in a week. The rise of temperature was less marked than before. Gradually the doses were raised until a maximum of .1 m.gm. was tolerated without reaction. She had no more haemoptysis during the two months she was in the hospital, and gained considerably in weight.

Case 4. — A school boy aged 16, suffering from tubercular disease of the fauces and the soft palate, of 6 months duration. Slight dullness at apex of right lung. No T.B. is the sputum. Open air treatment and inoculation of tuberculin for about two months improved his condition.
condition so much that he gained nearly 15 pounds in weight and his throat was apparently cured.

Case 5. ----- A Eurasian signaller, aged 28. He came with a history of fever, diarrhoea, dyspnoea and poor appetite. He was very much emaciated and anaemic. His temperature was sub-febrile going up to 99.8 to 100 in the evenings. On the right side of back between the spine and scapula the percussion note was distinctly dull and vocal fremitus was increased. He was subjected to tuberculin inoculations for nearly 6 months and his condition was so much improved that he was able to digest double the quantity of food he was taking before. There were no physical signs in the chest. He had neither fever nor diarrhoea and had gained about 28 pounds in weight.

Case 6. ----- A male patient aged 34. On admission there was well marked phthisis, left side. Tubercle bacilli present in the sputum. Temperature 100. Was put in bed in open air. Creasote was administered intermittently. Tuberculin injections were begun when the temperature gradually decreased. In 6 months time the symptoms --
symptoms improved and he was able to go home with considerable increase in weight, though the lung still showed some dullness on percussion and the breath sounds were not quite clear.

**Case 7.**——Child aged 10. Pleurisy with effusion on left side. On aspirating the chest about 10 ozs. of clear fluid was drawn. There was fever and diarrhoea. A week later fluid was again removed from the pleura. The temperature came down after the second aspiration. The injections were given weekly. After the third aspiration there was apparently no more collection of fluid and the other symptoms also improved very much.

**Case 8.**——Girl aged 8 years. Tubercular peritonitis, fever and marked wasting. There was no marked response to tuberculin inoculations. Was discharged after a month at parents' request.

**Case 9.**——Child aged 7. Tubercular disease of the hip——abscess, fever and emaciation. Abscess was incised and drained. After a time the injections were given. General condition greatly improved, in three months' time and abscess quite healed.
Case 10. ---- Young man aged 18. Phthisis, left, with tuberculosis of left elbow. Tuberculin injections with Bier's treatment for the elbow. The joint, however, became more swollen and painful. Finally amputation of the arm was performed. The chest condition subsequently improved somewhat and he was discharged at his request after 4 months in the hospital.

In a few cases of mixed infection that came under my care the effect of the injections was to aggravate the condition of the patients, but in such cases I soon discovered that two or three injections of anti-streptococeolic-serum had a marked effect in improving the general condition of the patients and preparing them for receiving the tuberculin injections subsequently.
VIII. Summary and Conclusions.

As to the very large question of the results of the vaccine treatment against tuberculosis it may be said that in phthisis, especially if early, and localised, and afebrile, treatment by T.R. in some cases may do much good, though it is often hard to eliminate the co-effects of fresh air and good food, &c. Some prefer T. R. made from the bovine bacillus. Others speak very highly of Beranek's tuberculin but as yet tuberculin has accomplished very little in phthisis and against the good it often produces must be discounted the harm which so powerful a double-edged weapon may sometimes cause. For we are only on the threshold of our knowledge of those intimate processes of immunity which may be stirred to their depths by vaccines such as tuberculin. One may succeed brilliantly or may damage seriously the delicate and mysterious machinery of immunity.

In the words of Dr. Philip of Edinburgh: "treatment by tuberculin demands especially favourable conditions. Even after successful inoculation while the feeble parasite is struggling to assert itself on the more or
or less resistant soil the conditions of environment determine the production of the disease."

Probably the best results are obtained by a combination of the sanatorium treatment with the use of tuberculin. No special climate is necessary for a sanatorium. Dr. Philip first proved the possibility of successfully treating pulmonary tuberculosis at home sanatoria and the possibility of dispensing with the Swiss mountains and the German forests. He is of the opinion that aero-therapy is a measure of universal applicability in all lands and that there is no climate specially favourable for its practice. He thinks that the sanatorium should be easily accessible. Dr. Galbraith of Edinburgh writes "The aim of the treatment is to fit the person for taking his place in the ranks of the workers and not to produce a crop of exotics to live under artificial conditions of climate or altitude. Thus a person, the subject of tubercular disease, should be treated under conditions, as little artificial in these respects as possible, and as nearly alike as practicable to the conditions under which he will afterwards have to live and work. This is now
now generally recognised and, all along, has been the guiding principle in the Edinburgh system. A public sanatorium must be easy of access from the districts which it is intended to serve."

In localised tuberculosis elsewhere than in the lungs, T. R. in tiny doses (1/5000 to 1/1000) at one or two weeks' intervals, with or without opsonic index, often produces striking improvement in chronic -- stationary or recurrent cases. More commonly -- absolutely no effect whatever seems to be produced or a occasionality the patient is temporarily upset.

Raw reports (February 1908) astonishingly good results in every kind of tubercular affections. Four cases out of six, of apparently tubercular meningitis, were cured and other results on the same scale with never the slightest bad effects. He gives 12 weekly -- injections increasing from .0001 to .01 m.gm. of T. R., human or bovine. On repeating his method in two cases of adult afebrile phthisis there was a decided improvement, but in a case of Lupus of the toe the benefit of the early doses was neutralised by the constitutional and local disturbances on increasing the dose to
to 1/1000 m.g. Similarly a child with bronchiectasis reacting to Calmette's test improved at first but seemed upset half way through the series of injections, which were then abandoned.

Latham of St. George's Hospital, London, demonstrated in last April the value of T. R. by mouth in doses of about 1/2000 m.g. at varying intervals. He has also indicated with the help of Drs. Inman and Spittal that the opsonic index in febrile cases generally varies inversely as the temperature and that a high or low index may be guessed from the clinical symptoms.

Very recently T. R. in doses of 1/5000 m.g. has been given per Os by Dr. Hector Mackenzie with good effect on the appetite and on tubercular glands in the neck. But the oral method has scarcely been worked out yet. In animals it has been shown experimentally that immunity may be produced in this way but only if the vaccine is given on an empty stomach.

E. C. Hort and Vere Pearson have supplemented
supplemented its action by horse serum (by mouth) with promising results.

The large dose method of tuberculin treatment, which has been in use for many years on the continent, is considered to have improved the curability of phthisis a little, and the sanatorium cases are rather less liable to relapse. But there has been very decided improvement in results. The tuberculin treatment of phthisis by any method is far more risky and uncertain than of other forms of chronic tubercular disease. In these latter cases it's cautious and experienced employment will often produce improvement and cure where other means have failed. But such brilliant results cannot always be expected.

In phthisis, whatever the method of treatment, success depends on early diagnosis. The closed cases before ulceration commenced, give very good results. There is a fatal misconception very prevalent in the profession that it is a sign of incompetance to be unable to diagnose phthisis in its earlier stages by physical signs. It cannot
cannot be too clearly recognised that the disease may be months before the most carefully trained ear can detect its presence. Hence, the vital importance of some form of tuberculin test. That the healing of unrecognised tubercular foci is of frequent occurrence is shown by their presence in 30 to 60% of post-mortems.

Probably the highest art in the treatment of phthisis consists in the control of the patients' own auto-inoculation as elaborated, by the brilliant work of Dr. Paterson and Dr. Inman at Frimley with the aid of the opsonic index. In a convalescent phthisical patient exercise will cause a liberation of toxin (tuberculin), as indicated by a rise of temperature and a fall of the index. Exercise is so gradually increased as to educate the patient to tolerate increasing doses of auto-toxin and thus to increase his resisting powers to tubercle. It is the tuberculin treatment, but the patient makes his own tuberculin. Looking back over the whole subject it is clear that the possibilities of preventive medicine in this disease are enormous. This is
is especially so, if it should turn out that tubercular cows' milk is the main source of infection and that inhalation of bacilli is of small account. For then it might be merely a matter of either vaccinating every calf against tubercle or killing every milch cow that reacted to tuberculin (some 30%). If this is too much expect as yet, then at all events the 2% of cows with tubercular udder should be slain without delay.

And even if, as is probable, tubercular cow's milk is, by no means, the only source of infection, a non-tubercular milk supply would probably enormously diminish the amount of tubercular diseases in children which now occupy about 1/3 of the beds in most of the children's Hospitals.

In India the necessity for such a whole-sale destruction of cattle is not needed, as the milk is generally boiled before use. And in China though tuberculosi is stated to be very prevalent, cow's milk is hardly used.
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Trivandrum

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DEPUTY SURGEON,
Mavalikara,
TRAVANCOORE.
PRESENT POSITION OF TUBERCULIN THERAPY.

A Thesis
by
V. Sankara Valiathan.