Review Article

Tuberculin Therapy — Echo from the Past

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Tuberculin, developed by Robert Koch, is a general name for the toxic products of Tubercle bacilli grown in culture. The products consist of soluble components and endotoxins of the cell body of the bacterium. Their selective affinity for tuberculous lesions indicated diagnostic potential which Koch utilized in designing the tuberculin test which continues to be in use. However its application in therapy, also introduced by Koch, underwent clinical trials in the first decade of 20th century and showed less than satisfactory results. Trials not with standing, general physicians used tuberculin in therapy extensively and many tuberculins appeared especially in Europe. Koch and the German School gave a scientific underpinning of active immunisation to tuberculin therapy and made efforts to standardise treatment protocols and dosage schedules. Meanwhile Wright introduced opsonic index as a guide and facilitator for tuberculin therapy though its essentiality remained doubtful.

The questions which attracted the keenest attention of investigators in tuberculosis in that period were the prime route of entry of tubercle bacilli in the body; interrelation between bacilli of human and bovine origin; and active immunisation induced by tuberculin.

A few illustrative cases of tuberculosis who underwent tuberculin therapy in a District hospital in Travancore (merged in Kerala) during 1913-14 are also reported.

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Tuberculin was developed by Robert Koch to destroy tubercle bacilli after his momentous discovery of the bacillus in 1882. Initially employed for treatment and diagnosis of tuberculosis by Koch, its therapeutic usefulness was seriously questioned in the first decade of the 20th century in Europe and Britain while its diagnostic role steadily gained recognition and "tuberculin test" became universally used to this day.

In the first decade of 20th century, Dr V Sankara Valiathan from Travancore, India studied medicine in the University of Edinburgh (MB ChB 1905; MD 1915) and wrote a thesis on "The present position of tuberculin therapy" in partial fulfilment of his MD requirements. This article retells the contents of his thesis in an abridged form with no deviation or alteration from the original. Sectional headings 1 to 8 comply with those in the original thesis. They hold a mirror to the status of tuberculin therapy in Europe and a Government hospital in Travancore (now part of Kerala) in early 20th Century.

Introduction :

Tuberculosis was known from the time of Hippocrates, but it was reserved for Robert Koch to make the epoch-making discovery of the tubercle bacilli grown in pure culture as its cause. He announced his brilliant discovery in March 1882, heralding a new era in the history of medicine. Koch next began the search for a remedy that would destroy the pathogenic bacteria in the living tissues. Years of search turned fruitless because the agents which destroyed the bacteria did not spare the healthy tissues either. He therefore took an untrodden path and made an important observation. When guinea pigs were inoculated with incremental doze of dead tubercle bacilli, the wound healed, but in 10-14 days a hard nodule appeared on the site, which broke down, ulcerated and refused to heal until the animal's death. If, on the other hand, the animal had

Editor's Comment :

- **Tuberculin is the name for 'toxic products' of tubercle bacillus grown upon artificial media.**
- **Tuberculin treatment is an immunological procedure which induces the body to produce antibodies.**
- **Koch & German school suggested active immunisation by tuberculin therapy & tried to standardise treatment.**
- **Wright & English school, on the other hand, introduced opsonic index as guide for tuberculin therapy.**
- **Studies in Tranvancore showed that tuberculin treatment was unsuccessful in full-fledged Pulmonary tuberculosis.**

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already been infected with tubercle bacilli, the wound would heal first but show no tendency to nodule formation: it would however develop ulceration followed by healing. Koch also observed that the same phenomena which appear after reinjection of living and dead bacteria could be reproduced by administering their extracts called tuberculin. In 1890, he claimed that he was "able to render animals immune against tubercle bacilli and to bring a standstill to the tuberculous process in animals" The extract consisted of a glycerine extract of tubercle bacilli evaporated to 1/10th of the volume in a water bath and then filtered through a porcelain filter.

Historical Outline :

Tuberculin : Is the general name for the toxic products of the tubercle bacillus grown upon artificial media. The toxic products are diffusible and soluble extractives and endotoxins of the cell body of bacteria. In man tuberculous lesions tend to be localised and dormant for months or years. Tuberculin has a selective action on these lesions, which it lacks against normal tissues. The selective action of tuberculin is both general and local; general action includes fever, rigor, and malaise, and local is typically seen in lupus where tuberculin picks out diseased tissues and spares the healed parts. This highlights the diagnostic potential of tuberculin. One could, for example, make a diagnosis of tuberculosis when tubercle bacilli are not detectable in incipient tuberculosis of the lung. The inflammatory response is a manifestation of an antigen – antigen body reaction where tuberculin is the antigen and anti- tuberculin is the antibody. Koch emphasised that tuberculin does not kill bacilli present in the tissues but affects only tissues harbouring the bacteria. The tissue response may be disintegration or sloughing.

Koch was encouraged by the early results of treatment of tuberculosis of skin, glands, bone and joints with tuberculin. Soon patients with pulmonary tuberculosis were also recruited and different dosage regimes proposed. From initial results Koch concluded that in early stages pulmonary tuberculosis was curable; in advanced stages, improvement was possible.

The rosy view of tuberculin for treatment led to several clinical trials and the dramatic cure of lupus heightened the belief in the curative power of tuberculin. Before long, misguided enthusiasm led to the use of too large dozes in the treatment of advanced cases, resulting in severe reactions. The Brompton hospital report (1892) declared that tuberculin did not favourably influence the course of disease in the majority of cases. Tuberculin was practically abandoned as a therapeutic agent but survived as a diagnostic tool thanks to the febrile reaction it produced in a tuberculous individual. Osler's text book of Medicine (1901) stated "During the past few years, it (tuberculin test) has been employed extensively in the Johns Hopkins Hospital, both on the Medical and Surgical sides, with the most satisfactory results, and so far as I know, without any harmful results. In obscure internal lesions, joint cases, and in suspected tuberculosis of kidneys the use of tuberculin gives most valuable information".[2] In veterinary practice it found a permanent place for recognising concealed tuberculosis. It is a sobering thought that Koch had warned against the use of tuberculin for treatment of tuberculosis in the presence of other infections and emphasised that tuberculin acted solely by the process of active immunisation, radically differing from the passive administration of man-made antiserum. It was felt that 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 infections in pulmonary tuberculosis. By a coincidence, tuberculin was tried as a remedy when influenza pandemic (Spanish influenza) raged in Europe. This further eroded the validity of the clinical trial of tuberculin.

The Various Kinds of Tuberculin :

Following the original tuberculin of Koch, he introduced modified versions in response to feedback from the experience of earlier versions; other investigators brought out their tuberculins. Most of these modifications were related to process control or improvement.

A few tuberculins in regular use are listed

i. Old Tuberculin (TO): This was the first tuberculin developed by Koch from a glycerine broth of tubercle bacilli 6 – 12 months old. It was evaporated 1/10th of its volume and then filtered through a porcelain filter. It is practically a solution in glycerine of the extra cellular toxins produced by the organism.

ii. Koch's Original Tuberculin (TOA): Prepared exactly like TO but not concentrated to 1/10th volume.

iii. Albumose-Free Tuberculin: This was introduced by Koch to avoid the fever caused by albumoses. It is prepared by growing bacilli on media free from albumoses.

iv. New Tuberculin (TR): TO was believed to provide immunity against bacterial toxin only, not against the bacilli themselves, just like anti- tetanus serum. Koch's aim was to combine both forms of immunity and he therefore prepared a new form of tuberculin by breaking up bacilli by a mechanical process which contained the curative and immunising

substances of bacilli in a form suitable for injection. It produced no ill effects and could be used as a preliminary to a course of TO. It had immunising properties unquestionably.

v. New Tuberculin Bacillary-Emulsion (BE): This is new tuberculin by eliminating centrifugation in its making, which was expected to enhance durability.

vi. Sanitized Bacillary Emulsion (SBE): As suggested by Meyer, dried human bacilli mixed with tubercular serum and kept in incubators at 37°c for several days. Further processing to be carried out.

vii. Beraneck's Tuberculin (TBK): Contains all substances having immunising properties whether in culture fluid or in bacteria themselves.

viii. Carl Spengler's Immunising Substances

Koch and the German School :

In the first decade of twentieth century, Koch's discoveries of tubercle bacilli and the twin role of tuberculin in diagnosis and treatment dominated the practice of medicine in Europe. The foregoing discussion shows the dominance of tuberculin in theory and practice of tuberculosis and its impact on the emerging science of immunology. The German School led by Koch was identified with certain views outlined below:

- Absence of reaction to tuberculin test indicates successful immunisation against bacterial toxins, which favours survival. The detoxifying effect is signalled by signs such as disappearance of fever and headache, drop in rapid pulse rate, gain in weight and increased appetite.
- Tuberculin treatment is an immunological procedure in so far as it induces the body to produce antibodies and boosts body's natural production of antibodies.
- Opinions are divided on tuberculin therapy employing high and low dosage regimes. Experience in practice does not support the claim that larger doses of tuberculin have a necessary correlation with severe reactions. At the same time, use of small or tiny dozes at long intervals has proved ineffective and has raised the spectre of hyper- susceptibility. It would seem in the present state of knowledge and experience that the majority of cases can be managed successfully through tuberculin treatment without appreciable rise of temperature and without damage to general health. It is essential that tuberculin therapy is regularly monitored and regulated by attention to patient's temperature (limit 37Úc), loss of body weight and increase in pulse rate, which represent increased level of toxins.
- Too rapid increase of dosage of tuberculin may cause hyper susceptibility. This is harmful and indicates toxaemia requiring corrective treatment.
- A school of thought (Petruschky) has advocated a system of interrupted treatment for two years when tuberculin treatment is given for periods of 2 – 3 months when injections are given, alternating with pauses of 3 -4 months. Disappearance of skin reaction to tuberculin test, absence of fever, return of normal pulse and gain in weight could be regarded as an indication for the cessation of tuberculin treatment.
- About twenty European clinicians and medical scientists are on record in support of tuberculin therapy and even for establishing "tuberculin dispensaries".

Wright and the English School :

Wright's development of opsonic index in England is not an essential part of the therapeutic application of tuberculin. The earlier practice of using clinical signs including pulse, temperature, weight gain, local signs and long experience justify the claim that they are sufficient to regulate tuberculin therapy apart from opsonic index determinations. It should also be borne in mind that the complexity of Wright's method and the consequent high margin of error do detract from its general utility in medical practice. However Wright's work has brought into focus the active immunisation method in the treatment of tuberculosis.

By the first decade of the 20th century, the bactericidal action of blood serum outside the human body was established in the laboratory. Apart from direct bacteriolytic action, destruction also took place by agglutination of bacteria, which was believed to be caused by a specific substance called agglutinin. Wright believed that still another substance called opsonin prepares bacteria for ingestion by phagocytes. The exact relationship of opsonin to other antibodies such as agglutinin and antitoxin is not known. Wright had experimental evidence to show that there was a substance in serum which greatly increased phagocytosis. However it had not been isolated or characterised and its physico-chemical properties were debated. The opsonic theory holds that vaccines act by stimulating the immune system to produce more opsonin. It was believed that opsonic index would enable one to track the immunisation process and facilitate the injection schedule on the basis of the amount of opsonin present. Wright's elaboration of opsonic index involving positive and negative phases, auto-inoculation etc., became highly complicated, and very frequent estimations of the index – subject to frequent fluctuations – cast doubt on whether it could be used widely as a reliable guide to immunisation.

Opsonic index lacked practical value for a large percentage of practitioners.

Modern Experimental Work :

Modern studies on the nature of tubercle bacilli have focussed on three questions:

(1) How tubercle bacilli gain entry into the human body?

(2) Do human and bovine tubercle bacilli intercommunicate? interact?

(3) How does the induction of active immunity work for the patient with or without opsonic index?

i) Originally Koch had shown in experiments that lungs always became infected by direct inhalation of bacilli in dust. There was rethinking when it was urged by Von Behring that infant's bowel is the main portal of entry of tubercle bacilli, and adult tuberculosis is an activation of tubercular foci which were quiescent from infancy. In Calmette's laboratory it was found that lungs of rabbits made to breath smoke did not become blackened if their gullet had been ligated. These observations are supported by other experimental studies, which suggest that tubercle bacilli gain entry into the body through the bowel. They may be arrested at the level of mesenteric glands or may enter blood via thoracic duct. It should also be kept in mind that inhaled bacilli could be arrested in the mouth or upper respiratory passages and subsequently swallowed.

These discussions would clarify why non-pulmonary tuberculosis is dominant in children who have pulmonary infection rarely. The oral route of entry is of practical importance thanks to the consumption of milk obtained from tubercular cow especially when unboiled. In England 30% of milch cows are shown by tuberculin test to be tuberculous.

ii) Koch surprised the world when he declared that tubercle bacilli of human and bovine origins were two different organisms. However subsequent investigations confirmed his observation that humans are vulnerable to attack by both organisms. The infectivity of human and bovine tubercle bacillus for either or both species is so important an issue for public health that numerous research studies were carried out to unravel the inter relationship between the two organisms. Generalisations such as tuberculosis affecting the respiratory system is caused by human bacillus and that of the abdominal, bone and joint, military and children's is bovine are misplaced. However a few facts are known at this time:

- Calves can be infected by subcutaneous injection of human bacillus.
- Monkeys are infected by feeding tuberculous cow's milk.
- Enough evidence that tubercular cow's milk should never be used for human consumption.
- Direct evidence of the infection of human beings by tubercular cow's milk is scanty.
- Humans do not inherit tubercular infection.
- Milk must always be boiled before consumption to 95ÚC for 1 minute or 70ÚC for 30 minutes.

iii) Active immunisation occurs when an organism undergoes a change following the assimilation of bacterium or its products and produces specific protective antibodies (such as antitoxins). This form of immunisation is called active immunisation (Ehrlich) as the organism has to do work of its own to produce the antibodies. Passive immunisation occurs when specific antibodies made by one organism is injected into another who gets it free.

Behring injected a culture of human tubercle bacilli into calves whose antibody response is mild to the human bacillus. When calves mature, the cows supply pure milk, but its administration to patients in the hope that anti-tuberculous antibodies may be present in the milk and may protect the patients was futile. Many other attempts to induce passive immunity to tuberculosis were equally unsuccessful.

The chief hope of fighting established tuberculosis currently is centred on tuberculin, Koch's original tuberculin (TO) and new tuberculin (TR) being generally used. For therapeutic purposes, TR is the candidate of choice. Wright's method is also employed for treatment using minute dozes where the dosage and intervals between injections are determined by their effect on opsonic index. Alternately, tuberculin is administered on the same schedule without employing opsonic index. A detailed debate on the need and efficacy of using opsonic index in tuberculin therapeutics is superfluous in the present context. Suffice to say, the "opsonic doctrine is assailed by an increasing number of investigators whose attack combined with much practical shortcomings have tended to produce widespread distrust in the practical value of the opsonic index".

Clinical Trial :

A clinical trial of tuberculin therapy was conducted in the Quilon District Hospital of Travancore from 1913 – 1914. The local conditions conformed to the Edinburgh System in terms of open air, sunshine, good food and friendly attendants during hospitalisation. Effort was made to provide "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". Ten illustrative cases among those treated at the hospital were analysed to

provide an overall picture of tuberculin therapy in a public hospital which had no radiologic facility but did boast of a laboratory for bacteriological tests.

Patient profile —

Age : Seven adults and three children below 10 years.

Gender : Male – 6, Female – 2, Not indicated - 2

Diagnosis —

- Pulmonary Tuberculosis 5
- Pulmonary Tuberculosis – Abscess elbow 1
- Tuberculous peritonitis 1
- Abscess hip 1
- Intestinal tuberculosis 1
- Pleurisy with effusion 1

Treatment and results —

- Tuberculin injection weekly after admission when patient settles down; weekly injections of TR with increasing dosage; dosage/frequency determined by clinical signs

– fever, pulse, weight gain, return of appetite. Discharge when fever settles, pulse becomes normal, substantial gain in weight occurs and appetite returns. This happens in weeks or months.

- Thoracentesis used for pleural effusion in a child.
- A child 8 years with tuberculous peritonitis, severe wasting and fever showed no improvement and was taken away by parents.
- A man aged 18 years with pulmonary tuberculosis and tuberculous abscess in the left elbow deteriorated (probably due to mixed infection of the elbow) and had to have the left arm amputated. He was discharged on request.

During the period of clinical trial, Travancore had no Sanatoria for tuberculosis treatment.

Summary and Conclusions :

Though tuberculin treatment does much good in the early stage of phthisis its results in treating full-fledged tuberculosis of the lung are disappointing. It must also be noted that success of tuberculin treatment demands favourable conditions such as fresh air, sunshine, and good food. No wonder the best results of treatment are believed to be obtained by a combination of the sanatorium treatment and tuberculin. At the present time, a standard method of tuberculin treatment is hard to recommend for various categories of patients because the use of tiny doses (1/5000th to 1/1000) of TR at one or two weeks' intervals, with or without opsonic index, gives differing results in the hands of practitioners. This applies to other methods such as the administration of TR by mouth. A few generalisations are however possible such as the large dose method of tuberculin treatment on the continent for many years has improved the curability of pulmonary tuberculosis. Whatever the method of treatment, success depends on early diagnosis. Hence the importance of tuberculin test which can detect the presence of tubercular infection long before the signs of the infection become detectable by physical examination.

The role of exercise in the recovery phase of pulmonary tuberculosis has not received adequate appreciation. In a convalescent patient of tuberculosis, Paterson and Inman at Frimley noticed that physical exercise would cause the release of body's own tuberculin or toxin (autoinoculation) as indicated by fever and fall in opsonic index. If the exercise level is gradually raised, the patient would become accustomed to autoinoculation and increased body resistance to tubercle. This is tuberculin treatment, but the patient makes his own tuberculin. It is clear that the possibility of preventive medicine is therefore substantial in this disease. If it turns out that tuberculous cow's milk is the main source of infection and the inhalation of bacilli is of small account, vaccinating every calf against tubercle or killing every milch cow that tests positive on tuberculin would be a major step for prevention. A non-tubercular milk supply would enormously diminish the prevalence of disease in children. A simpler measure would be to boil milk before consumption as is being done in India.

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