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Chemotherapy of Tuberculosis

D. S. BAPAT*

TUBERCULOSIS is a common communicable disease which causes a relatively high rate of mortality. It is regarded as one of the worst scourges of civilized communities. All over the world, tuberculosis has been the cause of untold economic waste and social disaster. In India too, malnutrition of the populace, insanitary living conditions, poverty and inadequate medical help prepare a ready background for its spread. About 2.5 million persons suffer from tuberculosis in this sub-continent of ours, and about half a million fall a prey to it annually.

In 1882 Robert Koch first published his brilliant investigations on the tubercle bacillus and differentiated the human and bovine types. Under the microscope, tubercle bacilli appear like straight or curved rods with slightly rounded ends. In the bacterial cell a higher alcohol "Mykol" is present which resists the decolourizing action of acids and alcohols when the bacteria are stained. Hence the tubercle bacillus is termed "acid fast." Like all other bacteria, bacillus tuberculosis is also readily destroyed by heat, but it is very resistant to bactericidal agents. Marked resistance is shown to 5% phenol, 15% sulphuric acid, caustic soda and antiformia[1]. In the human body tubercle bacillus penetrates deep, (in lungs and in other organs), creates a protective sheath (caseation) and makes the approach of the drug rather difficult.

In 1870 Sir Joseph Lister first postulated the principle of 'Microbial origin of diseases' which meant that an infection arises out of the invasion of tissues by micro-organisms and that it can be combated either by preventing the organisms from reaching a wound or by inhibiting their growth on the injured surface by the use of certain drugs. Since then attempts have been continually made to find out antibacterial agents which will have a maximum parasitotropic action and minimum organotropic action. Accepting this guiding principle of chemotherapeutic approach first propounded by the 'Father of Modern Chemotherapy,' Paul Ehrlich, investigations in the field of antibacterial therapy of tuberculosis were started during the thirties of the present century.

In the early stages of the development of chemotherapy, the chemical agents did not have a wide span of action. Chemotherapy made progress by leaps and strides only during the last two decades, when the sulpha drugs and the antibiotics came to the forefront. The first really effective and practicable antibacterial therapy of tuberculosis was

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developed only during the last decade. It is proposed in this article to trace the development of antitubercular agents.

In olden days gold in colloidal form and gold salts were employed in the treatment of tuberculosis. Since the effective concentration of these required to arrest the growth of tuberculosis bacillus could not be safely obtained in the body and they were most toxic, they were soon found to have very little value in this connection.

Guaiacol and creosote, at one time, enjoyed a rather wide use in pulmonary tuberculosis. However, they are now completely discarded as there is practically no evidence to support their antitubercular activity.

The era of modern chemotherapeutic agents for tuberculosis started in 1943, when Dr. S. A. Waksman working at the Rutger University in America was successful in isolating the streptomycins from the extract of Streptomyces griseus. This was the crowning success at the end of patient and painstaking research work carried out by Dr. Waksman and his team from 1939 to 1942. Nearly 250 cultures of actinomycetes fungi were isolated from soil specimens.[2] Though as many as 100 specimens yielded extracts having antibiotic activity, streptomycin was found to be the best.

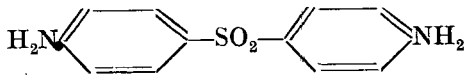
On industrial scale, 'streptomycin is biosynthesised by fermentation in a manner similar to penicillin. Streptomycin calcium chloride complex and dihydrostreptomycin are the forms of streptomycin used in common practice.

Streptomycin has a wide range of antibiotic activity. It is effective against a number of gram-negative and gram-positive organisms. Streptomycin exerts strong suppressive action on the course of tuberculosis by inhibiting the growth of the organisms in the pulmonary form; improvement results in about 50% of the cases. It is also effective in other tubercular involvements. The chief drawback of the streptomycins however is that drug-resistant strains develop readily. The streptomycins are not free from toxic effects. Apart from local irritation at the sight of injection other serious effects such as fatty infiltration of the liver, damage to kidneys, partial or complete impairment of hearing have been noticed on prolonged usage of streptomycin.[3] These difficulties have been overcome in recent times by attacking the bacteria with more than one weapon of chemotherapy. The combinations of P.A.S. (Para Amino Salicylic Acid) and streptomycin, and Conteben and streptomycin are generally employed.

In 1946 Lehman examining a series of derivatives of benzoic acid and salicylic acid (which were reported to increase the oxygen consumption rate of tubercle bacilli) found that *para*-aminosalicylic acid in concentrations of 2 parts per million inhibited the growth of the tubercle bacilli. It was also found effective in guinea-pigs experimentally infected with Micobacterium tuberculosis. P.A.S. is orally administered and relatively large doses can be tolerated. Although P.A.S. alone is valuable in the treatment of tuberculosis, it is now chiefly used in combination with streptomycin, as the combination considerably reduces the risk of development of streptomycin-resistant strains.

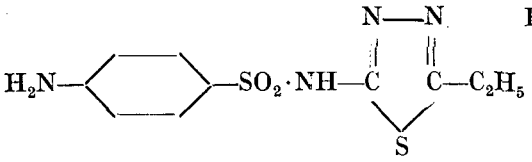
Several derivatives and analogues of P.A.S. have, in recent times, been studied with a view to find still better products. Phenyl-*para*-aminosalicylate is found to be more active. The benzoyl derivative of P.A.S. has been used in renal tuberculosis.[4]

Rist in 1940 observed the anti-tubercular activity of diamino diphenyl sulphone (D.D.S.).

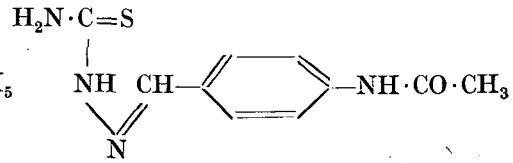


Since then it has been the subject of much investigation. Its clinical use is hindered by its greater toxicity. Its less toxic derivative "promin"—the sodium salt of pp'-diaminodiphenylsulphone-N-N'-di-(dextrosesulphonate) is found useful in inhibiting experimental tuberculosis in guinea-pigs. In human pulmonary tuberculosis, it has shown disappointing results. This group of compounds however, have shown more promising results in the treatment of human leprosy which is another ghastly disease caused by acid-fast bacteria.

Domagk in 1939 noted that sulphathiazole and 2-ethyl-5-sulphanil-amido thiadiazole (A) showed a specific but low antitubercular[5] activity. This attracted his attention towards thiosemicarbazones which were used as starting materials for the synthesis of sulphathiazoles.



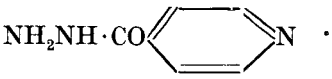
(A)



(B)

Of these, benzaldehyde thiosemicarbazone showed remarkable action when administered internally. Another thiosemicarbazone, Conteben (B), which is acetyl-p-aminobenzaldehyde thiosemicarbazone shows a clear inhibiting effect in dilutions of one in one million. This compound is now marketed under a variety of proprietory names. In manufacturing process, p-aminotoulene is either acetylated and then condensed with thiosemicarbazide or acetylation is carried out after the condensation. Though Conteben has a much smaller therapeutic dose (150 to 300 mgms. daily) its higher toxicity lays restrictions for its clinical use.

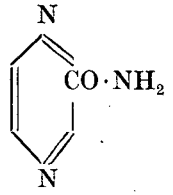
The discovery of *iso*-nicotinic acid hydrazide (I.N.H.) as a highly potent antitubercular agent was simultaneously announced in 1951 by three pharmaceutical firms, viz., Squibbs, Roche and Bayer. *iso*-Nicotinic acid hydrazide is in certain respects superior to streptomycin, P.A.S. and other antitubercular drugs. It shows a marked activity against tubercle bacilli growing intracellularly. It can be administered orally and it is not very costly.



(I.N.H.)

Its isopropyl derivative is on the market. The combinations I.N.H.-P.A.S. and I.N.H.-Streptomycin are also on the market.

The latest compound on the list of antitubercular drugs is Pyrazinamide. Its development is the result of the observation that Nicotinamide shows an inhibit-



ing property on cultures of tube[illegible] bacilli. Pyrazinamide has shown promi[illegible] ing results in cases of streptomycin-resistant strains.

Although a good number of highly effective substances are available for the treatment of tuberculosis in the chemotherapeutic armamentarium, the situation is far from satisfactory. While with one

drug there is the danger of resistant strain being developed, with the other there is the inconvenience of gulping large oral doses or of its being costly and out of reach of the poor sufferer. It is to be hoped that the intensive work going on in the various parts of the world, may soon evolve an ideal drug to eradicate tuberculosis, the Public Enemy Number One !

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Recent Developments in the Dyeing Technique

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IN recent years considerable amount of literature has been published on the subject of dyeing with vat colours. The application of vat colours to cellulosic fibres in package form as well as to fabrics by continuous methods and to wool and other synthetic fibres has called for many improvements in the usual methods of dyeing. Continuous method of dyeing which is being widely employed in modern times, yields not only greater production at low cost in the shortest possible time, but also ensures minimum damage to the material as the period of contact with the various chemicals is short. Temperature plays an important part in the rate of dye absorption and in the degree of penetration—they being increased with increase in temperature. This fact is made use of in the modern continuous dyeing methods. However, it has been the experience in the vat colour dyeing that the rate of exhaustion of the dye-bath is much higher than the rate of penetration into the interior of the fibre. This lack of balance causes uneven surface dyeing, particularly while dyeing in package form. In order to equalise these two rates of absorption and penetration in the process of dyeing, starting the dyeing at low temperatures and slowly raising the temperature of the dye-bath is practised as the rate of absorption is practically negligible at low temperatures. There have been many improvements[1] in this direction. The first is the use of retarding agents which lower down the rate of exhaustion. Such retarding agents are glue, sulphite liquor, paragol O, albetex P.O., dispersol V.L., etc. Another suggestion made to balance the rates of dye absorption and penetration is the addition of certain solvents to the dye-bath, such as methylated spirit, carbitol, butyl-carbitol, etc. which increase the rate of penetration by forming nearly molecular solutions of the dye. However, the high cost of these solvents prevents their commercial application. Yet another method for satisfactory dyeing makes use of the poor affinity of the acid-leuco-compound of the vat dye, unlike the sodium salt which exhibits

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