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THE TREATMENT OF PULMONARY TUBERCULOSIS

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The treatment of pulmonary tuberculosis may be likened to a pendulum which swings from one extreme to the other over the years, and which, during the last 10 years, has been passing through a phase in which the disease is treated with an ever-increasing number of antituberculous drugs. With every month that passes new variants are being added to the tried favourites; new techniques of administration are being advocated, and still newer drugs are being added to the list. This clinical appraisal is presented in the hope that it may shed some light on present-day drugs and regimes of administration.

Apart from the general principles involved in the treatment of any infectious disease *viz.* isolation, rest and feeding, it is now possible to assess more accurately the value of the various antituberculous drugs and to advocate certain lines of treatment based on world-wide experience.

DRUG THERAPY

Whatever drugs are selected, the patient's response to these should be backed up by clinical, laboratory and radiological assessment. It is useless to use a certain drug because it has a tuberculostatic or tuberculocidal effect—the aim must be eradication of the infection with the best possible means available. In general, drug therapy falls into two main sections: (1) that dealing with the known and proved agents, and (2) that dealing with the newer agents.

1. *Known and Proved Agents*

It is generally accepted that streptomycin, isonicotinic acid hydrazide (INAH) and para-aminosalicylic acid (PAS) should be used in the treatment of pulmonary tuberculosis. Their effect, dosage and method of administration have been the subject of numerous papers and it is possible now to advocate an optimal regime. But, although these drugs are the therapeutic agents of choice, they have certain disadvantages because (1) they can all produce a resistant strain of tubercle bacilli and (2) they all produce symptoms of toxicity or allergy in the patient.

Streptomycin. Recent research into the emergence of resistant strains of bacilli produced by the intermittent method of administration have shown that the most efficacious way to give this drug is to give *daily* doses of 1 g. by deep intramuscular injection. Emergence of resistant strains which could develop in 6 weeks under the old regime of 1 g. twice weekly has been abolished or delayed for longer periods by this method. It is also widely accepted, on the basis of controlled experiments, that this drug should never be used alone—the combination streptomycin/INAH or streptomycin/PAS is more effective than the administration of each drug on its own.

The following toxic effects may occur: (1) Permanent damage to the auditory branch of the VIII nerve. This occurs in 6—10% of all cases treated. In certain individuals the vestibular branch of the VIII nerve may be affected, leading to a disturbance of the proprioceptive sense. This is, however, now rare, since purification of the drug has eliminated what used to be a serious consequence of its administration. The dihydrosalt appears to have greater toxicity for the hearing mechanism. (2) Sensitization phenomena such as skin rashes still occur and sometimes prove troublesome. They are best treated by withdrawal, antihistaminics and test doses to determine whether streptomycin is really responsible. (3) Agranulocytosis has been reported.

Isonicotinic acid hydrazide (INAH). Initially administered alone, it is now widely recognized that this practice leads to rapid development of resistant strains, consequently INAH is always given in combination with either streptomycin or PAS or both. It is also being used in conjunction with some of the newer drugs. The optimal dosage can be regarded as between 3—5 mg. per kg. of body weight per day, given orally in divided doses. Absorption is very rapid. Parenteral administration leads to peak levels in pleural and cerebrospinal fluids and tissues more rapidly than oral intake.

The principal toxic manifestation has been a peripheral neuritis, the symptoms of which resemble those of a vitamin B6 (pyridoxine) deficiency. These effects are noted when doses higher than 5 mg. per kg. of body weight are employed; but they may appear in certain individuals at lower dosage levels. INAH is recognized as having some effect on carbohydrate metabolism, and various types of interference with the utilization of sugars, particularly in diabetics, have been reported. Allergic manifestations do occur, as with many other drugs; but these have not proved of great moment.

Para-aminosalicylic acid (PAS) is at present used almost exclusively in association with other more potent antimicrobial agents such as streptomycin and INAH. Although it may be employed intravenously, intramuscularly, intrapleurally, or even intrathecally, oral dosage proves the most practical. The optimum dosage lies between 10—15 g. per day (average 12 g. per day) in divided doses. Strains of resistant bacilli develop in patients treated with this drug; but emergence of these strains is slow and treatment can be carried on for months or years.

The most common toxic effect is digestive disturbance—anorexia, nausea, vomiting and diarrhoea. In certain indivi-

duals these may be of such magnitude as to require cessation of therapy. Other more serious side-effects are hypokalaemia, a goitrogenic effect, severe allergic reaction and signs of liver damage as shown by reduction in blood prothrombin and cholesterol, and by jaundice. These effects require withdrawal of the drug and change to another regime.

Combinations of Treatment. As each of the above drugs was discovered, it was used alone, and like all new weapons proved effective initially, but it soon lost that effectiveness through the emergence of drug resistance. Various investigators tried different combinations of these drugs, and it is now accepted: that (1) streptomycin-INAH is the most effective combination; that (2) streptomycin-PAS is useful in long-term policy; that (3) Streptomycin-PAS-INAH is now probably the most useful combination and the least likely to cause the emergence of drug resistant strains in the previously untreated individual and that (4) INAH-PAS can be given to cases where long-term drug cover is required, or where the facilities do not exist to give daily injections.

When using combinations of these 3 drugs, it is essential to request regular laboratory tests for the emergence of drug resistance in the organisms. In this way, time is not wasted in continuing treatment regimes which are ineffective, and at the earliest possible moment, a change can be made to a drug, or combination of drugs, to which the bacilli have not been previously exposed.

2. *Newer Agents*

In considering the drugs listed below it is as well to bear in mind that these, while having tuberculostatic properties, are not to be regarded as more efficacious than the first group. By comparison they are less potent than streptomycin or combined therapy—and in some cases are more toxic.

They can advantageously be employed, after drug resistance to streptomycin-INAH or streptomycin-PAS has emerged, for a period of several weeks or even months, to try to eliminate the resistant bacilli from the host—a change back to the streptomycin-INAH or streptomycin-PAS regime may then be made. The determining factor in the prolonged use of these 'intermediate' drugs is their toxic effect on the host.

Penicillin is ineffective against tubercle bacilli but is mentioned because in pyogenic complications of the disease, e.g. empyema, it exerts its usual beneficial action on suppurative infections.

Oxytetracycline. Good results have been reported in clinical treatment with oxytetracycline in conjunction with streptomycin. Its effectiveness appears to be like that of PAS in delaying the emergence of resistance to streptomycin. Its main drawback is the high ($\pm$4 g. per day) dosage and attendant intestinal upset.

Viomycin is employed by some in the re-treatment of cases after unsatisfactory results with other drugs, rather than in the initial therapy of tuberculosis. Its use is thus restricted to cases where neither streptomycin nor INAH can be used to advantage because of intolerance to these agents or high degrees of bacterial resistance. Some success has attended its use in this way; but its dosage and effectiveness are limited by its toxicity. Its unfavourable action is manifested by headache, nausea and other symptoms of malaise.

Cycloserine is apparently less active than either streptomycin or INAH, but it has been reported effective as a single medicament in patients not previously treated with chemotherapy. Combined with standard daily doses of INAH or 2 g. of streptomycin per week it has led to definite improvement in patients whose clinical course was unfavourable on other regimes. In doses of 0·5 g. daily combined with 4 mg. of INAH per kg. of body weight per day, it constitutes an effective therapeutic regime of low toxicity.

Drug resistance occurs as rapidly, and to the same degree as in streptomycin and INAH and has been correlated with loss of clinical effectiveness. Toxic effects are psychogenic reactions in patients with psychotic backgrounds, hyperreflexia and mild epileptiform convulsions. The convulsions seem directly related to the size of the dose.

SURGICAL PROCEDURES

In a discussion of the treatment of pulmonary tuberculosis mention must be made of the part played by minor and major surgical procedures in the control of the disease.

Minor surgical procedures (collapse therapy). These procedures have to a large extent fallen into disuse through the effectiveness of chemotherapy but they should not be completely disregarded in the scheme of treatment since they may hasten the ultimate aim—that of control.

In brief they are: (1) phrenic crush, (2) artificial pneumothorax and (3) artificial pneumoperitoneum. These procedures are all aimed at influencing the disease process in the affected lung.

Major surgical procedures are widely employed and are directed towards effecting a permanent cure by removal of diseased tissue. They are all employed after a reasonable time has been devoted to chemotherapy and are followed by at least 12 months further chemotherapy. The operations performed range from (*a*) segmental resection of a portion of a lobe, to (*b*) lobectomy, and/or (*c*) pneumonectomy, followed by (*d*) thoracoplasty.

Modern anaesthesia and post-operative care have reduced the mortality and it is possible for bilateral surgery to be carried out on cases which were, some 10 years ago, regarded as hopeless. Not every case of pulmonary tuberculosis can, however, be regarded as suitable for surgery; the selection of cases requires thorough investigation and consideration by a team of physicians and surgeons.

COMMON COMPLICATIONS

The following are some of the common complications which occur during the course of the illness and brief notes on their treatment.

1. *Cough.* Unproductive irritating cough can be controlled in many cases by the use of expectorant mixtures, inhalations, or in the worst cases, by the administration of romilar, or a similar product. Productive cough should not be suppressed, but great relief from exhausting spasms can be obtained by postural drainage.

2. *Haemoptysis* is a most alarming symptom which usually responds to a subcutaneous dose of 1/6—1/4 gr. of morphia, followed by a sedative mixture such as mist. pot. brom. et chloral $\frac{1}{2}$ fl. oz. 4 hourly. In mild blood-staining of the sputum, the sedative mixture and strict bed rest may be sufficient to control the bleeding.

If the bleeding is more than staining of the sputum, it is better to give the morphia and at the same time administer *one* of the following coagulants: Adrenosem 2 c.c. intramuscularly or 2·5 mg. orally, or adrenoxyl in similar doses

(these two preparations may be given 4 hourly); koagamin 3 c.c. intravenously followed by 2 c.c. intramuscularly 2 hourly up to a total of 10—15 c.c. or Congo red 1% 10 c.c. intravenously.

Only in the most severe cases is transfusion necessary and then the blood should be given slowly, because too rapid administration may cause a rise in blood pressure and start the haemoptysis again.

3. *Diabetes mellitus.* This is a common complication of pulmonary tuberculosis and often proves difficult to control. It is best treated by giving soluble insulin, since the insulin requirements of the patient vary with the progress of the lung disease, and stabilization is best effected by using a short-acting insulin while the lung disease is active. Once the lung disease has settled down it is usually possible to switch to a medium-acting insulin; while in a few cases, a long-acting preparation may be used once the patient has returned to work.

4. *Drug rashes* are of infinite variety and may prove extremely troublesome. They are usually associated with streptomycin sensitivity and are best treated by withdrawal of all drugs and the administration of antihistaminics. Once the rash has been controlled, each drug is restarted separately while careful watch is kept for the reappearance of the rash. Desensitization can be attempted but may be nullified by the appearance of drug-resistant bacilli. The elimination of the offender is, therefore, the safest procedure to adopt; other drug combinations can then be tried.

5. *Spontaneous pneumothorax*, if sudden and massive, may lead to death from mediastinal shift. Preliminary needling of the air space and the taking of manometric pressures after the withdrawal of some air, will indicate, by the failure to maintain a negative pressure after aspiration, whether a fistula is present. In this case intubation and underwater drainage is necessary. If a negative pressure is maintained, expectant treatment can be adopted.

6. *Pleural effusion* may cause severe distress if there is a massive accumulation. Needling and aspiration of a sample of fluid should be done early. If the fluid is straw-coloured and clear, aspiration by syringe until no more can be withdrawn, is indicated. If the fluid is at all hazy or turbid the presence of an empyema is indicated. Intubation with an underwater drain is now the method of choice for the pus must be drained. Daily instillations of 1 g. of streptomycin and 1 mega of penicillin are indicated until the underlying lung has fully expanded. If this does not occur, major surgery—decortication—is the next step.

7. *Pericardial effusion* may be a distressing complication and requires aspiration with the instillation of streptomycin and penicillin.