CHEMOTHERAPY OF TUBERCULOSIS: TRIUMPH AND TRAGEDY

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The evolution of the chemotherapy of tuberculosis is a triumph of medical research. Its application in practice is a human and medical tragedy.

Chemotherapy can be highly effective. With a particular regimen of streptomycin, isoniazid and PAS it is possible, in patients who have cultures of tubercle bacilli sensitive to these drugs, to obtain persistent bacteriological quiescence in all cases. If chemotherapy is continued for long enough, at least 18 months and in the more extensive cases for two years, the risk of relapse during the next five years is very small, possibly between one and two percent. Thus, it may reasonably be claimed that bacteriological 'cure' is now possible. If the patient has cultures which are not sensitive to these three drugs, the treatment is a little more difficult; but with good bacteriological facilities and an adequate supply of all the many anti-tuberculosis drugs that are now available, it should be possible to treat these patients efficiently as well.

The so-called 'triple-drug' regimen consists of the following. For the first three months the patient is treated with streptomycin 1g. or 0.75 g. intramuscularly daily together with isoniazid 150 mg. twice daily and sodium PAS 6 g. twice daily. The isoniazid and PAS are given by mouth; and it is better to give a preparation which contains both these drugs so that the patient cannot take one of them without taking the other. At the end of three months, the frequency of the streptomycin dosage can be reduced to 1 g. three times a week. This continues for a further three months. At the end of this six month period of triple-drug treatment the

sputum will be negative on culture in all but a very small proportion of cases. The intensity of the regimen is now reduced, so that the patient receives only isoniazid and PAS in the doses previously prescribed. This oral treatment continues for a further year or 18 months, so that the total period of treatment is 18 months or two years.

Unfortunately, this highly effective regimen of chemotherapy has some disadvantages. First, it is expensive. Both streptomycin and PAS are relatively expensive drugs. The amount of money available in a country for the treatment of tuberculosis may not be sufficient for these two drugs to be used in a daily regimen. Isoniazid, on the other hand, is cheap. Secondly, a regimen that demands daily injections for three months and injections three times a week for a further three months requires a high degree of organization of the treatment services and a large number of people. In many countries neither the people nor the organization are at present available. Finally, the regimen demands high degree of co-operation on the part of the patients. They must continue taking drugs by mouth without supervision for very long periods. A small amount of irregularity of drug-taking is probably not harmful: but no-one knows how much irregularity is harmless and the patients must be persuaded to take the drugs regularly throughout the whole period. Again, a highly efficient medical service is needed in order to ensure a high degree of co-operation.

Because of these disadvantages of the triple-drug regimen, attempts have been made to find less expensive and more acceptable regimens. Such regimens have been found; but none of them have so far been shown to be as effective as the expensive triple-drug regimen of streptomycin, isoniazid and PAS.

In East Africa, the British Medical Research Council carried out a series of controlled clinical trials using thiacetazone as a companion drug to isoniazid in place of PAS. Thiacetazone had been used to treat tuberculosis in Germany just after the 1939-45 war. No controlled clinical trial was done and moreover, the early reports of toxic effects from the drug were so alarming that few physicians used it in Europe or elsewhere. But the drug

had one great advantage. It is cheap. The carefully controlled trials in East Africa showed that, in patients with isoniazid-sensitive cultures, a regimen of 300 mg. of isoniazid and 150 mg. thiacetazone, given in a single dose is as effective as the widely used regimen of isoniazid PAS. With both regimens about 80% of patients with sensitive cultures obtained bacteriological quiescence after one year's treatment. Thiacetazone did have some toxic effects; but the number of patients who had to stop treatment because of them was no greater than the number of patients who had to stop because of the toxic effects of the isoniazid-PAS regimen.

Further controlled trials showed that the results could be improved by giving streptomycin together with the isoniazid and thiacetazone for the first six weeks. It was also found that the toxicity of thiacetazone and the tolerance of the patients for the regimen varied in different parts of the world. In some countries there appeared to be very little toxicity; in others quite a lot. The regimen has also been studied in the Tuberculosis Chemotherapy Centre at Madras with similar results to those obtained in East Africa. The regimen appears to be acceptable for Indian patients and to be a good substitute for the isoniazid-PAS regimen. It is much cheaper.

At the Tuberculosis Chemotherapy Centre in Madras another regimen has been studied. This consists of giving 1 g. of streptomycin together with 650 mg. isoniazid (15 mg./kg. body weight) on two days each week. In patients with cultures sensitive to both these drugs the results are very good. From 90-95% have obtained bacteriological quiescence after one year's treatment. The treatment is not too expensive for widespread use. It has the great advantage that the taking of the drug can be completely supervised. The patient can come to the clinic and have the streptomycin injection. At the same time the isoniazid can be swallowed and can be seen to be swallowed. Thus it is a completely supervised method of treatment. The disadvantage is that it is still necessary for the patients to co-operate. He need not so much co-operate in taking drugs. But he needs to co-operate in coming to the clinic or in being available for the injections to be given at his home. Thus the intermittent regimen solves one problem but leaves the other unsolved. Further

experience of the isoniazid-thiacetazone regimen and the intermittent streptomycin-high dose isoniazid regimen is required in many parts of the world. It may be that in some areas and in some conditions better results are obtained with an unsupervised oral regimen than with an intermittent supervised one, because the patients co-operate better in the unsupervised regimen.

In some areas the intermittent regimen may be quite impossible to carry out because of the distances the patients would have to travel twice weekly to have their injections. But it is not necessary to use one regimen to the exclusion of another. The regimen can be selected that is most likely to be effective in individual patients or in patients in a particular area of the country.

Further clinical trial are being carried out by the British Medical Research Council, the Tuberculosis Chemotherapy Centre in Madras and the International Union against Tuberculosis. There will be obvious advantage in being able to give the streptomycin and isoniazid only once weekly. But the trials in Madras suggest that this is not an effective enough regimen. However, there is hope that a more intensive regimen for short initial period followed by a weekly regimen, may eventually be evolved that will be both effective and possible to administer in countries where money and trained people are short.

Even in such countries it is now possible to treat tuberculosis highly effectively with limited resources. Why then is it not treated effectively? Here lies the tragedy of the chemotherapy of tuberculosis.

Tuberculosis chemotherapy presented the medical profession with an entirely new problem. This was not realised until many years after the drugs had become available, and by this time much harm had been. In some other diseases, such as diabetes and myxoedema, the patient has had to take drugs for long periods without daily supervision. But in these diseases the consequences of irregular treatment could easily be recognised by the patient himself within a short period. The symptoms of the disease would rapidly return if treatment was stopped. But with the tuberculosis the situation is quite different. After a relatively short time of chemotherapy the patient feels better. If he then stops the treatment he will not immediately

begin to feel worse; there may be an interval of several months or even years before the warning symptoms return. Thus the incentive to continue regular treatment in tuberculosis must be different from the incentive in other diseases that require long continued treatment. The patients do not keep on regularly day after day taking drugs merely because the doctor tells them to do so. They must be persuaded and helped. It is impossible to lay down universally applicable rules for persuading patients to continue treatment. So much depends on the social environment in which the patients are being treated. Intelligent patients require a different approach to the subject from unintelligent ones. Long established social customs and beliefs must be considered.

One rule, however, is universally applicable. This is that it must be made as easy as possible for the patients to obtain the drugs. Can we really expect the patient to remain co-operative if he has to wait four or five hours in a crowded clinic merely to see the doctor for one or two minutes and then receive a supply of drugs? Can we obtain and keep co-operation if the doctors treat the patients as inferior beings? Clinics are run for the benefit of the patients, not for the doctors, nurses and technicians. The primary objective is to treat patients properly, not to earn as much money as possible in the shortest possible time.

Patients cannot be expected to continue treatment for long periods if they have to buy their own drugs and are so poor that they cannot do so without going short of food. It is essential that anti tuberculosis drugs should be provided by the health services without charge to the individual patient.

In countries with too few doctors, it is not possible to restrict the treatment of tuberculosis to specially trained staff in special clinics. The general practitioners and the doctors working in primary health centres in the rural areas must take part. But to do so effectively they must be given adequate guidance about the principles of chemotherapy and as much help as possible given to them so that they can prescribe the right drug regimens for their patients without charge and detect and follow up defaulters. Treatment that aims mainly at increasing the income of the doctor or of the pharmacy and

pharmaceutical firms is likely to be bad. The patient and the community are more important than the medical profession and the pharmaceutical industry. At the same time, the doctors must have the opportunity of earning a reasonable salary whilst at the same time treating the tuberculosis patients well.

If antituberculosis drugs can be bought in the markets and the drug stores by anyone with money to buy them, it is not surprising that they are misused. Such misuse can do great harm. A few weeks of self-medication with isoniazid bought in the market for a cough may well produce isoniazid-resistant cultures and make impossible to treat the patient effectively in the future. If the intermittent streptomycin-isoniazid treatment is supplemented by the patient buying streptomycin injections himself because he considers twice a week is not enough treatment, streptomycin-resistant cultures may appear and this highly effective intermittent regimen be spoilt.

The harm that has been done by unregulated chemotherapy, failure to obtain the co-operation of patients, and indiscriminate use of drugs by doctors and para-medical personnel is shown by the proportion of patients with resistant cultures who present themselves at clinics for treatment. Thus, in some countries, both in Europe and other continents, there are clinics where up to 50% of the patients presenting themselves for treatment have resistant cultures through previous bad chemotherapy. In some countries such patients cannot be treated effectively at all. In others the drugs and facilities are available; but the treatment with these so-called 'second-line' drugs is arduous for the patient and difficult for the doctor. It is also very expensive.

To remedy all these faults of practical chemotherapy is an enormous task. So many factors are involved. It is not a simple matter of making recommendations and regulations. To suggest a solution to the problem in a particular country would require an intimate knowledge of the structure of the health service, the financial resources of the country, the social environment of the patient, the intellectual and ethical qualities of the

doctors and the availability of all types of staff. The first essential in any country should be to build up the will to control tuberculosis, not only in administrators and tuberculosis specialists, but also in the whole community. If the will to control the disease is absent it cannot be controlled.

This is the tragedy of the chemotherapy of tuberculosis. The scientists in the medical profession and the pharmaceutical industry have done their work well. They have discovered and tested a dozen antituberculosis drugs in the past 25 years. Throughout the world many lives have been saved through their efforts. But so much more could have been done if more thought had been given to the problems of chemotherapy in the field. The world malaria campaign is in some countries entering the phase of eradication. This has been a great achievement. But the problems of eradicating malaria are simple compared with the problems of eradicating tuberculosis. With malaria you have to deal primarily with insects; with tuberculosis one deals with men. It is easier to control mosquitoes than human beings. If as much thought were given to the problems of patients as people as is given to chest x-rays and preparations of their sputum, many of the difficulties would disappear and in time so would the disease itself.