Drug Treatment of Disease

DRUG TREATMENT OF TUBERCULOSIS

II. TREATMENT OF PATIENTS WITH TUBERCLE BACILLI RESISTANT TO STANDARD CHEMOTHERAPY

BY

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As indicated in the previous article,* treatment of tuberculosis with standard chemotherapy is highly successful provided that the patient's organisms are initially sensitive to the drugs used. It is therefore unethical to carry out large-scale trials of newer drugs on such patients, at least until it has been established that there is some probability that the newer drug will be superior to streptomycin, P.A.S., or isoniazid. Because of this the newer drugs have been investigated on a much smaller scale and usually in patients whose tubercle bacilli are already resistant to standard chemotherapy. There have been ethical and other difficulties in carrying out strictly controlled trials. In consequence the scientific data available on the newer drugs are very much less reliable than those relating to standard chemotherapy.

Newer Chemotherapeutic Agents

Before considering what combinations of drugs to use in patients with tubercle bacilli resistant to one or more of the standard drugs, some of the newer drugs will be listed and brief information given about them. The drugs with the most powerful antituberculous action are probably pyrazinamide and alpha-ethylthioisonicotinamide (1314 or ethionamide), while viomycin, kanamycin, cycloserine, and the tetracycline group have a weaker action.

Pyrazinamide

Pyrazinamide is a relatively powerful antituberculous drug whose administration has two major defects—liver toxicity, which has occasionally proved fatal, and the rapid emergence of drug-resistant organisms. Because of its potential toxicity, it should be used only in hospital, at least initially, and liver function tests should be carried out every two weeks. Should any abnormality be shown by the tests it is wise to stop the drug at least temporarily. It is given orally in a dose of 40 mg./kg./day divided into two equal doses with a maximum of 1.5 g. twice a day.

Pyrazinamide resistance often emerges within six weeks if the drug is given alone. There is good evidence that such resistance is prevented if pyrazinamide is given with isoniazid, provided the patient's organisms are initially sensitive to both drugs. There is less evidence about the value of streptomycin or P.A.S. in this respect, but it is reasonably probable that if they are given in adequate daily dosage they will be effective. Tetracycline drugs, cycloserine, or 1314 (at least in a dose of 0.5 g. daily) may fail to prevent pyrazinamide resistance in a relatively high proportion of severe cases.

1314 (alpha-ethylthio-iso-nicotinamide or ethionamide)

Although at the time of writing 1314 is available only for research purposes in Great Britain it is likely soon

to be on the market. There is no doubt that it is a relatively powerful antituberculous drug. Its major side-effect is nausea, which can be very troublesome. The optimal dose is at present uncertain. It is given orally, and the dosage has varied from 0.25 g. twice daily to 0.5 g. twice daily. Nausea is commoner when a dose of 1 g. daily is used, but it seems possible that a dose as low as 0.5 g. daily may be insufficient to prevent resistance to a companion drug. Suppositories are being investigated. Though resistance develops rapidly when 1314 is given alone, it seems probable that it can be prevented by standard doses of streptomycin, isoniazid, or P.A.S. Combination with tetracycline or cycloserine may result in a fairly high proportion of failures, at least in severe cases. There is less information about viomycin and kanamycin, but neither seems likely to be a successful companion drug. One can summarize by saying that 1314 is certainly a useful drug but its exact place in antituberculous chemotherapy is not yet established.

Viomycin

Viomycin is an antibiotic given by intramuscular injection. It can cause giddiness or deafness and can also give rise to renal damage. Such effects are rare when the drug is given in doses of 1 g. twice a day on two days in the week and are not a serious problem even when a similar dosage is given on three days in the week. It is not a very powerful drug. Organisms resistant to it may emerge if it is given alone, but this can be prevented, or at least deferred for many months, by combining the twice-weekly dosage mentioned above with tetracycline in a dose of 2 g. twice daily. Though there is little detailed evidence, it seems probable that daily cycloserine might equally delay the emergence of viomycin resistance. In the case of other newer drugs, it is more probable that viomycin will in the first place fail to prevent the emergence of resistance to the second drug with the subsequent emergence of resistance to viomycin also. Kanamycin seems likely to be similar in action to viomycin and has similar limitations. There is often cross-resistance between them.

Cycloserine

Cycloserine is a relatively weak drug. It is given orally. With doses of more than 1 g. daily toxic effects have been a serious problem. Psychotic symptoms may occur within a few days of starting treatment, and convulsions have been reported fairly frequently. It has been thought that some patients on the verge of cor pulmonale have been precipitated into cardiac failure. In a dose of 0.5 g. twice daily by the mouth toxic effects have been less common. Lower doses are probably less effective, but it is thought that complications are rarer if treatment is begun with a dose of 0.25 g. twice daily, gradually increasing to a dose of 0.5 g. twice daily over

*Published in the *Journal* last week at p. 370.

a period of up to two weeks. Cycloserine resistance emerges less readily than with some of the other drugs and in our experience has not emerged when the drug was combined with 2 g. tetracycline twice daily. Cycloserine is relatively ineffective in preventing the emergence of resistance to pyrazinamide or to 1314.

Tetracyclines

The tetracycline drugs have only a very weak antituberculous action, but there is evidence to suggest their value when given in the high dosage of 2 g. twice daily in delaying or preventing the emergence of resistance to streptomycin (when this is given twice weekly), isoniazid, viomycin, and perhaps cycloserine. With doses lower than 2 g. twice daily they are much less effective in this respect. Some diarrhoea is quite common in the first couple of weeks of treatment, but usually it then decreases and becomes very much less troublesome. A few patients are unable to tolerate the high dosage necessary.

Drug Combinations in Patients with Tubercle Bacilli Resistant to the Standard Drugs

It must be clear from the foregoing account that most of the newer drugs are more toxic, and often less effective, than streptomycin, P.A.S., or isoniazid. They are also much more expensive. Owing to the ethical problems of testing, we are less informed about them. The following suggestions must be read with these limitations in mind.

The Patient Who Has Had Previous "Doubtful" Chemotherapy

If the patient has had previous chemotherapy it is always possible that his organisms are now drug-resistant, for if he is in need of further treatment it is likely that there has been some error in the original therapy. The presence of drug-resistant bacilli becomes more probable if he is known to have received intermittent streptomycin with daily isoniazid or P.A.S. If he has been treated as an out-patient he may well have failed to take his drugs in the rhythms and doses advised.

It is unwise to start such a patient on all three drugs. If his organisms are already resistant to two of them they may well become resistant to the third also. It is wise to treat him in the first place with some form of "holding" chemotherapy until the results of resistance tests become available in two to three months. Viomycin 2 g. in two divided doses on two days in the week together with tetracycline 2 g. twice daily is a suitable combination. It is not highly effective but it does usually prevent deterioration and allows the patient to hold his own and perhaps even improve. It is also relatively free from risk of toxicity. In such a patient it is of course very important indeed that drug-resistance tests should be carried out on more than one specimen of sputum and that they should be thorough. Any laboratory error may result in the patient losing the use of further drugs.

If the resistance tests show any degree of loss of sensitivity to one of the standard drugs this drug should not be relied on to prevent resistance to a second drug used in combination. It is very likely to fail. It may sometimes be justifiable, if there is only a low or doubtful degree of resistance, to use the drug in question, but only in *addition* to another combination of two or more drugs known to be mutually effective in preventing the emergence of resistant organisms.

The Patient with Tubercle Bacilli Resistant to Streptomycin Only

P.A.S. plus isoniazid should be used. In that case it is wise to use the P.A.S. in a dose of 5 g. of the sodium salt four times daily together with isoniazid 100 mg. twice a day. After three successive negative cultures have been obtained it is justifiable to reduce the dose of P.A.S. to 5 g. twice daily. If the disease is very extensive, it may perhaps be unwise to rely only on P.A.S. plus isoniazid, which may sometimes fail in such cases. It is as well to add a third effective drug such as viomycin or pyrazinamide.

The Patient with Tubercle Bacilli Resistant to P.A.S. Only

In patients under the age of 40 the correct treatment should be 1 g. streptomycin daily combined with 100 mg. isoniazid twice daily; in patients over that age there is a risk of vestibular damage with such a dose of streptomycin, and it may be justifiable to lower this to 0.5 g. or 0.75 g. daily. In a very severe case it is probably wise to accept the risk of vestibular damage and to give the full dose of 1 g., at least for the first few weeks.

The Patient with Organisms Resistant to Isoniazid Only

The patient should be treated with daily streptomycin 1 g. together with sodium P.A.S. 5 g. four times daily. If only 5 or 10 g. P.A.S. is given daily, streptomycin-resistant organisms may emerge in a substantial number of cases, and the organisms are likely to become P.A.S.-resistant later. The problem of streptomycin dosage in older people is similar to that discussed in the previous paragraph.

The Patient Whose Tubercle Bacilli are Resistant to Both Streptomycin and P.A.S.

The combination of pyrazinamide (20 mg./kg. twice daily with a maximum of 1.5 g. twice daily) with isoniazid (100 mg. twice daily) is probably the most powerful. In severe cases the risk of pyrazinamide toxicity should probably be taken. In very mild cases it may be justifiable to use viomycin plus tetracycline. It is possible that a combination of isoniazid plus 1314 may prove as effective and less risky than the pyrazinamide-isoniazid combination already mentioned, but there is not yet sufficient evidence on this point.

The Patient whose Tubercle Bacilli are Resistant to Both P.A.S. and Isoniazid

The combination of streptomycin (1 g. daily) and pyrazinamide in the doses already mentioned may well be the best, though there is not much evidence about the value of streptomycin in preventing pyrazinamide resistance. It may be that streptomycin plus 1314 will prove as effective and less risky, but this is not yet established. If either of these combinations is used, and if the case is a severe one, it may be wise in the present state of our knowledge to add a third drug, such as tetracycline or cycloserine. Alternatively streptomycin may be combined with both pyrazinamide and 1314.

The Patient whose Tubercle Bacilli are Resistant to Both Streptomycin and Isoniazid

It is uncertain whether P.A.S. would be adequate to prevent the development of resistance to pyrazinamide or to 1314. The best treatment would probably be to combine P.A.S. in the highest tolerated doses with pyrazinamide and also to use cycloserine, viomycin, or 1314.

The Patient whose Organisms are Resistant to Streptomycin, P.A.S., and Isoniazid

Such patients present a formidable problem, and no drug combination so far tested can give a guarantee of arrest of the disease and permanent conversion of the sputum to negative. Viomycin plus tetracycline may sometimes succeed in making those with milder disease fit for surgical operation, but it is unlikely to achieve sputum conversion on its own. Cycloserine plus tetracycline has similar limitations, in addition to the risk of toxicity from cycloserine. There have been a number of failures, with the emergence of drug resistance, on combinations of cycloserine plus pyrazinamide, cycloserine plus 1314, and pyrazinamide plus 1314. It is possible that the success rate can be improved by using three drugs in combination. Pyrazinamide together with 1314, if possible 0.5 g. twice daily, and viomycin 2 g., twice or three times weekly, may well be the best combination, though there is inadequate evidence regarding it. Cycloserine is perhaps best avoided as the third drug in order to reduce the number of pills which the patient may have to take and to avoid adding the toxicity of cycloserine to that of 1314 and pyrazinamide.

Drug Cover for Surgery

It must be clear from the foregoing paragraphs that none of the therapeutic combinations recommended are likely to be as effective as the standard drug combinations. In addition, patients with resistant organisms often have chronic and extensive disease. The probability of failure of chemotherapy and the emergence of drug resistance is therefore relatively high. In such patients resectional surgery, if it is feasible, is often indicated. The best time to carry this out in the individual case is a matter of judgment. In general, after three months' chemotherapy the patient's bacterial population will have been considerably reduced. If the sputum has become consistently less positive, even though negative cultures have not yet been obtained, it may provisionally be assumed that the tubercle bacilli are not yet drug-resistant. The chemotherapy in use should therefore be able to prevent infectious complications of the operation. Nevertheless, to be on the safe side it is probably wise to add an additional drug as operation cover. It is seldom possible to remove all the tuberculous disease, so it is very important to continue chemotherapy afterwards. The minimum duration should be one year after the first of a series of consistently negative sputum cultures, but in a severe case and if no drug toxicity emerges it is wise to continue for a total of two years regardless of when the operation was carried out.

Conclusions

The treatment of a patient with drug-resistant organisms is always a difficult matter requiring careful judgment of all the clinical, bacteriological and surgical factors involved. It is essential that the resistance tests, which will determine the chemotherapy used, should be carried out with skill and care and that wherever possible a decision should be based on more than one test. The physician must be capable of critical evaluation of the bacteriological results. The surgeon will often have to be consulted. It may be justifiable to ask him to take bigger risks than would normally be permissible, because the prognosis with chemotherapy alone, especially in the patient whose organisms are resistant to all three of the standard drugs, is so uncertain. Nevertheless, if all

concerned, including the patient himself, are prepared to take sufficient trouble, many of these unfortunate people can be salvaged.

NOTE.—References to original work on which some of these recommendations are based may be found in Crofton, J. (1960). *Brit. med. Bull.*, 16, 550

I am glad to acknowledge my debt to many colleagues, including Drs. P. D'Arcy Hart, the late Dr. Marc Daniels, and Dr. D. A. Mitchison of the Medical Research Council, and, in Edinburgh, Drs. I. W. B. Grant, N. W. Horne, J. D. Ross, Sheila Stewart, F. W. A. Turnbull, A. T. Wallace, and J. Williamson. Most of the Edinburgh research was financed by generous grants from the Royal Victoria Hospital Tuberculosis Trust.

AN APPRAISAL OF PSYCHIATRY IN GENERAL PRACTICE

BY

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The flood of mental illness with which the G.P. has to contend presents problems that are hard to solve. Some observers can see no solution apart from a fundamental change in either the patients or the doctors. In the meantime the immediate problem remains and becomes more pressing—namely, how to help the doctors as they now are to deal with the patients who actually consult them.

Psychotherapy

Strictly speaking, "psychotherapy" should mean all methods of treating the mind, but by custom it refers only to treatment by personal discussion between patient and doctor, and here it is used in this sense. The nature of the discussion and of any guidance and explanation offered to the patient varies widely, as do the duration and frequency of these interviews.

Each school of psychopathology believes in general that only psychotherapy practised within the framework of its own particular set of beliefs can be of real value. However, a non-partisan observer will hardly agree. The value of a frank discussion of one's personal problems and an airing of one's inner feelings has always been recognized. It has often been provided by organized religion, sometimes as part of an act of confession. In our modern secular society it is not surprising that the physician is frequently expected to take over this function, which was previously performed by the priest; it is, however, a function which the physician is often most reluctant to fulfil.

Nevertheless, psychotherapy by G.P.s is finding many strong advocates within the medical profession, particularly since Balint (1957) described his methods of training G.P.s at the Tavistock Clinic. One must admire his achievement of inducing G.P.s to continue to attend weekly seminars over a period of years. On the other hand, he reports that half of them did prematurely stop attending, and it appears from the lengthy case-histories he gives that more than half the patients remained ill despite many hours of work on