

## Late Results of Treatment of Chronic Drug-resistant Pulmonary Tuberculosis

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Patients with active pulmonary tuberculosis of many years' duration are thought to have a reduced chance of being cured if they harbour tubercle bacilli resistant to streptomycin, para-aminosalicylic acid (P.A.S.), and isoniazid. Three reasons are often given for this poor prognosis. Some patients cannot tolerate prolonged treatment with alternative chemotherapy—ethionamide, pyrazinamide, and cycloserine (the "second-line" drugs); the drugs may be less effective in eliminating tubercle bacilli from the sputum; and they may fail to prevent the emergence of resistant strains.

The preliminary results of the treatment of 26 patients by means of the second-line drugs have previously been described (Somner and Brace, 1962). We feel that a further report is justifiable because we believe we have demonstrated that second-line drugs can be tolerated by patients over prolonged periods, can eliminate tubercle bacilli from the sputum in nearly all cases, and can prevent the emergence of resistant strains.

In the earlier report we stated that these patients had had tuberculosis for many years and that they had gradually lost faith in the ability of chemotherapy to achieve a satisfactory outcome. Furthermore, as a result of methods of sensitivity-testing that were subsequently proved inadequate in the early and middle 1950s some tubercle bacilli were reported as "sensitive" which were in fact resistant to the standard drugs, streptomycin, P.A.S., and isoniazid. In consequence physicians were often encouraged to persist with chemotherapy which could offer little hope of cure, and the patient finally became convinced of its inability to achieve success. Any new drug programme, perhaps even less pleasant than the standard drugs, was therefore received with apathy, and before being embarked upon necessitated most careful consideration by patient and physician.

### Patients

Our study began in 1960 and was limited to 26 patients whose sputum was persistently positive in spite of chemotherapy with standard drugs over several years. Careful sensitivity-testing by a method of doubling dilution confirmed that 24 had cultures resistant to all three standard drugs and two had cultures resistant to two standard drugs. A number of other patients, found to have cultures resistant to one drug only, were excluded from the study because, with proper management, it should still be possible to render them sputum-negative with standard drugs. The background to these 26 patients suffering from chronic sputum-positive tuberculosis can best be illustrated by three observations. First, the duration of tuberculosis was a long one—a total of 324 years for the 26 patients, or an average of 12 years each since the disease was first diagnosed. Secondly, over half were diagnosed as having tuberculosis 10 to 15 years ago, at a time when chemotherapy was not fully evaluated, when

therapy with a single drug was accepted, and when bacterial resistance was little understood. Thirdly, the extent of sputum-positivity can be judged from the results of six cultures carried out during the year before the study was begun—22 of the 26 patients were positive on all six cultures, two were positive on five cultures, one on four cultures, and one on two cultures. Finally, chest radiographs revealed bilateral disease in 24 and cavitation in 22, and all radiographs were thought to show moderately or far advanced disease according to the classification of the National Tuberculosis Association of the U.S.A.

### Treatment

*Ethionamide* was given as 1 g. daily (0.5 g. morning and evening). It was often impossible to maintain this daily dose because of intolerance, and reluctantly it was reduced to 0.75 g. or 0.5 g. daily for many patients.

*Pyrazinamide* was given on a weight basis. Patients of 10 st. (63 kg.) and over received 3 g. daily (1.5 g. morning and evening), of 8 to 10 st. (50–63 kg.), 2.5 g. daily (1.25 g. morning and evening), and those weighing less than 8 st. (50 kg.) received 2 g. daily (1 g. morning and evening). It was nearly always possible to maintain the full dosage provided significant elevation of the serum transaminase was not encountered.

*Cycloserine* was also given on a weight basis. Patients weighing over 11 st. (70 kg.) received 1 g. daily (0.5 g. morning and evening), between 8 and 11 st. (50–70 kg.) received 0.75 g. daily (0.25 g. morning and 0.5 g. in the evening), and under 8 st. (50 kg.) 0.5 g. daily (0.25 g. morning and evening). Depression and lack of well-being frequently necessitated some reduction of dosage.

Eighteen of the 26 patients received initially all three drugs together, but often it was impossible to maintain treatment with all three drugs at full dosage because some patients pressed for a reduction regardless of whether the physician thought it necessary or not. With two exceptions (Cases 5 and 6) a significant reduction was not permitted unless the sputum cultures had become negative at the time.

Seven of the 18 patients received three drugs throughout the course of two years' treatment, five received them for the first six months or more but for less than 12 months, and three received them for less than six months from the beginning of treatment. All of these 15 patients completed a total course of two years' treatment. The remaining three patients (Cases 1, 4, and 5) died within the first few months of treatment and are discussed under "treatment failures."

Eight of the 26 patients started treatment with two drugs only—namely, ethionamide and pyrazinamide. The initial omission of cycloserine was due to the fact that most of the patients reported in this paper were included in a controlled trial organized by the Research Committee of the British Tuberculosis Association to assess the value of treatment of resistant tuberculosis with ethionamide and pyrazinamide and the addition of cycloserine to one group but not the other.

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Of these eight patients one (Case 2) died after three months' treatment and one received ethionamide and pyrazinamide only for 24 months. In two patients raised serum transaminase levels necessitated the substitution of cycloserine for pyrazinamide in a two-drug régime. In four patients the two drugs were given for 6 to 12 months and were then replaced by a three-drug régime (by the addition of cycloserine (two cases), kanamycin (one case), or tetracycline (one case)) when it became apparent that a three-drug régime was likely to be associated with less drug-resistance than a two-drug régime. The addition of a third drug at this stage would not generally be advised because of the possibility of resistance to it developing when resistance to ethionamide and pyrazinamide was already present.

### Duration of Treatment

It was our aim that all patients should receive a two-year course of treatment. Treatment of this duration was completed in the 22 patients who survived, but was not achieved in the remaining four patients because of death. All the patients started treatment in hospital and none of the survivors were discharged until culture-negative.

In a short paper like this it is impossible to detail all the alterations of treatment in the successfully treated patients, particularly when they were out-patients. Furthermore, it would not necessarily be a true assessment of the amount of treatment received, because from experience with other out-patients treated for long periods there is reason to suspect that a variable proportion of the drugs would not be taken.

Apart from reduction of dosage of drugs, confined mostly to ethionamide, it was sometimes necessary to interrupt all treatment temporarily so as to give the patient a respite and to maintain his good will. These interruptions were rarely made in hospital, but were more frequent in those at home who had received the longest periods of treatment. Furthermore, they were nearly always made after the patient had been sputum-negative for a long time, and were not viewed with the same concern as would have been the case had the sputum been positive.

## Results

### Treatment Failures

The failures which occurred during the course of the prescribed chemotherapy numbered four.

*Case 1.*—A man aged 59 being treated with ethionamide, pyrazinamide, and cycloserine discharged himself from hospital after six weeks' treatment, discontinued the drugs, and died.

*Case 2.*—A man aged 73 received ethionamide and pyrazinamide and left hospital against medical advice after eight weeks' treatment. At home he took drugs irregularly for three months and died after a cerebral thrombosis.

*Case 4.*—A man aged 69 received ethionamide, pyrazinamide, and cycloserine in hospital for five months. The last three sputum cultures taken in hospital were negative. One week after returning home he committed suicide. Cycloserine was thought to have contributed to his death.

*Case 5.*—A man aged 64 received ethionamide, pyrazinamide, and cycloserine, but the last-mentioned drug was discontinued after only two weeks because of a convulsion attributed to it. He became culture-negative during the seventh month of treatment. The cultures remained negative for a further 11 months, after which he died of a streptococcal empyema. He refused treatment for this condition, fearing that it was a further relapse of his tuberculosis.

(Case 3—previously reported as an early failure of treatment (Somner and Brace, 1962)—has continued treatment and is now classified as a treatment success.)

### Treatment Successes

Cases by which treatment was successful at the end of the course of prescribed chemotherapy numbered 22. These patients completed two years' chemotherapy and all 22 became culture-negative. The Table shows the rate of sputum conversion by smear and culture (the sputum is recorded as negative when the first of at least three consecutive negative results was obtained). Sputum-negativity was usually achieved remarkably early. At the end of three months' treatment 21 of the 22 patients were smear-negative and culture-negative, the other patient becoming negative by the fifth month. Occasionally sputum smears continued to be positive while cultures from the same specimens were negative.

*Bacteriological Findings in the 22 Patients Regarded as "Treatment Successes"*

Month	Smear			Culture		
	Total	Pos.	Neg.	Total	Pos.	Neg.
0	22	22	0	22	22	0
1	22	6	16	22	13	9
2	22	5	17	22	5	17
3	22	2	20	22	1*	21
4	22	1*	21	22	1*	21
5	22	1*	21	22	0	22
6	22	1*	21	22	0	22
7	22	0	22	22	0	22

\* See text.

Of these 22 patients nine completed their course of chemotherapy during 1962, eight during 1963, and the remaining five by the end of 1964. At the completion of treatment all 22 patients were culture-negative.

### Extent of Treatment Success at April 1965

One month after completion of treatment one patient died of cor pulmonale after an acute respiratory infection. Many years previously he had undergone a pneumonectomy as part of the treatment for tuberculosis, and this considerably reduced the respiratory reserve.

A second patient (marked with an asterisk in the Table), who under treatment took longer to become smear-negative and culture-negative than any of the other patients, discontinued chemotherapy in January 1963 and became smear-positive and culture-positive again in April 1963. After he left hospital he admitted having taken chemotherapy irregularly because he felt so ill taking the drugs and had considerable arthralgia due to pyrazinamide. Even so, further sensitivity tests showed that the tubercle bacilli were still sensitive to ethionamide, cycloserine, and pyrazinamide. He declined further treatment. However, he was readmitted to hospital in June 1964 with a severe respiratory infection, and, after recovery from it, agreed to a further course of ethionamide and cycloserine, without pyrazinamide. The persistently positive sputum again became negative on culture at the third month, but two weeks later he refused further treatment. At the time of writing he had again relapsed and was sputum-positive.

The other 20 patients have remained negative. All were seen at regular intervals of three to four months and the sputum was tested by culture. Eleven patients remained negative 25 to 36 months after treatment was stopped. Six remained negative 13 to 24 months after cessation of treatment, and three remained negative for periods up to 12 months after treatment was stopped.

In our previous report (Somner and Brace, 1962) we referred to two patients—Cases 6 and 7—who, because of mismanagement of their treatment, had become sputum-positive. These patients were readmitted to hospital, where treatment was successfully completed. They are now included in the group of 20 patients referred to in the preceding paragraph.

*Case 6.*—A man aged 60 was treated with all three drugs initially in 1961, but pyrazinamide was discarded after one month because of rising transaminase levels. Ethionamide and cycloserine were continued and viomycin (2 g. on two days a week for two months and 1 g. on three days a week for three months) was added. After four months' treatment in hospital he returned home, and reduced the dose of ethionamide and cycloserine by half because he believed they aggravated a "frozen shoulder." Sputum cultures became negative two months after the start of treatment, but were repeatedly positive at the seventh month as a result of taking the reduced dose of ethionamide and cycloserine for two months. He was readmitted to hospital (for 13 months) and received a two-year course of ethionamide and cycloserine (organisms remained sensitive) plus kanamycin (1 g. daily for four weeks and 2 g. twice weekly for five weeks) initially. Sputum conversion occurred one month after the resumption of treatment; since then all cultures have been negative.

*Case 7.*—A man aged 53 received all three drugs in hospital and became culture-negative at two months. He should have continued with the three drugs at home, but early in 1962 the hospital pharmacist reported that the patient was not collecting sufficient drugs from the pharmacy to meet his requirements. Careful discussion with the patient on several occasions failed to reveal that he was not taking the correct amount of drugs. After negative cultures for eight consecutive months two cultures in April and May 1962 were returned positive, showing full sensitivity to ethionamide, pyrazinamide, and cycloserine. Retention of sensitivity supported the view that relapse was due to failure to take the drugs. The patient was warned of the gravity of his actions and instructed to stop treatment; but he may have taken some form of chemotherapy on his own initiative, because on readmission to hospital for treatment five cultures showed a high degree of resistance to ethionamide (and to thiacetazone). Rearranged chemotherapy consisted of daily pyrazinamide and cycloserine for two years, with kanamycin (2 g. twice a week for one month and 1 g. daily for another month) initially. At one month cultures became negative again and have remained so since the completion of two years' chemotherapy; but once again the pharmacist reported that the patient was not collecting enough drugs to meet his requirements.

In summary, 20 patients (77%) were alive and sputum-negative one to three years after completion of a two-year course of chemotherapy. Five patients died from a variety of causes, and one was alive and the sputum positive because he cannot tolerate treatment.

### Bacterial Resistance

Sensitivity tests were carried out on three pretreatment sputum specimens in all patients by methods detailed in an earlier report by the British Tuberculosis Association (1963). The tubercle bacilli from all 26 patients were fully sensitive to ethionamide, pyrazinamide, and cycloserine.

During the course of treatment two patients developed resistance to ethionamide (and to thiacetazone, with which there is cross-resistance). One case (Case 7) is described above. The other started treatment with ethionamide and pyrazinamide, became culture-negative at the third month, but in the fourth month produced positive cultures resistant to ethionamide (and to thiacetazone). Thereafter followed a three-year course of pyrazinamide (to which he remained sensitive) and cycloserine, with tetracycline 4 g. daily (2 g. twice daily) given for the first six months. Cultures became negative in the first month and have remained so.

### Side-effects of Drugs

These effects usually constitute the main obstacle to successful treatment with the second-line drugs, both by their frequency and by their unpleasantness. In general, patients attached unpleasant symptoms to all three drugs, and in order of unpleasantness, ethionamide, cycloserine, and pyrazinamide. Space does not permit discussion of them here, but some

aspects are published in our earlier report (Somner and Brace, 1962) and a fuller report is to be published elsewhere.

The great majority of the side-effects are unpleasant, particularly if they extend over 12 to 24 months, but seldom call for abandonment of treatment. There are two exceptions—namely, the effect of pyrazinamide and, less often, ethionamide upon the liver, and the possibility that the use of cycloserine may result in suicidal tendencies and central and peripheral neuropathy.

In this series of patients liver damage was usually assessed by the elevation of the serum glutamic oxaloacetic acid transaminase (S.G.O.T.) and serum bilirubin, the former being of greater value. A sustained and significant elevation of S.G.O.T. occurred in nine patients, and pyrazinamide or ethionamide was stopped temporarily. But in all except two the drugs were cautiously reintroduced once the S.G.O.T. had returned to normal, and the course of treatment was usually completed. So long as the S.G.O.T. level does not rise suddenly, we think it is justifiable to maintain the patient on pyrazinamide and ethionamide in the presence of a slowly rising S.G.O.T., and we are prepared to carry on with the drugs when the S.G.O.T. is over 40 units, so long as it does not constantly exceed 80 units. In view of the serious loss to the patient by the withdrawal of either pyrazinamide or ethionamide, we feel this should be taken into account before either drug is finally abandoned. Jaundice was not encountered in this series as a result of continuing pyrazinamide or ethionamide after the serum transaminase was found to be raised.

### Discussion

We believe this report shows that good results can be obtained from the treatment of chronic pulmonary tuberculosis in which the tubercle bacilli are resistant to the standard drugs—streptomycin, P.A.S., and isoniazid. We also believe that this can be achieved not merely by the substitution of ethionamide, pyrazinamide, and cycloserine for the standard drugs; it requires also the development of an unusually strong doctor-patient relationship of confidence and discipline.

We have described the treatment of 26 patients suffering from chronic drug-resistant tuberculosis, living in towns along the north bank of the River Tyne (Wallsend, North Shields, Tynemouth) and in adjacent towns in South-east Northumberland. Twenty-four had cultures resistant to all three standard drugs, and in two the cultures were resistant to two of the three drugs. Because of the good results which followed treatment with second-line drugs, we now believe we have largely eliminated chronic resistant pulmonary tuberculosis in the area. Apart from the one remaining sputum-positive patient reported in this series, there were two others who remained unconvinced of the benefits of a negative sputum and would not co-operate with us, and are not included in this survey because treatment was never started.

In analysing the results it is necessary to look at the fate of all 26 patients who started treatment. Four died before treatment could be completed: two refused more than a few weeks' treatment, left hospital, and died, one committed suicide, and the fourth died of a non-tuberculous empyema. Two patients completed two years' treatment; of these one subsequently died of cor pulmonale, and the other relapsed, admitting that he had taken inadequate treatment during the two-year course. Thus 20 patients (77%) were successfully treated with two years of chemotherapy and remained sputum-negative for a further one to three years after treatment was completed.

Zierski (1964), in Poland, has had equally good results in a much larger series of patients, and he supports the view that a three-drug programme gives better results than a two-drug programme. Jančík *et al.* (1963), in Czechoslovakia, also reported good results with the second-line drugs and empha-

sized that better results were obtained with the three-drug régime than with two drugs. Further reports from these authors after their patients have completed their treatment will be awaited with great interest. Though many reports have been made regarding the efficacy of the second-line drugs, most authors refer only to the short-term results from treatment given over a few months, and very few report a series of patients given periods of two years' continuous treatment.

Side-effects of the three second-line drugs form the main obstacle to successful treatment. Space does not permit a full report of these side-effects, but there are several fundamental aspects of management which must be emphasized. It is common to encounter a wide variety of symptoms associated with any new form of treatment. Apart from tests to detect the hepatotoxic effect of pyrazinamide and ethionamide, no effort was made to elicit complaints of the drugs, nor were patients encouraged to attribute any symptom to a particular drug when symptoms arose. When symptoms were mentioned which might be attributable to the new drugs no attempt was made to withdraw the drugs to see if the symptoms disappeared. Most important of all, even if one or more symptoms were found to be due to a particular drug, this information was not particularly helpful because the last thing we wished to do was to withdraw that drug from the patient's treatment programme.

For all of these patients resort to second-line drugs held out their only chance of cure. Over many years they failed to respond to treatment with standard drugs, usually because of the development of drug resistance. This was usually unrecognized because the tests were carried out by methods not designed to detect low degrees of bacterial resistance. When resistance to one or more of the standard drugs has developed or is strongly suspected, it is usually unwise, and often disastrous, to combine second-line drugs with any of the standard drugs in the hope that the latter might prevent the emergence of resistance to the second-line drugs, unless there is absolute confidence in the reliability of the sensitivity tests. In general it is felt that the second-line drug programme is of such vital importance to the patient that it should be so constructed that the emergence of resistance is prevented by the simultaneous use of ethionamide, pyrazinamide, and cycloserine, without reliance upon one or more of the standard drugs, at least for the first year of treatment.

Not all our patients received all three second-line drugs together, but we would now recommend this in future, at least until the sputum cultures are consistently negative and preferably for at least the first year of treatment. This view is based largely upon the findings of the two trials of the British Tuberculosis Association (1961, 1963), in which it was shown that a lower incidence of drug resistance emerged when all three second-line drugs were given together instead of two drugs. Finally, we feel it is absolutely essential that the drugs be given continuously for two years, because there is likely to be a high risk of relapse of the disease with chemotherapy of short duration. Horne (1964) reported that relapse occurred in 70% of patients receiving standard chemotherapy for six months or less, whereas it occurred in only 0.2% of those receiving it for 18 months or more. Relapse is often associated with the discovery of resistance, and our patients, already resistant to the standard drugs, cannot afford to become resistant to any of the second-line drugs. Should resistance to the second-line drugs develop because of inadequate chemotherapy, it may not be easy to detect it because

of the much greater difficulty in performing and interpreting the sensitivity tests—thus it becomes a more formidable task to replan a further course of treatment with these drugs. To avoid such a calamity we think it wise to insist that these patients should receive a two-year course of chemotherapy. If only two drugs are administered during the second year of treatment ethionamide should always be given, combined with pyrazinamide whenever possible. Cycloserine should be the companion drug to ethionamide only when pyrazinamide is unacceptable because of hepatotoxicity or arthralgia.

Finally, it should be emphasized that to obtain good results much time must be spent in convincing the patient of the need to have continuous and prolonged treatment. Because of the frequency of side-effects, these good results often seemed more encouraging to us than to the patients during the course of the treatment, and they sometimes regarded the cure as worse than the disease. The doctor-patient relationship is often put to considerable strain, and tactful but firm handling of the situation is required lest the patient refuse further treatment.

### Summary

Twenty-six patients with active pulmonary tuberculosis of many years' duration were found to harbour tubercle bacilli resistant to the standard drugs—streptomycin, para-aminosalicylic acid, and isoniazid. These patients are usually regarded as having poor prospects for cure of their disease.

By the use of ethionamide, pyrazinamide, and cycloserine 22 patients were rendered and maintained culture-negative throughout a two-year course of treatment. Treatment of this duration was not achieved in the remaining four patients because of death.

Of the 22 patients who completed two years' treatment one subsequently died of cor pulmonale and one had a relapse of tuberculosis due to failure to take all the drugs prescribed. The other 20 patients remained culture-negative—11 for 25–36 months after stopping treatment, six for 13–24 months, and three for up to 12 months after the two-year course.

In spite of the difficulty in getting patients to take two years' treatment with "second-line" drugs, we believe that the results are sufficiently good to encourage chest physicians to make efforts to render sputum-negative all patients with resistant tuberculosis.

We are grateful to the Research Committee of the British Tuberculosis Association for permission to report upon the findings of those patients who formed part of the controlled trial of ethionamide, pyrazinamide, and cycloserine in resistant tuberculosis. We are indebted to our colleagues, Dr. C. D. Jobling (North Shields), Drs. Sheila Stewart and A. T. Wallace (Edinburgh), and Dr. R. W. Riddell (London), and their laboratory staffs for all the bacteriological investigations and sensitivity tests, and we are also indebted to the nursing staff of the Hadrian Hospital, Wallsend upon Tyne, for their care of the patients. We also wish to thank Mrs. Constance Davison for considerable secretarial assistance in this work.

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