ADVANCED PULMONARY TUBERCULOSIS WITH PERSISTENT CAVITATION

PRELIMINARY REPORT ON PROLONGED CHEMOTHERAPY

BY

A. C. DOUGLAS, M.B., M.R.C.P.Ed.

Registrar

AND

N. W. HORNE, M.B., F.R.C.P.Ed.

Consultant Physician and Lecturer in Tuberculosis

(From the Tuberculosis Unit, City Hospital, Edinburgh,
and the Department of Tuberculosis and Diseases of
the Respiratory System, University of Edinburgh)

The value of chemotherapy as a definitive measure in cases of recent minimal and moderately extensive pulmonary tuberculosis and as an integral part of the pre- and post-operative care of cases requiring surgical treatment is now universally recognized. There remains, however, a type of case with extensive disease which, for various reasons, is unsuitable for surgical treatment. Chemotherapy in such cases was initially employed on a tentative basis as no definitive treatment for the control of the disease was thought possible, and early opinion was averse to its use in chronic pulmonary tuberculosis because of the likelihood of the development of bacterial resistance. With the evolution of chemotherapy that has taken place in recent years, however, many of the objections to the use of prolonged chemotherapy in such cases are no longer valid.

Clarke (1952) has defined the goal of tuberculosis treatment as the patient "whose disease is inactive, who is financially independent, and who is no risk to his family or colleagues," and described an attempt to achieve this with chemotherapy on an ambulant basis in chronic sputum-positive cases. Dooneief and Hite (1954) have described a series of 52 cases of tuberculosis

treated with indefinitely prolonged chemotherapy, 6 of which were far-advanced cases of active pulmonary tuberculosis; and several reports of so-called "open-cavity healing" in pulmonary tuberculosis have been recorded in the Spanish and French literature (Purriel *et al.*, 1953; Bernard and Carraud, 1953; Galy *et al.*, 1953; Pruvost *et al.*, 1953; Simonin *et al.*, 1953; Bernou, 1953).

This paper records our own experience with indefinitely prolonged chemotherapy in six cases of extensive pulmonary tuberculosis with gross cavitation. The cases recorded are the most advanced examples of this type treated by long-term chemotherapy alone in this unit in the last three years, and form part of a more extensive study of the value of this type of therapy in advanced

FIG. 1.—Case 1. Pre-treatment radiograph taken on December 22, 1953.

FIG. 2.—Case 1. Radiograph taken on July 4, 1955.

TABLE I.—Clinical Details of Cases Described

Case No.	Sex and Age	Chemotherapy			Time taken to become Sputum-negative (Culture) (Months)	Time Elapsed since last Positive Sputum Culture (Months)	Weight Gain since Starting Treatment lb. kg.
		Drugs	Duration (Months)	Total Duration (Months)			
1	F 29	SH SP 20 PH	2 8 9†	19†	2	17	25 11.3
2	F 30	SH S ₂ H 12 PH	6 2 29†	37†	2	35*	15 6.8
3	F 37	SH 12 PH	11 7†	18†	2	16	39 17.7
4	F 48	SH 12 PH	16 1†	17†	2	15	69 31.3
5	M 57	SP SH 12 PH	2½ 12 11†	25½†	4½	21	27 12.2
6	M 68	T ₁ H SH	3 17†	20†	3	17	24 10.9

SH=Streptomycin 1 g. daily plus isoniazid 100 mg. twice a day.

SP=Streptomycin 1 g. daily plus P.A.S. (sodium salt) 20 g. daily.

S₂H=Streptomycin 1 g. thrice weekly plus isoniazid 100 mg. twice a day.

T₁H=Oxytetracycline 1 g. daily plus isoniazid 100 mg. twice a day.

12PH=P.A.S. (sodium salt) 12 g. daily plus isoniazid 100 mg. twice a day.

20 PH=P.A.S. (sodium salt) 20 g. daily plus isoniazid 100 mg. twice a day.

* An isolated positive culture was obtained at 14 months.

† Treatment being continued.

pulmonary disease. Surgical treatment was regarded as impracticable in all cases because of the extent of the disease, respiratory insufficiency, or age. The types of chemotherapeutic regimes used, the time taken to achieve sputum conversion, and the duration of sputum-negativity are shown in Table I. Radiographs of the chest at the onset of treatment and at the most recent review are shown in respect of Cases 1, 3, and 4 (Figs. 1-6).

Material and Methods

Six patients suffering from far-advanced pulmonary tuberculosis with gross cavitation—all acutely ill on admission to hospital—were treated initially with chemotherapy in association with rest in bed followed by continued chemotherapy on an ambulant basis. The duration of complete rest in bed was about six months in every case, after which the patient was allowed up progressively.

All showed tubercle bacilli in the sputum in direct film and on culture at the beginning of treatment. Pre-treatment cultures from all cases, with one exception (Case 6), were fully sensitive to streptomycin, *para*-aminosalicylic acid (P.A.S.), and isoniazid according to the standards used in the Medical Research Council trials (M.R.C. 1953b). Sputum was examined at monthly intervals thereafter and radiographs of the chest were taken every second month while the patient was in hospital. Out-patient observation has been continued at three-monthly intervals approximately.

All cases were given long-term chemotherapy, the details of which are shown in Table I. It is our practice not to alter therapeutic regimes unless there are specific reasons for doing so, such as drug resistance. The types of chemotherapy used in six cases and the reasons for changing chemotherapy are detailed below.

FIG. 3.—Case 3. Pre-treatment radiograph taken on January 8, 1954.

FIG. 4.—Case 3. Radiograph taken on June 15, 1955.

FIG. 5.—Case 4. Pre-treatment radiograph taken on March 2, 1954.

FIG. 6.—Case 4. Radiograph taken on August 22, 1955.

Four of the six cases received chemotherapy initially in the form of streptomycin sulphate, 1 g. daily intramuscularly, along with either isoniazid, 100 mg. twice daily, or P.A.S. (sodium salt), 20 g. daily, in four divided doses for periods varying from 6 to 14½ months. Isoniazid was substituted for P.A.S. after 2½ months in one patient (Case 5) because of intolerable nausea, and P.A.S. was substituted for isoniazid after two months in another (Case 1) because of slight mental disturbance which was thought to be due to an isoniazid effect in a predisposed toxic subject. One patient (Case 2), following a course of six months of daily streptomycin plus isoniazid, had a short period of streptomycin, 1 g. thrice weekly, along with daily isoniazid at a time when the possibility of the emergence of drug-resistant strains with this regime was not fully appreciated. One patient (Case 6) had a six-weeks course of streptomycin plus P.A.S. followed by P.A.S. alone for two months before admission to hospital. In view of the previous chemotherapy, doubts were expressed regarding sensitivity to P.A.S. and streptomycin, and he was given isoniazid, 100 mg. twice daily, along with oxytetracycline, 1 g. daily, for three months. He became sputum-negative on this regime, and when the organisms were found to be sensitive to streptomycin and isoniazid and doubtfully resistant to P.A.S., daily streptomycin plus isoniazid was given, and this form of therapy has been continued. With this exception, therefore, P.A.S. or isoniazid was given with daily streptomycin initially in all cases.

Maintenance chemotherapy in five of the six cases is being given in the form of P.A.S. (sodium salt), 12 g. daily (4 cases) or 20 g. daily (1 case), along with isoniazid, 200 mg. daily, conveniently prescribed in cachets containing both drugs.

Results

Marked clinical and radiological improvement was noted in every case, though gross radiological changes including cavitation persisted. All showed satisfactory increases in weight (see Table I). The sputum became negative on culture in all cases within five months, the cases receiving streptomycin plus isoniazid becoming sputum-negative at two months. All cases have been maintained sputum-negative for periods varying from 15 to 35 months, with the exception of an isolated positive culture obtained from Case 2 after 14 months of chemotherapy. This latter finding followed an upper respiratory infection, and the organisms obtained were still sensitive to streptomycin, P.A.S., and isoniazid. Six subsequent cultures of sputum from this patient have been negative.

Only one patient (Case 3) has required specific treatment for non-tuberculous respiratory infection since discharge from hospital. No evidence of P.A.S.-induced thyroid dysfunction has been noted in any of the cases on maintenance treatment with P.A.S. plus isoniazid, nor has there been any toxic effect from long-term treatment with streptomycin.

The patients have all been living at home for at least six months, some for much longer. Three (Cases 2, 3, and 4) are housewives and manage their homes unaided. The remaining female patient (Case 1) is now engaged in light employment. One male patient (Case 6) is retired and able to enjoy his retirement. The other (Case 5) is incapacitated for any work by reason of chronic bronchitis and emphysema. The results of tests for maximum breathing capacity carried out in July, 1955, in five of the cases are shown in Table II. Functional respiratory capacity in all cases, with the exception of that already mentioned, is adequate for their mode of life.

TABLE II.—Results of Respiratory Function Tests

Case No.	Maximum Breathing Capacity	
	Actual L./Min.	Predicted L. Min.
1	33	92
2	41	90
3	42	85
4	34	78
6	35	81

Discussion

Extensive trials of chemotherapy in pulmonary tuberculosis (M.R.C., 1948, 1952, 1953a, 1953c, 1954, 1955) have formulated the basis for a rational approach to its use in

the acute forms of the disease and in association with surgical treatment. Chemotherapy has not yet, however, been generally accorded a definitive role in the treatment of the chronic case and especially in the type of case with extensive disease where other active measures may not be possible. The primary aim of chemotherapy in pulmonary tuberculosis is to render the sputum bacteriologically negative for tubercle bacilli, and if it can be shown to succeed in this aim in cases of extensive chronic pulmonary tuberculosis where no other measures are feasible then clearly all forms of tuberculosis of the lungs can be brought within the scope of treatment and every patient can have hope of bacteriological "cure." If this were so, the benefit to the individual would be immense, and a major public health measure would be available for the further control of the disease; for the main problem with regard to the control of tuberculosis in the community is still the chronic sputum-positive case. We believe that chemotherapy, effectively used, can result in sputum conversion even in the most advanced cases of pulmonary tuberculosis, provided such factors as overwhelming toxæmia or cor pulmonale do not decide the issue before anti-tuberculosis drugs have had time to come into effect, and provided the patient's organisms are not primarily drug-resistant to more than one of the three main chemotherapeutic drugs—streptomycin, P.A.S., and isoniazid.

The necessity for using a combination of drugs in the treatment of tuberculosis is now widely, if not universally, accepted. It has been shown (M.R.C., 1953a) that streptomycin along with P.A.S. or isoniazid is the most effective means of bringing the disease under control and that the daily administration of streptomycin (1 g.) along with daily P.A.S. (20 g. of the sodium salt) or isoniazid (200 mg.) offers the best use of these drugs. Five of the cases in the present series had a period of such treatment until sputum conversion was achieved and for 4 to 14 months thereafter. It is obviously of paramount importance in the type of case described in this report to select a combination of drugs which continues to be effective for as long as possible; and with regard to drug combinations of streptomycin with P.A.S. or isoniazid it has become increasingly recognized that both drugs must be administered daily if the development of bacterial resistance is best to be avoided. We would not agree with Rothstein and Johnson (1954) that there is a place for the regimen of streptomycin once a week in the prolonged treatment of tuberculosis.

Deuschle *et al.* (1954) maintain that the development of isoniazid resistance may be of no untoward significance to the patient, and advocate the use of isoniazid alone in certain circumstances. This view is also expressed by Oestreicher *et al.* (1955). Even if it is true that the pathogenic potentialities of most isoniazid-resistant mutants are strictly limited in an important manner for most tuberculous patients, it must be borne in mind that such organisms are capable of producing disease in other individuals (Katz *et al.*, 1954; Murdoch and Grant, 1955). We agree with Scadding (1955) when he states: "Until unequivocal results are available from such investigations the wise physician will continue to treat his patients on the supposition that isoniazid-resistance is unfavourable, and to plan antibacterial treatment in such a way as to minimize the risk of the emergence of resistant bacilli." We believe that one of the major misfortunes that can befall the tuberculous patient under treatment is the development of bacterial resistance, and especially is this so where other active measures are, for any reason, precluded.

Two of the cases in this report had, for short periods, types of chemotherapy—streptomycin, 1 g. three times weekly, along with isoniazid, 100 mg. twice a day (Case 2) and oxytetracycline, 1 g. daily, along with isoniazid 100 mg. twice a day (Case 6)—which fall short of present-day standards but which fortunately did not preclude long-term treatment although maintenance therapy in one (Case 6) has necessitated daily injections.

Maintenance chemotherapy in five of the cases described was a combination of P.A.S. and isoniazid. This combination

is particularly suitable as maintenance treatment in a scheme of indefinitely prolonged chemotherapy, and can be conveniently prescribed in the form of cachets containing both drugs. Primary or induced resistance to any of the three standard antituberculosis drugs, and especially to P.A.S. or isoniazid, naturally introduces problems in maintenance therapy. One patient (Case 6) whose maintenance treatment required a daily injection exemplifies this. Joiner *et al.* (1954) found P.A.S., 10 g. daily, along with isoniazid, 250 mg. daily, disappointing in the treatment *ab initio* of a small series of cases with chronic fibrocaceous pulmonary tuberculosis because of the emergence of resistant strains of the organism. Such findings, however, if substantiated, do not necessarily invalidate the use of P.A.S. plus isoniazid in maintenance treatment of such cases after the preliminary use of streptomycin along with P.A.S. or isoniazid for a sufficient period to reduce the bacterial population to a low level. In the cases described in this report sputum negativity is being successfully maintained in spite of the presence of gross radiological change with open cavitation by the daily administration of P.A.S. in 12-g. or 20-g. dosage along with 200 mg. of isoniazid.

It is still too early to assess the long-term results in the cases described. The likelihood of maintaining sputum negativity, however, seems promising.

Other major potential hazards in this type of case include haemoptysis and the development of secondary pulmonary infection. Haemoptysis, initially present in all cases, has not occurred in any after the first month of treatment. Auerbach (1955), in a study of pulmonary lesions after chemotherapy, mentions greatly decreased tendency to pulmonary haemorrhage as one of the most dramatic effects resulting from prolonged chemotherapy and suggests reasons for this phenomenon.

Grossly destroyed pulmonary tissue provides a *locus minoris resistentiae* for the establishment of secondary infection which must be regarded as a particular hazard for the type of case under discussion. With this in mind, patients were advised on leaving hospital to seek medical advice early should upper respiratory infection occur. It is interesting to note, however, that only one patient has so far required specific treatment for secondary respiratory infection, and that on one occasion only. The possible development of amyloid disease and late cor pulmonale are problems for future assessment.

One further important problem remains. How long must chemotherapy be maintained; and, indeed, is it ever possible to sterilize tuberculous lesions by drug treatment? Myers (1955) expresses doubt that this can be achieved with the drugs at present available, and it may be that certain cases will require chemotherapy which is literally indefinitely prolonged. Numerous reports have been published on this aspect of the problem, and further study is required before this crucial aspect of the problem of long-term chemotherapy can be elucidated. The fact that a positive culture was isolated in one of the above cases after fourteen months' treatment suggests that in this type of case treatment for so short a time is inadequate.

Summary

Six cases of advanced pulmonary tuberculosis are described. All had gross cavitation and were treated by long-term chemotherapy alone because of the extent of the disease, respiratory insufficiency, or advanced years. The patients have been rendered sputum-negative for periods of 16 to 35 months and enabled to take their place in the community once more.

The chemotherapy used is described and the problems of long-term chemotherapy in such cases are discussed.

We are indebted to Dr. J. Williamson for permission to record Case 4, to Mrs. M. Beaton for the respiratory function tests, and to Dr. A. Wallace for the bacteriological work.

REFERENCES

- Auerbach, O. (1955). *Amer. Rev. Tuberc.*, **71**, 165.
 Bernard, E., and Carraud, J. (1953). *Rev. Tuberc. (Paris)*, **17**, 1021.
 Bernou, A. (1953). *Ibid.*, **17**, 1055.
 Clarke, O. (1952). *British Medical Journal*, **2**, 644.
 Deuschle, K., Ormond, L., Elmendorf, D., Muschenheim, C., and McDermott, W. (1954). *Amer. Rev. Tuberc.*, **70**, 228.
 Dooneief, A. S., and Hite, K. E. (1954). *Ibid.*, **70**, 219.
 Galy, P., Bérard, M., Arzibehaute, R., Touraine, R. G., and De Saint-Florent (1953). *Rev. Tuberc. (Paris)*, **17**, 1037.
 Joiner, C. L., Maclean, K. S., Carroll, J. D., Marsh, K., Collard, P., and Knox, R. (1954). *Lancet*, **2**, 663.
 Katz, S., Storey, P. B., and McCormick, G. F. (1954). *Amer. Rev. Tuberc.*, **70**, 881.
 Medical Research Council (1948). *British Medical Journal*, **2**, 769.
 — (1952). *Ibid.*, **2**, 735.
 — (1953a). *Ibid.*, **1**, 521.
 — (1953b). *Lancet*, **2**, 213.
 — (1953c). *British Medical Journal*, **2**, 1005.
 — (1954). *Thorax*, **9**, 254.
 — (1955). *British Medical Journal*, **1**, 435.
 Murdoch, J. McC., and Grant, I. W. B. (1955). *Lancet*, **2**, 587.
 Myers, J. A. (1955). *Amer. Rev. Tuberc.*, **71**, 885.
 Oestreicher, R., Dressler, S. H., Russell, W. F., Grow, J. B., and Middlebrook, G. (1955). *Ibid.*, **71**, 390.
 Pruvost, P., Delarue, J., Meyer, A., and Depierre (1953). *Rev. Tuberc. (Paris)*, **17**, 1046.
 Purriel, P., Casamayou, E., Muras, O., Piovano, C., and Ruggiero, C. (1953). *Thorax*, **2**, 115.
 Rothstein, E., and Johnston, M. P. (1954). *Amer. Rev. Tuberc.*, **69**, 980.
 Scadding, J. G. (1955). *Lancet*, **2**, 99.
 Simonin, Girard, Lochar, and Sadoul (1953). *Rev. Tuberc. (Paris)*, **17**, 1051.

CLINICAL APPLICATION OF AN ASSAY OF THYROID-STIMULATING HORMONE IN RELATION TO EXOPHTHALMOS

BY

I. C. GILLILAND, M.D., M.R.C.P.

Lecturer and Physician, Department of Medicine

AND

J. I. STRUDWICK, B.Sc.

Research Assistant, Department of Chemical Pathology

Postgraduate Medical School of London

The aetiology of the exophthalmos that frequently occurs in relation to thyroid disorders has not yet been elucidated and treatment is consequently unsatisfactory and largely empirical. The exophthalmos is commonly held to be the result of an excessive secretion of thyroid-stimulating hormone (T.S.H.) by the pituitary gland. This was first suggested by the experimental work of Marine and Rosen (1934) on rabbits, and of Smelser (1937) on guinea-pigs. They showed that it was possible to produce both thyroid overactivity and exophthalmos in animals by injection of a pituitary extract rich in T.S.H. The similarity of these experimental findings to the clinical conditions encountered in man suggested that both the thyroid overactivity and the exophthalmos were caused by the one factor, the T.S.H. of the pituitary. Conflicting results, however, have been obtained by numerous observers using different assay procedures to estimate the T.S.H. in the blood and urine of patients suffering from thyroid and ophthalmopathic disorders. Many of these procedures were difficult or were complicated by the fact that excess thyroxine in the serum might affect the test animals. For this reason a new method for clinical assay has been developed which would not be affected by the presence of excess thyroid hormone, and this report is based upon the results obtained.

Method

The method has been described in detail elsewhere (Gilliland and Strudwick, 1953). It is based on the discharge of