general practice. Of 50 patients with leg ulcers, 84% have been healed within a few months.

We thank Dr. Inge Birger for stimulating our interest in this method; Sister Deane and Sister Norman for their enthusiastic treatment of these patients; and Mr. A. Booker for the photographs.

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THE RESULTS OF CHEMOTHERAPY IN THE TREATMENT OF TUBERCULOUS PLEURAL EFFUSIONS

BY

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The ultimate results of the treatment of tuberculous pleural effusions by chemotherapy are uncertain and have been little investigated (Crofton, 1956). Anti-tuberculosis drugs are used in the hope of abating early symptoms, of hastening the absorption of the effusion, and of preventing later and more serious tuberculous sequelae. Their variable effect upon these early manifestations has often been described (Gerocarni, 1949; Chu, 1949; Moyer, 1949; Danopoulos and Melissinos, 1951; Bauce and Vannini, 1951; Stadler, 1951; Emerson, 1955). In contrast, only two studies have been published which have attempted to assess their long-term prophylactic value (Emerson, 1955; Falk and Stead, 1956), although streptomycin and para-aminosalicylic acid have been used in treatment since 1947.

From 20 to 30% of patients who have suffered from primary tuberculous pleural effusions eventually develop fresh pulmonary and extrapulmonary tuberculous lesions (Robson, 1952; Emerson, 1954). Bed-rest at the time of the effusion has generally been ineffective in preventing this (Emerson, 1954), although success has often been claimed (Roper and Waring, 1955). The chief aim of the present study has been to assess the efficacy of chemotherapy in preventing this high incidence of post-primary tuberculosis. The investigation is retrospective: a control trial at the present time would be quite unethical.

Material

Sources.—Full records and radiographs were obtained of all patients with tuberculous pleural effusions who had been treated in the country branch of the London Chest Hospital from 1949 to 1953. They came largely from east and north-eastern London, and had been diagnosed at clinics or hospitals in that area. Some had been treated for short periods in these latter before being transferred.

Diagnosis.—Cases were studied only if the lung fields were clear on radiographs taken during the whole time that the effusion was present. Where a parenchymatous lesion was seen or a non-tuberculous cause was suspected, these cases were discarded. In all, an effusion of varying size was present, the fluid was invariably and predominantly lymphocytic, and the Mantoux test was positive to 1 or 10 international units of old tuberculin. Of the 56 cases finally studied, there was a family or contact history of tuberculosis in 16. Tubercle bacilli were isolated from the pleural fluid, sputum,

or gastric washings in only 15 patients; though not a high proportion, this finding is comparable to those of many other series where laboratory search for tubercle bacilli has not been exhaustive (Thompson, 1946).

Follow-up.—Because the great majority of tuberculous lesions develop during the first two or three years after the effusion (Thompson 1946; Emerson, 1954; Roper and Waring, 1955; Wynn-Williams and Shaw, 1955), only patients who had been observed for at least 2½ years were included. Many patients were still attending at the out-patient departments of the London Chest Hospital or at their original hospital or chest clinic. Those who had not been so observed were recalled to their local chest clinic, were examined, and a chest x-ray film was taken. In addition, most of them answered a letter inquiring for specific details of health since their original treatment. All the original suitable patients were thus traced, except four who eluded all inquiry; none of these last had received chemotherapy. The proportion followed for various periods is given in Table I; the majority have been observed for over five years since their effusion.

TABLE I.—Follow-up

Duration	No. of Cases		
	Chemotherapy	Relatively Untreated	Total
2½–3½ years ..	6	3	9
3½–4½ " ..	3	4	7
4½–7 " ..	15	25	40

TABLE II.—Comparison of Groups

	No. of Cases	
	Chemotherapy	Relatively Untreated
Male	12	9
Female	12	23
Age 16–20 years	7	16
" 21–30 "	15	14
" 31 and over	2	2
Family or close-contact history ..	8	8
Size of effusion*:		
Up to dome of diaphragm ..	5	5
" hilum	7	13
Above "	12	14

* There were no bilateral effusions.

Division of Material.—After analysis of the records the cases were divided into two groups according to whether they had received efficient chemotherapy or not. In the first there were 24 patients who had received various forms of effective chemotherapy in addition to bed-rest, while, in the second, 32 had been treated by bed-rest alone. Features of the two groups are compared in Table II. They are not completely matched, but most of the differences are probably not of major importance. So far as the retrospective nature of the study permits, therefore, a comparison may be made between the effects of bed-rest alone and of bed-rest with chemotherapy in these patients. There was concurrence in time of both groups, and the duration of follow-up was proportionately equal in both (see Table I); but there was a tendency for more of the effusions with severe manifestations to be treated with chemotherapy.

Treatment

Both groups were treated initially with strict bed-rest, which lasted for an average of three months. In the chemotherapy group drugs were given for periods ranging from

TABLE III.—Chemotherapy

Type	No. of Cases
Streptomycin 1 g. and para-aminosalicylic acid 15–20 g. daily ..	17
" " three times weekly and para-aminosalicylic acid 15 g. daily	2
Streptomycin 1 g. and isoniazid 300 mg. daily	3
Para-aminosalicylic acid 15 g. and isoniazid 300 mg. daily ..	2

2½ to 6 months. The types of chemotherapy are shown in Table III: most were treated with daily streptomycin and para-aminosalicylic acid.

Certain patients who had been treated with what is now recognized as inadequate chemotherapy were included in the "relatively untreated" group. Seven had received para-aminosalicylic acid alone; two had subsequent tuberculous lesions. One had been given streptomycin alone and one isoniazid alone.

Most effusions had been aspirated early, and in some cases streptomycin or para-aminosalicylic acid had been inserted intrapleurally. Unfortunately, recorded details of these procedures were not adequate enough to allow analysis.

Results

Early.—The subsidence of pyrexia, of the erythrocyte sedimentation rate, and of the effusion in the two groups are compared in the Chart. There was surprisingly little difference in the rates of subsidence of all three features. More

Showing subsidence of early manifestations with and without chemotherapy. —, Chemotherapy group; ----, Relatively untreated group.

of the relatively untreated patients had normal temperatures and sedimentation rates by the time that treatment began. Nevertheless, a small proportion of these cases continued with fever, a raised sedimentation rate, and persistent fluid for some time longer than any of the chemotherapy group, though in general it was those with more severe symptoms who were treated with anti-tuberculosis drugs.

Late.—Subsequent forms of tuberculosis developed in 9 cases (28%) of those treated with bed-rest alone, in contrast to 2 (8%) of those treated by chemotherapy in addition. The relevant data are shown in Table IV. The cases were

TABLE IV.—Tuberculosis Morbidity

Years After Effusion	Chemotherapy Group		Relatively Untreated Group	
	No. of Cases	Type of Tuberculosis	No. of Cases	Type of Tuberculosis
1	1	Pleural effusion*	5	{ 2 pleural effusions* 3 infiltrations†
2	0		0	
3	0		3	
4	0	Infiltration†	1	{ 2 infiltrations† 1 Tb. ovary Infiltration†
5	1		0	

* An effusion reappeared on the same or opposite side several months after the primary effusion had completely absorbed.
† Pulmonary.

distributed proportionately through the age and sex groups and through the three divisions in size of the effusions. Only one had a family or contact history of tuberculosis. It is of interest that the pulmonary lesions were all fresh minimal infiltrations, as was the experience of Roper and Waring (1955).

In 28 patients there was permanent pleural thickening—in 16 from the relatively untreated patients and 12 from the chemotherapy group. In most there was obliteration of the costophrenic angle, and a line of thickened pleura was visible, continuing thence up the chest wall, the diaphragm often being distorted. In a few there was much more marked thickening. None complained of dyspnoea, despite specific questioning, so that this pleural thickening was not of clinical importance so far.

Discussion

The 56 patients described here do not form a large series. Nevertheless, they provide a homogeneous group because they were drawn from the same population, were treated under identical conditions apart from the choice of therapy, and largely concurred both in time and in the duration and completeness of follow-up. Conclusions may therefore be of more validity than this small number might at first suggest.

In this series the effect of chemotherapy during the early stages of primary tuberculous pleural effusions has been disappointing. Similar experiences have been recorded before (Moyer, 1949; Bariéty and Lesobre, 1951). Some have found that the length of fever was often, but by no means invariably, reduced, although neither the level of the erythrocyte sedimentation rate nor the duration of the effusion was affected (Chu, 1949; Gerocarni, 1949; Bauce and Vannini, 1951; Emerson, 1955). Certainly in the present series pyrexia had persisted in some patients despite bed-rest, but subsided quickly when anti-tuberculosis drugs were given. Further, there were a few patients treated by bed-rest alone whose symptoms and effusions continued for longer than any of the chemotherapy group, although those with severe manifestations were most often included in the latter; therefore these drugs probably helped to abate symptoms in such patients. Nevertheless, in most patients the symptoms subsided as quickly with bed-rest alone as when chemotherapy was added. No definite conclusions are possible because of the original bias in selection of the cases (see above).

In its remoter effects chemotherapy was more successful. Only two (8%) of the treated group developed fresh tuberculous disease, as compared with nine (28%) of the bed-rest cases. This difference is unlikely to be due to chance, the standard error being 9.0. Further, there could have been no selection of these cases originally, for there is no way of foretelling which patients with pleural effusions will develop further tuberculosis. Any bias might be against the chemotherapy group, because this was loaded with the more severe effusions. Most of the whole series had been followed for five years or more, a period during which the vast majority of subsequent tuberculous lesions are known to develop (Thompson, 1946; Robson, 1952; Mitchell, 1953; Emerson, 1954; Roper and Waring, 1955). Consequently these results may well indicate the incidence of fresh tuberculosis that may be expected in primary tuberculous pleural effusions which have been treated by short-term chemotherapy—that is, for under six months: the two cases reported here had had daily streptomycin and para-aminosalicylic acid for 2½ and 4½ months. Similar results were found in the American Veterans Administration co-operative study (Robins and Livings, 1955; Falk and Stead, 1956), though in this study a large proportion of patients who had been treated were lost in the follow-up, among other faults. Emerson (1955) found no cases of subsequent tuberculosis in patients without initial parenchymatous lesions, but his follow-up was for less than three years in almost all. Bariéty and Lesobre (1951) have reported several cases where subsequent tuberculosis developed despite brief chemotherapy. Conversely, tuberculous pleural effusions have developed while other tuberculous lesions were being treated by chemotherapy (Trocmé, 1950; Bariéty and Lesobre, 1951; Emerson, 1955).

Short-term chemotherapy is therefore partially but not completely effective. It may be deduced that if anti-tuberculosis drugs are given for a longer period, perhaps one year,

it is possible that all subsequent development of tuberculosis will be prevented. The superiority of this long-term chemotherapy has become very widely recognized in other forms of tuberculosis (Hoyle *et al.*, 1955; Borthwick, 1956; Ross and Kay, 1956).

It is disappointing that residual pleural thickening was as common among those treated with chemotherapy as among those treated without. Possibly early aspiration (Mackay-Dick and Rothnie, 1954) or the administration of corticosteroids (Sors and Trocmé, 1954; Bruel *et al.*, 1955) might lessen this complication, which nevertheless did not cause any disability to patients so affected in this series.

Conclusions and Summary

Anti-tuberculosis chemotherapy should be given to all patients with primary tuberculous pleural effusions. Its chief effect is to prevent the development of subsequent forms of tuberculosis: for complete suppression it is probable that treatment should last for at least one year. It is less effective in the early manifestations of the effusion, and does not reduce the incidence of residual pleural thickening.

The frequency of post-primary tuberculosis following the use of chemotherapy in primary tuberculous effusions has been assessed in only two published series.

In the present investigation 56 patients with such effusions and without obvious parenchymatous foci at the time have been followed, most of them for over five years. Thirty-two were treated with bed-rest alone and in nine (28%) subsequent forms of tuberculosis developed. Twenty-four had received chemotherapy for periods of from two and a half to six months in addition; in most, daily streptomycin and para-aminosalicylic acid were given. Only two patients (8%) developed forms of tuberculosis later. Residual pleural thickening was equally common in both groups.

Chemotherapy had little effect upon the early manifestations, but there was bias in the original selection of cases.

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OESOPHAGEAL OBSTRUCTION AND COMA DUE TO NODULAR GOITRE

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Although pressure effects on adjacent organs are common when the thyroid becomes enlarged, it is unusual to find severe dysphagia or disturbances of consciousness associated with a benign nodular goitre. The case to be reported here is that of a woman with goitre who presented as a case of coma with complete oesophageal obstruction.

Case Report

An unmarried woman aged 45 was admitted to the Royal Free Hospital on December 3, 1954, having been unconscious for several hours. The patient, whose history was obtained from her sister, had been mentally retarded from infancy, and at the age of 22 years started to have epileptic attacks. She had major fits at about three-monthly intervals, always at night, and also two or three attacks of petit mal each month.

In 1951 she had a respiratory infection with cough, sputum, and fever lasting a fortnight. During this illness, after a bout of coughing, she had her first breathless attack which lasted an hour and during which she went blue in the face. Subsequently she became breathless on climbing stairs. About once in two months she had an attack of breathlessness associated with cyanosis and stridor, usually brought on by excitement or coughing.

Three weeks before admission she had her first major attack during the day and fell into the fire, suffering second-degree burns on the back, for which she was admitted to another hospital. After this fit she had stridor, was breathless, and became navy-blue in the face. On discharge, eighteen days later, she had a "cold" and a non-productive cough.

On the morning of December 3 she had a bout of coughing and became cyanosed, but stridor was not noticed. She improved after $\frac{1}{2}$ gr. of "omnopon," given by her doctor. In the evening the symptoms recurred, she vomited and lapsed into coma.

Clinical State.—On admission to the Royal Free Hospital the same evening she was still comatose. There was navy-blue cyanosis, maximal in the head and neck, with marked inspiratory and expiratory stridor. The jugular veins were distended but not pulsating. The thyroid was moderately enlarged and nodular, with retrosternal dullness. The trachea was displaced to the left. The accessory muscles of respiration were in use and coarse rales were heard at both lung bases. Apart from the raised jugular venous pressure and a tachycardia of 108 there were no abnormal cardiovascular signs. No response was obtained to painful stimuli; there was no papilloedema; the limbs were flaccid, with diminished tendon jerks; the plantar responses could not be obtained.

Progress and Treatment

Soon after admission an endotracheal tube was passed, through which about 20 ml. of mucous fluid was aspirated. The cyanosis disappeared after the administration of oxygen through the tube, but there was no other improvement. She had three fits in the first hour, and during the second hour had a grand-mal attack lasting ten to fifteen minutes. After an injection of 10 ml. of paraldehyde intramuscularly no further attacks occurred.