RESULTS OF TREATMENT OF PNEUMOCONIOSIS COMPLICATED BY TUBERCULOSIS

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Most patients who suffer from infectious pneumoconio-tuberculosis die within a few years. Antituberculous chemotherapy has been found to be singularly ineffective in these patients. Most of the published studies have described little more than a palliative effect. This is in striking contrast to the almost invariable success with which patients with uncomplicated pulmonary tuberculosis can be treated. We report here on our experience, which suggests, contrary to other writers, that similar success can be obtained in patients suffering from advanced pneumoconiosis in addition to tuberculosis.

The Patients

Selection of Cases.—There were in all 29 cases of pneumoconiosis complicated by tuberculosis treated in Bangour Hospital, West Lothian; Southfield Hospital, and the City Hospital, Edinburgh, between 1953 and 1958. Of these, one was excluded because he had left the district and could not be traced. Three others were also excluded because they had only recently come under observation. Otherwise there have been no exclusions. There remained, therefore, 25 patients for analysis.

Diagnosis.—Of these 25 patients, 17 were coal-miners with anthracotuberculosis, and the remaining eight suffered from silicotuberculosis. Tubercle bacilli were cultured from sputum in each case, and in most cases were found on direct smear as well. Twenty-four of the patients had been awarded pensions by the Pneumoconiosis Medical Panel of the Ministry of Pensions and National Insurance. The remaining patient had not applied for a pension.

Age.—The patients' ages ranged from 44 to 79 years, the average being 59.3 years.

Duration of Exposure to Dust.—This ranged from 16 to 63 years (average 35.9 years). Exposure was longer in coal-miners (average 41.1 years) than in workers exposed to siliceous dust (average 25.0 years).

Radiological Appearance on Diagnosis.—Eighteen cases were classified as breaking-down progressive massive fibrosis, while the remaining seven were classified as unmodified tuberculosis on a background of simple pneumoconiosis. The differentiation between these two groups was not easy except in those cases where x-ray films were available before the development of tuberculosis. Otherwise weight was given to the density of the pulmonary opacities, the presence or absence of distortion of the pulmonary architecture by fibrosis, the occurrence of inky-black sputum, and the radiological response to treatment. The categories of pneumoconiosis (Fletcher, 1955) were:

Simple	...	...	...	...	...	...	7
Progressive massive fibrosis.	Category A	...	...	...	...	...	2
"	"	"	"	"	"	"	4
"	"	"	"	"	"	"	3
"	"	"	"	"	"	"	9

Categories A to D indicate increasing degrees of severity. Most cases therefore had very extensive disease.

Sensitivity of *M. tuberculosis*.—In every case sensitivity of the patient's organisms was determined towards *para*-aminosalicylic acid (P.A.S.), streptomycin, and isoniazid at the beginning of treatment. One case showed initial resistance to streptomycin (ratio > 16). All the other cases showed sensitivity to the three drugs—that is, sensitivity ratios of up to and including two for streptomycin, up to four for P.A.S., and for isoniazid a growth of less than 20 colonies in a concentration of 0.2 µg. of isoniazid per ml.

Treatment

All patients were treated in hospital for a period of from one to 12 months, the average stay being eight months.

Chemotherapy.—All patients received chemotherapy. Only one had previously had drug treatment. Twenty were treated initially with streptomycin, P.A.S., and isoniazid combined, for an average period of 6.5 months. Streptomycin 1 g. was given daily in 12 cases, thrice weekly in seven, and twice weekly in one. Of the remaining five patients, two had streptomycin and isoniazid daily, one had streptomycin and P.A.S. daily, one had streptomycin thrice weekly with daily P.A.S., and one had P.A.S. and isoniazid daily. P.A.S. was given in a dose of 5 g. two to four times a day. The sodium salt was used except in two patients who showed gastro-intestinal intolerance and who were given calcium B-P.A.S. Isoniazid was also given daily in two doses of 100 to 200 mg. After discharge, P.A.S. and isoniazid were given in a cachet combining both drugs, to a total of 5 g. of P.A.S. and 100 mg. of isoniazid twice daily. At the time of reporting, 13 patients had completed treatment with chemotherapy. In these cases the minimum period of treatment was nine months, and the maximum 49 months (average 25.2 months).

Ferric Chloride Test for P.A.S. in Urine.—This test (Simpson, 1956) was performed in 17 patients for whom P.A.S. and isoniazid had been prescribed as out-patients. It was positive in 38 out of 47 tests (80.9%).

Surgical Treatment.—In one patient the right apico-posterior segment was resected. The sputum had converted to culture-negative before operation, but after eight months of treatment there was still some caseation in the specimen.

Results

Sputum conversion occurred in every case, consistently negative cultures being obtained. The time taken for this to happen varied from one to eight months, the average being 3.1 months (see Table). In only two cases were positive cultures subsequently obtained from patients showing sputum conversion. In one of these the patient left hospital against advice at the end of five months and thereafter did not take chemotherapy regularly. He has been readmitted recently, and the sensitivity tests show that his

Time Taken to Convert the Sputum to Culture Negative

Months of Treatment	1	2	3	4	5	6	7	8	
No. of patients converting	8	3*	5†	2	4	2	0	1	Total 25

* One patient refused further treatment after five months and relapsed.

† A positive culture was again obtained in one patient at the eighth month but none has been found since (see text).

organisms are still fully sensitive to P.A.S. and isoniazid, with which drugs he is again being treated. His organisms were primarily resistant to streptomycin. The other, who had urogenital tuberculosis in addition to advanced silicotuberculosis, had initially been treated with streptomycin 1 g. thrice weekly, P.A.S. 5 g. twice daily, and isoniazid 100 mg. twice daily. Unfortunately streptomycin had to be discontinued after five months because of toxicity. While still in hospital this patient relapsed at the eighth month, when tubercle bacilli were again cultured from the sputum and urine, and cold abscesses appeared in the chest wall and scrotum. His sputum again became negative when viomycin 2 g. twice weekly and oxytetracycline 4 g. daily were added to P.A.S. and isoniazid, it being feared that resistance had emerged. The organisms were found to be fully sensitive, however, and his sputum has subsequently remained negative for eight months. The explanation of this relapse may be that P.A.S. and isoniazid alone were insufficient to suppress the exceptionally large bacterial population present in this case.

Including the second case described above, there are 20 patients whose sputum is consistently negative on culture; the period of negativity ranges from 5 to 48 months (average 22.5 months). Four of the remaining five patients have died from other causes, though their sputum had become persistently negative, and the first patient described above has not yet converted. Thirteen patients who have completed chemotherapy have all remained culture-negative for a period ranging from 1 to 37 months (average 8.9 months) since stopping chemotherapy.

Radiological Change.—In six cases there was no radiological change; 10 showed slight improvement, and eight moderate improvement. In the case of the uncooperative patient there was deterioration. In 19 cases there were cavities on diagnosis, and these closed in four. The remaining 15 still have cavities. The seven cases of tuberculosis complicating simple pneumoconiosis appeared to fare better radiologically as six out of seven showed improvement, while in the group with progressive massive fibrosis 12 out of 18 showed improvement. Three out of the four instances of cavity closure occurred in the former group.

Deaths.—Four patients died, 37 months, 15 months, 14 months, and 7 months from the start of treatment. The respective causes of death were gastric carcinoma, cor pulmonale, non-tuberculous bronchopneumonia, and bronchial carcinoma. Post-mortem examinations were performed on the three patients who died at 37, 14, and 7 months, and there was no residual pathological evidence of active pulmonary tuberculosis in any of them.

Effects of Treatment on Working Capacity.—Only eight patients were working at the time of diagnosis. One was engaged in heavy industry, two were doing medium work, and five were doing light work. At the time of reporting, 10 patients had become fit for work following treatment, this being light work in all cases.

Discussion

So far as sputum conversion is concerned, our results are identical to those which can be obtained with uncomplicated tuberculosis (Ross *et al.*, 1958). All 25 patients have ultimately converted except for one patient who refused treatment after five months and subsequently relapsed; he is again under treatment. These results are more encouraging than those of other authors.

Early chemotherapeutic regimes often gave rise to drug resistance, with consequent failure or relapse. These dangers may be particularly great in pneumoconiotuberculosis, where the bacterial population is large and relatively inaccessible because of the avascularity of the lesions. It is not surprising that many authors reported little more than temporary symptomatic improvement, without sputum conversion or prolongation of survival (Boselli and Lusardi, 1950; Lang, 1951; Van Mechelen, 1951; Stojadinović and Stojadinović, 1952; Theodos and Gordon, 1952; Cox, 1953; Cohen and Glinsky, 1953). The best results were those of Moyer (1952), who obtained sputum conversion in 5 out of 13 patients with streptomycin alone or combined with P.A.S.

It is disturbing that later authors, even the most recent, have been unable to obtain substantially better results. Kilpatrick *et al.* (1954) found that only three out of 26 of their patients survived more than two years from the beginning of treatment; while Carpenter and Cochrane (1956), working in the same unit, could convert the sputum of only 1 out of 12 patients. Cogo and Casati's (1954) results were similar in their 15 cases. Only 7 out of 45 patients treated by Worth and Heinz (1956) remained permanently negative. Eight out of 10 patients of Courtois *et al.* (1956) converted, but six relapsed soon after treatment was stopped and further treatment gave little benefit.

Soloveva (1957) and Evers (1957) obtained good results only in the early stages of the disease, but even so a large proportion relapsed. Planques and Bollinelli (1957) had similar experiences, but Amsler (1957) was more optimistic, though he did not give any details. Even with various resection procedures in addition, Andrews *et al.* (1958) converted the sputum of only 3 out of 13 patients. Sadler (1958) obtained permanent conversion in each of five patients who had simple pneumoconiosis with superimposed tuberculosis; in contrast, only 2 out of 17 patients with progressive massive fibrosis and a positive sputum were converted. Morrow and Kantor (1958) found that in only 6 out of 22 patients did the sputum become permanently negative.

We consider that the reason for the failure that has been so widely reported in pneumoconiotuberculosis has been the incorrect use of chemotherapy. Most of Morrow and Kantor's (1958) patients received streptomycin 1 g. only twice weekly, with isoniazid 300 mg. daily, usually for at least nine months. Three of Sadler's (1958) patients had the acceptable combination of daily streptomycin, isoniazid, and P.A.S. for at least the first few months, while one had the same drugs three times weekly. The remainder of his patients received undefined "various standard courses" of these three drugs for at least nine months. Courtois *et al.* (1956) gave streptomycin as either 1 g. daily or 2 g. twice weekly, with daily isoniazid and P.A.S. for six months. Those patients who relapsed were re-treated without success and often with the emergence of isoniazid-resistance. Soloveva (1957) found that drug-resistance was difficult to prevent. Details given by all the other more recent authors mentioned above are too scanty to allow analysis.

There are clear causes of failure in the forms of treatment detailed above. Pre-treatment sensitivity tests were not described in any of these papers, nor was it usually stated whether previous chemotherapy had been given or not. There may have been initial resistance in some cases, and consequently resistance to the

remaining drugs of the combination might sometimes have emerged. Morrow and Kantor's combination of streptomycin twice weekly with isoniazid daily is notoriously apt to allow resistance to emerge (Medical Research Council, 1953), particularly when extensive disease is present. Though re-treatment failed in the patients of Courtois *et al.*, resistance sometimes emerged to isoniazid and not to streptomycin or to P.A.S., although all three were being given together. If the accuracy of the sensitivity results is accepted, it is difficult to explain this except as a result of the patients' failure to take P.A.S. (Simpson, 1956). The isoniazid might then be unprotected, if the streptomycin of the combination is being given only twice weekly. Even when there is full sensitivity and good combinations are given, there is a risk of relapse if chemotherapy is given for less than a year, particularly in far-advanced disease (Ross *et al.*, 1958). That this is also the case with pneumoconiotuberculosis is obvious from the results already quoted. These various problems have been discussed in detail elsewhere so far as they concern uncomplicated pulmonary tuberculosis (Ross *et al.*, 1958; Crofton, 1958).

It has been widely agreed that chemotherapy brings no radiographic change in these cases, even when the sputum is converted. Some definite though slight resolution was seen in more than half of our cases. In only one of these with progressive massive fibrosis was there cavity closure, though this did not affect sputum conversion in the remainder.

Unfortunately antituberculous chemotherapy cannot remove the dangers of non-tuberculous pulmonary infection and cor pulmonale which are present in patients with progressive massive fibrosis. Of our patients one died from each of these causes. Progressive massive fibrosis does not necessarily greatly reduce the expectation of life (Carpenter and Cochrane, 1956), and our patients should not fare worse than those who have never had tuberculosis. Though all our patients felt better after treatment, there was little change in their exercise tolerance and capacity for work.

A third of our patients have not yet finished treatment and only a half have been observed for a few months or more since stopping treatment. Nevertheless, though our results cannot yet be final, sputum conversion has conformed so closely to that seen in uncomplicated pulmonary tuberculosis (Crofton, 1958) that relapse in the future seems very unlikely. Many of our cases have already exceeded the two years within which 88% of the patients of Kilpatrick *et al.* (1954) died. Further, in three patients who died from other causes, post-mortem examination did not show any residual foci of active tuberculosis.

Methods of Treatment

We believe that the normal principles of antituberculous chemotherapy apply in the same way whether pneumoconiosis is present or not. Initial sensitivity tests and the previous chemotherapeutic history must guide treatment. Initially we give streptomycin 1 g. daily with P.A.S. 15 to 20 g. and isoniazid 200 mg. daily, and always in hospital. When full sensitivity of the organisms is proved the streptomycin can be reduced to 1 g. thrice weekly. Though almost all of the patients will be in the age groups where vestibular toxicity is likely, 15 of our patients did receive daily streptomycin for an average of five months without such toxicity, except in one case. Once the sputum has become persistently negative on

culture, discharge from hospital is considered; and after discharge treatment as out-patient is continued. Combined cachets are prescribed, of P.A.S. to a total of 5 g. twice daily and isoniazid to a total of 100 mg. twice daily. These reduce but do not eliminate the danger of the patient taking an inadequate dose, with subsequent resistance. We test the patient's urine occasionally for P.A.S. to make sure he is taking the cachets. Although we gave calcium B-PAS to two patients, we would now use only preparations which give adequate levels of P.A.S. in the blood. As there are usually open cavities left in these patients, we give a minimum of two years of continuous chemotherapy.

When resistance to two or more standard drugs is present, less reliable chemotherapy has to be used and surgery should be considered. Otherwise surgery has little place in the treatment of the patients.

Summary and Conclusions

Antituberculous chemotherapy has hitherto been regarded as having little permanent effect in advanced pneumoconiosis complicated by open tuberculosis.

Our experience has been more encouraging, and we have found that these patients can be treated as successfully as those with uncomplicated pulmonary tuberculosis. Sputum conversion to negative should approximate 100%, though no great radiological change can be expected.

All cases of pneumoconiotuberculosis that were admitted into three Scottish hospitals from 1953 to 1958 have been analysed. There were 25 patients, 18 of whom had progressive massive fibrosis. In all, except one who defaulted and another who relapsed temporarily, the sputum has become consistently negative. Twenty were treated initially with daily or intermittent streptomycin together with daily P.A.S. and isoniazid. The remainder received combinations of two drugs. After conversion, out-patient treatment with P.A.S. and isoniazid was given. The mean duration of chemotherapy has been 25 months. Though eight patients are still continuing chemotherapy, in half this has been completed, and during a mean period of 8.9 months afterwards none has relapsed. Four have died from non-tuberculous causes.

There has been slight radiographic resolution in more than half of the patients, but cavity closure was obtained in only one of those with progressive massive fibrosis.

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PERSISTENCE OF HAEMOGLOBIN "BART'S" BEYOND INFANCY IN A CHILD WITH THALASSAEMIA

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Haemoglobin "Bart's" (Ager and Lehmann, 1958) was found in a newborn infant of mixed ancestry (Spanish, West-Indian, Negro, Chinese). Its electrophoretic mobility at alkaline pH was slower than that of haemoglobin H and faster than that of haemoglobin J, resembling that of haemoglobin N. On chromatography at pH 6 it moved faster than any hitherto known variant. This pigment was adjudged to be an abnormal foetal haemoglobin because of its absence in both parents, because its resistance to alkali denaturation was intermediate between that of haemoglobin A and haemoglobin F, and because its ultra-violet spectrum was of the foetal type. Haemoglobin "Bart's" was seen to disappear as the child grew older, and at the age of 6 months it had disappeared completely.

The possibility was considered that a haemoglobin discovered in early infancy in a Greek child (Fessas and Papaspyrou, 1957) was identical with "Bart's." This pigment migrated more slowly than J on paper electrophoresis at alkaline pH, and was not alkali-resistant. These two findings might have been due to the fact that the haemoglobins of Fessas and Papaspyrou had been in about half the concentration of that of the "Bart's" component. However, dilution of a haemoglobin containing 24% "Bart's" and a mixture of foetal and adult haemoglobin, with an equal amount of haemoglobin A, did not alter the mobility of the fast component. Samples of infants' blood containing haemoglobin "Bart's" and sent to us by Dr. F. Vella from Singapore, Dr. S. Tuchinda from Thailand, and Dr. R. Schneider from Galveston, Texas, contained amounts of "Bart's" varying from < 10% to > 20%. The mobility on paper electrophoresis at alkaline pH was in all cases greater than that of J, and the isolated fraction was denatured more slowly than haemoglobin A and faster than haemoglobin F.

By the courtesy of Dr. F. Vella we have recently examined a haemoglobin from an infant suffering from anaemia. There was 15% of a "fast-moving" haemoglobin whose ultra-violet spectrum was of the foetal type. This haemoglobin moved on paper and starch electrophoresis at alkaline pH similar to J and more slowly than "Bart's." It may well be possible that we were here dealing with an abnormally large proportion of the pigment described by Fessas and Papaspyrou (1957). The haemoglobin sample was in the carboxy form and could therefore not be tested for resistance to alkali denaturation. Some of the fast-moving fraction was eluted from filter paper after electrophoresis, oxygenated for two hours, treated with sodium metabisulphite, and again briefly reoxygenated. This sample showed then an increased resistance to alkali denaturation, which had not been noted in their foetal variant by Fessas and Papaspyrou. However, we do not think that too much reliance can be placed on a result under these circumstances.

The present communication is intended to report yet another resemblance between haemoglobin "Bart's" and haemoglobin F—its persistence beyond the age of infancy in a child with thalassaemia. The patient, a boy aged 9 years, showed some degree of infantilism

FIG. 1.—Stained film of the patient's blood. Moderate hypochromia, aniso-poikilocytosis, some macrocytes, and a few target cells are present.

FIG. 2.—Hanging strip paper electrophoresis at pH 8.6, comparing the patient's haemoglobin with haemoglobin from the original infant with haemoglobin "Bart's," then aged 3 months, and showing 15% of the abnormal foetal pigment. The difference in the position between the two slow-moving fractions (A + F) is due to the higher haemoglobin F content in the baby's blood.