Long Term Results Of Drug - Treated Pulmonary Tuberculosis

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During the last decade, antibiotics and chemotherapeutic agents have changed completely the treatment and outlook of pulmonary tuberculosis. In the majority of cases, the immediate results have been gratifying to physician and patient alike, but in such a disease as tuberculosis the final assessment of any form of treatment should rest more on the relapse rate than on the immediate results. This paper deals with 60 patients, all women, who started treatment during 1953 and 1954, and who have been followed up to the end of 1961. They are all women as they happen to belong to a hospital division.

Selection of patients

The patients under review consist of all types of pulmonary tuberculosis; but, they are "selected" in a way in that

(a) all have been treated in the wards and out-patient department of a hospital;
(b) all started treatment in 1953 and 1954
(c) none had ever had any anti-tuberculosis drugs before.

The advantages of hospital treatment are obvious: treatment is carried out under supervision, patients are more likely to take the drugs, follow-up can be better controlled, and therefore, the evaluation of results is more reliable. Only patients who started treatment during 1953 and 1954 have been selected, as a follow-up of at least 5 years from the end of treatment would increase the significance of the relapse rate. The fact that none had had any drugs before is of major importance in assessing the value of the treatment concerned.

Classification of patients and extent of disease

Patients were classified into A or B depending on the absence or presence of tubercle bacilli in the sputum, exudates etc., but "grouping" into 1, 2 or 3, was based more on the radiological findings, as suggested by Foster-Carter (Foster-Carter et al, 1952, Hoyle C., Nicholson H., Dawson J., 1955).

Eleven patients belonged to Class A and 49 to Class B, grouped as follows:

A1	2	patients
A2	5	"
A3	3	"
B1	2	"
B2	23	"
B3	25	"

Age of patients on admission. Table I gives the age-group distribution in years.

Duration of illness. This is very difficult to postulate with anything like certainty in pulmonary tuberculosis, as the disease may have been smouldering for a long time without producing any overt symptoms. This insidiousness of onset was again emphasized in the present patients by the fact that, in spite of the extent of the radiological findings, no less than 31 started to complain of any symptoms not earlier than six months before admission to hospital; 6 patients had no symptoms at all and were discovered on routine X-Ray examination -3 as prospective emigrants and 3 as contacts. Ten, 9 and 3 patients

had been feeling unwell for one, two and five years respectively; one was first diagnosed as having tuberculosis thirty years ago and the present illness was a relapse.

Complications on admission. Sixteen patients had a complicating condition or another disease; of these 9 had Diabetes Mellitus complicated by another condition as follows:—

Diabetic Coma, purpura	1
Arteriosclerosis	1
Hypertension	2
Nephrosclerosis	1
Ischaemic heart disease, Cerebral thrombosis	1
Ischaemic heart disease, Duodenal ulcer	1
Spontaneous hydropneumothorax	1
Undulant fever (Brucella Melitensis)	1

The other seven patients had

Disseminated Tuberculosis (lungs, ulna, five lumbar vertebrae, bilateral psoas abscess)	1
Undulant fever	1
Chronic nephritis	1
Third degree uterine prolapse severe microcytic anaemia	1
Squamous cell carcinoma of face	1
Mental deficiency	1

Three other patients were in the early months of pregnancy.

Methods of assessing progress

The traditional investigations — temperature taking, weight, E.S.R. bacteriology of the sputum and/or of the gastric contents, serial X-Ray — were carried out in every case, but final assessment was entirely guided by the last two objective criteria, i.e. bacteriological conversion and radiological improvement.

Fever. The absence of fever does not rule out active or extensive tuberculosis, and temperature taking has now very little value in following the progress of the disease, except during the acute phase of the illness; the following are the highest temperatures recorded on admission in the 60 patients:

98.4° F.	21 patients
99° F.	13 "
100° F.	6 "
102° F.	9 "
103° F.	7 "
104° F.	4 "

Weight. Patients were weighed on admission and again at weekly intervals. With very few exceptions, their weight was found to be below the average local normal standard.

E.S.R. This was estimated by the Westergren method and was read after one hour. It was repeated monthly and was found to be a good index of the activity, extent and progress of the disease. In fact only 3 patients had an E.S.R. below 10mm. on admission — classification A1, B1 and A2 respectively.

E.S.R. (1st. hour) of 60 patients on admission.

Below 10mm.	in 3 patients.
Between 10 — 19mm.	in 11 patients
20 — 39mm.	in 18 "
40 — 59mm.	in 20 "
60 — 79mm.	in 4 "
80 — 99mm.	in 2 "
100 — 120mm.	in 2 "

Sputum. Direct (Ziehl-Nielsen) bacteriological examination of the sputum, including counts per field, was done on admission and repeated monthly thereafter. Culture and/or guineapig inoculation (sputum or gastric contents) were carried out if smears turned out negative on repeated examination. Tubercle bacilli were found in 48 patients, as follows:

Sputum, direct, in 38.

Gastric contents, culture, in 6.

Gastric contents, guineapig, in 1.

Gastric contents, culture and guineapig, in 2.

Pleural fluid, culture, in 1.

Radiological Findings. A postero-anterior X-Ray was carried out routinely, repeated monthly, or more frequently in special cases. A "lateral" or tomogram was done when considered necessary.

Of the 60 patients, 4 had only one zone in one lung involved, 32 had unilateral or bilateral lesions in two or three zones, and 24 patients had bilateral disease involving four or more zones. 42 patients had cavities, 20, 11, 4, 1, and 6 having one, two, three, four and multiple cavities respectively.

Cavities were graded into small (1cm. or less), medium (1cm. to 2cm.), or large (2cm. to 6cm.), according to the size of their largest diameter: 10, 15, and 17 patients had small, medium and large covities respectively.

The total number of cavities present in the 42 patients was 70, 38 in the right lung and 32 in the left, the majority being in the upper zones (right upper zone 22, middle zone 16; left upper zone 24, middle zone 8). In the present series no cavities were present in the lower zone.

Treatment

Bed Rest. All patients were kept in bed at least for the first six months, being allowed up only to wash and for toilet purposes, whenever their physical condition permitted. When cavities were present, rest in bed was enforced as long as the covities remained open and for a further 3 months after their closure.

Drugs. One of the three possible combinations of the three anti-tuberculosis drugs — Streptomycin, PAS and INAH — was given continuously from one to two years, except in one patient when treatment had to be stopped after six months because of side effects and in two others who died five and six months after admission to hospital. Table II gives the duration of treatment in months in the 60 patients.

The routine procedure was to give Streptomycin 1G coupled with PAS 12-15G or INAH 200 mgm. daily for at least six months or until sputum conversion and/or cavity closure, whichever was the longer period. During the next three months, Streptomycin was reduced to 1G three times weekly, and reduced further to 1G. twice weekly for the following three months. In those patients who received more than one year of the drug, treatment was continued with PAS 10-12G. and INAH 200 mgm. daily either as in- or as out-patients.

During in-patient treatment the Streptomycin-PAS combination was used on 28, the Streptomycin-INAH on 39, and the PAS-INAH combination on 19 occasions.

Ir the older age groups this schedule had to be somewhat modified because of their greater tendency to Streptomycin neurotoxicity. Streptomycin, therefore, was only given daily during the acute phase of the illness, say for a month or two, and then it was reduced to three times weekly. Since March 1953 whenever Streptomycin had to be given intermittently, in the presence of a positive sputum and/or an open cavity it was always coupled with PAS and not with INAH to lessen the danger of emergence of resistant strains of bacilli. (M.R.C. 1953., Editorial B.M.J., 1953).

Triple drug therapy was never used; it must be remembered however, that these patients were receiving the drugs for the first time, and in 1953 and 1954 the local incidence of primary drug resistance in untreated patients was not yet of any significance.

Toxic reactions and side-effects. It was not found necessary to withold permanently drug therapy because of side-effects, toxic reaction, or for any other reason, except in one patient. Even when these appeared, it was always possible to continue treatment with a different combination of drugs. The only

patient in whom treatment had to be abandoned altogether had chronic seborrheic alopecia and showed skin sensitivity reactions to all the three drugs. Desensitization in this patient was not attempted as she was below average intelligence and uncooperative. Desensitization to Streptomycin, however, was carried out successfully in another patient who became allergic (swelling, pain and erythema at the site of injection) to this drug, and who had already exhibited allergy to PAS, in the form of fever, cervical adenopathy and a rash. Ten other patients showed reactions to Streptomycin: 5 headache, 3 paraesthesias around the mouth, 2 vertigo. Headache and vertigo usually appeared when treatment had been going on for some months and was more frequent in the older age groups; in all these patients streptomycin was substituted by PAS or INAH. In one patient vertigo was permanent. Paraesthesias around the mouth, in the form of pins and needles, appeared in younger patients early on in treatment and usually following immediately after the injection; the drug was continued and the complaints disappeared as treatment went on. Three others had pruritus and an erythematous rash due to PAS and in each case the drug was replaced. In the dosage used, 12-15G. daily, gastrointestinal complaints after PAS were remarkably uncommon and mild, and they could be controlled either by giving the mixture after meals or by replacing it with cachets. Except the one patient already mentioned, none had any toxic reactions or side-effects attributed to INAH.

Examination of urine, blood count and picture and liver function tests were done periodically; no alterations due to drugs were noted.

Other treatment. Other treatment beside rest in bed and drugs was found necessary in 7 patients: artificial pneumothorax. 2; thoracoplasty, 2; phrenic crush, 1; aspiration of psoas abscess and immobilization in a plaster bed, 1; aspiration of a spontaneous hydropneumothorax, 1.

The patients who had Undulant Fever were given orthodox chlortetracyclin therapy in addition to the other drugs.

RESULTS OF IN-PATIENT TREATMENT. Fever subsided rapidly and was down to normal after a few days; it never took longer than three weeks to settle down. Cough and sputum likewise disappeared very quickly, even when cavity remained large.

With two exceptions, one of whom had a carcinoma of the face, all gained weight rapidly even those who eventually died.

The E.S.R. improved concurrently with the disappearance of the toxaemia and with the radiological improvement.

Progressive decrease in the number of bacilli per field was noted almost weekly; in some cases, sputum conversion occurred after the first three months of treatment.

Radiological improvement was fairly rapid, and as would be expected, the "soft" shadows produced by the exudative lesions were the first to disappear, clearing up completely by the end of the third month. Cavity closure, in the majority of cases, took longer. Whether a cavity closes or not with drugs alone, depends to a great extent, apart from the state of the bronchus, on the amount of lung-tissue destroyed and of the structure of its walls; one thing is certain, to prognosticate about the fate of a cavity before anti-bacterial treatment is well under way may lead to surprises, pleasant and unpleasant. A giant tension cavity will very often close in no time with drugs and rest in bed, while a small fibrotic one will not close at all. In the present series one such tension cavity, and in the apex of the lower lobe of the left lung, vanished after only

three weeks of treatment. "Calcification" of the nodular shadows perhaps appeared earlier than formerly, and miliary shadows, more often than not, disappeared completely. Healing was more frequently by resolution than by fibrosis unless there was extensive disease.

The three pregnant women had normal deliveries and healthy babies, and the pregnancies did not effect their pulmonary condition. The two patients who had Undulant Fever did well and there was no relapse.

Duration of stay in hospital. The average stay in hospital was 15 months, the extremes being 6 and 24 months. Patients were kept in hospital from 4 to 5 months after being allowed out of bed, sending them home for the week-ends and on public holidays. This had the double purpose of getting them acclimatized to Sanatorium regime when up and about, and of observing the reaction of their disease to increased activity.

Deaths. Five patients all belonging to Class B 3 died while in hospital. Their ages at the time were, 41, 54, 59, 67, 71 years. In only one patient was death directly attributable to pulmonary tuberculosis, an old "chronic" who had an associated cor pulmonale. In two others, both diabetics, the tuberculosis had reached the quiescent stage and they were due for discharge: one died of a second attack of coronary thrombosis and the other of cerebral haemorrhage. In the other two the tuberculosis had improved, but one died of an inoperable carcinoma of the face, and the other, who had diabetes, ischaemic heart disease and cerebral thrombosis died in congestive heart failure.

Condition of survivals at time of discharge (55 patients)

Weight. With only one exception, who maintained the same weight throughout, all patients had gained from 2 to 5 stones in weight.

E.S.R. This was normal in 48 patients; in six it was above 20mm. and in one, above 80mm. Of the six who had an E.S.R. above 20mm. all were sputum negative, but two had only had 8 months of the drugs and were discharged partly at request continuing treatment as out-patients, one had had extensive bilateral disease and the lesions were not yet fully calcified, and another had had only 6 months treatment, when this had to be stopped because of allergic skin manifestations. The single patient who had an E.S.R. above 80mm. had active disease, an open cavity and positive sputum.

Sputum Conversion.

Bacteriological tests carried out before discharge from hospital consisted of repeated culture of, and/or guineapig inoculation with, the gastric contents as very few had any available sputum at that time.

Of the 55 patients discharged, 45 had positive bacteriological findings on admission, and of these only one had a positive sputum when she left hospital.

Cavity closure. Of the survivals, 38 had cavities on admission. In 32 patients the cavities closed with rest in bed and drugs; 5 had to have collapse measures (2 artificial pneumothorax, 2 thoracoplasty, 1 phrenic crush) all with successful results. One left hospital at request with an open cavity and a positive sputum. Cavity closure was controlled by tomograms in every case. There were no "open negative" cases.

Out-patients follow-up of 55 patients

50 of the 55 patients discharged have been followed up for about 5 to 6 years after the termination of treatment; of these, 48 have remained well and 2 have had a radiological relapse, but both

responded well to a second course of the drugs. Three died, two in ureamia following chronic renal disease 5 and 3 years after they left hospital with no evidence of reactivation of the tuberculosis, and the other one, aged 54 years, of pulmonary tuberculosis; she was the one who left hospital at request with an open cavity and a positive sputum.

Two patients never attended the clinic after leaving hospital and could not be traced

End results

Of the 60 patients who started treatment during 1953 and 1954 and who were having anti-tuberculosis drugs for the first time, 50 are now living and well (end of 1961); 8 died, 2 from pulmonary tuberculosis, 6 from other causes; two could not be traced, but had left hospital with their disease in the quiescent stage.

Comment

Relapses. The two patients who relapsed had had bilateral disease involving three or more lung zones with cavities in the upper lobes and a positive sputum on direct smear. One had had 12 and the other 15 months of continuous drugs while still in hospital; in one the relapse occurred one year and in the other 4 months after stopping treatment. No tubercle bacilli could be discovered either in the sputum or in the gastric contents, on smear and culture, and in both the relapse was radiological, at the site of the original lesion and consisting of "softening" of the nodular shadow which had undergone "hardening." In one, the relapse occurred during the fifth month of pregnancy and in the other it followed an abortion. Both were re-treated as outpatients and responded promptly to PAS and Isoniazid. These patients were insufficiently treated; considering the extent of their original lesions, both should have had at least 18 months of the drugs from the start.

Hospital stay. A stay in hospital for 15 months may appear long by present day standards. Even in Ross's series, which consisted mainly of advanced and far advanced cases (B.2 and B.3 in the present series), the average stay in hospital was only ten months (Ross et al, 1958). At the same time, one cannot but agree that the longer the hospital stay the shorter the period of "self medication" with all its drawbacks (Dixon et al 1957; Lancet, E., 1958; Ireland, 1960; Luntz and Austin, 1960).

Perhaps the point at issue today would not be the duration of hospital stay, but whether hospitalisation is really necessary. It is readily granted that present-day treatment permits a more liberal approach to tuberculosis; at the same time, however, one should remember that drug-resistance is practically non existent in hospital treated patients. "In avoiding resistance to drugs it was important to see that the regimes laid down were understood and carried out by the patients, who varied considerably in intelligence. There was a danger that treatment might be regarded too lightly and admission to hospital was desireable in the first instance." (Scadding J.G. 1958)

Tuberculosis is *still* an infectious disease. Although some workers have shown that the results of domiciliary and hospital treatment may not differ very much where the patient is concerned, yet the risk to contacts of those treated at home is relatively high, especially among the young. As the International Union against Tuberculosis puts it *"institutional treatment is desireable in all sputum positive cases,* mainly to ensure that the patient takes his chemotherapy and to decrease the danger to others." (XV International Tuberculosis Conference 1959). Inspite of growing tendency to a shorter hos-

pital stay and to domiciliary treatment, it is still the practice of the writer to extend hospitalization to one year, thus making sure that patients have had at least on year of proper drug treatment. Although many more factors bearing on the relapse rate of tuberculosis have yet to be established, sufficient evidence has now accumulated to prove that as regards drug treatment the relapse rate is inversely proportional to its duration (Low, 1956; Crofton, 1959).

Rest in bed. In some of the present patients, this may have been prolonged unduly. Recent controlled trials have shown that patients with "mild" pulmonary tuberculosis (sputum negative on direct smear, cavity not more than 2 cm. in diameter) may be treated at work with good results (Tuberculosis Society of Scotland, 1960). However, it is also a fact that cavities close earlier with rest (Ross & Kay, 1956); the earlier the cavity closes the more rapid is sputum conversion and the emergence of drug-resistance is less likely. Weir, Schless O'Connor & Weiser who treated 105 patients in hospital conclude that control of physical activity is not necessary for successful treatment of pulmonary tuberculosis which includes adequate chemotherapy. But out of 46 of their patients with cavities, 24 had to undergo resectional surgery for residual cavities after 5 to 11 months of treatment (Weir et al, 1961). In the present series, out of 39 of the 42 patients with cavities (excluding the one patient who left hospital at request and the two who died in the early phase of treatment — all three considered as unsuitable for any kind of surgery), only 5 had to have other treatment for the closure of cavities, besides drugs and rest in bed. It is felt that rest in bed must have contributed to the high rate of cavity closure by conservative measures in these patients.

Treatment. In the present series, the duration of drug treatment, from one to two years, is compatible with modern ideas, except that today, even in the less severe case, one is more inclined towards the longer period. In all other respects, during the last years, treatment has been modified to conform to accepted standards. Since 1955 drug sensitivity tests have been carried out routinely in *all* our patients before and during treatment, all the three standard drugs have been given until the results of these tests were available, and Isoniazid always formed part of the drug combination.

It is unjustifiable, especially today, to speak of the drug treatment of tuberculosis and to draw any conclusions thereon without including bacterial sensitivity. In the patients under review sensitivity tests were not done regularly enough to warrant inclusion in this report; however, as already stated, in 1953 and 1954 the local incidence of primary drug resistance was not yet of any significance, and from the response to treatment and the results obtained in the present series one is justified to assume that the bacilli remained sensitive throughout treatment. The 2 patients who died of tuberculosis would have done so irrespective of the drug sensitivity of their bacteria.

Summary

Sixty women suffering from Pulmonary Tuberculosis started treatment between January 1953 and December 1954.

All were treated in hospital (some continuing treatment as out-patients) with a combination of two of the three standard drugs (Streptomycin plus P.A.S. or Isoniazid, or P.A.S. plus Isoniazid), and rest in bed; all were having the drugs for the first time.

Fifty-seven patients completed from one to two years of treatment; two died within six months of admission to hos-

pital, one from malignant disease, the other from chronic pulmonary tuberculosis and cor pulmonale; in another patient treatment had to be suspended after six months because of drug allergy.

Forty-two patients had cavities, three being unsuitable for any kind of active treatment; in thirty-four, the covities closed by conservative measures only (i.e. drugs and rest in bed), in the other five collapse therapy had to be used, with successful results.

By the end of 1961, of the 57 patients who had completed from one to two years of treatment, 50 were alive and well, including 2 who had relapsed but who did well on re-treatment; one other patient in whom treatment had to be suspended after six months because of allergic reactions was also alive and well. Six had died, one from pulmonary tuberculosis (this patient had left hospital against advice), 5 from other causes. Two others could not be traced, but at the time of their discharge from hospital their disease was in the quiescent stage.