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# The Results of Treatment with Streptomycin Plus Pyrazinamide in Patients with Active Pulmonary Tuberculosis Despite Prolonged Treatment with Isoniazid Plus PAS

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There have been a number of reports on the use of pyrazinamide in combination with other drugs in the treatment of pulmonary tuberculosis. It has been used in combination with isoniazid (Donnerberg et al., 1957; United States Public Health Service, 1959a), with cycloserine (Schwartz & Moyer, 1957; Toguri & Atwell, 1958) and with viomycin (Pfeutze & Pyle, 1957) in the treatment of patients who had failed to attain quiescence with previous antituberculosis chemotherapy. It has also been used successfully in the treatment of newly-diagnosed disease in combination with isoniazid, with daily and bi-weekly streptomycin and with PAS (Muschenheim et al., 1954; Allison, 1959; Tucker & Matthews, 1959; United States Public Health Service, 1959b). A major disadvantage of pyrazinamide, however, is the occurrence of hepatic toxicity, which sometimes results in jaundice or death, especially since liver function tests do not always give adequate warning of impending hepatic damage (American Trudeau Society, 1957 ; Potter &, Chang, 1955 ; Spengos & Cuizon, 1958 ; United States Public Health Service, 1959a). In a controlled study, the United States Public Health Service (1959a) reported hepatic toxicity of between 2% and 3% in a 12 week period with daily dosages of 25 or 40 mg of pyrazinamide per kg body weight. In a 24 week period the toxicity increased to 6.6% with the larger dose but remained unaltered with the 25 mg dose. Joint pains, elevation of the serum uric acid and frank clinical gout have also been reported (Yaeger et al., 1952 ; Cullen et al., 1956).

This report presents the findings during a year or more of observation of 20 South Indian patients who, after an initial course of isoniazid plus PAS, were treated with streptomycin plus pyrazinamide for active pulmonary tuberculosis. The combination of streptomycin plus pyrazinamide was chosen, first, because of its likely therapeutic effectiveness, since all the patients had streptomycin-sensitive strains of bacilli, secondly, because it presented an opportunity to study *supervised* drug administration in domiciliary patients in a community in which the self-administration of antituberculosis drugs could not be depended on (Fox, 1958 ; Tuberculosis Chemotherapy Centre, 1959, 1960 ; Velu et al., 1960). The patients were either unsuitable for or unwilling to undergo surgery.

Up to 30 January 1959, 22 patients were admitted to treatment with the combination of streptomycin plus pyrazinamide ; 2 have been excluded because

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their treatment was interrupted early in its course ; 1 patient developed an amoebic hepatitis with an abscess which ruptured into the lung 6 weeks after the start of the new regimen and it was considered inadvisable to continue pyrazinamide ; the other patient absconded from Madras in the second month of treatment as he was wanted by the police. All the 20 cases were excreting tubercle bacilli when the streptomycin plus pyrazinamide regimen was started. In 16 the disease had previously failed to attain a quiescent state on the standard combination of isoniazid plus sodium-para-aminosalicylate (the daily dose of isoniazid ranged from 150 to 200 mg and the daily dose of PAS (sodium salt) from 7.5 to 10 g, according to the patient's body weight) given in this Centre for periods varying from 9 to 25 months. The remaining 4, after achieving quiescence, had relapsed bacteriologically with radiographic spreads of the disease. Of the 20 patients, 17 had had a recent radiographic deterioration, 2 had had a clearcut clinical deterioration associated with an haemoptysis and the remaining patient still had a positive sputum after 2 years of treatment with isoniazid plus PAS. Thus, all the 20 cases were treatment failures of a standard combined chemotherapy. When the original treatment began, 14 had sensitive organisms to both isoniazid and PAS, 4 had isoniazid-resistant organisms, and 2 (who received their treatment in the first pilot study in the Centre) had no sensitivity results at that time.

It was the intention in the study reported here to treat every patient with streptomycin plus pyrazinamide for a minimum of a year and, provided the patient would cooperate, for a period of up to 2 years. If, however, the sputum remained persistently positive after 6 months of treatment the case was reviewed. Because of the possibility of toxicity, treatment with the combination was stopped if it was considered, in the light of the radiographic and bacteriological response (including the streptomycin sensitivity test results), that there was no reasonable likelihood that further improvement would result from continuing the regimen.

**The treatment regimen**

The standard regimen was streptomycin sulphate 1 g daily (i. e. 24 to 32 mg per kg body weight) in a single intramuscular injection on 6 days a week, plus pyrazinamide 1 to 1.5 g daily (30 to 40 mg per kg body weight) in 1 dose. The pyrazinamide was given 6 days a week under direct supervision in the clinic and 1 dose was given to be taken at home on Sundays.

In 7 patients it became necessary to reduce the daily dosage of streptomycin to 15 mg per kg because of the development of giddiness.

The majority of the patients were treated entirely under ambulatory domiciliary conditions, but 4 patients spent part of the period in sanatorium, during which time they received streptomycin on all 7 days of the week.

**Routine examinations**

The patients were examined clinically and radiographically at monthly intervals. At each month 2 overnight sputum specimens were examined by smear and culture and a pair of laryngeal swabs by culture. A streptomycin sensitivity test was performed on a positive culture at each month, when 1 was available. The bacteriological techniques have been described elsewhere (Tuberculosis Chemotherapy Centre, 1959). The urine was examined for bilirubin twice a week using a simple test (Sobotka et al., 1953) if the result was positive, a simple spectroscopic examination for urobilin was performed (Harrison, 1957).

There are few centres in India that have access to liver function tests ; if the present study was to have any bearing on the current tuberculosis problem in India it

was therefore essential to know whether pyrazinamide could be used without undue risk in the absence of such tests. For this reason, no special tests of liver function were undertaken in this study.

### Condition at the start of treatment with streptomycin plus pyrazinamide

The patients' ages ranged from 18 to 51. Three were under 20 years, 9 were aged 20 to 29 years, 5 were aged 30 to 39 years and 3 were older. Fourteen were males and 6 were females.

The majority of the patients had advanced disease. Thus, on postero-anterior radiography, 16 had moderate or extensive cavitation and only 2 had no evidence of cavitation. All except 1 patient had 3 or more lung zones involved in disease, 12 having 5 or 6 lung-zone involvement. The positivity of the sputum was graded on the basis of smear and culture examination of a single overnight collection specimen. The specimens in all 20 patients were positive, 18 on both smear and culture and 2 only on culture ; 14 had 3-plus (heavy) or 2-plus (moderate) positive smears. All, as already mentioned, had streptomycin-sensitive strains of bacilli.

## RESULTS

### Cooperation of the patients

The cooperation of the patients in accepting treatment was remarkably good. It was necessary to give some patients limited financial assistance, as explained in an earlier report (Tuberculosis Chemotherapy Centre, 1959). Most of the patients were given money for fares since they had to attend the clinic 6 days a week for many months and travel up to 5 miles each way under tropical conditions. In all, 17 patients received an average of Rs. 5.84 a month for fares, or an average of Rs. 4.96 per month for the whole series of 20. Even so, patients occasionally failed to attend for their injection, but no patient had an interruption of chemotherapy of more than a few days at any time.

### Treatment changes during the year

Seven patients had their treatment changed in the second 6 months, 6 in the eighth month and 1 in the tenth month. In only 1 of these patients was there evidence of radiographic deterioration. The others had their treatment changed because the sputum was positive and it was considered they would not improve further either radiographically or bacteriologically.

### Radiographic changes

In the first 6 months, 17 of the 20 patients showed radiographic improvement; in 9 of these patients it was classified as moderate or considerable by an independent assessor (Dr. Raj Narain). Two patients showed no change and 1 patient had deteriorated radiographically. Considering the 13 patients who continued on the streptomycin-pyrazinamide regimen for a full year, 9 showed radiographic improvement over the period, 2 no change and 2 had deteriorated.

### Bacterial content of the sputum

The average number of culture examinations was 2.7 per month, the range being 1.8 to 3.8 per month.

There was a rapid and striking fall in the bacterial content of the sputum in the early months (Table 1); at 2 months only 1 of the 20 patients yielded a positive culture. By 3 months the position had changed and 7 patients yielded positive cultures. Again, at 6 months, 7 patients yielded positive cultures, 5 specimens being

TABLE 1

*Presence of Tubercle Bacilli in Multiple Specimens taken at Monthly Intervals*

| Months after start of chemotherapy | Number of patients with treatment changed | Total patients on initially-prescribed regimen with culture examinations | Patients with at least 1 positive culture | | | Patients with all cultures negative* | |
|---|---|---|---|---|---|---|---|
| | | | Smear positive | All smears negative | On laryngeal swab only | No. | % of the 0 patient admitted to study |
| 0 | 0 | 20 | 18 | 2 | 0 | 0 | *0* |
| 1 | 0 | 19 | 4 | 3 | 0 | 12 | *60* |
| 2 | 0 | 20 | 0 | 1 | 0 | 19 | *95* |
| 3 | 0 | 20 | 1 | 5 | 1 | 13 | *65* |
| 4 | 0 | 20 | 3 | 4 | 1 | 12 | *60* |
| 5 | 0 | 20 | 5 | 3 | 1 | 11 | *55* |
| 6 | 0 | 20 | 5 | 2 | 0 | 13 | *65* |
| 7 | 0 | 20 | 6 | 1 | 2 | 11 | *5.5* |
| 8 | 6 | 14 | 2 | 1 | 1 | 10 | *50* |
| 9 | 6 | 14 | 0 | 1 | 2 | 11 | *55* |
| 10 | 7 | 13 | 3 | 0 | 0 | 10 | *50* |
| 11 | 7 | 13 | 2 | 1 | 0 | 10 | *50* |
| 12 | 7 | 13 | 1 | 2 | 0 | 10 | *50* |

* Even if the smear was positive

TABLE 2

*Bacteriological Status at 12 Months According to the Condition on Admission to Study*

| Condition on admission to study | | Total patients | Bacteriological status at 12 months | |
|---|---|---|---|---|
| | | | Quiescent | Active, relapsed or treatment changed |
| Extent of Cavitation | Extensive | 4 | 3 | 1 |
| | Moderate | 12 | 3 | 9 |
| | Slight | 2 | 2 | 0 |
| | Nil | 2 | 2 | 0 |
| Number of lung zones involved in disease | 6 | 7 | 3 | 4 |
| | 5 | 5 | 3 | 2 |
| | 4 | 4 | 3 | 1 |
| | 3 or 2 | 4 | 1 | 3 |
| Bacterial content of sputum on smear examination | 3-plus | 7 | 4 | 3 |
| | 2-plus | 7 | 4 | 3 |
| | 1-plus | 4 | 0 | 4 |
| | Negative | 2 | 2 | 0 |

positive on smear examination also. By 9 months 6 patients had had their treatment changed because of bacteriological relapse and, of the remaining 14, 3 yielded positive cultures. The position was essentially unchanged at 12 months.

**Sensitivity test results**

(a) *Streptomycin sensitivity tests :* At 1 month 1 of 6 strains was streptomycin-resistant. At 2 months the only positive culture from the 20 patients was resistant. Both at 3 and at 6 months 6 of 7 cultures were streptomycin-resistant. From 7 months onwards all the positive cultures were resistant.

In all, 10 patients yielded streptomycin-resistant strains, 1 for the first time at 1 month, 1 first at 2 months, 4 at 3 months, 2 at 4 months, 1 at 7 months and 1 at 8 months. In 7 of 8 patients in whom the first resistant strain was obtained at 3 months or later, this strain was also the first positive bacteriological finding following 1 or more months of culture negativity. Thus, in this group of patients, there was a very clear "fall and rise" phenomenon, i.e. a fall in the bacterial content of the sputum followed by a rise in its content associated with the emergence of streptomycin-resistant organisms. In each of the 10 patients with streptomycin resistance at any time during the year, the first resistant strain (resistance ratio of 8 or more) which emerged was highly resistant, that is, had a resistance ratio of 100 or more.

(b) *Pyrazinamide sensitivity tests:* Considerable difficulty was experienced in the Centre's laboratory with the standardisation of pyrazinamide sensitivity tests and reliable results are not available for these patients, either before or during treatment.

**Assessment of the bacteriological status at one year**

At 1 year, 10 of the 20 patients had bacteriologically quiescent disease, 7 having been bacteriologically negative from the first month onwards and 3 from the second month. Two patients, after periods of culture negativity of 3 and 7 months, respectively, had relapsed to bacteriological positivity. One patient had bacteriologically active disease throughout the year. The-remaining 7 patients had had their treatment changed, because they were consistently bacteriologically positive and were considered unlikely to derive further benefit. (One had also had a radiographic deterioration when treatment was changed.)

**Prognostic value of the clinical features at the start of treatment with streptomycin plus pyrazinamide**

The bacteriological status at 12 months is set out in Table 2 in relation to the radiographic features and the bacterial content of the sputum at the start of treatment. Bacteriological quiescence was attained in 3 of the 4 patients with extensive cavitation and in 3 of the 12 patients with moderate cavitation. Six of the 12 patients with 5 or 6 lung zones involved in disease attained quiescence. Four of the 7 patients with a 3-plus bacterial content of the sputum on smear examination attained quiescence and so did 4 of 7 with a 2-plus bacterial content. It may be concluded that patients with extensive disease and large bacterial populations were capable of attaining quiescence. A striking feature was the ability of the combination to sterilise major cavitated lesions even though the cavities remained open. Two cases are illustrated in figures 1 to 4. Of the 4 patients who had had isoniazid-resistant strains when treatment with isoniazid plus PAS was begun, 2 had quiescent disease after a year of treatment with streptomycin plus pyrazinamide.

**Drug toxicity**

(a) *Streptomycin:* In all, 9 patients complained of giddiness. This responded to anti-histamine drugs in 2, but in 7 patients the dosage of streptomycin was reduced to 15

mg per kg body weight for the rest of the period of treatment. Some patients complained of pain at the site of the injections, but in no case was treatment interrupted because of this.

(b) *Pyrazinamide :* No patient developed symptoms or signs suggestive of liver toxicity. A weak positive finding for bilirubin in the urine was reported in 6 patients. In this Centre such a finding was not uncommon in tuberculous patients under investigation prior to treatment and, since the spectroscopic test for urobilin was negative, these results were ignored. Five patients had transient joint pains in the early months which responded to symptomatic treatment.

**Continuation of treatment with streptomycin plus pyrazinamide for a second year**

In 13 patients treatment was continued into the second year. Of these, 3 had active disease at 1 year; the combination was stopped for these 3 patients after 17, 16 and 14 months, respectively, since it was considered that they would derive no benefit from further treatment. In 2 of these patients a radiographic spread had occurred during treatment with the combination.

The remaining 10 patients had quiescent disease at 1 year and have remained quiescent. Treatment was discontinued in 1 patient after the completion of 26 months and in 3 patients after the completion of 2 years. One patient stopped the treatment of his own accord after 15 months. In 1 patient the treatment was stopped after 13 months because of persisting giddiness; this patient, a male aged 48, provided the only example of serious toxicity to the combination encountered in the whole series. Four more patients are still receiving treatment and have so far completed 23, 20, 17 and 15 months, respectively.

## DISCUSSION

The United States Public Health Service (1959b) has reported that streptomycin plus pyrazinamide daily is a valuable combination in the treatment of fresh cases of pulmonary tuberculosis. The present study reports the use of this combination in 20 patients, all of whom had previously failed to respond to prolonged treatment with the combination of isoniazid plus PAS and were unsuitable or unwilling for surgery. It has shown that streptomycin plus pyrazinamide has a place in the treatment of such cases, for 10 patients attained bacteriological quiescence at the end of a year. The results are not as good as those reported by the United States Public Health Service (1959b) but are favourable in comparison with the general experience of the retreatment of failure cases with new combinations of drugs. Of the 10 patients whose disease became quiescent 8 had been previously treated *at home* with isoniazid plus PAS. A study already reported from this Centre (Tuberculosis Chemotherapy Centre, 1959) has shown that bacteriological quiescence can be attained in a high proportion of patients treated at home. The present report demonstrates that patients who have failed to respond to the combination of isoniazid plus PAS may subsequently still attain quiescence with streptomycin plus pyrazinamide (the results of domiciliary chemotherapy with isoniazid plus PAS can thus be improved upon). It may be argued that better overall results could be obtained by treating from the outset *all* patients with streptomycin, isoniazid and PAS daily for several months and only then continuing with 2-drug therapy. On the other hand, it is much more simple under domiciliary conditions to organise a service on the basis of the administration of an oral combination and then to treat with streptomycin plus pyrazinamide the comparatively small proportion of patients who fail to respond.

A striking feature of the study was the rapid sputum conversion in the 10 patients who attained quiescence; 7 had converted by 1 month and the remaining 3 by 2 months. It is, therefore, easy to differentiate between patients who are responding successfully and those who are not, for the latter usually show a clearcut "fall and rise" phenomenon of the bacterial content of the sputum (Mitchison, 1950; Joiner et al., 1952; Coates et al., 1953; Wallace et al., 1954) in the early months, associated with the emergence of highly streptomycin-resistant organisms. The prolonged treatment of patients who are not likely to show substantial benefit from the combination can therefore be avoided.

Although treatment with the combination in this series was long-term (4 patients with quiescent disease having so far completed 2 years of uninterrupted treatment) and although the patients were drawn from a malnourished section of the community (Tuberculosis Chemotherapy Centre, 1959) there was no clinical evidence of hepatic damage. It has proved possible to use pyrazinamide in a daily dosage of 30 to 40 mg per kg body weight, in the absence of liver function tests, without complications, so that the findings have relevance to Indian conditions, for special laboratory facilities are at present not generally available here. (A further considerable series of patients is under treatment with the combination and hepatic toxicity has so far not been encountered in them either.)

Finally, the study has demonstrated that it is possible to persuade Indian patients to cooperate for periods of 1 to 2 years in ambulatory daily supervised drug administration, which includes streptomycin injections, given especially favorable clinic facilities for the supervision of the patients and the administration of the treatment. In view of the difficulties encountered with the long-term *self-administration* of oral medicaments (WHO Expert Committee on Rheumatic Diseases, 1957; Fox, 1958; Tuberculosis Chemotherapy Centre, 1959; 1960; Velu et al., 1960), this observation raises the possibility that, if effective *intermittent* antituberculosis regimens become available, the organisation of entirely supervised drug-administration might be developed in mass campaigns against tuberculosis, as has been done in the field of leprosy (Lauret et al., 1956; Ross Innes, Personal communication, 1958).

Information on a further series of patients receiving the combination is accumulating and will be reported later.

## SUMMARY

(1) Twenty patients with chronic pulmonary tuberculosis and organisms sensitive to streptomycin were treated with daily streptomycin plus pyrazinamide, the majority attending a clinic daily for the therapy; all had previously been treated with isoniazid plus PAS,

(2) Treatment was stopped in 7 patients after 8 to 10 months because the disease was still active.

(3) Of the 20 patients 13 completed a year's treatment, and 10 attained bacteriological quiescence.

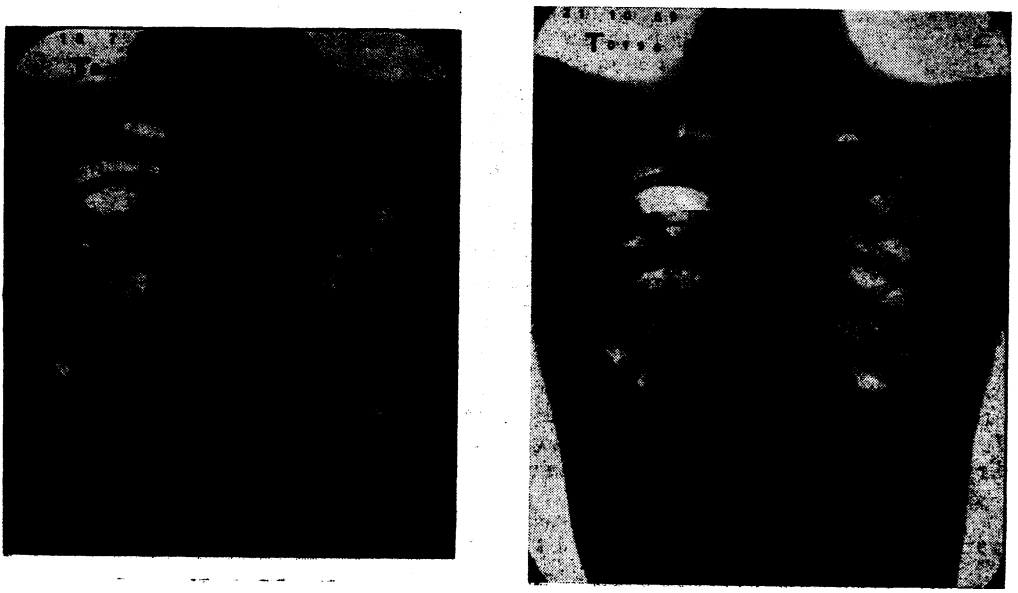
(4) Sputum conversion was very rapid in the patients who attained bacteriological quiescence.

(5) A clearcut "fall and rise" phenomenon associated with a high level of streptomycin resistance was present in the patients whose response was unsatisfactory.

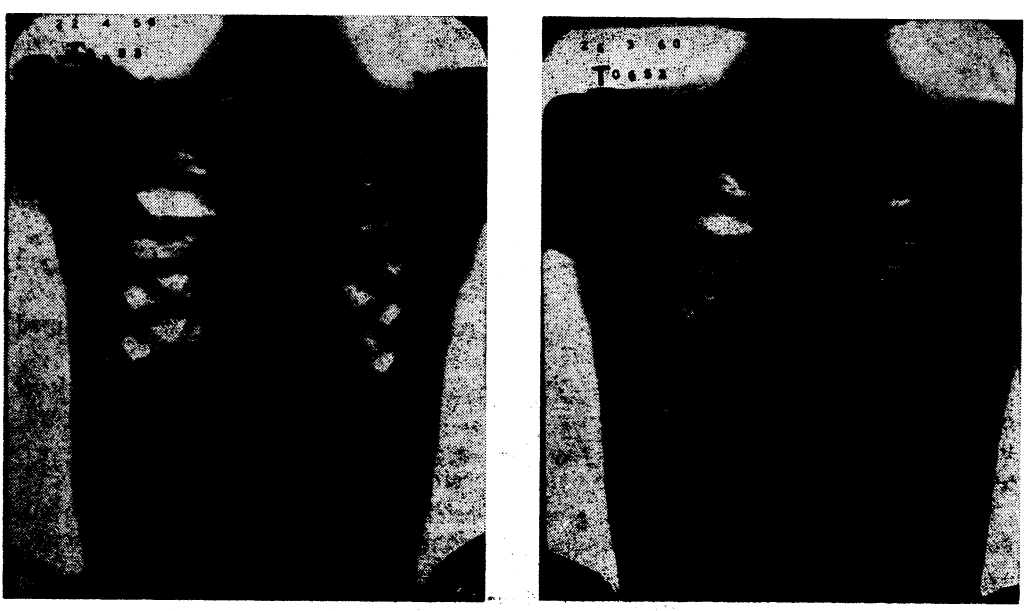
(6) Toxicity was not a problem with either drug.

(7) It is possible in India, given especially favorable clinic facilities, to administer long-term daily streptomycm and pyrazinamide under ambulatory conditions,

**Case No. T.0194—Male, aged 18 years**



**Case No. T.0653 –Male, aged 34 years**



## ILLUSTRATIVE CASES

### Case No. T.0194–Male, aged 18 years

This patient had extensive bilateral pulmonary tuberculosis which responded initially to the combination of isoniazid plus PAS. In the twelfth month, due to a slowly deteriorating lesion (see figure l), treatment with daily streptomycin plus pyrazinamide was commenced, Within a month the sputum became negative and remained so thereafter. Treatment was stopped after 26 months on the combination (see figure 2). During this period 73 consecutive negative cultures were obtained. The patient travelled 10 miles daily for treatment and, in the last 6 months, was in full-time employment.

*Comment :* This case illustrates the rapid disappearance of tubercle bacilli from the sputum and the maintenance of bacteriological negativity, despite persisting extensive residual cavitation after 26 months of treatment with the combination of streptomycin plus pyrazinamide.

Case No. T.0653–Male, aged 34 years

This patient had extensive bilateral pulmonary tuberculosis which responded initially to the combination of isoniazid plus PAS. In the seventeenth month the patient had an haemoptysis and the radiograph at this stage showed a deteriorating lesion (see figure 3). Treatment with daily streptomycin plus pyrazinamide was commenced in sanatorium. Within 2 months the sputum became negative and remained so thereafter. The patient was discharged from sanatorium after 9 months and has so far completed 23 months on the regimen (see figure 4). All the 57 cultures since the second month have been negative. The patient has been back in full-time employment for the last 13 months.

*Comment:* This case also illustrates the rapid disappearance of tubercle bacilli from the sputum and persisting bacteriological negativity, despite extensive residual cavitation after 23 months of treatment with the combination of streptomycin plus pyrazinamide.

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