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# TREATMENT OF PULMONARY TUBERCULOSIS WITH STREPTOMYCIN AND PARA-AMINO-SALICYLIC ACID

## A MEDICAL RESEARCH COUNCIL INVESTIGATION

*(Made with the co-operation of the British Tuberculosis Association Research Committee)*

A controlled investigation into the effects of *para*-amino-salicylic acid (P.A.S.) in the treatment of pulmonary tuberculosis has been completed, and the following is a report of the results. The inquiry was planned and directed by a joint subcommittee of the Medical Research Council's Streptomycin in Tuberculosis Trials Committee and the British Tuberculosis Association's Research Committee. The Subcommittee was composed of the following members: Dr. Geoffrey Marshall (chairman), Professor R. Cruickshank, Dr. Marc Daniels, Dr. W. Pointon Dick, Professor F. R. G. Heaf, Professor A. Bradford Hill, Dr. J. V. Hurford, Dr. K. Perry, Dr. J. G. Scadding, Dr. W. E. Snell, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out, and the clinicians and pathologists co-operating in the trial, were as follows:

*Brompton Hospital, London.*—Clinicians: Dr. J. R. Bignall, Dr. J. W. Crofton (working under the direction of the honorary staff of Brompton Hospital). Pathologists: Dr. J. W. Clegg, Dr. T. D. M. Martin.

*Clare Hall County Hospital, Herts.*—Clinician: Dr. T. A. W. Edwards. Pathologists: Dr. H. Loewenthal, Dr. R. F. Welch.

*Colindale Hospital, London.*—Clinicians: Dr. M. Hemming, Dr. W. C. Harris. Pathologists: Dr. J. L. Hamilton-Paterson, Dr. E. D. Hoare.

*Fazakerley Sanatorium, Liverpool.*—Clinicians: Dr. O. F. Thomas, Dr. J. Hamilton Gifford. Pathologists: Professor A. W. Downie, Dr. C. A. St. Hill.

*Harefield County Hospital, Middlesex.*—Clinicians: Dr. L. E. Houghton, Dr. G. P. Maher-Loughnan. Pathologist: Dr. E. Nassau.

*King George V Sanatorium, Surrey.*—Clinicians: Dr. J. V. Hurford, Dr. W. D. Moore. Pathologist: Dr. N. P. L. Wildy.

*London Chest Hospital, London.*—Clinician: Dr. L. J. Grant. Pathologist: Dr. W. I. Leslie.

*London Hospital Annexe, Essex.*—Clinicians: Dr. K. Perry, Dr. N. Lloyd Rusby, Dr. D. C. L. Beatty. Pathologist: Dr. F. C. O. Valentine.

*Sully Hospital, Glamorgan.*—Clinician: Dr. L. R. West. Pathologist: Dr. Ruth L. Milne.

*Yardley Green Hospital, Birmingham.*—Clinician: Dr. Hector J. T. Ross. Pathologist: Dr. B. R. Sandiford.

The clinicians met periodically under the chairmanship of Dr. Geoffrey Marshall, and the pathologists under the chairmanship of Professor R. Cruickshank. The Medical Research Council's Tuberculosis Research Unit was responsible for the co-ordination of the trial and Professor Bradford Hill for its statistical design; Dr. Marc Daniels, of the Unit's staff, analysed the results and prepared the report for the Committee. The radiological results were assessed by a panel composed of Dr. A. F. Foster Carter, Dr. P. Kerley, and Dr. G. Simon.

### Introduction

In 1948 the Medical Research Council received requests, from the Ministry of Health and from the British Tuberculosis Association, to organize clinical trials of P.A.S. in pulmonary tuberculosis. Favourable effects of the drug had been reported from Sweden by Lehmann (1946). Early observations in this country by different workers were conflicting, and, as a decisive answer had been reached for streptomycin by the method of controlled clinical trial (M.R.C., 1948a), it was agreed by clinicians in doubt about the value of P.A.S. that the method should be applied to trial of this drug.

It was clear, in view of the proved efficacy of streptomycin in the forms of pulmonary tuberculosis considered most suitable for chemotherapy trials, that an investigation with a control group treated by bed-rest only would no longer be possible. The Committee decided, therefore, to compare the effect of P.A.S. treatment in one group of patients with the effect of streptomycin in another group having similar disease. Further, it seemed possible that the combination of P.A.S. with streptomycin might delay or prevent the emergence of streptomycin resistance. Accordingly it was decided to have three concurrent groups, the treatment being in one group P.A.S. alone (P group), in a second streptomycin alone (S group), and in the third streptomycin plus P.A.S. (SP group). Finally, though retrospective comparisons are subject to error, it was hoped that, since exactly the same type of disease as in the first trial was selected, it would also be possible to compare the results in this investigation with those of the control group treated by bed-rest alone in the first trial (M.R.C., 1948a). The inclusion of a streptomycin group in the present trials would afford evidence of the validity of such a comparison between the first and second trials. The first patients were admitted in December, 1948, and by October, 1949, 183 patients had been accepted. In December, 1949, results concerning streptomycin resistance were already so striking that an interim communication was made (M.R.C., 1949). The present report is the full analysis of the trial.

### Plan and Conduct of the Trial

The methods of the investigation were similar in nearly all respects to those of the first trial. They were fully described in the report of that trial; briefly they were as follows:

The type of case to be investigated was acute progressive bilateral pulmonary tuberculosis, believed to be of recent origin, bacteriologically proved, unsuitable for collapse therapy, age group 15 to 30. Letters were sent, through the Regional Hospital Boards, to chest physicians and

medical superintendents of general hospitals in the areas from which the chosen centres could receive patients; the letters outlined the proposed scheme and asked that particulars and *x*-ray films of possibly suitable patients should be sent to the Tuberculosis Research Unit. Particulars and films of cases submitted were considered by the Committee's selection panel, who decided if a case came within the limits of the definition. When a patient had been accepted as suitable, arrangements were made through the Regional Hospital Board for admission to one of the centres; these patients were given high priority, and nearly all were admitted to the respective centre within two weeks of approval.

After acceptance by the panel, the determination of the treatment group (P, S, or SP) in each case was made by reference to a randomly constructed list (based upon random sampling numbers) held confidentially in the Tuberculosis Research Unit. Patients were not told that they were taking part in a special investigation. After admission each patient was under observation for at least one week before treatment for the trial started; during that week all prescribed preliminary examinations were carried out. Clinical observations were entered on standard record forms designed particularly for this trial; these forms provided for details of history, examination on admission, monthly routine re-examinations with assessment of progress since last examination, observation of toxic reactions, temperature and treatment records, and finally a pathological record form. Instructions on required frequency of examinations were given. The nature of the treatment to be followed in each group was laid down, and is described under "Treatment."

When six months' observation had been completed in the required number of cases, all records and *x*-ray films were sent to the M.R.C. Tuberculosis Research Unit for analysis. The analysis presented here is therefore based on all available material from the centres at which the patients were treated, but has been made independently of those centres. The basic analysis was submitted to the clinicians and pathologists at the centres; the comments and discussion in this report represent a consensus of opinion of all those concerned.

## Number of Patients in the Trial

166 patients were available for the analysis of results: 59 in the group treated with P.A.S. (P group), 54 treated with streptomycin (S group), and 53 treated with streptomycin and P.A.S. (SP group). 183 had been accepted, but 12 did not enter the trial, and 5 were later excluded. Of the 12 who did not enter, 3 had died while awaiting admission; 2 died within three days after admission (treatment had not begun); 2 refused to enter hospital; 3 were, after further examination on admission, considered unsuitable for the trial (one of these would have been in the P group, two in the SP group); 2 left hospital after a few days against medical advice. In 5 other patients treatment for the trial was started, but the cases were excluded from the analysis for the following reasons. In one case (P group) the physician in charge decided after a week that the patient should have streptomycin in addition. Two patients—one in the P group, one in the S—left after a month: one was worried about domestic affairs, and the other was discharged because totally uncooperative. In 2 other cases —one in the P group and one SP—treatment was stopped within the first month because of severe toxic reactions; strictly, this should be regarded as a failure of treatment, though it has not been possible to take it into account in the analysis; these cases are described later (see "Toxicity").

## Condition on Admission

Table I shows the condition of patients before the start of treatment, as reflected by their general condition (assessment by the clinician in charge), temperature, and sedimentation rate (Westergren, 200 mm., reading at one hour).

TABLE I.—*Condition on Admission*

| General Condition | Group P | Group S | Group SP | Average Evening Temp. in First Week* | Group P | Group S | Group SP | Sedimentation Rate | Group P | Group S | Group SP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Good.. | 7 | 7 | 8 | Afebrile† .. | 5 | 4 | 7 | 0–10 | 1 | 1 | 1 |
| Fair .. | 27 | 25 | 23 | Less than 99° F. (37·2° C.) but febrile | 20 | 17 | 13 | 11–20 | 2 | 1 | 3 |
| Poor .. | 25 | 22 | 22 | 99–99·9° F. (37·2–37·75° C.) | 18 | 18 | 19 | 21–50 | 23 | 18 | 26 |
| | | | | 100° F.+ (37·8° C.+) | 16 | 15 | 14 | 51+ | 33 | 34 | 22 |
| Total | 59 | 54 | 53 | Total .. | 59 | 54 | 53 | Total | 59 | 54 | 52‡ |

* Temperature taken by mouth.
† A patient was considered afebrile if *all* temperatures recorded were below 99° F. (37·2° C.).
‡ Sedimentation rate not done in one case.

The data indicate that clinically most of the patients were fairly ill, and that the distribution of cases was about equal in the three groups. The SP group had less cases with a sedimentation rate above 50.

Though the main analysis here will be concerned with a comparison of results in these three groups, there is some interest in comparing the results with those obtained in the first M.R.C. trial of streptomycin in pulmonary tuberculosis. The interest particularly concerns a comparison of the results in the P group of the present trial and the control group in the first trial, since there is no other available method of assessing the effects of P.A.S. treatment as compared with treatment by bed-rest alone. It is useful, therefore, to consider how the cases in this trial compare with those admitted to the first streptomycin trial. In the first trial, on admission the general condition was considered to be poor in 50% of the 107 patients and fair in 35%; in the second trial, reported here, the corresponding figures are 42% and 45% of the 166 patients. The sedimentation rate on admission was, in the first trial, above 50 in 61% and between 21 and 50 in 34%; in the second trial it was above 50 in 54% and between 21 and 50 in 41%. The figures suggest that the patients in the second trial were not quite so severely ill as those in the first, but the differences are not significant.

In Table II are set out the main data concerning condition on admission of patients in the control group (C group) of the first trial, alongside those in the P group of the present trial. It can be seen that, judging by the factors listed, the group C and the group P patients are closely comparable.

### X-ray Classification

As in the first trial, the panel of clinicians who were appointed to select cases for the trial adhered so far as was possible to the definition laid down. Cases in which cavitation constituted the predominant lesion were excluded, and so also were cases which, though bilateral, had only a small amount of disease in one lung. The main conditions were that the lesions should be extensive, that they should appear from both the history and the *x*-ray appearances to be of fairly recent origin, and that in the judgment of the panel the patients could reasonably be regarded as unsuitable for collapse therapy at least for some months. As in the first trial, however, it was found that there were variations within the limits of the definition:

TABLE II.—*Condition on Admission. Comparison with First Trial*

| General Condition | C Group 1st Trial | | P Group 2nd Trial | | Max. Evening Temp. in First Week* | C Group 1st Trial | | P Group 2nd Trial | | Sedimentation Rate | C Group 1st Trial | | P Group 2nd Trial | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | | No. | % | No. | % | | No. | % | No. | % |
| Good .. .. | 8 | *15* | 7 | *12* | 98–98·9° F. (36·7–37·15° C.) | 4 | *8* | 5 | *8* | 0–10 .. | 0 | *0* | *1* | *2* |
| Fair .. .. | 20 | *39* | 27 | *46* | 99–99·9° F. (37·2–37·75° C.) | 12 | *23* | 21 | *36* | 11–20 .. | 2 | *4* | 2 | *3* |
| Poor .. .. | 24 | *46* | 25 | *42* | 100–100·9° F. (37·8–38·85° C.) | 17 | *33* | 13 | *22* | 21–50 .. | 20 | *39* | 23 | *39* |
| | | | | | 101° F.+ (38·3° C.+) | 19 | *36* | 20 | *34* | 51+ .. | 29 | *57* | 33 | *56* |
| Total .. | 52 | *100* | 59 | *100* | Total .. | 52 | *100* | 59 | *100* | Total .. | 51† | *100* | 59 | *100* |

* Not comparable with Table I, in which figures are based on *average* evening temperature. † Examination not done in one case.

many cases accepted for the trial had less extensive lesions than others, and many had much cavitation, while others had none or very little. Nevertheless, an assessment of the degree of cavitation, made on an arbitrary basis by one radiologist who viewed all the films, shows that distribution on the basis of extent of cavitation was similar throughout the three groups (Table III).

TABLE III.—*Extent of Cavitation*

| Group | Total | Extent of Cavitation on Admission* | | | |
|---|---|---|---|---|---|
| | | Nil | One-plus | Two-plus | Three-plus |
| P .. | 59 | 9 | 16 | 26 | 8 |
| S .. | 54 | 5 | 21 | 21 | 7 |
| SP .. | 53 | 9 | 19 | 18 | 7 |
| Total | 166 | 23 | 56 | 65 | 22 |

* Assessment on a single film before treatment started. Tomograms were not taken into account.

In the first trial a simpler classification was used, based on whether gross cavitation (large or multiple cavities) was present or absent: of the 107 patients, 62 (58%) showed large or multiple cavities in the film taken on admission. If categories 2-plus and 3-plus in Table III are regarded as corresponding to the group showing large or multiple cavities in the first trial, the distribution appears to be similar: 87 of 166 cases, or 52%, were thus classified. Taking specifically again the C and P groups: of the 52 C cases in the first trial, 30 (58%) had gross cavitation; of the 59 P cases in the second trial, 34 (again 58%) had 2-plus or 3-plus cavitation.

On the basis of the data concerning condition on admission and the *x*-ray classification, added to the fact that the same panel of clinicians selected the cases on the same criteria as before, it may be concluded that the two series are reasonably comparable.

## Treatment

### A. First Three Months

Treatment of the three groups in the present trial was as follows:

*P group.*—20 g. daily of the sodium salt of P.A.S. by mouth, in four doses of 5 g. at 8 a.m., noon, 4 p.m., and 8 p.m. The P.A.S. was given in solution suitably flavoured, and only in capsules if not tolerated in solution.

*S group.*—Streptomycin* only, 1 g. (1 million units) a day, in one dose by intramuscular injection at 8 a.m.

*SP group.*—P.A.S. plus streptomycin,* in doses as for the two other groups.

Treatment in each case started at the end of a preliminary observation week, during which all initial examinations were made, and was given in each group for three months continuously. It was recommended that no other treatment apart from bed-rest be given during these three months unless the condition should so change that other measures became necessary and urgent. In fact, artificial pneumothorax was induced in one SP case in the third month.

*The streptomycin used was in the form of the sulphate, obtained from one manufacturer.

### B. Second Three Months

The recommended procedure was that the three months of chemotherapy should be followed by a month of observation on bed-rest alone. At the end of this period—that is, four months after the start of treatment for this trial—any other treatment might be initiated. This decision was taken on the basis of experience already acquired with chemotherapy; it was felt that in many cases collapse therapy could not reasonably be withheld beyond this time. The additional treatment given in this period may be considered under the headings of (1) collapse therapy, and (2) streptomycin in the P group.

(1) *Collapse Therapy.*—Collapse therapy was applied in 20 P cases, 22 S cases, and 22 SP cases; pneumonectomy was performed in one P case and one SP case. Although it was recommended that collapse therapy should not be applied before the fifth month, exception was to be made for patients believed to require collapse therapy urgently before that time. In the P group it was begun in the fourth month in 7 cases and in the fifth or sixth month in the others. In the S group 6 were begun in the fourth month, and in the SP group 7; in addition, one (already mentioned) was begun in the third month in the SP group. Thus, although there was more frequent departure from the recommended procedure than expected, it occurred fairly equally in all three treatment groups. The details of collapse therapy applied are shown in Table IV.

TABLE IV.—*Collapse Therapy and Chest Surgery Initiated During the Trial*

| | P | S | SP |
|---|---|---|---|
| Artificial pneumothorax { Maintained .. .. | 10 | 5 | 12 |
| Artificial pneumothorax { Abandoned .. .. | 4 | 4 | 4 |
| Artificial pneumoperitoneum .. .. .. | 7* | 13 | 8* |
| Thoracoplasty .. .. .. .. .. .. | 1 | 0 | 0 |
| Pneumonectomy .. .. .. .. .. | 1 | 0 | 1 |
| Total patients with collapse therapy or pneumonectomy .. .. .. .. .. .. .. | 21 | 22 | 23 |

* Two P cases and 2 SP cases after abandoned artificial pneumothorax.

(2) *Streptomycin.*—Four patients in the P group were given streptomycin after the end of their three months of treatment for the trial. To one patient streptomycin was given for six weeks, starting a week after the three-months period, and an artificial pneumoperitoneum was induced five days later. During the first three months her general condition was thought to have improved slightly, but she had lost weight and the E.S.R. remained high (75); in the fourth month she made considerable improvement, gained 10 lb. (4.5 kg.), and the E.S.R. came down. In another

case streptomycin and P.A.S. were given in the fifth and sixth months; in the fourth month there had been definite clinical deterioration, but after the new course of therapy the patient improved rapidly. In a third case, also, there was definite improvement during a course of combined streptomycin and P.A.S. therapy in the fourth and fifth months. The fourth patient was given streptomycin at 4½ months, and pneumonectomy was performed two weeks later. In the first three cases there was improvement that might well be attributed to streptomycin treatment. Though allowance for these cases cannot be made in the analysis, it should be remembered that by the addition of streptomycin treatment the overall results in the P group were slightly better than they would otherwise have been.

### Toxicity

Giddiness was recorded during treatment in 12% of patients having streptomycin, either alone or with P.A.S., but in only one patient was the symptom severe. Caloric tests of vestibular function were not carried out regularly. One patient having streptomycin alone had a slight transient rash.

Three patients having P.A.S. alone developed rashes during treatment. In two the rash was not severe and treatment could be continued. The other patient developed an extensive rash at the end of the fourth week; it was accompanied by a high fever, and treatment had to be stopped; this case has been excluded from the main analysis.

Four patients in the SP group developed rashes. It is not known whether the rashes were due to streptomycin or P.A.S. In two the rash subsided rapidly. In another there was a marked toxic reaction 3½ weeks after starting treatment; the symptoms responded dramatically to cessation of chemotherapy and did not reappear on its resumption three weeks later. In a fourth there was a very intense toxic general reaction from the 24th day; after several attempts to resume the prescribed therapy, each producing a marked reaction, dihydrostreptomycin was given and was well tolerated. This case is excluded from the main analysis.

Gastro-intestinal symptoms were common in those having P.A.S., being recorded in 58% of the P group and 51% of the SP group. The recorded incidence varied widely between the centres: in some centres slight symptoms were not noted. In most centres the symptoms occurred slightly more often in women than in men. Nausea at some period during treatment was recorded in 38% of all those having P.A.S.; diarrhoea was recorded in 33% and vomiting in 24%. In only one instance was it necessary to reduce the daily dose of P.A.S., and the gastro-intestinal symptoms did not cause treatment to be stopped in any patient in either treatment group.

### Results at End of Six Months

#### Mortality

In each group of the present trial one patient died within the treatment period: one P case on the eighth day, one S case in the seventh week, one SP case in the third week. Five other deaths occurred subsequently: one in the P group in the fourth month, one in the S group in the fifth month, and three more in the S group in the sixth month. The differences in mortality are not statistically significant. The occurrence of deaths in the S group in the fifth and sixth months is similar to what was observed in the S group in the first trial, when four deaths occurred in the same period. The fatality rate of 3% in the P group is considerably lower than that of the control group in the first streptomycin trial, which was 27%; the difference is significant.

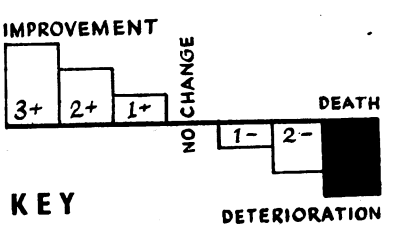
### Results Based on Assessment of Radiological Appearances

TABLE V.—*Assessment of Radiological Appearance at Six Months as Compared with Appearance on Admission*

| Second Trial: Radiological Assessment | P Group No. | P Group % | S Group No. | S Group % | SP Group No. | SP Group % | First Trial: Radiological Assessment | Control Group No. | Control Group % | Streptomycin Group No. | Streptomycin Group % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Improvement: | | | | | | | | | | | |
| Three-plus | 1 | 2 | 9 | 17 | 7 | 13 | Considerable improvement | 4 | 8 | 28 | 51 |
| Two-plus.. | 12 | 20 | 21 | 39 | 20 | 38 | Moderate or slight improvement | 13 | 25 | 10 | 18 |
| One-plus.. | 20 | 34 | 10 | 18 | 19 | 36 | | | | | |
| No material change | 20 | 34 | 3* | 6 | 3 | 6 | No material change | 3 | 6 | 2 | 4 |
| Deterioration: | | | | | | | Moderate or slight deterioration | 12 | 23 | 5 | 9 |
| One-minus | 4 | 7 | 5 | 9 | 2 | 4 | | | | | |
| Two-minus | 0 | — | 1 | 2 | 1 | 2 | Considerable deterioration | 6 | 11 | 6 | 11 |
| Deaths .. | 2 | 3 | 5 | 9 | 1 | 2 | Deaths | 14 | 27 | 4 | 7 |
| Total .. | 59 | 100 | 54 | 100 | 53 | 101 | Total | 52 | 100 | 55 | 100 |

* Includes one patient discharged at 4 months; the assessment at that date was "no change."

Considering first of all the results in the present series on the basis of *x* ray assessment (Table V and Fig. 1), the first outstanding fact is that in all three of these groups of patients, admitted with severe progressive disease, the majority had shown improvement at the end of six months. Secondly, improvement was noted in more patients of the groups receiving streptomycin than of the group receiving P.A.S. only: the total improved were 56% in the P group, 74% in the S group, 87% in the SP group. Furthermore, in the patients receiving streptomycin the proportion showing 2-plus or 3-plus improvement was greater than in the group receiving P.A.S. alone: roughly half the former and slightly less than a quarter of the latter showed improvement




Key to Charts 1, 2, and 3.

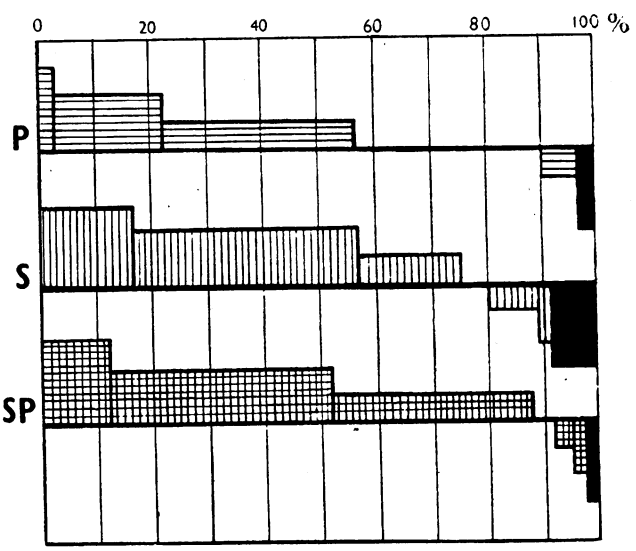



FIG. 1.—Assessment of radiological appearance at six months compared with appearance at start of chemotherapy

of this degree. The difference is statistically significant. It is reflected conversely by the large number in the P group (34%) who showed no material change over the six months, as compared with 6% in both the S and the SP groups. Summarizing, while results were good in all groups, they were definitely less good in the P group than in the two others. So far as the difference between the S and SP groups is concerned, while the proportion of patients showing improvement, and among these considerable improvement, was high in both groups, the overall improvement was higher in the SP group than in the S group. In the SP group one patient died and three others deteriorated; in the S group five died and six others deteriorated. These differences, however, are below the level of statistical significance.

Coming now to a comparison with the results of the first trial, it is here again striking that the group receiving only P.A.S. showed far better results than the control group of patients with similar disease but treated by bed-rest alone, though it must be remembered that three P cases were apparently improved by streptomycin given in the later months. Of the control group 33% showed improvement, compared with 56% of the P group; 61% had at the end of six months deteriorated or died, compared with only 10% of the P group. It is obvious that, while the patients receiving only P.A.S. fared definitely less well than those receiving streptomycin, they fared very much better than if they had been treated by bed-rest alone.

TABLE VI.—*Radiological Assessment at Six Months. Results Related to Condition on Admission*

| Average Temp. During Week Before Treatment Started | Cavitation | Group | Total | Radiological Assessment at 6 Months: Improvement 3-plus or 2-plus | Improvement 1-plus | No Change | Deterioration | Deaths |
|---|---|---|---|---|---|---|---|---|
| 100° F.+ .. | Gross | P | 14 | 1 | 5 | 3 | 3 | 2 |
| | | S | 9 | 3 | 0 | 1 | 2 | 3 |
| | | SP | 7 | 4 | 0 | 0 | 2 | 1 |
| | Other | P | 2 | 0 | 1 | 1 | 0 | 0 |
| | | S | 6 | 2 | 2 | 0 | 0 | 2 |
| | | SP | 7 | 2 | 3 | 1 | 1 | 0 |
| | Total | P | 16 | 1 | 6 | 4 | 3 | 2 |
| | | S | 15 | 5 | 2 | 1 | 2 | 5 |
| | | SP | 14 | 6 | 3 | 1 | 3 | 1 |
| 99–99·9° F. | Gross | P | 9 | 1 | 5 | 2 | 1 | 0 |
| | | S | 12 | 6 | 4 | 1 | 1 | 0 |
| | | SP | 10 | 4 | 5 | 1 | 0 | 0 |
| | Other | P | 9 | 0 | 3 | 6 | 0 | 0 |
| | | S | 6 | 3 | 3 | 0 | 0 | 0 |
| | | SP | 9 | 5 | 4 | 0 | 0 | 0 |
| | Total | P | 18 | 1 | 8 | 8 | 1 | 0 |
| | | S | 18 | 9 | 7 | 1 | 1 | 0 |
| | | SP | 19 | 9 | 9 | 1 | 0 | 0 |
| Less than 99° F. | Gross | P | 11 | 4 | 3 | 4 | 0 | 0 |
| | | S | 7 | 4 | 1 | 1 | 1 | 0 |
| | | SP | 8 | 5 | 2 | 1 | 0 | 0 |
| | Other | P | 14 | 7 | 3 | 4 | 0 | 0 |
| | | S | 14 | 12 | 0 | 0 | 2 | 0 |
| | | SP | 12 | 9 | 3 | 0 | 0 | 0 |
| | Total | P | 25 | 11 | 6 | 8 | 0 | 0 |
| | | S | 21 | 16 | 1 | 1 | 3 | 0 |
| | | SP | 20 | 14 | 5 | 1 | 0 | 0 |

### Results Related to Condition on Admission

It is interesting to consider the effects of the three types of treatment in relation to the clinical condition of the patients at the start of treatment. The two most important single factors of variation in condition within each group were the temperature and the extent of cavitation. In Table VI the results of *x*-ray assessment at six months after the start of treatment are shown in relation to the temperature and extent of cavitation on admission. To simplify the figures, those with cavitation classified as 2-plus or 3-plus are here grouped as having "gross" cavitation, while those classified as 1-plus or with no cavitation have been grouped under "other" cases.

Table VI shows that in all three treatment groups the worst results were in the patients whose average temperature at the start of treatment was over 100° F. (37.8° C.), and all the deaths occurred among such cases. Within this group the results were particularly bad among the patients who had gross cavitation. By chance the P group had a larger number of these patients with gross cavitation and high temperatures than occurred in the other two groups. It should be noted that only in the least febrile patients was considerable improvement (2-plus or 3-plus) seen in the P group on a scale comparable with the groups receiving streptomycin; here 11 of 25 P patients showed considerable improvement, compared with 16 of 21 S patients and 14 of 20 SP patients. Among those with average temperatures over 99° F. (37.2° C.), only two out of 34 P patients showed considerable improvement, compared with 14 of 33 S patients and 15 of 33 SP patients.

As might be expected, the results were generally less good among patients with gross cavitation than among the others.

### Results in Men and Women

The results, considered separately for men and women, are shown in Table VII and Fig. 2. The results were better in women than in men; the differences in results for all men and all women are statistically significant, and the same trends appear in each of the three treatment groups. In each group more deteriorated or died among the men than among the women, and fewer improved. Three-plus improvement was seen in 4% of the men and in 15% of the women; 2- or 3-plus improvement was seen in 30% of the men and in 52% of the women. The results in the 30 women in the SP group were remarkable: there was

TABLE VII.—*Radiological Assessment at Six Months. Results Related to Sex*

| Group | Sex | Total | | Radiological Assessment at Six Months: Improvement 3-plus | | Improvement 2-plus | | Improvement 1-plus | | No Change | | Deterioration 1-minus | | Deterioration 2-minus | | Deaths | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| P | M | 30 | *100* | 0 | *0* | 5 | *17* | 10 | *33* | 11 | *37* | 3 | *10* | 0 | *0* | 1 | *3* |
| | F | 29 | *99* | 1 | *3* | 7 | *24* | 10 | *35* | 9 | *31* | 1 | *3* | 0 | *0* | 1 | *3* |
| S | M | 20 | *100* | 1 | *5* | 8 | *40* | 5 | *25* | 1 | *5* | 2 | *10* | 0 | *0* | 3 | *15* |
| | F | 34 | *101* | 8 | *24* | 13 | *38* | 5 | *15* | 2 | *6* | 3 | *9* | 1 | *3* | 2 | *6* |
| SP | M | 23 | *99* | 2 | *9* | 6 | *26* | 10 | *43* | 2 | *9* | 1 | *4* | 1 | *4* | 1 | *4* |
| | F | 30 | *100* | 5 | *17* | 14 | *47* | 9 | *30* | 1 | *3* | 1 | *3* | 0 | *0* | 0 | *0* |
| All | M | 73 | *99* | 3 | *4* | 19 | *26* | 25 | *34* | 14 | *19* | 6 | *8* | 1 | *1* | 5 | *7* |
| | F | 93 | *100* | 14 | *15* | 34 | *37* | 24 | *26* | 12 | *13* | 5 | *5* | 1 | *1* | 3 | *3* |

deterioration in only one case; 28 improved, and in 19 of them the improvement was 2- or 3-plus.

Only persons aged 15–30 were included in this trial; the same differences between results in males and females appear within the separate age groups 15–19, 20–24, and 25–30. On analysis of the data concerning condition on admission there is no disparity between the two sexes to account for the difference in results; while on the one hand more men had temperatures of 100° F. or over (30% compared with 23% of women), on the other hand more women had 3-plus cavitation (18% compared with 7% of men). From the data available on serum drug levels in this trial, there is no indication that the levels reached were higher or were maintained longer in women than in men.

There was a greater proportion of men in the P group than in the other two, and this could have weighted the

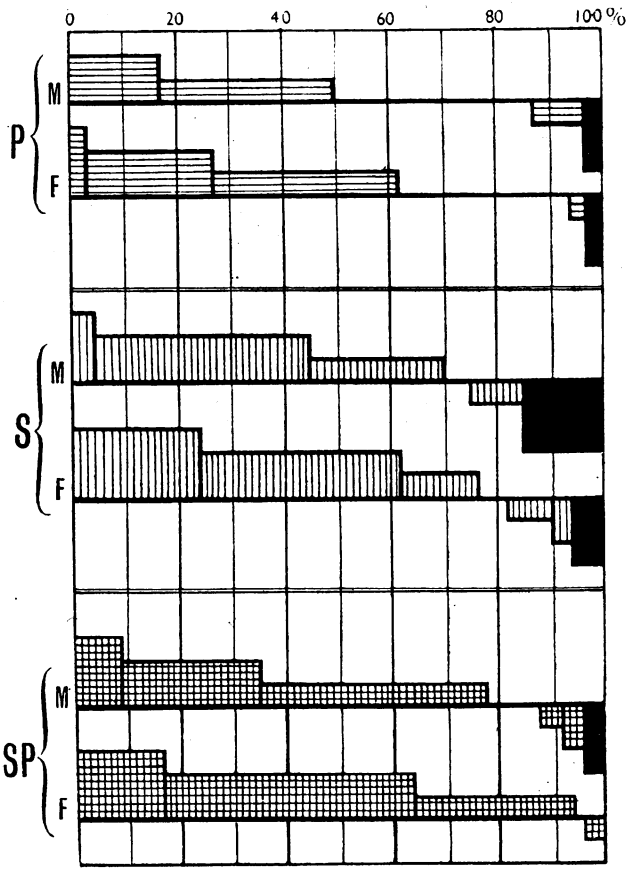



FIG. 2.—Assessment of radiological appearance at six months compared with appearance at start of chemotherapy. Males and females.

results unfavourably in the P group; but the differences between results in males and females in this group are smaller than in the others, and the weighting is negligible.

It is interesting to note that in the first trial a higher mortality in males than in females occurred in both S and C groups, but the differences were not large enough to be significant.

## Clinical Changes during the Period of Trial

### Division of Periods for Assessment

Assessment of changes has been made to cover four separate periods: the first two months, the third month, the fourth month, and the last two months. It was thought useful to analyse what was happening before the end of the three-month treatment period; assessment at one month would have yielded little result, as changes were then not yet evident, especially as regards *x*-ray appearances; the first period of two months was therefore chosen, and a further period of one month carrying on to the end of treatment. The fourth month had been prescribed as a month for observation after the end of treatment, and it was requested that, where possible, other treatment should not be introduced at that time. Finally, during the last two months of the six months for the trial, clinicians were at liberty to institute any other form of therapy. It was therefore necessary to have a separate assessment for the fourth month and for the last two months.

### General Condition

As in the previous trial, the assessment of changes in the general condition was made by clinicians in charge of the patients, and constituted an overall impression based on clinical facts and on the patient's appearance and feeling of well- or ill-being.

It is obvious from Table VIII that in all three groups the great majority of patients improved. So far as the overall improvement in the six months is concerned, there is little difference between the three groups except in

TABLE VIII.—*Progress in General Condition after Start of Treatment*

| Period (months from start of treatment) | Group | Total | Improvement | | No Change | Deterioration | Deaths |
|---|---|---|---|---|---|---|---|
| | | | 2-plus | 1-plus | | | |
| 0–2 | P | 59 | 5 | 43 | 7 | 3 | 1 |
| | S | 54 | 13 | 38 | 2 | 0 | 1 |
| | SP | 53 | 20 | 26 | 4 | 2 | 1 |
| 2–3 | P | 58 | 0 | 26 | 28 | 4 | 0 |
| | S | 53 | 1 | 31 | 20 | 1 | 0 |
| | SP | 52 | 2 | 34 | 14 | 2 | 0 |
| 0–3 | P | 59 | 7 | 43 | 5 | 3 | 1 |
| | S | 54 | 17 | 35 | 1 | 0 | 1 |
| | SP | 53 | 23 | 25 | 2 | 2 | 1 |
| 3–4 | P | 58 | 2* | 23 | 26 | 6 | 1 |
| | S | 53 | 0 | 21 | 23 | 9 | 0 |
| | SP | 52 | 0 | 35 | 15 | 2 | 0 |
| 0–4 | P | 59 | 11* | 38 | 7 | 1 | 2 |
| | S | 54 | 20 | 29 | 2 | 2 | 1 |
| | SP | 53 | 31 | 18 | 2 | 1 | 1 |
| 4–6 | P | 57 | 2† | 28 | 25 | 2 | 0 |
| | S | 52 | 1 | 16 | 22 | 9 | 4 |
| | SP | 52 | 14 | 24 | 17 | 7 | 0 |
| 0–6 | P | 59 | 29† | 33 | 3 | 2 | 2 |
| | S | 53 | 34 | 20 | 1 | 3 | 5 |
| | SP | 53 | 4 | 15 | 0 | 3 | 1 |

* Marked improvement followed streptomycin treatment in one case.
† Marked improvement followed SP treatment in two cases.

the proportion showing marked improvement, which was greatest in the SP group and least in the P group. Another important fact is that marked improvement occurred earlier in the groups receiving streptomycin than in the P group; in the first two months only 5 patients in the P group showed marked improvement, compared with 13 S patients and 20 SP patients. Finally, clinical deterioration occurred most frequently after treatment had stopped, and more in the S group than in the two other groups: in the fourth month deterioration was seen in 9 S patients, compared with 2 SP patients and 7 P patients (including one death); in the last two months clinical deterioration occurred in 13 S patients (including 4 deaths), compared with 7 SP and 2 P patients. The statistical significance of these differences is doubtful, and account must be taken of the effect of streptomycin treatment given in 4 P cases.

Comparing the results with those of the control group in the first trial, we find that deterioration was seen there in 50% of patients (including 27% deaths), compared with 6.8% in the P group of the second trial (including 3.4% deaths).

### Temperature

Patients were regarded as afebrile if their evening temperatures were below 99° F. every day for a week before the date considered. Table IX shows, for patients who were febrile on admission, the results at successive periods after the start of treatment.

TABLE IX.—*Temperature Changes in Patients Febrile on Admission*

| Average Evening Temperature During Week Following Admission | Group | Total | No. of Patients Afebrile at End of: | | | |
|---|---|---|---|---|---|---|
| | | | 2 Months | 3 Months | 4 Months | 6 Months |
| Less than 99° F. .. | P | 20 | 15 | 15 | 16 | 16 |
| | S | 17 | 15 | 13 | 13 | 15 |
| | SP | 13 | 9 | 9 | 11 | 10 |
| 99–99·9° F. .. | P | 18 | 10 | 11 | 11 | 14 |
| | S | 18 | 14 | 12 | 11 | 11 |
| | SP | 19 | 12 | 13 | 17 | 14 |
| 100° F.+ .. .. | P | 16 | 4 | 1 | 4 | 5 |
| | S | 15 | 5 | 6 | 2 | 5 |
| | SP | 14 | 7 | 7 | 7 | 8 |

There is very little difference between the groups. Response of temperature to treatment was rapid in all three groups. Almost the maximum effect was obtained in the first two months, at which time 29 of the P group, 34 of the S group, and 28 of the SP group were afebrile. As might be expected, the results were least impressive in the patients most febrile on admission; in these cases the SP patients fared perhaps better than the others, but the differences are too small to be significant.

### Weight

The overall weight changes are shown in Table X. During the three-months treatment period there was good weight gain in all three groups, but particularly in the S group. The smaller gain in the other two can be ascribed to the digestive disturbance caused by P.A.S. treatment in the large dosage given. Seventeen S patients each gained 14 lb. (6.35 kg.) or more during this period, compared with 11 P patients and 6 SP patients.

During the following three months there was a reversal of this picture. The average gain during this period was 8.4 lb. (3.8 kg.) in the SP group, 6.2 lb. (2.8 kg.) in the P group, and 2.6 lb. (1.1 kg.) in the S group. Seven SP patients gained 14 lb. or more, compared with 5 P patients and 4 S patients.

Over the whole six-month period there was no significant difference in average weight gain in the three groups. The numbers who gained 14 lb. or more were: in the P group 23, in the S group 19, and in the SP group 27.

### Sedimentation Rate

A fall in the sedimentation rate after the start of treatment was seen in all three treatment groups. It occurred more rapidly in the SP group than in the other two, and at the end of six months twice as many of the SP group had sedimentation rates within normal limits as in the other two groups. The difference is significant. The results appear to be no better in the S group than in the P group.

TABLE XI.—*Changes in Sedimentation Rate (Westergren)*

| | Group | Total | Sedimentation Rate | | | | Deaths |
|---|---|---|---|---|---|---|---|
| | | | 0–10 | 11–20 | 21–50 | 51+ | |
| At start of treatment | P | 59 | 1 | 2 | 23 | 33 | — |
| | S | 54 | 1 | 1 | 18 | 34 | — |
| | SP | 52* | 1 | 3 | 26 | 22 | — |
| At 2 months | P | 59 | 5 | 13 | 24 | 16 | 1 |
| | S | 54 | 6 | 11 | 13 | 23 | 1 |
| | SP | 53 | 11 | 12 | 18 | 11 | 1 |
| At 3 months | P | 59 | 8 | 13 | 25 | 12 | 1 |
| | S | 54 | 9 | 8 | 19 | 17 | 1 |
| | SP | 53 | 11 | 14 | 18 | 9 | 1 |
| At 4 months | P | 59 | 7 | 11 | 21 | 18 | 2 |
| | S | 54 | 8 | 7 | 23 | 15 | 1 |
| | SP | 53 | 15 | 14 | 16 | 7 | 1 |
| At 6 months | P | 59 | 11 | 16 | 17 | 13 | 2 |
| | S | 53* | 11 | 8 | 18 | 11 | 5 |
| | SP | 53 | 21 | 9 | 18 | 4 | 1 |

* Result not recorded in one case.

### Changes in Radiological Appearances during Period of Trial

As in the first trial, chest radiographs of all patients in the trial were viewed by an independent panel, composed of two radiologists and one clinician. The clinician was medical superintendent of a sanatorium to which some of the patients from one centre were sent after the trial; apart from this, members of the panel were not acquainted with any of the cases involved. Assessment was made in the same way as before, except that under "improvement" and "deterioration" three degrees of change were allowed. In fact, no films were classed as showing deterioration 3-minus. The measure of agreement was much the same as that found before, and the same method of dealing with cases of disagreement was adopted.

The results are tabulated in Table XII, and shown graphically in Fig. 3.

The overall results for the six months (0–6) have already been discussed. Considering now the changes at different periods of the six months, though on the whole most patients in each group fared well throughout the trial, certain differences emerge. During the three-months treatment period very few cases deteriorated, but the number of patients who improved was significantly greater in the two groups receiving streptomycin than in that receiving P.A.S. only, and in this group the number showing no radiological change was correspondingly higher. These differences are statistically significant.

During the month following the end of treatment (3–4 months), death occurred in one P case and deterioration

TABLE X.—*Weight Changes**

| Period | Treatment Group | No. of Patients Weighed | No. of Patients Showing Weight Change | | | | | | | Total Gain in Weight (All Patients) (lb.) | Average Gain in Weight per Patient (lb.) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lost Weight | | | No Change | Gained Weight | | | | |
| | | | 14 lb. or More | 7–13 lb. | Less than 7 lb. | | Less than 7 lb. | 7–13 lb. | 14 lb. or More | | |
| First three months | P | 58 | 0 | 4 | 4 | 4 | 22 | 13 | 11 | +370 | +6·4 |
| | S | 52 | 0 | 1 | 4 | 1 | 13 | 16 | 17 | +556 | +10·7 |
| | SP | 49 | 1 | 3 | 2 | 1 | 16 | 20 | 6 | +292 | +6·0 |
| Second three months | P | 56 | 0 | 1 | 10 | 2 | 14 | 24 | 5 | +348 | +6·2 |
| | S | 48 | 0 | 3 | 12 | 3 | 20 | 6 | 4 | +127 | +2·6 |
| | SP | 49 | 0 | 0 | 4 | 0 | 18 | 20 | 7 | +414 | +8·4 |
| Six months | P | 56 | 0 | 2 | 3 | 0 | 9 | 19 | 23 | +714 | +12·8 |
| | S | 48 | 2 | 0 | 3 | 1 | 6 | 17 | 19 | +676 | +14·1 |
| | SP | 49 | 0 | 2 | 1 | 1 | 5 | 13 | 27 | +706 | +14·4 |

* For conversion into metric weights, 1 lb. = 454 g.

TABLE XII.—*Changes in the Radiological Picture*

| Interval | Group | Total | | Radiological Assessment: Improvement 3-plus | | Improvement 2-plus | | Improvement 1-plus | | No Change 0 | | Deterioration 1-minus | | Deterioration 2-minus | | Died | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| 0–2 Admission to end of 2 months | P | 59 | 100 | 0 | 0 | 1 | 1·7 | 21 | 35·6 | 34 | 57·6 | 2 | 3·4 | 0 | 0 | 1 | 1·7 |
| | S | 54 | 100 | 0 | 0 | 5 | 9·3 | 24 | 44·4 | 21 | 38·9 | 3 | 5·6 | 0 | 0 | 1 | 1·8 |
| | SP | 53 | 100 | 0 | 0 | 2 | 3·8 | 24 | 45·3 | 26 | 49·1 | 0 | 0 | 0 | 0 | 1 | 1·9 |
| 2–3 months .. | P | 58 | 100 | 0 | 0 | 0 | 0 | 14 | 24·1 | 43 | 74·1 | 1 | 1·7 | 0 | 0 | 0 | 0 |
| | S | 53 | 100 | 0 | 0 | 0 | 0 | 21 | 39·6 | 31 | 58·5 | 1 | 1·9 | 0 | 0 | 0 | 0 |
| | SP | 52 | 100 | 0 | 0 | 0 | 0 | 25 | 48·1 | 26 | 50·0 | 1 | 1·9 | 0 | 0 | 0 | 0 |
| 0–3 months .. | P | 59 | 100 | 0 | 0 | 5 | 8·5 | 23 | 39·0 | 27 | 45·8 | 3 | 5·1 | 0 | 0 | 1 | 1·7 |
| | S | 54 | 100 | 1 | 1·8 | 11 | 20·4 | 26 | 48·2 | 13 | 24·1 | 1 | 1·8 | 1 | 1·8 | 1 | 1·8 |
| | SP | 53 | 100 | 0 | 0 | 9 | 17·0 | 31 | 58·5 | 11 | 20·8 | 1 | 1·9 | 0 | 0 | 1 | 1·9 |
| 3–4 months .. | P | 58 | 100 | 0 | 0 | 0 | 0 | 7 | 12·1 | 50 | 86·2 | 0 | 0 | 0 | 0 | 1 | 1·7 |
| | S | 53 | 100 | 0 | 0 | 0 | 0 | 14 | 26·4 | 36 | 67·9 | 3 | 5·7 | 0 | 0 | 0 | 0 |
| | SP | 52 | 100 | 0 | 0 | 0 | 0 | 17 | 32·7 | 35 | 67·3 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0–4 months .. | P | 59 | 100 | 0 | 0 | 8 | 13·6 | 22 | 37·3 | 24 | 40·7 | 3 | 5·1 | 0 | 0 | 2 | 3·4 |
| | S | 54 | 100 | 3 | 5·6 | 16 | 29·6 | 21 | 38·9 | 10 | 18·5 | 1 | 1·8 | 2 | 3·7 | 1 | 1·8 |
| | SP | 53 | 100 | 2 | 3·8 | 14 | 26·4 | 26 | 49·1 | 9 | 17·0 | 1 | 1·9 | 0 | 0 | 1 | 1·9 |
| 4–6 months .. | P | 57 | 100 | 0 | 0 | 0 | 0 | 18 | 31·6 | 34 | 59·6 | 5 | 8·8 | 0 | 0 | 0 | 0 |
| | S | 52* | 100 | 0 | 0 | 1 | 1·9 | 23 | 44·2 | 16 | 30·8 | 6 | 11·6 | 2 | 3·8 | 4 | 7·7 |
| | SP | 52 | 100 | 0 | 0 | 0 | 0 | 28 | 53·8 | 19 | 36·5 | 4 | 7·7 | 1 | 1·9 | 0 | 0 |
| 0–6 months .. | P | 59 | 100 | 1 | 1·7 | 12 | 20·3 | 20 | 33·9 | 20 | 33·9 | 4 | 6·8 | 0 | 0 | 2 | 3·4 |
| | S | 54 | 100 | 9 | 16·7 | 21 | 38·9 | 10 | 18·5 | 3† | 5·6 | 5 | 9·3 | 1 | 1·9 | 5 | 9·3 |
| | SP | 53 | 100 | 7 | 13·2 | 20 | 37·7 | 19 | 35·9 | 3 | 5·7 | 2 | 3·8 | 1 | 1·9 | 1 | 1·9 |

* One patient was discharged at 4 months. † Includes assessment of one case at 4 months.

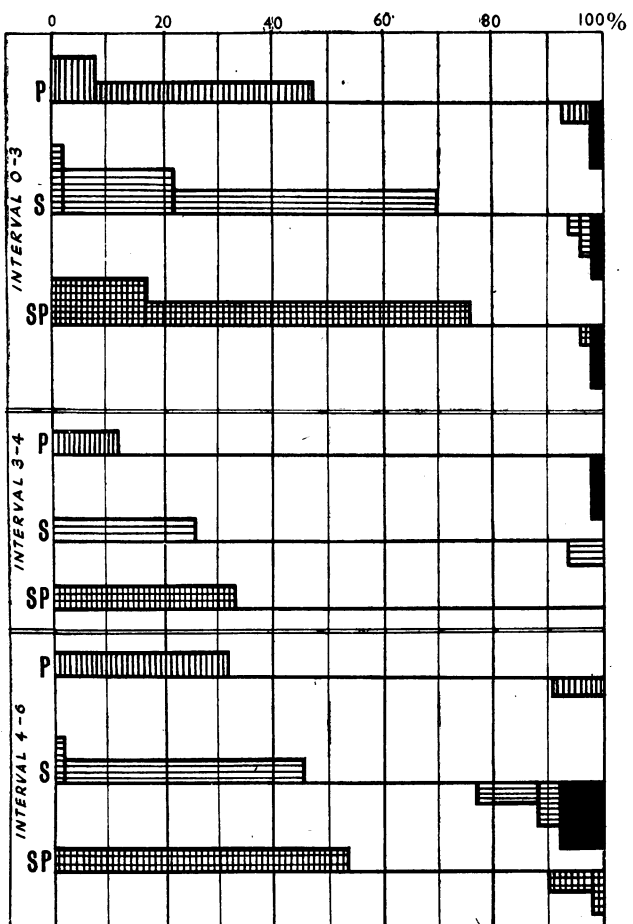



FIG. 3.—Changes in the radiological picture in succeeding periods.

in 3 S cases. During this month the number showing improvement was in all groups lower than in the previous month, and again higher in the S and SP groups than in the P group. At the end of the fourth month 51% of P patients were better than at the start of treatment, compared with 74% of S patients and 79% of SP patients. The group receiving only P.A.S. had fared much better than the original control group, of whom only 18% had shown improvement at the end of four months; deterioration or death had occurred in 56% of the controls and in only 8% of the P cases. It is important to note that the difference was striking already at this stage, and was therefore unconnected with the greater use of collapse therapy in this trial than in the first.

In the last two months, though again in the P group there were twice as many showing no material radiological change as in the streptomycin groups, the most interesting difference in the three groups is in the number of S cases deteriorating. In this period the only deaths occurred in this group: a total of 23.1% of S cases deteriorated or died, compared with 8.8% of the P patients and 9.6% of the SP patients. Here again, however, it is difficult to assess the significance of the difference, since 4 additional P cases might have deteriorated during this period had they not received streptomycin. In the same period in the first series, deterioration or death occurred in 36% of control cases and 38% of streptomycin cases.

### Bacteriology: (A) Bacterial Content of Sputum

Sputum was tested by direct examination and culture, on admission and twice a month or more often during the six-months period. Where there was no sputum, material from gastric lavage and/or laryngeal swab was cultured. Specimens positive on direct examination or on culture were obtained from all patients before or shortly after treatment started. In Table XIII are grouped the results of all *examinations* made during successive months after the start of treatment. The only results excluded are those where a specimen was negative on direct examination and was not cultured. The great majority under the heading "positive direct examination" were positive on culture as well as on microscopical examination. The negative results are shown graphically in Fig. 4.

The results in the SP group are seen to be consistently better than in the other two groups, in respect both of the proportion of specimens giving negative cultures and of the proportion of positives which were positive on culture only. There is little difference between the S and P groups, except in the last two months, in the proportion of specimens giving negative cultures; there was then a rise in the S group and a fall in the P group.

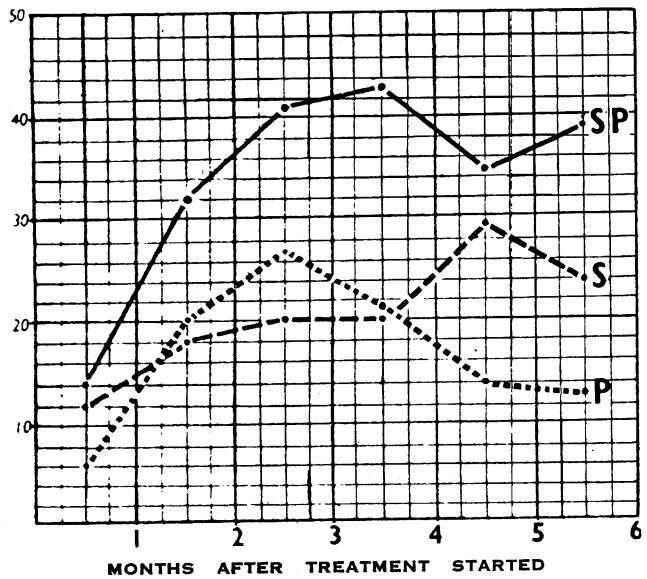



FIG. 4.—Negative results (percentage negative cultures of total specimens examined) in succeeding months in the three treatment groups.

TABLE XIII.—*Presence of Tubercle Bacilli*

| Time | Group | Total Patients from Whom Specimens were Examined | Total Specimens Examined | | D+ Positive Direct Examination | | C+ Negative Direct Examination Positive Culture | | C− Negative Direct Examination and Culture | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | No. | % | No. | % | No. | % | No. | % |
| On admission | P | 59 | 59 | 100 | 54 | 91 | 5 | 9 | 0 | 0 |
| | S | 54 | 54 | 100 | 46 | 85 | 8 | 15 | 0 | 0 |
| | SP | 53 | 53 | 100 | 45 | 85 | 8 | 15 | 0 | 0 |
| 1st month | P | 52 | 104 | 100 | 75 | 72 | 23 | 22 | 6 | 6 |
| | S | 53 | 118 | 100 | 84 | 71 | 20 | 17 | 14 | 12 |
| | SP | 53 | 114 | 100 | 71 | 62 | 27 | 24 | 16 | 14 |
| 2nd month | P | 58 | 132 | 100 | 83 | 63 | 23 | 17 | 26 | 20 |
| | S | 54 | 131 | 100 | 76 | 58 | 32 | 24 | 23 | 18 |
| | SP | 52 | 126 | 100 | 53 | 42 | 32 | 26 | 41 | 32 |
| 3rd month | P | 56 | 150 | 100 | 74 | 50 | 35 | 23 | 41 | 27 |
| | S | 53 | 147 | 100 | 87 | 59 | 31 | 21 | 29 | 20 |
| | SP | 52 | 133 | 100 | 42 | 32 | 36 | 27 | 55 | 41 |
| 4th month | P | 57 | 135 | 100 | 67 | 50 | 40 | 29 | 28 | 21 |
| | S | 53 | 119 | 100 | 69 | 58 | 26 | 22 | 24 | 20 |
| | SP | 52 | 114 | 100 | 31 | 27 | 34 | 30 | 49 | 43 |
| 5th month | P | 55 | 125 | 100 | 72 | 58 | 35 | 24 | 18 | 14 |
| | S | 50 | 103 | 100 | 54 | 52 | 19 | 19 | 30 | 29 |
| | SP | 50 | 107 | 100 | 37 | 35 | 33 | 30 | 37 | 65 |
| 6th month | P | 50 | 99 | 100 | 56 | 57 | 30 | 30 | 13 | 13 |
| | S | 48 | 84 | 100 | 46 | 55 | 18 | 21 | 20 | 24 |
| | SP | 46 | 90 | 100 | 37 | 41 | 18 | 20 | 35 | 39 |

In Table XIV are shown, for successive months after the start of treatment, the numbers of *patients* who gave only negative results throughout the respective month.

Considering the bacteriological results in this way, it is seen that, except in the first month, the results were consistently best in the SP group and least good in the P group. In the fourth month, following the termination of treatment, 14 (27%) of 52 SP cases were negative, compared with 7 (13%) of 53 S cases and 6 (11%) of 57 P cases. In the sixth month the percentage of negative cases was 33 in the SP group, 19 in the S group, and 8 in the P group. The results are significantly better in the SP group than in the two others

If we consider now the number who were persistently positive throughout the three months of chemotherapy, the results are as follows: 28 (48%) in the P group, 32 (60%) in the S group, and 16 (31%) in the SP group.

In conclusion there can be no doubt that, so far as the effect of the chemotherapy on bacterial content of sputum was concerned, the results were best in the patients who received both streptomycin and P.A.S.

TABLE XIV.—*Number of Patients with Negative Results (Direct Examination and Culture) Throughout Successive Months*

| Month After Treatment Started | Group | Total Patients from whom Specimens were Examined (A) | No. of Patients Giving Only Negative Results (B) | Total Specimens Examined in B | Percentage Patients Negative B/A |
|---|---|---|---|---|---|
| First | P | 52 | 1 | 3 | 2 |
| | S | 53 | 5 | 7 | 9 |
| | SP | 53 | 1 | 1 | 2 |
| Second | P | 58 | 6 | 14 | 10 |
| | S | 54 | 8 | 17 | 15 |
| | SP | 52 | 10 | 20 | 19 |
| Third | P | 56 | 5 | 13 | 9 |
| | S | 53 | 6 | 14 | 11 |
| | SP | 52 | 15 | 27 | 29 |
| Fourth | P | 57 | 6 | 12 | 11 |
| | S | 53 | 7 | 10 | 13 |
| | SP | 52 | 14 | 25 | 27 |
| Fifth | P | 55 | 4 | 9 | 7 |
| | S | 50 | 9 | 22 | 18 |
| | SP | 50 | 12 | 24 | 24 |
| Sixth | P | 50 | 4 | 6 | 8 |
| | S | 48 | 9 | 16 | 19 |
| | SP | 46 | 15 | 28 | 33 |

## (B) Bacterial Drug Resistance

### Streptomycin Sensitivity

One of the most important objects of the trial was to estimate the effect of combined streptomycin and P.A.S. treatment on the development of streptomycin resistance. Arrangements were made to examine for streptomycin sensitivity as many as possible of the positive cultures isolated from patients in the groups receiving streptomycin treatment. The technique employed was the same as that previously reported (M.R.C., 1948b). All strains isolated before the start of streptomycin therapy showed sensitivity similar to that of the standard strain H37Rv. In Table XV are summarized the results of the streptomycin sensitivity tests in each of the six months. The results are designated by the resistance ratio (R.R.), which is the ratio of the minimum concentration of streptomycin to which the tubercle bacilli of the patient are sensitive, to the corresponding figure for the standard strain H37Rv.* The result recorded for each case is that for the specimen with the highest degree of streptomycin resistance in the respective month. The results are shown graphically in Fig. 5.

The results referred to in an interim communication (M.R.C., 1949) have been fully confirmed. There is, between the S and SP groups, a remarkable difference in the emergence of streptomycin resistance. If we consider those strains with a resistance ratio over 8, we find that the proportion of cases producing such strains rose to a maximum of 70% in the fourth month in the group receiving streptomycin only, and a maximum of 9% in the fifth month in the group receiving streptomycin plus P.A.S. The difference is pronounced in each successive month, and there can be no doubt of its significance. The very low proportion of resistant strains was maintained in the SP group to the end of the six months. It is interesting to observe also that in respect of those strains with a resistance ratio between 4 and 8 the proportion was higher in the patients receiving streptomycin alone. At the end of the six months 89% of the SP patients producing positive cultures had completely sensitive strains, and only 21% of the S patients.

*1. Streptomycin Resistance in SP patients*

Four patients in this group became negative shortly after treatment started, and one other patient died. The

*A strain with R.R. less than 4 is considered to be completely sensitive.

TABLE XV.—*Streptomycin Resistance in the S and SP Groups, in Successive Months After the Start of Treatment*

| Interval After Treatment Started | Group | Total* Examined (Cases) | Cases Giving Negative Cultures | Cases with Positive Cultures Examined for Sensitivity | | Streptomycin Resistance Ratio† (Highest Recorded During the Month) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Less than 4 | | 4–8 | | 9–99 | | 100+ | |
| | | | | No. | % | No. | % | No. | % | No. | % | No. | % |
| 1 month .. | S | 49 | 5 | 44 | *100* | 37 | *84* | 4 | *9* | 3 | *7* | 0 | *0* |
| | SP | 45 | 1 | 44 | *100* | 42 | *95* | 2 | *5* | 0 | *0* | 0 | *0* |
| 2 months .. | S | 51 | 8 | 43 | *100* | 18 | *42* | 13 | *30* | 5 | *12* | 7 | *16* |
| | SP | 48 | 10 | 38 | *100* | 35 | *92* | 2 | *5* | 1 | *3* | 0 | *0* |
| 3 months .. | S | 53 | 6 | 47 | *100* | 12 | *26* | 8 | *17* | 10 | *21* | 17 | *36* |
| | SP | 48 | 15 | 33 | *100* | 29 | *88* | 2 | *6* | 1 | *3* | 1 | *3* |
| 4 months .. | S | 49 | 9 | 40 | *100* | 6 | *15* | 6 | *15* | 10 | *25* | 18 | *45* |
| | SP | 47 | 14 | 33 | *100* | 26 | *79* | 5 | *15* | 1 | *3* | 1 | *3* |
| 5 months .. | S | 49 | 9 | 40 | *100* | 6 | *15* | 10 | *25* | 8 | *20* | 16 | *40* |
| | SP | 48 | 12 | 36 | *100* | 30 | *83* | 3 | *8* | 1 | *3* | 2 | *6* |
| 6 months .. | S | 43 | 9 | 34 | *100* | 7 | *21* | 6 | *18* | 9 | *26* | 12 | *35* |
| | SP | 43 | 15 | 28 | *100* | 25 | *89* | 2 | *7* | 0 | *0* | 1 | *4* |

* The total includes all with negative cultures throughout the month, or with positive cultures of which at least one was examined for sensitivity. Excluded are those for whom no specimen was available and those for whom no specimen was fully examined in the respective month.

† The ratio of the minimum concentration of streptomycin to which the tubercle bacilli of the patient are sensitive, to the corresponding figure for the standard strain H37Rv.

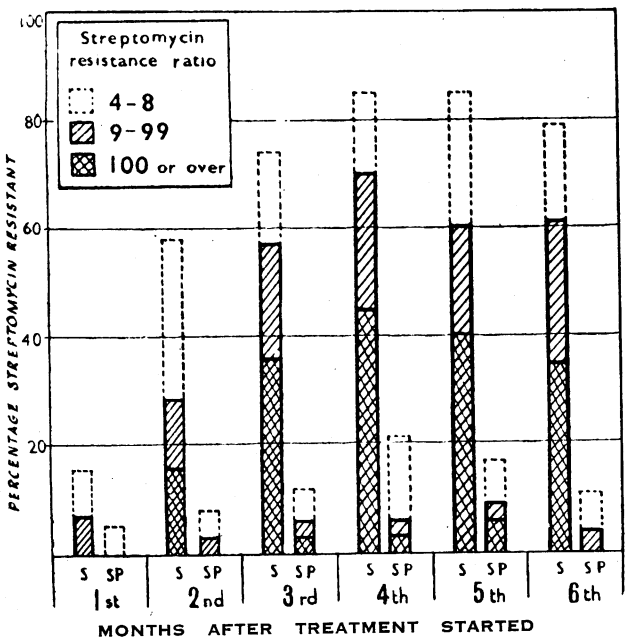



FIG. 5.—Percentage of cases with streptomycin-resistant strains in succeeding months.

following analysis relates to the remaining 48 patients. In 36 cases (75%) all strains isolated were completely sensitive. In 7 cases, strains with a resistance ratio between 4 and 8 were isolated at some time. In 5 of the 7 the R.R. was only 4. In another case all cultures were negative until the end of the fourth month, when the R.R. of a positive culture was 8; in subsequent cultures the R.R. varied between 2 and 8. In another the R.R. was 8 for three consecutive cultures after the middle of the third month, previous cultures having been sensitive.

Five patients produced at some time cultures with R.R. above 8 (Table XVI). In 2 of the 5 cases there was only a single resistant culture, and subsequent ones were sensitive. The resistance ratio of the single culture was in one of these patients (Case 72) 400, and appeared at four and a half months; in the other patient (Case 82) 20, and appeared at three months. A third patient (Case 75) produced three consecutive resistant cultures, after which other cultures were sensitive; the ratio of the first resistant culture, produced at seven weeks, was 20, of the next 20, and of the third 100. Cultures from the fourth patient (Case 143) at a little over four months after start of treatment had an R.R. of 24, a month later 200, and at six months 100. The fifth patient (Case 93) had at three months a culture with R.R. over 125, two weeks later one completely sensitive, and four weeks after this one with R.R. over 2,500. No further cultures were obtained from this patient. It is of interest to record that this was the only SP case in which P.A.S. resistance also was demonstrated in the strains isolated. It is reported, however, that the cultures in this case were very atypical in appearance; moreover, two cultures did not produce typical tuberculous lesions in guinea-pigs six weeks after inoculation, but both gave rise to a local abscess, in the pus of which acid-fast organisms were demonstrated.

In 2 of these 5 cases there had been extensive cavitation (3-plus) on admission, in 2 only 1-plus, and in one none; there is no indication, therefore, that resistance arose more frequently in patients with gross cavitation. Nor is there any significant indication of clinical deterioration connected with the drug resistance demonstrated in these cases. Radiological deterioration was recorded in the last two

TABLE XVI.—*Streptomycin Resistance in SP Group*

| Case No. | Condition on Admission | | | | Streptomycin Resistance | | *X*-ray Assessment at 6 Months | Course |
|---|---|---|---|---|---|---|---|---|
| | General Condition | Average Evening Temperature | E.S.R. | *X*-ray Extent of Cavitation | Time of Emergence (Weeks After Treatment Started) | Resistance Ratio | | |
| 72 | Fair | 99·6° F. | 35 | 3+ | 20 | 400 (single culture) | Improvement 2-plus | Improved during treatment. Clinical relapse in 6th month, without radiological deterioration |
| 82 | Poor | 102·1° F. | 27 | 3+ | 14 | 20 (single culture) | Deterioration 1-minus | Clinical improvement throughout. Radiologically, no change for 4 months, then slight deterioration |
| 75 | Poor | 99·1° F. | 37 | 0 | 7 | 20–100 | Improvement 3-plus | Improved throughout in all respects |
| 143 | Fair | 100° F. | 116 | 1+ | 18 | 24–200 | Improvement 2-plus | Improved throughout, except that, after being afebrile, at 6 months temperature was occasionally over 99 |
| 93 | Fair | 99·9° F. | 24 | 1+ | 12 | 125–2,500 | Improvement 3-plus | Improved throughout in all respects |

months only in Case 82, with no clinical relapse. In Case 72 there was a clinical relapse at five months, without radiological deterioration.

Summarizing, though streptomycin resistance with R.R. above 8 was demonstrated in 5 cases, in 3 of these the last strains isolated were sensitive, and one of the 2 others appears to have been abnormal and showed great variations in sensitivity.

### 2. *Streptomycin Resistance in S patients*

In 3 S cases examinations were persistently negative after the first week of treatment, and in one case after the first month. One patient died in the second month. The analysis of streptomycin resistance in the S group relates to the remaining 49 patients. In only 4 of the 49 cases (8%) were all strains completely sensitive. In 12 other cases the R.R. was never more than 4 to 8. Strains more resistant were produced in all of the remaining 33 cases.

In 13 of the 33 cases the R.R. was over 8 but less than 100. In 3 of the 13 there was reduction of resistance in that for the last strains from these patients the R.R. was not over 8; in 2 of the 3 cases the R.R. had risen to 16, and the reversion occurred in the fifth and sixth months; in the other case the R.R. was over 64, and reverted to 8 in the fifth month.

In the remaining 20 cases strains were isolated which had an R.R. of 100 or more. Reduction of drug resistance was observed in 4 of these: one reverted to complete sensitivity after producing strains with R.R. over 2,000; in another, strains with R.R. only 6 emerged in the fifth month, after previous strains which had been up to 200; in the other 2 cases the resistance ratio dropped from 128 and 400 to 16 and 25.

As in the first series, the development of resistance was related to the severity of disease present at the start of treatment. Marked streptomycin resistance (R.R. 100 or over) emerged in 15 of the 24 cases with gross cavitation (2- or 3- plus), and in only 5 of the 25 others. It was seen in 8 of the 13 cases with average temperature over 100° F. (37.8° C.) on admission, in 8 of the 18 with temperature of 99–99.9° (37.2–37.75°), and in 4 of the 18 with lower temperatures. The high proportion of acutely ill patients among those whose tubercle bacilli subsequently became highly resistant, and the difficulty of ascribing the poor prognosis in these patients to their initial condition or to the drug resistance, were discussed in the report of the first trial. It is of particular interest to consider this point again, in view of the results of combined therapy. Were the better results of combined treatment due simply to an additive therapeutic effect, or were they also due to the prevention of drug resistance?

Within the S group we can relate the prognosis to both the clinical condition and the emergence of streptomycin resistance. The data are set out in Table XVII and Fig. 6.

It can be seen that within each of the clinical groups—highly febrile, not highly febrile but having gross cavitation, and others—results were less good in those patients who developed a high degree of drug resistance. Though the figures are small, they show the same trend in all groups. It is noteworthy that, of the 16 patients with R.R. less than 9, the two who did not show improvement at the end of six months were two of the 6 patients whose R.R. reached 8 at some time. In other words, all 10 patients whose R.R. was always less than 8 improved; in 9 of the 10 the improvement was 2-plus or 3-plus (this is shown in the adjusted totals of Table XVII). At the other end of the scale, 9 of the 20 patients with R.R. over 99

TABLE XVII.—*Results in S Group Related to Clinical Condition at Entry to Trial and Subsequent Emergence of Streptomycin Resistance*

| Clinical Condition | Streptomycin Resistance Ratio | Total | Results at 6 months. X-ray Assessment | | | | Death |
|---|---|---|---|---|---|---|---|
| | | | Improvement | | No Change | Deterioration | |
| | | | 3+ or 2+ | 1+ | | | |
| High fever (average temp. 100° F.+) | Less than 9 | 2 | 1 | 0 | 0 | 1 | 0 |
| | 9–99 | 3 | 1 | 2 | 0 | 0 | 0 |
| | 100+ | 8 | 2 | 0 | 1 | 1 | 4 |
| Gross cavitation but temp. below 100° F. | Less than 9 | 4 | 3 | 0 | 1 | 0 | 0 |
| | 9–99 | 6 | 3 | 3 | 0 | 0 | 0 |
| | 100+ | 8 | 3 | 2 | 1 | 2 | 0 |
| Other patients | Less than 9 | 10 | 9 | 1 | 0 | 0 | 0 |
| | 9–99 | 4 | 2 | 2 | 0 | 0 | 0 |
| | 100+ | 4 | 2 | 0 | 0 | 2 | 0 |
| Total .. | Less than 9 | 16 | 13 | 1 | 1 | 1 | 0 |
| | 9–99 | 13 | 6 | 7 | 0 | 0 | 0 |
| | 100+ | 20 | 7 | 2 | 2 | 5 | 4 |
| If R.R. = 8 is taken as lower limit of resistance, results are: .. | Less than 8 | 10 | 9 | 1 | 0 | 0 | 0 |
| | 8–99 | 19 | 10 | 7 | 1 | 1 | 0 |
| | 100+ | 20 | 7 | 2 | 2 | 5 | 4 |

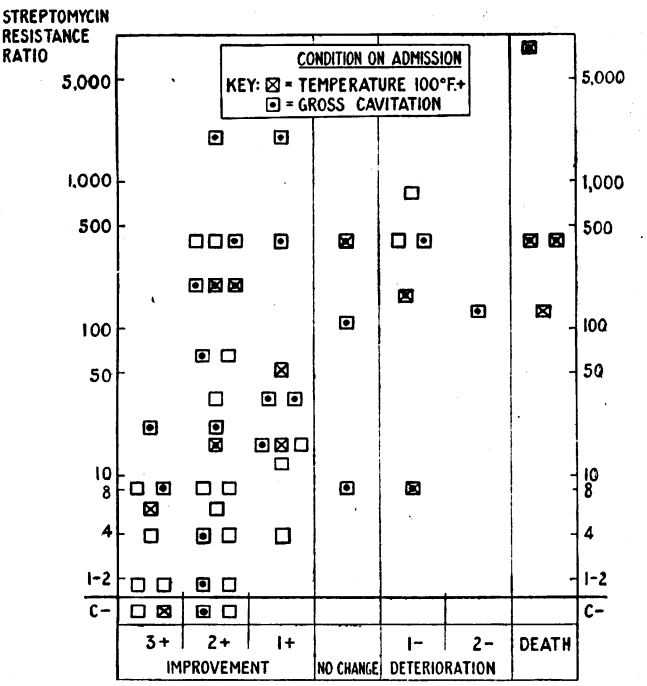



FIG. 6.—Streptomycin resistance related to radiological assessment at six months and to condition on admission. Each square represents one case. C−: Culture negative after first month of treatment.

deteriorated, and the 4 deaths occurred in this group. Of the 12 S patients who deteriorated or died in the last two months (see Table XII), in 9 the R.R. had previously risen to over 100. In one of the remaining 3 the R.R. reached 12, in another 8, and the last remained sensitive throughout. It is highly probable, considering these facts, that streptomycin resistance was responsible or partly responsible for failure of the drug to prevent deterioration, and that the better results of combined treatment were due in part to the maintenance of streptomycin sensitivity.

The number of cases in which later less resistant strains were isolated is too small to show any difference in clinical results. One of the 8 died. The relevant details were analysed to see if there was less reversion to sensitivity in cases with gross cavitation; but, although none of the 8 cases had cavitation classified as 3-plus on admission, here

again figures are too small to be significant. Possible association of reversion with collapse therapy was also investigated, but in only one case did reversion occur shortly after the induction of collapse treatment. It is, however, interesting to note that, in the patient who died, a first drop of the resistance ratio from 128 to 16 occurred after a spontaneous pneumothorax. It was unfortunately not possible to get post-mortem specimens in this case to test for sensitivity, as permission for necropsy was refused.

#### P.A.S. Sensitivity

P.A.S. sensitivity was not studied as thoroughly as streptomycin sensitivity, partly because of early impressions that P.A.S. resistance rarely occurs, and partly because tests were regarded as not very reliable. The test still does not give results as satisfactory and constant as the test for streptomycin sensitivity. Tests checked by different observers have in a few cases given widely different results. The technique was similar to that employed for streptomycin sensitivity tests. The normal range of sensitivity by this method is between 0.12 and 1.0 $\mu$g. P.A.S. per ml.

For 22 of the 59 P patients there is no information on P.A.S. sensitivity after the first month of treatment. The following analysis relates to the remaining 37 cases. In 25 of these the resistance ratio was never above 8. Resistant strains were isolated from the remaining 12 cases. In 4 of these, however, only a single resistant strain was found. In one of the 4 a strain with a resistance ratio of 40 emerged at four months; 8 sensitive strains preceded it, and 4 sensitive strains followed. In 3 other cases a single resistant strain emerged near the end of the six months' trial period, having been preceded by several sensitive ones. In one of the 3, tests by a second pathologist gave results as resistant (R.R. 16) for all strains throughout the six months, including the first one.

Eight cases produced resistant strains on more than one occasion, with R.R. varying between 20 and 800. In 2 of the 8 cases resistance emerged between six and seven weeks after treatment started; in 5 others the interval was 10 to 13 weeks; in one it was 16 weeks. In 2 cases sensitive strains were again isolated before the end of six months. No significant difference in prognosis was found between the patients from whom P.A.S.-resistant strains were isolated and the others.

Because of the unsatisfactory test, it may be questioned if any importance should be attached to these results, but it should be noted that the finding of resistant strains on more than one occasion occurred in 8 of the 24 cases with gross cavitation (2- or 3-plus), and in none of the 13 others (only cases tested for sensitivity are included in these totals); this difference is statistically significant.

In the SP group, information on P.A.S. sensitivity after the first month is available for 30 cases. In all but 2 cases the strains were sensitive throughout. In one a single strain with a resistance ratio of 40 was isolated in the sixth month, followed by a sensitive strain two weeks later. In another patient (Case 93 already mentioned) resistance to both P.A.S. and streptomycin was found; this patient responded well to treatment, and did not deteriorate later.

## Discussion

The present trial has shown clearly the beneficial effect of P.A.S. treatment alone in acute progressive pulmonary tuberculosis, confirming the reports of Swedish authors, and in particular the results of a controlled clinical investigation recently reported by the Swedish National Association against Tuberculosis (1950). Our patients given P.A.S. alone fared much better than a comparable group with similar disease in our first streptomycin trial, treated by bed-rest alone (M.R.C., 1948a). Whereas at the end of six months 27% of the control cases in the first trial had died and the condition of another 34% had deteriorated on radiological assessment, only 3% of the present P group died and the condition of another 7% deteriorated on the same basis in this period. Improvement in the general condition, where it occurred during P.A.S. therapy, was rapid, with fall of temperature, reduction of sedimentation rate, and weight gain; radiological improvement was less impressive in its degree.

P.A.S. alone was, however, less effective than streptomycin alone. Although the radiological condition deteriorated in only a few of the P.A.S.-treated patients, in 34% there was no appreciable radiological change during the six months' observation; the comparable figure in the patients receiving streptomycin was 6%. On the other hand, less than a quarter of the P cases, but more than half of the S group, showed radiological improvement of considerable degree (2-plus or 3-plus). The difference was noted particularly in febrile patients; for those with average temperatures of 99° F. or more on admission, considerable radiological improvement was evident in only 6% of the P group and in over 40% of the S group. Fewer P cases than S cases became bacteriologically negative. The differences in the clinical improvement were less obvious: response of temperature and of sedimentation rate to treatment was equally rapid in the two groups, and average weight gain over the six months was similar. Improvement in general condition was, however, less, and occurred later, in the P group than in the S group.

When the two groups receiving streptomycin (S and SP) are compared, the outstanding difference is in the emergence of streptomycin-resistant strains of tubercle bacilli. Streptomycin resistance (as judged by a "resistance ratio" greater than 8) was detected in 33 of the 49 S cases from which results were available from the first month onwards, whereas streptomycin-resistant strains occurred in only 5 of the 48 SP cases (in 4 of these 5 cases resistance emerged late in treatment or after its cessation; in 2 of them only a single resistant culture was obtained, subsequent cultures being sensitive). The association of P.A.S. with streptomycin had therefore a most marked effect in delaying or preventing the emergence of streptomycin-resistant variants of the infecting organisms. Similar results have been reported by Karlson and his co-workers (1949) and from the extensive trials of the Veterans Administration (1949, 1950). At the Ninth Streptomycin Conference of the Veterans Administration the following results were reported from Fitzsimons General Hospital, Denver, Colorado: in a group of 95 patients treated with streptomycin every three days and P.A.S. daily, none developed streptomycin resistance, compared with 33% of 97 patients treated only with streptomycin every three days and 76% of 66 patients treated only with streptomycin daily (the evaluation was made after 120 days of therapy). Although the course of the combined therapy in the present series was only three months, the effect in preventing the development of streptomycin resistance continued until the end of the sixth month. The present results were obtained with a high dose of P.A.S. —namely, 20 g. of the sodium salt—a dose which caused digestive discomfort. It is not known if lower doses would have an equal effect on streptomycin resistance: an M.R.C. trial designed to answer this question is in progress.

The therapeutic differences between the two streptomycin-treated groups were not great; most of them do not satisfy tests of statistical significance, though the improvement was, on the whole, somewhat greater in the patients who received P.A.S. as well as streptomycin than in those who received streptomycin alone. Radiologically, 74% of the S cases and 87% of the SP cases improved; but "considerable" improvement was noted in a larger proportion of the S group. The sedimentation rate was normal at six months in 40% of the SP group and in 21% of the S group; among patients febrile on admission slightly more of the SP than of the S group became afebrile. The clearest effect of combined treatment, apart from that on drug resistance, was on the bacterial content of the sputum: throughout the period of the trial, after the first month of therapy, more SP than S cases were converted to negative; in the sixth month, 33% of SP cases were bacteriologically negative, compared with 19% of S cases.

As in our first trial, failure of chemotherapy after emergence of drug resistance was evident in that, among the patients receiving streptomycin only, the disease pursued a less favourable course in cases producing resistant strains than in the others; this was still so after taking into account differences in severity of disease on admission. The clinical relapses in the fifth and sixth months occurred particularly in resistant cases. Though the figures involved are small, the total evidence, including that of the first trial, makes it probable that the prevention of streptomycin resistance was in part responsible for the rather more favourable clinical results which were associated with combined therapy. On the other hand, in many patients from whom resistant strains were isolated improvement continued even when the resistance ratio was over 100. Moreover, from a few of the cases producing resistant strains sensitive cultures were isolated later. Drug resistance therefore must not be overstressed as a factor in prognosis. Strains from one lesion may be resistant while those from another in the same patient may be sensitive; and the patient's own recuperative powers may be sufficient to cope with the drug-resistant bacilli remaining after elimination of the more sensitive organisms.

P.A.S. resistance was observed in several of the cases on P.A.S. therapy only. Although the present methods of testing are thought to be unsatisfactory, there is no doubt that such resistance can develop, albeit less frequently than streptomycin resistance. This risk must certainly be taken into account when planning the use of P.A.S.

It is now possible to adjudge the place of P.A.S. in the chemotherapy of pulmonary tuberculosis, although it must be emphasized that the comparisons in the present trial apply to the results of treatment given for equal short periods—namely, three months with each drug; no comment can be made on the possible effects of more prolonged P.A.S. or combined therapy. Leaving aside the types of disease in which chemotherapy could have little appreciable effect, P.A.S. given alone has a place in the treatment of cases which show apparently complete streptomycin resistance. The most important conclusion concerns the use of combined therapy. In view of its effect on streptomycin resistance, it is obvious that the addition of P.A.S. prolongs the period of effective streptomycin treatment. As used at present, the main object of any chemotherapy in pulmonary tuberculosis is to prepare selected cases for collapse treatment or chest surgery; in appropriate cases combined therapy should be continued until this objective is achieved, whether this is a matter of weeks or months; the gains may be only transitory, and there should be no delay in the use of other measures at the opportune moment. Combination of P.A.S. with streptomycin not only renders effective administration of streptomycin possible for longer periods than previously, but probably permits also of repeated effective courses. The use of chemotherapy thereby becomes justifiable for a wider range of lesions. There has been much discussion on the advisability of giving streptomycin to patients with lesions which might be expected to heal without either collapse treatment or chemotherapy. The main argument against streptomycin alone in such cases has been that the development of drug resistance might prejudice the prognosis should there be a relapse with more severe disease at a later date. This argument is now less valid, and the extension of chemotherapy to early or small lesions is worth investigation; but evaluation of the results will be extremely difficult. It should still be remembered, moreover, that neither P.A.S. nor streptomycin is without toxicity, and that the emergence of streptomycin resistance is not entirely prevented by combined therapy.

## Summary

166 patients with acute progressive bilateral pulmonary tuberculosis were studied in a clinical trial of P.A.S. and streptomycin.

59 patients were treated with P.A.S. (P group), 54 with streptomycin (S group), and 53 with both streptomycin and P.A.S. (SP group). Patients were assigned to a treatment group by random selection.

P.A.S. was given in the form of the sodium salt, 20 g. daily. The daily dose of streptomycin was 1 g. Chemotherapy was given for three months, and observation for the trial continued for a further three months.

Patients treated only with P.A.S. fared much better than patients with similar disease treated without chemotherapy in the first M.R.C. trial of streptomycin in pulmonary tuberculosis.

P.A.S. was less effective than streptomycin. In 34% of the P group there was no appreciable radiological change, compared with 6% of the S group. Marked radiological improvement (2- or 3-plus) was seen in 22% of the P group and in 56% of the S group. The difference was greatest in febrile patients.

Improvement was somewhat greater in the SP group than in the S group, but the differences are small. The proportion of cases becoming bacteriologically negative was highest in the SP group. The outstanding effect of combined therapy was on emergence of drug resistance. Strains with a streptomycin resistance ratio above 8 were isolated in 33 of 49 S cases, and in only 5 of 48 SP cases; in 2 of these 5 there was only a single resistant culture.

Deterioration in the S group was related to the emergence of streptomycin resistance.

The Committee wishes to express its gratitude to all the clinicians and pathologists of the centres for their constant co-operation, and is also much indebted to the nursing staff and laboratory technicians of the centres.

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The Association of Psychiatric Social Workers has published the fourth number of its annual journal, *British Journal of Psychiatric Social Work*, copies of which may be obtained for 3s. 6d. from the association at 1, Park Crescent, London, W.1. It includes articles on the work and training of psychiatric social workers and news of interest to them.