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Meeting in Geneva on May 19 to discuss birth control, the World Health Organization decided not to follow further the proposal put forward by the Norwegian delegate to study the "health aspects" of the world population problem (*New York Times*, May 20). This was because delegates from several predominantly Roman Catholic countries had said that action in this field would endanger the whole existence of W.H.O. Dr. Karl Evang had suggested they should look into the possibility of government propagation of birth-control methods in over-populated countries. The Belgian delegate put forward a counter-proposal forbidding any action of this sort. Had this been accepted it would have put a stop to the work already being done by W.H.O. in India and various other countries on family planning. The question was debated for two days, and then all the delegates agreed to drop the whole matter without a vote, in the interests of harmony. Secretariat officials said afterwards that they did not consider themselves bound in any way to stop advising governments on family planning as a result of this discussion. Only a formal decision by the Assembly could do this. In a letter to *The Times* on May 23, Lord Horder, commenting on the Roman Catholic threat of a mass walk-out in the event of acceptance of Norway's proposals, says that by their action they have possibly "prevented action which might have saved millions of lives." The problem of population, he writes, increases with every hour of every day and, without the knowledge of birth control, can be solved only by disease and other means involving much human suffering.

# THE PREVENTION OF STREPTOMYCIN RESISTANCE BY COMBINED CHEMOTHERAPY

## A MEDICAL RESEARCH COUNCIL INVESTIGATION

The value of chemotherapy, combining streptomycin and P.A.S., in the treatment of certain forms of pulmonary tuberculosis was demonstrated in a Medical Research Council (1950) report of a controlled investigation. In particular it was shown that association of P.A.S. with streptomycin substantially reduced the risk of development of drug resistance. The daily dose of P.A.S. used was 20 g. of the sodium salt, a dose which produced gastro-intestinal discomfort in more than half the patients. It was decided to investigate whether smaller doses of P.A.S. would have the same effect on drug resistance: that investigation has been completed, and the results are reported here. The inquiry was planned and directed, as the previous trial, by a joint subcommittee of the Medical Research Council's Streptomycin in Tuberculosis Trials Committee and the British Tuberculosis Association's Research Committee, and the centres at which the work was carried out were the same as before.*

It was decided to have three concurrent groups, with the same type of disease as in the previous trial, and to use the same daily dose of streptomycin for all groups, but different doses of P.A.S. (5, 10, or 20 g.). The main analysis would concentrate on the results of streptomycin sensitivity tests. Since these would give a clear numerical differentiation, smaller groups were needed than for the previous trial, and the collection of cases, which had started in November, 1949, was stopped at the end of December, 1950, with 115 patients in the investigation.

*Members of the Joint Subcommittee: Sir Geoffrey Marshall (chairman), Professor R. Cruickshank, Dr. Marc Daniels, 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).

Centres, clinicians, and pathologists collaborating:

*Brompton Hospital, London.*—Clinician: Dr. J. R. Bignall (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. W. E. Snell, Dr. G. O'Malley, Dr. W. C. Harris. Pathologists: Dr. J. L. Hamilton-Paterson, Dr. E. D. Hoare.

*Aintree Hospital (late 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, Dr. J. Sumner. Pathologist: Dr. E. Nassau.

*King George V Sanatorium, Surrey.*—Clinicians: Dr. J. V. Hurford, Dr. M. Francis. 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.

Dr. Marc Daniels, of the M.R.C. Tuberculosis Research Unit, was responsible for the co-ordination of the trial, and he also analysed the results and prepared the report for the Committee. Professor A. Bradford Hill was responsible for the statistical design of the trial. The radiological results were assessed by Dr. G. Simon.

### Plan and Conduct of the Trial

The methods employed were similar to those of the previous combined chemotherapy trial and of the initial streptomycin trial. The type of case to be investigated was defined as follows: acute progressive bilateral pulmonary tuberculosis, believed to be of recent origin, bacteriologically proved, unsuitable for collapse therapy, age group 15–30. 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.

After acceptance by the panel the determination of the treatment group in each case was made by reference to a list (based upon random sampling numbers) held confidentially in the Tuberculosis Research Unit. After admission each patient was kept 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. When six months' observation had been completed in the required number of cases, all records and *x*-ray films were sent to the 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. Changes in *x*-ray appearance were assessed without the assessor having any knowledge of the treatment given.

### Number of Patients in the Trial

The records of 115 patients were available for the analysis of results; for 42 of them the daily dose of sodium P.A.S. was 20 g. (group SP 20), for 39 it was 10 g. (SP 10), and for 34 it was 5 g. (SP 5).

A total of 133 cases had been accepted by the panel (46 SP 20, 46 SP 10, 41 SP 5), but for various reasons 18 were omitted from the study. Thus four cases were excluded after acceptance because they were never confirmed bacteriologically and therefore failed to meet the criteria of admission. Eight were excluded because it was found after acceptance that they had already been treated with streptomycin or P.A.S., or both; this would have affected the results of sensitivity tests. One patient refused treatment, and another took his own discharge after six weeks' treatment. Two died before treatment could be started. In two cases the physician under whose care the patient was admitted decided that collapse therapy was necessary immediately in addition to the chemotherapy prescribed for the trial.

### Condition on Admission

In Table I is shown, for the three treatment groups, the condition of the patients before treatment started, as reflected by their general condition (assessment by the clinician in charge), temperature (Fahrenheit, by mouth), sedimentation rate (Westergren, 200 mm. reading at one hour), and extent of cavitation as assessed on one single film, without tomograms.

As in the previous trials, the data indicate that clinically most of the patients were fairly ill, and in about half of them radiography revealed gross cavitation (2-plus or 3-plus). The distribution was similar in the three groups; there were rather more severely ill patients in the SP 10 group, but the differences are not statistically significant.

TABLE I.—*Condition of Patients on Admission*

| | SP 20* | | SP 10† | | SP 5‡ | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Total | 42 | *100* | 39 | *100* | 34 | *100* |
| General condition: | | | | | | |
| Good | 2 | *5* | 3 | *8* | 1 | *3* |
| Fair | 23 | *55* | 17 | *44* | 21 | *62* |
| Poor | 17 | *40* | 19 | *49* | 12 | *35* |
| Average evening temp. in first week:§ | | | | | | |
| Afebrile‖ | 5 | *12* | 6 | *15* | 8 | *24* |
| Less than 99° F. (37·2° C.), but febrile | 14 | *33* | 9 | *23* | 7 | *21* |
| 99–99·9° F. (37·2–37·75° C.) | 16 | *38* | 14 | *36* | 15 | *44* |
| 100° F.+ (37·8° C.+) | 7 | *17* | 10 | *26* | 4 | *12* |
| Sedimentation rate: | | | | | | |
| 0–10 | 0 | *0* | 0 | *0* | 2 | *6* |
| 11–20 | 2 | *5* | 4 | *10* | 2 | *6* |
| 21–50 | 20 | *48* | 17 | *44* | 13 | *38* |
| 51+ | 20 | *48* | 18 | *46* | 17 | *50* |
| Cavitation: | | | | | | |
| Nil | 3 | *7* | 5 | *13* | 8 | *24* |
| 1-plus | 19 | *45* | 10 | *26* | 9 | *26* |
| 2-plus | 16 | *38* | 22 | *56* | 11 | *32* |
| 3-plus | 4 | *10* | 2 | *5* | 6 | *18* |

* SP 20. Group treated with 1 g. streptomycin and 20 g. P.A.S. (sodium salt) daily.
† SP 10. Group treated with 1 g. streptomycin and 10 g. P.A.S. (sodium salt) daily.
‡ SP 5. Group treated with 1 g. streptomycin and 5 g. P.A.S. (sodium salt) daily.
§ Temperature taken by mouth.
‖ A patient was considered afebrile if *all* temperatures recorded were below 99° F.

### Treatment

#### A. First Three Months

All patients were treated by rest in bed, and all had streptomycin, 1 g. daily, by intramuscular injection at 8 a.m. In addition, sodium P.A.S. was given in daily doses of 20 g., 10 g., and 5 g. for the SP 20, SP 10, and SP 5 groups respectively; it was given by mouth, in four divided doses, at 8 a.m., noon, 4 p.m., and 8 p.m.

Treatment in each case started at the end of a preliminary observation week, and continued for three months. It was recommended that during these three months no treatment should be given other than rest in bed and the prescribed chemotherapy, unless the condition so changed that other measures became urgent and desirable. In fact, artificial pneumoperitoneum was induced in the second month of treatment in two cases, both in the SP 10 group.

#### B. Second Three Months

In the protocols of the trial it was suggested that during the second three-months period any other treatment considered appropriate might be initiated by the clinician in charge of the patient; it was strongly recommended that any further chemotherapy combining the two drugs should not be different from that given in the first three months.

*Additional Chemotherapy.*—Chemotherapy was continued during this period in 14 cases: seven in the SP 20 group, three in the SP 10, and four in the SP 5. Further details of these cases are given in the study of sensitivity results.

*Collapse Therapy.*—Collapse therapy was applied in 36 cases (Table II). In 22 cases it was induced in the fourth month, shortly after the end of the prescribed chemotherapy course.

TABLE II.—*Collapse Therapy*

| | SP 20 | SP 10 | SP 5 |
|---|---|---|---|
| Artificial pneumothorax maintained | 3 | 1 | 3 |
| ,, ,, abandoned | 0 | 2 | 2 |
| ,, pneumoperitoneum | 11 | 9 | 5 |
| | 14 (33%) | 12 (31%) | 10 (29%) |

### Toxicity

No severe vestibular disturbance was noted. Giddiness was recorded in 8 of the 115 cases (7%)—five in the first month and three in the second. One of the cases occurred

in the SP 5 group, three in the SP 10, and four in the SP 20.

Apart from rashes accompanying febrile toxic reactions described below, and apart from some dryness and scaliness of the skin noted in many cases, a rash was observed in seven cases—three on the smallest dose of P.A.S. and four on the highest dose. Treatment was not stopped and the rash subsided, in four cases after administration of antihistamines, though whether the latter was responsible for the improvement is not clear.

Gastro-intestinal symptoms were infrequent and mild in the two groups on smaller doses of P.A.S.: four (12%) of the SP 5 group and six (15%) of the SP 10 had loose stools in the first or second month. In the group receiving 20 g. of P.A.S. the incidence was much greater; gastro-intestinal symptoms were recorded in 22 cases (52%): in five there was diarrhoea persisting on and off throughout treatment, in nine loose stools, in seven nausea, and in six vomiting. However, in only one of these cases was the disturbance severe enough to demand reduction of the dose; the daily dose was reduced to 10 g. in the third month.

In five cases there were in the third or fourth week of treatment febrile toxic reactions which necessitated temporary cessation of treatment. In one case in the SP 20 group the reaction was attributable to P.A.S.: on the 23rd day a papular rash developed and the temperature rose, the reaction subsiding when P.A.S. was stopped; P.A.S. treatment was started again with 2.5 g. daily, and it was possible to lead up slowly again to the full dose of 20 g. without mishap. In one case (SP 10 group) the streptomycin was definitely responsible: the temperature rose again each time a streptomycin injection was given; finally, dihydrostreptomycin was substituted and was well tolerated. In three cases (one SP 5 and two SP 10) the toxic reaction was attributable to both drugs; desensitization was undertaken to streptomycin and then to P.A.S., and both drugs were then well tolerated.

## Clinical Results

The trial was designed especially to answer questions concerning streptomycin sensitivity. It was expected from the outset that in clinical results there would be little difference between the three groups, since in the previous trial the difference between the group receiving streptomycin only and the one receiving streptomycin plus 20 g. of P.A.S. had been small. Accordingly the clinical analysis which follows is much briefer than that for the previous trial.

*Mortality.*—Two patients died; both were in the group receiving 5 g. of P.A.S. daily. One of them had improved during the first three months, but got rapidly worse subsequently, and died in the sixth month; the other showed no response to chemotherapy, and died in the fifth month.

*Radiological Assessment.*—The changes in radiological appearance at three months and six months are shown in Table III. There was no significant difference between the three groups, either at the end of the three-months course of chemotherapy or after three more months of observation. Nearly 90% of these patients with acute progressive tuberculosis who were at first thought to be unsuitable for collapse therapy had improved at the end of six months; the improvement was considerable (2-plus or 3-plus) in half of them. The results for men and women were analysed separately and, contrary to the findings of the previous trial, the difference was here in favour of the men: 59% showed considerable improvement, compared with 45% of the women. The difference, however, is not statistically significant.

TABLE III.—*Assessment of Radiological Appearance at Three Months and Six Months Compared with Appearance on Admission*

| | At 3 Months | | | | | | At 6 Months | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SP 20 | | SP 10 | | SP 5 | | SP 20 | | SP 10 | | SP 5 | |
| | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Improvement: | | | | | | | | | | | | |
| 3-plus | 0 | *0* | 0 | *0* | 1 | *3* | 4 | *10* | 7 | *18* | 4 | *12* |
| 2-plus | 2 | *5* | 2 | *5* | 1 | *3* | 18 | *44* | 12 | *31* | 15 | *44* |
| 1-plus | 22 | *52* | 19 | *49* | 22 | *65* | 14 | *34* | 15 | *38* | 11 | *32* |
| No change | 18 | *43* | 15 | *38* | 8 | *24* | 4 | *10* | 4 | *10* | 2 | *6* |
| Deterioration | 0 | *0* | 3 | *8* | 2 | *6* | 1 | *2* | 1 | *3* | 0 | *0* |
| Death .. | 0 | *0* | 0 | *0* | 0 | *0* | 0 | *0* | 0 | *0* | 2 | *6* |
| Total | 42 | *100* | 39 | *100* | 34 | *101* | 41* | *100* | 39 | *100* | 34 | *100* |

* One *x*-ray film missing.

*General Condition.*—The general condition at the end of six months was thought by the clinician in charge to have improved in all but four of the SP 5 group, all but four of the SP 10 group, and all but two of the SP 20 group. The improvement was considerable in 56%, 49%, and 52% respectively.

*Temperature.*—In Table IV are shown the number of patients who, febrile at the start of treatment, had become afebrile at the end of three months and six months. Here again there is no appreciable difference between the three groups. In general the results were most favourable in those with average temperature under 100° F. (37.8° C.); 56 of the 75 such patients (75%) were afebrile at the end of three months' treatment, compared with only 5 of 21 (24%) more acutely febrile cases.

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

| Average Evening Temperature During Week Following Admission | Group | Total | No. of Patients Afebrile at: 3 Months | | 6 Months | |
|---|---|---|---|---|---|---|
| | | | No. | % | No. | % |
| Less than 99° F. (37·2° C.) | SP 5 | 7 | 5 | *71* | 5 | *71* |
| | SP 10 | 9 | 7 | *78* | 8 | *89* |
| | SP 20 | 14 | 10 | *71* | 11 | *79* |
| 99–99·9° F. (37·2–37·75° C.) | SP 5 | 15 | 12 | *80* | 11 | *73* |
| | SP 10 | 14 | 11 | *79* | 8 | *57* |
| | SP 20 | 16 | 11 | *69* | 11 | *69* |
| 100° F.+ (37·8° C.+) .. | SP 5 | 4 | 1 | *25* | 1 | *25* |
| | SP 10 | 10 | 2 | *20* | 1 | *10* |
| | SP 20 | 7 | 2 | *29* | 3 | *43* |
| All febrile cases .. .. | SP 5 | 26 | 18 | *69* | 17 | *65* |
| | SP 10 | 33 | 20 | *61* | 17 | *52* |
| | SP 20 | 37 | 23 | *62* | 25 | *68* |

*Sedimentation Rate.*—The data on sedimentation rate in Table V show somewhat better results in the SP 5 group than in the other two—53% normal at six months against 41% in SP 10 and 34% in SP 20; but the difference is not significant. The total number of patients with an E.S.R. within normal limits was two before treatment started, 32 (28%) at the end of three months, and 48 (42%) at six months.

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

| | Group | Total | Sedimentation Rate 0–10 | 11–20 | 21–50 | 51+ | Deaths |
|---|---|---|---|---|---|---|---|
| At start of treatment | SP 5 | 34 | 2 | 2 | 13 | 17 | — |
| | SP 10 | 39 | — | 4 | 17 | 18 | — |
| | SP 20 | 42 | — | 2 | 20 | 20 | — |
| At 3 months .. | SP 5 | 34 | 11 | 9 | 8 | 6 | — |
| | SP 10 | 39 | 14 | 6 | 15 | 4 | — |
| | SP 20 | 42 | 7 | 17 | 11 | 7 | — |
| ,, 6 ,, .. | SP 5 | 43 | 18 | 5 | 6 | 3 | 2 |
| | SP 10 | 39 | 16 | 4 | 15 | 4 | — |
| | SP 20 | 41* | 14 | 10 | 12 | 5 | — |

* No result available for one patient.

## Bacterial Content of Sputum

Sputum was examined on entry and twice a month by smear and culture; if there was no sputum, or the smear examination was negative, material was cultured from a laryngeal swab or gastric lavage. No case was to be declared

bacteriologically negative unless these examinations had been done. The results of these examinations are set out in Tables VI and VII.

TABLE VI.—*Presence of Tubercle Bacilli*

| Time | Group | Total Patients from Whom Specimens were Examined | Total Specimens Examined | | Positive Direct Examination | | Negative Direct Examination Positive Culture | | Negative Direct Examination and Culture | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | No. | % | No. | % | No. | % | No. | % |
| On admission | SP 5 | 34 | 34 | *100* | 26 | *77* | 8 | *23* | 0 | *0* |
| | SP 10 | 39 | 39 | *100* | 35 | *90* | 4 | *10* | 0 | *0* |
| | SP 20 | 42 | 42 | *100* | 33 | *79* | 9 | *21* | 0 | *0* |
| 1st month | SP 5 | 34 | 74 | *100* | 37 | *50* | 29 | *39* | 8 | *11* |
| | SP 10 | 38 | 79 | *100* | 56 | *71* | 13 | *16* | 10 | *13* |
| | SP 20 | 40 | 87 | *100* | 59 | *68* | 16 | *18* | 12 | *14* |
| 2nd month | SP 5 | 34 | 79 | *100* | 26 | *33* | 30 | *38* | 23 | *29* |
| | SP 10 | 37 | 85 | *100* | 42 | *49* | 28 | *33* | 15 | *18* |
| | SP 20 | 40 | 94 | *100* | 51 | *54* | 26 | *28* | 17 | *18* |
| 3rd month | SP 5 | 30 | 70 | *100* | 19 | *27* | 19 | *27* | 32 | *46* |
| | SP 10 | 38 | 84 | *101* | 30 | *36* | 25 | *30* | 29 | *35* |
| | SP 20 | 41 | 98 | *100* | 29 | *30* | 24 | *24* | 45 | *46* |
| 4th month | SP 5 | 33 | 73 | *100* | 17 | *23* | 16 | *22* | 40 | *55* |
| | SP 10 | 38 | 82 | *101* | 16 | *20* | 27 | *33* | 39 | *48* |
| | SP 20 | 40 | 86 | *100* | 23 | *27* | 14 | *16* | 49 | *57* |
| 5th month | SP 5 | 32 | 70 | *100* | 26 | *37* | 20 | *29* | 24 | *34* |
| | SP 10 | 39 | 79 | *100* | 35 | *44* | 14 | *18* | 30 | *38* |
| | SP 20 | 37 | 84 | *100* | 26 | *31* | 24 | *29* | 34 | *40* |
| 6th month | SP 5 | 32 | 71 | *100* | 24 | *34* | 14 | *20* | 33 | *46* |
| | SP 10 | 36 | 70 | *100* | 34 | *49* | 14 | *20* | 22 | *31* |
| | SP 20 | 38 | 81 | *101* | 33 | *41* | 20 | *25* | 28 | *35* |

TABLE VII.—*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 | SP 5 | 34 | 0 | 0 | 0 |
| | SP 10 | 38 | 2 | 4 | 5 |
| | SP 20 | 40 | 1 | 1 | 3 |
| Second | SP 5 | 34 | 4 | 8 | 12 |
| | SP 10 | 37 | 5 | 8 | 14 |
| | SP 20 | 40 | 1 | 2 | 3 |
| Third | SP 5 | 30 | 7 | 21 | 23 |
| | SP 10 | 38 | 9 | 18 | 24 |
| | SP 20 | 41 | 12 | 24 | 29 |
| Fourth | SP 5 | 33 | 13 | 32 | 39 |
| | SP 10 | 38 | 15 | 31 | 39 |
| | SP 20 | 40 | 18 | 35 | 45 |
| Fifth | SP 5 | 32 | 7 | 21 | 22 |
| | SP 10 | 39 | 10 | 21 | 26 |
| | SP 20 | 37 | 9 | 17 | 24 |
| Sixth | SP 5 | 32 | 10 | 28 | 31 |
| | SP 10 | 36 | 9 | 16 | 25 |
| | SP 20 | 38 | 7 | 16 | 18 |

There is no significant difference between the three groups. All were positive on admission. In all three the percentage of negative examinations rose steadily: 11–14% in the first month, 18–29% in the second, 35–46% in the third, until it reached 48–57% in the fourth month—that is, shortly after the three-months course of chemotherapy. It subsequently fell to 31–46% in the sixth month.

The results are similar when analysed in terms of the proportion of patients for whom all examinations were negative for tubercle bacilli throughout a month. The proportion of negative cases rose to 39–45% in the fourth month, and fell subsequently to 18–31% in the sixth month.

### Streptomycin Sensitivity

Strains isolated on admission, and subsequently at least once a month, were tested for streptomycin sensitivity. The technique employed was the same as that previously reported.

All strains isolated before the start of chemotherapy showed sensitivity similar to that of the standard strain H37Rv. The results in succeeding months are set out in Table VIII and shown graphically in the Chart. As in the previous report, the results are designated by the resistance ratio (R.R.)—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. There was some indication in the previous trial that where the resistance ratio is less than eight the strain

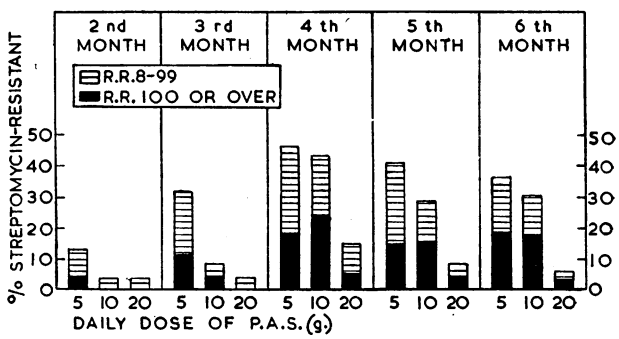


Chart showing percentage of cases with streptomycin-resistant strains in succeeding months after treatment started. All patients were treated for three months with daily streptomycin, 1 g., and P.A.S., 5, 10, or 20 g.

may be considered "sensitive"; accordingly the categories in this analysis are "sensitive" (less than eight), "moderately resistant" (8–99), and "strongly resistant" (100+). The result recorded in Table VIII for each case is that for the specimen with the highest degree of streptomycin resistance in the respective month.

In the first three months differences appear between the group receiving only 5 g. of P.A.S. and the other two groups: in the third month 32% of SP 5 cases had resistant strains, against 8% in the SP 10 group, and 4% in the SP 20 group. Subsequently the figures rise in both the SP 5 and SP 10 groups, and the percentage of resistant strains remains very low only in the group treated with 20 g. P.A.S. Thus the percentage of resistant cases in the fourth month was 47% in the SP 5 group, 43% in the SP 10, and only 15% in the SP 20; in the fifth month the corresponding figures were 41%, 28%, and 8% respectively; and in the sixth month 36%, 30%, and 7%. The difference between the group on the high P.A.S. dose and the others is even greater if we include only those strongly resistant. The conclusion must be that the dose of 20 g. of P.A.S. is much more effective in preventing or delaying the emergence of streptomycin resistance than doses of 5 or 10 g.

If only the cases giving strongly resistant strains are considered, in the SP 20 group of 42 patients there was only one such case; several cultures gave the same result. In the SP 10 group of 39 patients there were six cases: in four of these strongly resistant strains were isolated on several occasions; in a fifth there was an isolated one, followed by a strain with R.R. 8; in a sixth a single resistant strain was isolated in the sixth month. In the SP 5 group, among 34 patients there were seven cases: five were repeatedly highly resistant; in a sixth there was an isolated resistant culture, followed by a sensitive one; in a seventh, again, a single resistant strain in the sixth month. If these results are grouped for highly resistant strains, in 4 of the 14 cases it was an isolated observation, and in two of the four reversion to sensitivity or to R.R. 8 was observed.

Reversion to sensitivity was observed much more often in respect of moderately resistant strains, and in all three groups. In the SP 20 group there were six cases with moderately resistant strains: in five of them it was a single observation; in two of the five, sensitive strains were isolated subsequently. In the SP 10 group there were eight cases, and reversion to sensitivity was observed in seven of them. In the SP 5 group there were nine cases: five reverted to sensitivity, one other had a single resistant strain, and in three several resistant strains were isolated. If these results

TABLE VIII.—*Streptomycin Resistance in the Three Treatment Groups, in Successive Months after the Start of Treatment*

| Month 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 8 (Sensitive) | | 8–99 (Moderately Resistant) | | 100+ (Strongly Resistant) | |
| | | | | No. | % | No. | % | No. | % | No. | % |
| First .. .. | SP 5 | 28 | 0 | 28 | *100* | 27 | *96* | 1 | *4* | 0 | *0* |
| | SP 10 | 33 | 2 | 31 | *100* | 30 | *97* | 1 | *3* | 0 | *0* |
| | SP 20 | 34 | 1 | 33 | *100* | 32 | *97* | 1 | *3* | 0 | *0* |
| Second .. | SP 5 | 27 | 4 | 23 | *100* | 20 | *87* | 2 | *9* | 1 | *4* |
| | SP 10 | 35 | 5 | 30 | *100* | 29 | *97* | 1 | *3* | 0 | *0* |
| | SP 20 | 38 | 1 | 37 | *100* | 36 | *97* | 1 | *3* | 0 | *0* |
| Third .. | SP 5 | 26 | 7 | 19 | *100* | 13 | *68* | 4 | *21* | 2 | *11* |
| | SP 10 | 33 | 9 | 24 | *100* | 22 | *92* | 1 | *4* | 1 | *4* |
| | SP 20 | 34 | 12 | 22 | *99* | 21 | *95* | 1 | *4* | 0 | *0* |
| Fourth .. | SP 5 | 30 | 13 | 17 | *100* | 9 | *53* | 5 | *29* | 3 | *18* |
| | SP 10 | 36 | 15 | 21 | *100* | 12 | *57* | 4 | *19* | 5 | *24* |
| | SP 20 | 37 | 18 | 19 | *99* | 16 | *84* | 2 | *10* | 1 | *5* |
| Fifth .. .. | SP 5 | 29 | 7 | 22 | *100* | 13 | *59* | 6 | *27* | 3 | *14* |
| | SP 10 | 35 | 10 | 25 | *100* | 18 | *72* | 3 | *12* | 4 | *16* |
| | SP 20 | 33 | 9 | 24 | *100* | 22 | *92* | 1 | *4* | 1 | *4* |
| Sixth .. .. | SP 5 | 32 | 10 | 22 | *100* | 14 | *64* | 4 | *18* | 4 | *18* |
| | SP 10 | 32 | 9 | 23 | *100* | 16 | *70* | 3 | *13* | 4 | *17* |
| | SP 20 | 37 | 7 | 30 | *99* | 28 | *93* | 1 | *3* | 1 | *3* |

*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 in the respective month was fully examined.

† 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.

are grouped for moderately resistant strains, reversion to sensitivity was observed in 14 of the 23 cases, and in four others a single resistant culture was isolated.

It is interesting to consider whether the continuation of chemotherapy after the first three months may have affected the streptomycin sensitivity. Resistant strains were isolated from 3 of the 14 patients who had further chemotherapy. One, on 5 g. of P.A.S., was resistant from the second month of treatment; another was resistant from the beginning of the fourth month, but treatment had been stopped at the end of the third month, and was not resumed till the end of the fourth; in neither of these cases, therefore, was the continuation of chemotherapy responsible for emergence of resistant strains. In a third case (No. 27) chemotherapy was continued throughout the six months; cultures were negative from the first until the fifth month, when strains with R.R. over 16 were isolated.

In this series it is difficult to relate the clinical results to the emergence of streptomycin resistance, since improvement was observed in so high a proportion of cases, and the proportion developing streptomycin resistance was relatively low. Furthermore, as in previous series, resistance was observed most frequently in those most acutely ill: strongly resistant strains were isolated from 5 of 20 patients acutely febrile on admission—average temperature, 100° F.+ (37.8° C.+)—from 6 of 45 patients not acutely febrile but with gross cavitation, and from 3 of 46 other patients. The combined results for all three treatment groups are given in Table IX.

TABLE IX.—*Radiological Results Related to Streptomycin Resistance and to Condition on Entry*

| Clinical Condition | Streptomycin-resistance Ratio* | Total | Results at 6 Months. X-ray Assessment | | | | Deaths |
|---|---|---|---|---|---|---|---|
| | | | Improvement | | No Change | Deterioration | |
| | | | 3+ or 2+ | 1+ | | | |
| Temp. 100° F.+ (37·8° C.+) | Less than 8 | 8 | 5 | 2 | 0 | 1 | 0 |
| | 8-99 | 7 | 2 | 3 | 2 | 0 | 0 |
| | 100+ | 5 | 0 | 3 | 0 | 0 | 2 |
| Temp. less than 100° F. but cavitation + | Less than 8 | 32 | 15 | 14 | 2‡ | 1 | 0 |
| | 8–99 | 7 | 4 | 3 | 0 | 0 | 0 |
| | 100+ | 6 | 3 | 1 | 2 | 0 | 0 |
| Others .. | Less than 8 | 34 | 22 | 9 | 3 | 0 | 0 |
| | 8–99 | 9 | 5 | 3 | 1 | 0 | 0 |
| | 100+ | 3 | 2 | 1 | 0 | 0 | 0 |
| Total† .. | Less than 8 | 74 | 42 | 25 | 5 | 2 | 0 |
| | 8–89 | 23 | 11 | 9 | 3 | 0 | 0 |
| | 100+ | 14 | 5 | 5 | 2 | 0 | 2 |

* Highest recorded at any time in the six months.

† For two cases that showed considerable improvement, and one with moderate improvement, sensitivity results are not available after the first month.

## P.A.S. Sensitivity

The results of P.A.S.-sensitivity tests can conveniently be considered for all groups together, since very few resistant strains were isolated. The technique was similar to that employed for streptomycin-sensitivity tests. All but one were sensitive before the start of treatment. Strains from 87 patients (32, 28, and 27 in the SP 20, SP 10, and SP 5 groups respectively) were tested for P.A.S. sensitivity after treatment started; in the second month strains from 48 cases were tested, in the third 42, in the fourth 36, in the fifth 43, and in the sixth 46.

After the first month P.A.S.-resistant strains were isolated from three cases only. In two, both on 20 g. of P.A.S. daily, this was a single observation, with R.R. 40 (in the second month in one case, in the third month in the other); later strains were sensitive. The third case, in the SP 5 group, had a moderately resistant strain (R.R. 16) before treatment started; the only other culture tested was in the fifth month, and gave an R.R. 33; the streptomycin sensitivity was normal throughout.

## Discussion

Emergence of drug-resistant organisms is one of the limiting factors in the present increasing range of antibacterial agents. Since the first demonstrations of the development of streptomycin-resistant organisms in pulmonary tuberculosis, ways have been sought to prevent this potentially dangerous change in character of the infective organism. One of the most effective ways found has been the association of P.A.S. with streptomycin, a daily dose of 20 g. of the sodium salt reducing the risk considerably. However, this high dose produces much gastric discomfort, and the investigation reported here was undertaken to determine if smaller doses of P.A.S. would be equally effective in reducing the risk of streptomycin resistance.

Three groups of patients with similar pulmonary disease (acute rapidly progressive bilateral pulmonary tuberculosis) received for three months 1 g. of streptomycin daily and 20, 10, or 5 g. daily of the sodium salt of P.A.S. Allocation to one or the other of the three groups was made by random selection, and the three were observed and treated in similar conditions. It was found that clinical results of treatment were uniformly good in all three groups: in general condition, temperature, and sedimentation rate, changes were similar; the same applies to the proportion

of cases becoming tubercle-negative and to the *x*-ray changes. Similar numbers in the three groups became suitable for collapse therapy.

Results of streptomycin-sensitivity tests, however, show clear differences between the groups; in the first three months very few of the cases on 10 or 20 g. of P.A.S. developed drug-resistant strains, whereas of those on only 5 g. one in three had resistant strains in the third month. Subsequently the percentages of resistant strains rose in both the groups on small doses of P.A.S., and remained low only in the group on 20 g. daily: in the fourth month the proportion of resistant cases was 47% in the SP 5 group, 43% in the SP 10, and only 15% in the SP 20; these differences persisted in subsequent months. There is no doubt that the dose of 20 g. is much more effective in preventing emergence of streptomycin resistance than are doses of 10 or 5 g., and that in adults the higher dose should be administered if it is tolerated. The clinical significance of these results is discussed elsewhere in this issue by Daniels and Bradford Hill (1952).

Other methods of preventing emergence of streptomycin resistance have not been investigated here, though one at least has been reported to be most effective. Administration of streptomycin every third or fourth day reduces the risk of emergence of streptomycin resistance and, it is claimed, without loss of clinical effect; combination of this regime with daily administration of P.A.S. reduces the risk even further (Veterans Administration, 1949–50).

**Summary**

A series of 115 patients with acute progressive bilateral pulmonary tuberculosis unsuitable for collapse therapy were studied in a clinical trial of streptomycin and P.A.S. All were treated for three months with 1 g. of streptomycin daily; in addition, 42 were given 20 g. of P.A.S. daily (SP 20), 39 had 10 g. (SP 10), and 34 had 5 g. (SP 5). Patients were assigned to one or another treatment group by random selection.

Gastro-intestinal disturbance was infrequent (12–15%) and mild in the two groups on lower doses of P.A.S.; in the group receiving 20 g. of P.A.S. the incidence was 52%.

The radiological assessment of change at the end of six months shows no difference between the three groups. The proportion showing improvement was 87–88%. No differences were found between the groups in respect of changes in temperature, sedimentation rate, general condition, or bacterial content of sputum.

Analysis of results of streptomycin-sensitivity tests show significant differences between the groups. In the third month 32% of SP 5 cases had resistant strains, against 8% in the SP 10 group and 4% in the SP 20 group. Subsequently the figures rise in both groups on lower doses, and remain very low in the SP 20 group. In the fourth month the proportion of resistant cases was 47% in the SP 5 group, 43% in the SP 10, and 15% in the SP 20. In the sixth month the corresponding figures were 36%, 30%, and 7%.

Reversion to sensitivity was observed frequently, in all three groups, in cases with moderately resistant strains.

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Americans have started a national matching plan for placing new interns in hospital appointments. Students apply for internships and visit hospitals. Students and hospitals send confidential "ratings" to a national committee, which then matches them, and the student receives the internship he wants if the hospital's rating of him is satisfactory.

# CHEMOTHERAPY OF PULMONARY TUBERCULOSIS IN YOUNG ADULTS

## AN ANALYSIS OF THE COMBINED RESULTS OF THREE MEDICAL RESEARCH COUNCIL TRIALS

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During the period 1947 to 1951 three trials of chemotherapy of pulmonary tuberculosis in young adults were made under the direction of the Medical Research Council's Streptomycin in Tuberculosis Trials Committee. The first of these trials was designed to assess the efficacy of streptomycin itself. At that time the drug was available in only very small quantities, and it was thus possible to contrast the patients given streptomycin with similar patients treated by rest in bed only (M.R.C., 1948). In the second trial the newly discovered drug P.A.S. was brought under study, and its effects when used either alone or in combination with streptomycin were compared with the results given by streptomycin alone. It was clearly proved that the dose of 20 g. of P.A.S. daily would frequently prevent the development of streptomycin-resistant organisms (M.R.C., 1950). However, this dose often produced undesirable side-effects in the patient—nausea and vomiting—and a third trial was therefore set up to determine whether smaller doses of P.A.S. (5 or 10 g. daily) would be as effective as 20 g. in preventing the emergence of streptomycin-resistant strains. With the completion of this third trial (M.R.C., 1952) it is now possible to consider together the results of all three investigations.

The three trials were all designed in the same way. Clinicians and pathologists of several hospitals co-operated. The patients admitted to the trial had to conform to a particular definition (acute progressive bilateral pulmonary tuberculosis, believed to be of recent origin, bacteriologically proved, unsuitable for collapse therapy, age group 15–30); after acceptance by a panel the cases were randomly allocated to one or another treatment group; in each trial the different treatment groups were treated and observed concurrently; the clinical and radiological examinations and record-keeping were

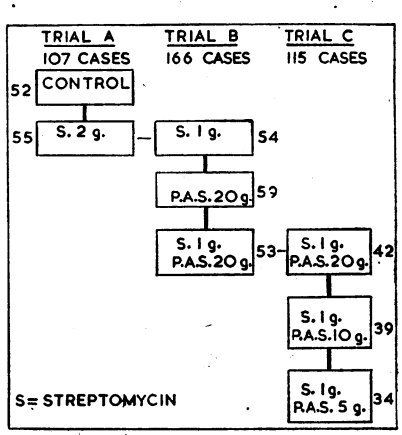


FIG. 1.—Diagram showing groups involved in the three trials.