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STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchison.

Colindale Hospital (L.C.C.), London.—Clinicians: Dr. J. V. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Snell; Pathologists (Central Public Health Laboratory): Dr. G. B. Forbes, Dr. H. D. Holt.

Harefield Hospital (M.C.C.), Harefield, Middlesex.—Clinicians: Dr. R. H. Brent, Dr. L. E. Houghton; Pathologist: Dr. E. Nassau.

Bangour Hospital, Bangour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reevie; Pathologist: Professor J. W. McLeod.

Northern Hospital (L.C.C.), Winchmore Hill, London.—Clinicians: Dr. F. A. Nash, Dr. R. Shoulman; Pathologists: Dr. J. M. Alston, Dr. A. Mohun.

Sully Hospital, Sully, Glam.—Clinicians: Dr. D. M. E. Thomas, Dr. L. R. West; Pathologist: Professor W. H. Tytler.

The clinicians of the centres met periodically as a working subcommittee under the chairmanship of Dr. Geoffrey Marshall; so also did the pathologists under the chairmanship of Dr. R. Cruickshank. Dr. Marc Daniels, of the Council's scientific staff, was responsible for the clinical co-ordination of the trials, and he also prepared the report for the Committee, with assistance from Dr. D. A. Mitchison on the analysis of laboratory results. For the purpose of final analysis the radiological findings were assessed by a panel composed of Dr. L. G. Blair, Dr. Peter Kerley, and Dr. Geoffrey S. Todd.

Introduction

When a special committee of the Medical Research Council undertook in September, 1946, to plan clinical trials of streptomycin in tuberculosis the main problem faced was that of investigating the effect of the drug in pulmonary tuberculosis. This antibiotic had been discovered two years previously by Waksman (Schatz, Bugie, and Waksman, 1944); in the intervening period its power of inhibiting tubercle bacilli *in vitro*, and the results of treatment in experimental tuberculous infection in guinea-pigs, had been reported; these results were strikingly better than those with any previous chemotherapeutic agent in tuberculosis. Preliminary results of trials in clinical tuberculosis had been published (Hinshaw and Feldman, 1945; Hinshaw, Feldman, and Pfuetze, 1946; Keefer *et al.*, 1946); the clinical results in pulmonary tuberculosis were encouraging but inconclusive.

The natural course of pulmonary tuberculosis is in fact so variable and unpredictable that evidence of improvement or cure following the use of a new drug in a few cases cannot be accepted as proof of the effect of that drug. The history of chemotherapeutic trials in tuberculosis is filled with errors due to empirical evaluation of drugs (Hart, 1946); the exaggerated claims made for gold treatment, persisting over 15 years, provide a spectacular example. It had become obvious that, in future, conclusions regarding the clinical effect of a new chemotherapeutic agent in tuberculosis could be considered valid only if based on adequately controlled clinical trials (Hinshaw and Feldman, 1944). The one controlled trial of gold treatment (and the only report of an adequately controlled trial in tuberculosis we have been able to find in the literature) reported negative therapeutic results (Amberson, McMahon, and Pinner, 1931). In 1946 no controlled trial of streptomycin in pulmonary tuberculosis had been undertaken in the U.S.A. The Committee of the Medical Research Council decided then that a part of the small supply of streptomycin allocated to it for research purposes would be best employed in a rigorously planned investigation with concurrent controls.

The many difficulties of planning and conducting a trial of this nature are important enough to warrant a full description here of the methods of the investigation.

Plan and Conduct of the Trial

Type of Case

A first prerequisite was that all patients in the trial should have a similar type of disease. To avoid having to make allowances for the effect of forms of therapy other than bed-rest, the type of disease was to be one not suitable for other forms of therapy. The estimated chances of spontaneous regression must be small. On the other hand, the type of lesion should be such as to offer some prospect of action by an effective chemotherapeutic agent; for this reason old-standing disease, and disease with thick-walled

cavities, should be excluded. Finally the age group must be reasonably limited, since the total number of patients in the trial could not be large.

Such closely defined features were considered indispensable, for it was realized that no two patients have an identical form of the disease, and it was desired to eliminate as many of the obvious variations as possible. For these several reasons the type of case to be investigated was defined as follows: acute progressive bilateral pulmonary tuberculosis of presumably recent origin, bacteriologically proved, unsuitable for collapse therapy, age group 15 to 25 (later extended to 30).

The selection of this type of disease constituted full justification for having a parallel series of patients treated only by bed-rest, since up to the present this would be considered the only suitable form of treatment for such cases. Additional justification lay in the fact that all the streptomycin available in the country was in any case being used, the rest of the supply being taken up for two rapidly fatal forms of the disease, miliary and meningeal tuberculosis.

Recruitment and Admission of Cases

Co-operation in the trial was obtained in the first place from Brompton Hospital (drawing on London County Council cases), Colindale Hospital (London County Council), and Harefield County Hospital (Middlesex County Council). The L.C.C. and the M.C.C. gave full co-operation, permitting recruitment of suitable cases from the areas served by them, covering a population of nearly six million persons. Accordingly letters were sent, through the tuberculosis departments of these authorities, to tuberculosis officers and to medical superintendents of general hospitals outlining the proposed trial and asking that particulars and *x*-ray films of possibly suitable patients be sent to the co-ordinator of the trials for consideration. Visits were paid to the tuberculosis clinics and hospitals to show by representative *x*-ray films the type of case sought and to explain in detail the nature of the controlled trial. When cases were submitted the clinical particulars and *x*-ray films were taken to the Committee's selection panel for consideration. When a patient had been accepted as suitable, request was made through the local authority for admission to one of the streptomycin centres; in spite of long waiting-lists these patients were given complete priority, and the majority were admitted within a week of approval.

The first patients to be accepted were admitted to the centres in January, 1947. At first the impression was that cases of the type defined are seen often. In fact, such cases are not common. As it became evident after three months that enough cases could not be found in the London and Middlesex areas, other authorities were approached. The Welsh National Memorial Association, the Department of Health for Scotland, and the Leeds Tuberculosis Service made available centres at Sully, Bangour, and Killingbeck, and cases were recruited to those centres from the respective areas. In addition, another centre was opened in the London area, at the Northern Hospital (L.C.C.).

By September, 1947, 109 patients had been accepted, and no more were admitted to this trial. Two patients had died within the preliminary observation week; these are excluded from the analysis. Of the remaining 107 patients 55 had been allocated to the streptomycin group and 52 to the control group.

The Control Scheme

Determination of whether a patient would be treated by streptomycin and bed-rest (S case) or by bed-rest alone (C case) was made by reference to a statistical series based on random sampling numbers drawn up for each sex at each centre by Professor Bradford Hill; the details of the series were unknown to any of the investigators or to the co-ordinator and were contained in a set of sealed envelopes, each bearing on the outside only the name of the hospital and a number. After acceptance of a patient by the panel, and before admission to the streptomycin centre, the appropriate numbered envelope was opened at the central office; the card inside told if the patient was to be an S or a C case, and this information was then given to the medical officer of the centre. Patients were not told before admission that they were to get special treatment. C patients did not know throughout their stay in hospital that they were control patients in a special study; they were in fact treated as they would have been in the past, the sole difference being that they had been admitted to the centre more rapidly than was normal. Usually they were not in the same wards as S patients, but the same regime was maintained

It was important for the success of the trial that the details of the control scheme should remain confidential. It is a matter of great credit to the many doctors concerned that this information was not made public throughout the 15 months of the trial, and the Committee is much indebted to them for their co-operation.

By definition, cases accepted for the trial were unsuitable for collapse therapy; clinicians were therefore asked to adopt collapse therapy only if the course of the disease so changed that some collapse measure became indispensable and urgent. In the S cases collapse therapy was in fact never applied during the four treatment months. It was given to five of the 52 C cases during that period.

Observation and Treatment Period

Each patient was to remain in bed at the centre for at least six months, and the results were to be assessed on the clinical status at the end of that period. In addition to the usual hospital records, clinical observations were entered on standard record forms designed particularly for this trial; these forms provided for details of history, criteria of acceptance, 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.

Clinicians and pathologists' meetings were held during the trials to discuss the work as it proceeded. The co-ordinator visited centres and was constantly in touch with the clinicians concerned to discuss the progress of the trial and the problems arising. The working subcommittee of pathologists established the technical laboratory procedures, discussed the findings at intervals, and arranged for independent checking of sensitivity tests of tubercle bacilli and streptomycin levels in the blood.

Analysis of Results

The general trend of results during the course of the trial was followed through the monthly reports from the centres. The analysis of results up to six months after the patient's admission is presented here; it is based on information from the standard record forms completed for each patient and on the *x*-ray films which have been made available by the hospitals concerned.

The films have been viewed by two radiologists and a clinician, each reading the films independently and not knowing if the films were of C or S cases. One of the radiologists had been attached to a centre taking part in the trial; the other two specialists had not been connected with the trial in any way. There was fair agreement among the three; at a final session they met to review and discuss

films on which there had been a difference of interpretation, and agreement was reached without difficulty on all films. The results of radiological assessment presented in the main analyses are the agreed results, but the separate reports and their differences are discussed under the heading "Changes in Radiological Picture."

Condition on Admission

Each patient was under observation at a centre for at least one week before streptomycin treatment or observation proper for the trial started. Data in Table I reflect the condition on admission.

TABLE I.—*Condition on Admission*

General Condition	S Group	C Group	Max. Evening Temp. in First Week*	S Group	C Group	Sedimentation Rate	S Group	C Group
Good .	8	8	98–98·9° F. (36·7–37·15° C.)	3	4	0–10	0	0
Fair ..	17	20	99–99·9° F. (37·2–37·75° C.)	13	12	11–20	3	2
Poor ..	30	24	100–100·9° F. (37·8–38·25° C.)	15	17	21–50	16	20
			101° F. (38·3° C.) +	24	19	51 +	36	29
Total	55	52	Total	55	52	Total	55	51†

* Temperature by mouth in all but six cases. †Examination not done in one case.

Thirty patients (54%) in the S group and 24 (46%) in the C group were in poor general condition at the start of the trial; of these, 20 and 17 respectively were considered to be desperately ill. Twenty-four S patients (44%) and 19 C patients (36%) had during the preliminary observation week maximum evening temperatures of 101° F. (38.3° C.) or over. In 36 S patients (65%) and 29 C patients (56%) the sedimentation rate (Westergren, 200 mm. reading at one hour) was over 50.

These data reflect the fairly acute clinical condition of most of the patients, though obviously the clinical picture was far from uniform in the 107 patients admitted to the trial. The data show also that random distribution has equalized the groups; if anything, there are more severe cases in the S group. There were 22 men and 33 women in the S group, 21 men and 31 women in the C group.

X-ray Classification

All cases conformed more or less to the type defined, but within the possible limits of the definition there were wide variations. All films showed opacities representing extensive infiltration of apparently recent origin; where there was room for doubt the length of history was taken into consideration as evidence of the age of the lesions.

It was thought at first that gross cavitation should be excluded, but this view was abandoned, as many otherwise suitable cases had large cavities. Thirty-two of the 55 S cases and 30 of the 52 C cases showed large or multiple cavities in the film taken on admission (tomography was not used as a routine); it must be stressed, however, that from their radiological appearance these seemed to be of recent development and that the lesions predominating in the lungs were bronchopneumonic in type.

In 19 S cases and in 19 C cases there was radiological evidence of segmental atelectasis.

Treatment

All S patients were given streptomycin* by the intramuscular route. The dose was 2 g. per day, given in four injections at six-hourly intervals. This dosage was adopted following exchange of correspondence with Dr. H. C. Hinshaw, of the Mayo Clinic, to whom the Committee is indebted for advice during the planning of the trial.

The original intention was to continue streptomycin treatment for six months. However, reports from observers in the U.S.A., and a growing impression in our own centres, indicated that the maximum effect of streptomycin was reached within the first three or four months, and it was therefore decided in July, 1947, to treat patients for four months only, but to continue observation to the end of six months from admission as for C patients. (One patient was treated with streptomycin for 6 months, 2 for 5½ months, 6 for 5 months, 5 for 4½ months; the remainder, 41 patients, were treated for 4 months.)

Patients in both groups were on bed-rest during the period of the trial, and were allowed only up to toilet where the general condition allowed. As already indicated, although patients admitted were considered unsuitable for collapse therapy, it was agreed that when the course of disease had so changed that collapse therapy was strongly indicated such treatment should be given. In 11 C patients collapse measures (artificial pneumoperitoneum with phrenic paralysis in 10 cases, pneumothorax in one) were induced at some time during the six months—three in the third month of observation, two in the fourth month, two in the fifth, and four in the last observation month. In seven of the 11 the course of the disease appears not to have been affected; in four there was deterioration before and improvement after induction of artificial pneumoperitoneum. Collapse therapy was induced in 11 S patients during the fifth or sixth month; in all but two the course of the disease was apparently unaltered.

Results at End of Six Months

Four of the 55 S patients (7%) and 14 of the 52 C patients (27%) died before the end of six months. The difference between the two series is statistically significant; the probability of it occurring by chance is less than one in a hundred.

Assessment of condition at the end of the six-months period should be based on a judicious combination of changes in the radiological picture, changes in general condition, temperature, weight, sedimentation rate, and bacillary content of the sputum. We have not attempted a numerical evaluation of the relative importance of each of these, and changes in them will be reported in turn. Appreciation of the clinical effects of the drug have not been lacking in the many reports published within the past two years. So far as possible, the analysis in this report will deal with the more readily measurable data only.

The following preliminary analysis is based on changes in the radiological picture alone, this being in our opinion the most important single factor to consider; it will be seen later that in the great majority of cases clinical and radiological changes followed similar trends.

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

Radiological Assessment	Streptomycin Group		Control Group	
Considerable improvement ..	28	*51%*	4	*8%*
Moderate or slight improvement	10	*18%*	13	*25%*
No material change	2	*4%*	3	*6%*
Moderate or slight deterioration	5	*9%*	12	*23%*
Considerable deterioration ..	6	*11%*	6	*11%*
Deaths	4	*7%*	14	*27%*
Total	55	*100%*	52	*100%*

The overall results given in Table II (extracted from Table IX) show differences between the two series that leave no room for doubt. The most outstanding difference

*The streptomycin used was in the form of the hydrochloride, obtained from one American producer. For technical particulars of the product see article in *Lancet*, 1948, **1**, 582.

is in the numbers who showed "considerable improvement" in the radiological picture—i.e., those for whom at the end of the six-months period there was a reasonable prospect of recovery. Twenty-eight of the S patients (51%) and only four of the C patients (8%) were considerably improved (the probability of such a difference occurring by chance is less than one in a million).

Results in men and women were similar, and need not be tabulated here. There was a higher mortality among males in both S and C groups; two of 22 male S patients died and eight of 21 male C patients, compared with two of 33 female S patients and six of 31 female C patients, but the difference is not significant.

Results Related to Condition on Admission

The next point to be considered is whether the prognosis was worse in those most acutely ill, and whether the difference between the S and C groups applies to the less or more acutely ill patients.

Temperature

TABLE III.—*Results at Six Months Related to Temperature on Admission*

Max. Evening Temp. during First Observation Week		Radiological Assessment at 6 Months: Improvement	No Change	Deterioration	Deaths	Total
98–98·9 °F. (36·7–37·15° C.)	S	3	0	0	0	3
	C	3	1	0	0	4
99–99·9° F. (37·2–37·75° C.)	S	9	1	3	0	13
	C	7	2	2	1	12
100–100·9° F. (37·8–38·25° C.)	S	13	0	2	0	15
	C	5	0	7	5	17
101° F. (38·3° C.)+	S	13	1	6	4	24
	C	2	0	9	8	19

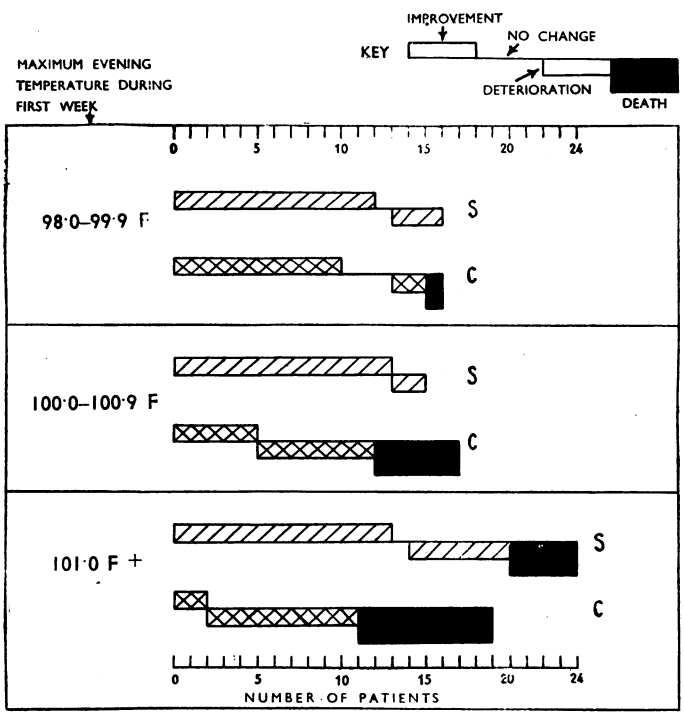

CHART I.—Results at six months (radiological assessment) related to temperature on admission.

The results in Table III, represented graphically in Chart I, show first what was to be expected—viz., in both groups the most grave prognosis was in the patients most febrile on admission; indeed, in the S group the only deaths were in patients who had on admission evening temperatures of 101° F. (38.3° C.) or over. A second, more important, point that emerges is that the superiority of results in the S group as a whole over the C group is almost entirely accounted for by the most febrile patients. Only seven (19%) of 36 C patients with a temperature of 100° F. (37.8° C.) or over were improved at the end of six months, compared with 26 (67%) of 39 S patients. Further analysis reveals that eight of the 24 S patients with a temperature of 101° or over showed considerable improvement, and none of the 19 C patients. In less febrile and in afebrile patients there is little difference in results between the two groups, though analysis shows that the number showing considerable improvement was greater in the S group.

Sedimentation Rate (E.S.R.)

Relation of results to the E.S.R. on admission shows the same trends. Of patients with an E.S.R. not higher than 50, 13 (68%) of 19 S patients were improved, compared with nine (41%) of 22 C patients. Eighteen (50%) of 36 S patients with E.S.R. over 50 were improved, compared with seven (24%) of 29 C patients.

Radiological Assessment on Admission

TABLE IV.—*Radiological Assessment at Six Months Related to Presence or Absence of Gross Cavitation on Admission*

X-Ray on Admission	Group	Total Cases	Radiological Assessment at 6 Months: Improvement: Considerable	Improvement: Slight or Moderate	No Change	Deterioration: Slight or Moderate	Deterioration: Considerable	Deaths
Cases with large or multiple cavities	S	32	11	7	2	4	4	4
	C	30	1	8	2	6	2	11
Other cases	S	23	17	3	0	1	2	0
	C	22	3	5	1	6	4	3

The data in Table IV show that in both S and C groups the results were better where there was no gross cavitation on admission. In the S cases with no gross cavitation the results were outstandingly good, with no deaths and 17 of 23 patients showing considerable improvement.

Clinical Changes During Period of Trial

General Condition

Assessment of changes in general condition is based on a combination of clinical facts, clinician's general impression, and patient's feeling of well- or ill-being. As such, it is mentioned only briefly here. At four months after admission the general condition had improved in 40 (73%) of the 55 S patients, compared with 26 (50%) of 52 C patients; only seven (13%) S patients were worse, whereas 10 (19%) C patients had died and another 13 (25%) were worse than on admission. At six months after admission the difference between the two groups was less; in 33 (60%) S patients and in 24 (46%) C patients the general condition was better than on admission: 13 S patients (24%) were worse and four others (7%) had died; 12 C patients (23%) were worse and 14 others (27%) had died.

Temperature

Three S patients and four C patients were afebrile on admission to the trial. The three S patients remained afebrile throughout, with the exception of a short slight pyrexial episode in one case. Two of the four C patients remained afebrile throughout; the other two had occasional low pyrexia, and one was still pyrexial at the end of the six

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CASES DEMONSTRATING "CONSIDERABLE IMPROVEMENT"

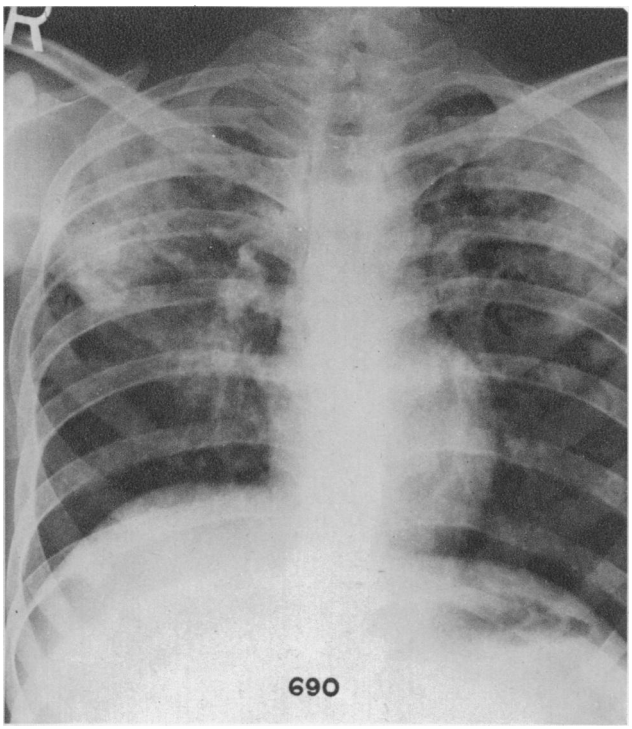

Fig. 1.—Case 69 (S). May 12, 1947.

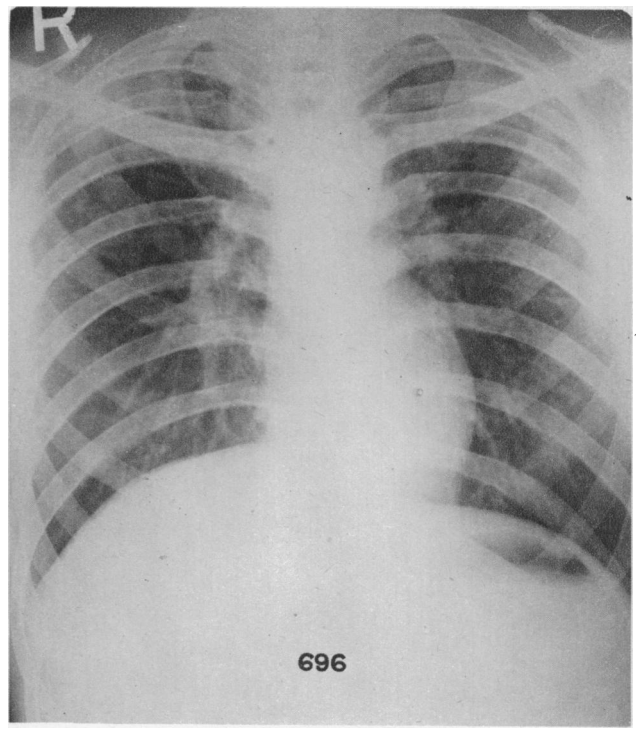

Fig. 2.—Case 69 (S). Nov. 17, 1947.

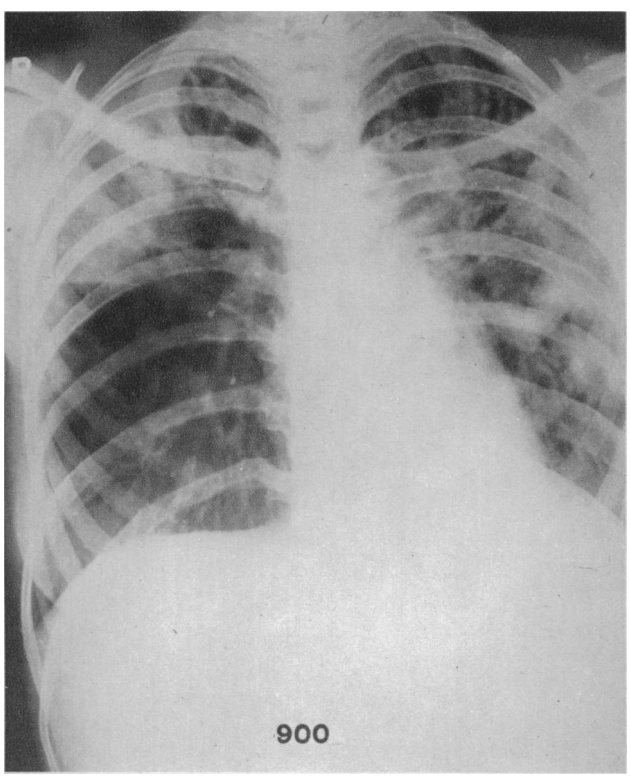

Fig. 3.—Case 90 (S). April 26, 1947.

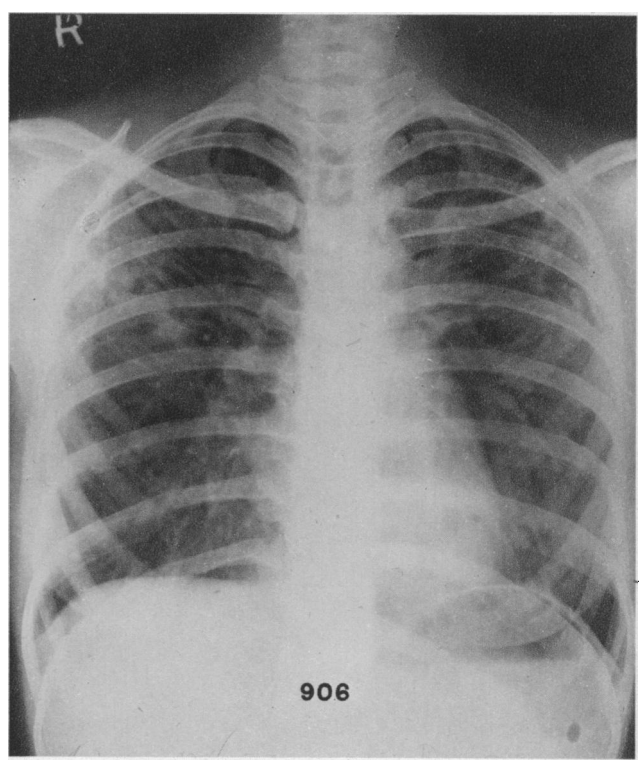

Fig. 4.—Case 90 (S). Nov. 5, 1947.

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CASES DEMONSTRATING "CONSIDERABLE IMPROVEMENT"

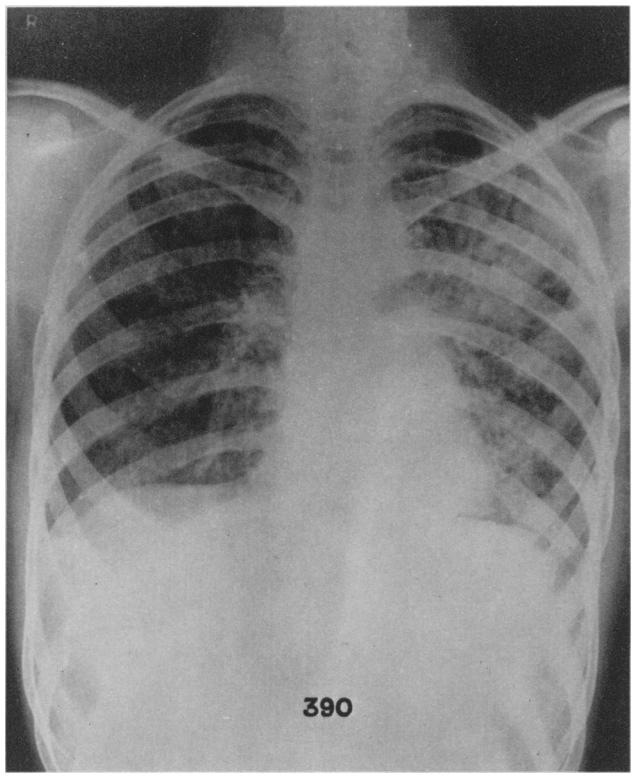

FIG. 5.—Case 39 (S). June 21, 1947.

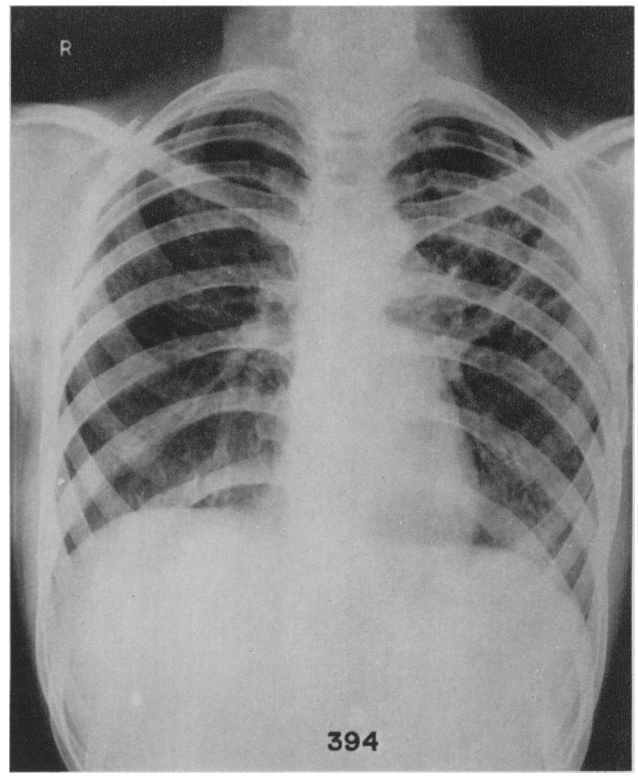

FIG. 6.—Case 39 (S). Oct. 20, 1947.

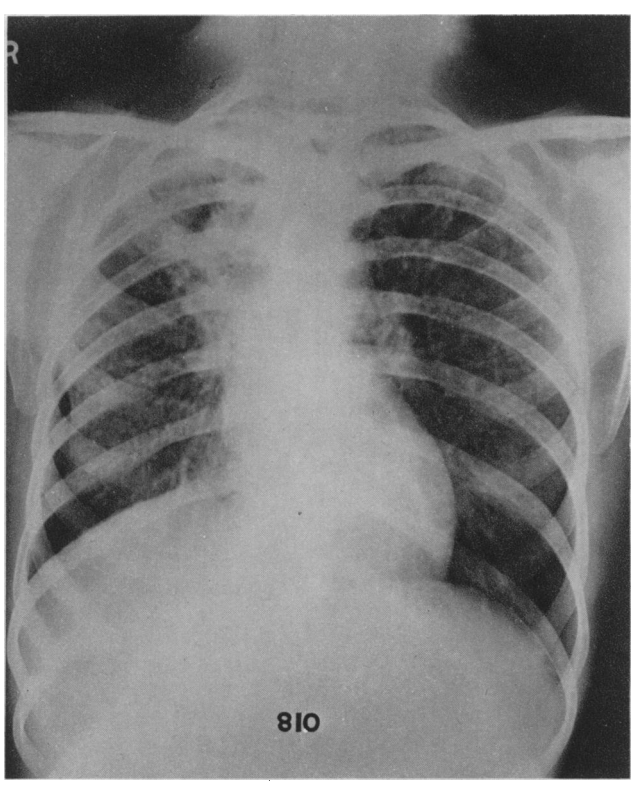

FIG. 7.—Case 81 (C). Feb. 27, 1947.

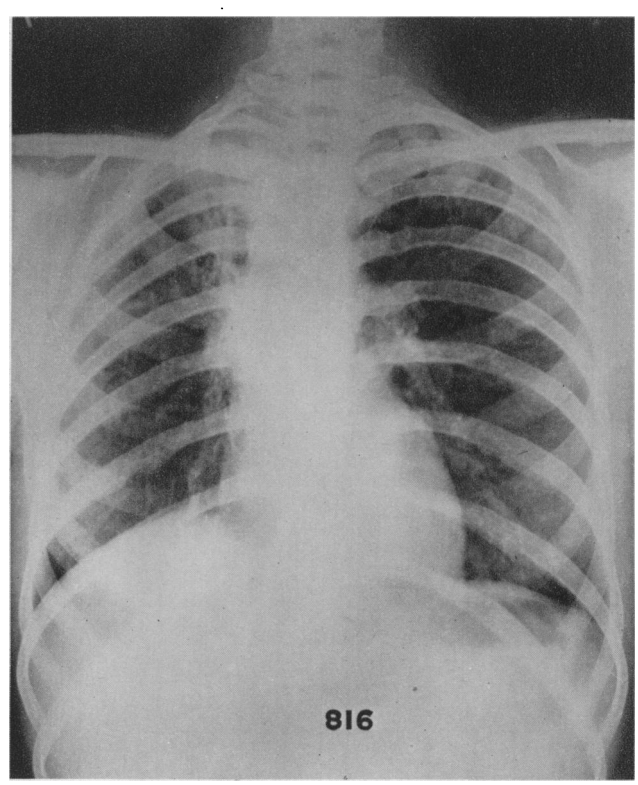

FIG. 8.—Case 81 (C). Aug. 27, 1947.

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CASES DEMONSTRATING "MODERATE IMPROVEMENT"

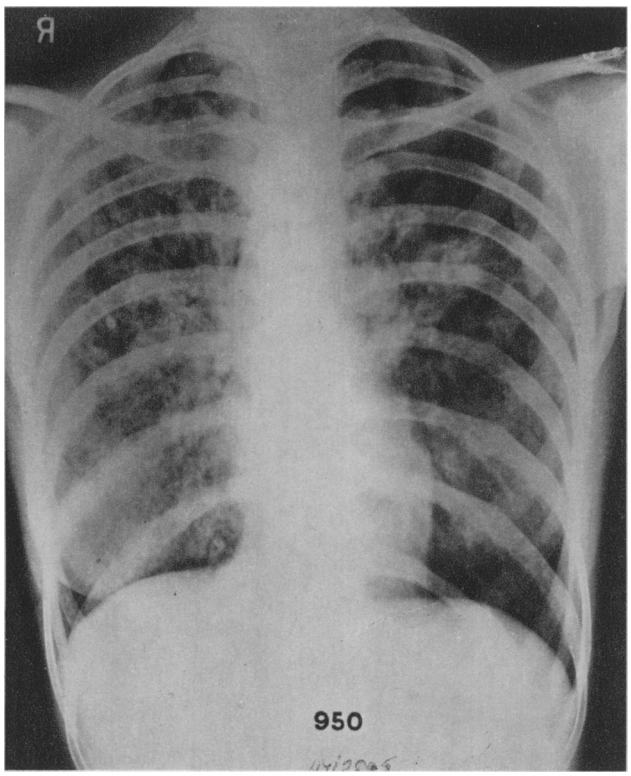

Fig. 9.—Case 95 (S). May 21, 1947.

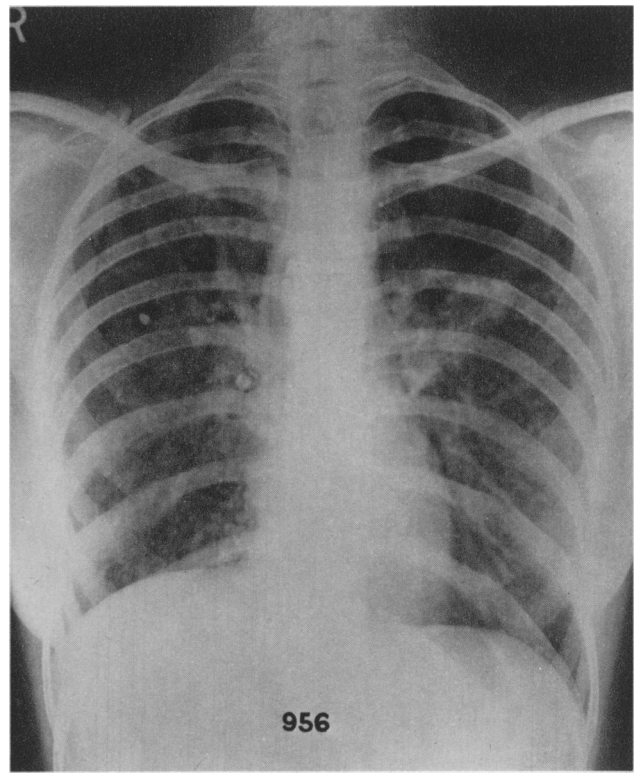

Fig. 10.—Case 95 (S). Nov. 21, 1947.

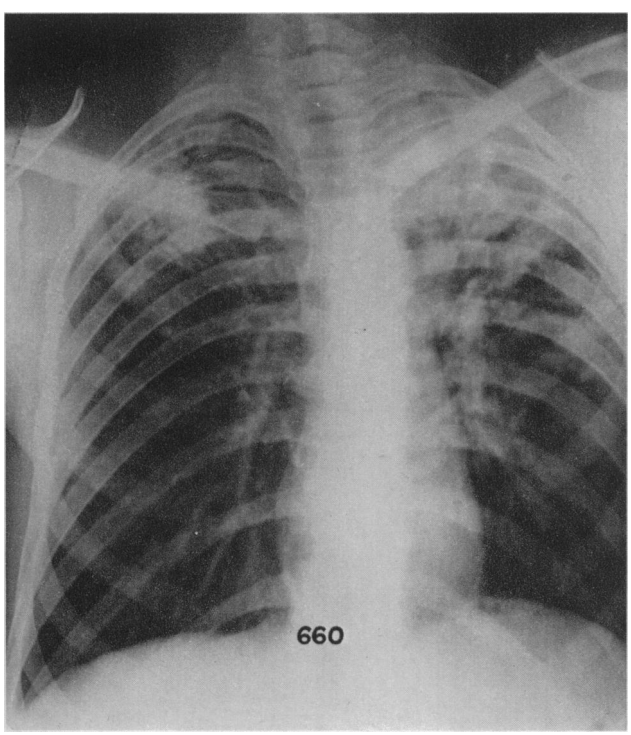

Fig. 11.—Case 66 (C). April 11, 1947.

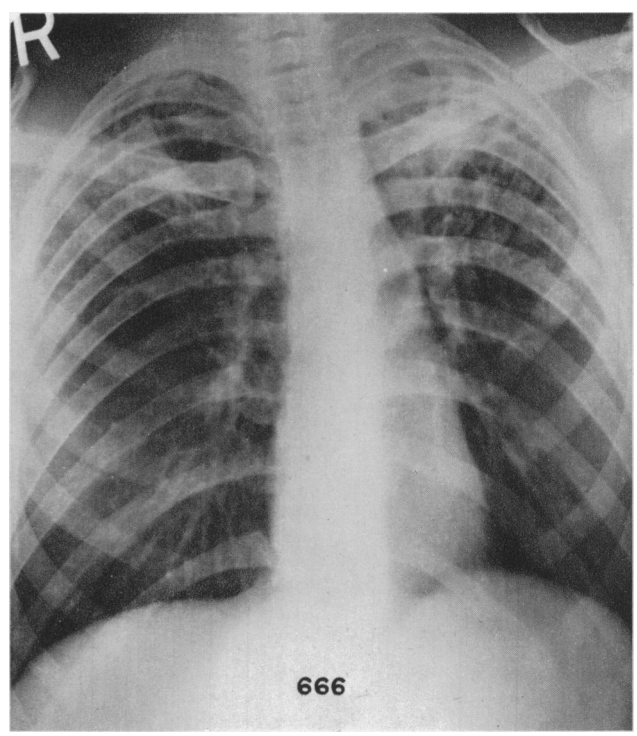

Fig. 12.—Case 66 (C). Oct. 15, 1947.

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S CASES: IMPROVEMENT AND SUBSEQUENT DETERIORATION

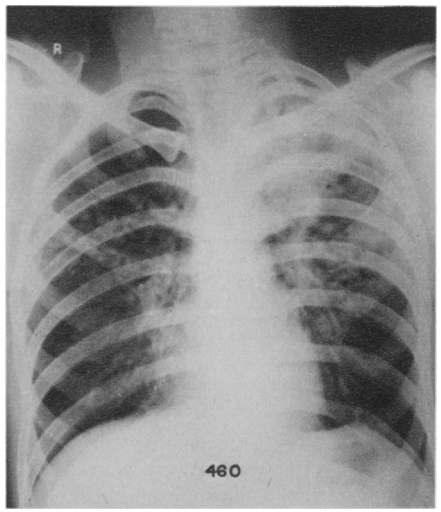

FIG. 13.—Case 40. Jan. 30, 1947.

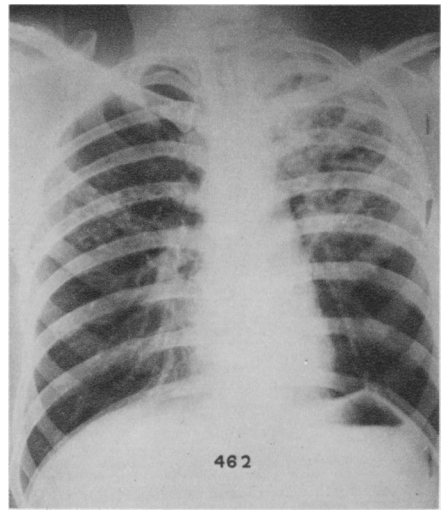

FIG. 14.—Case 46. March 26, 1947.

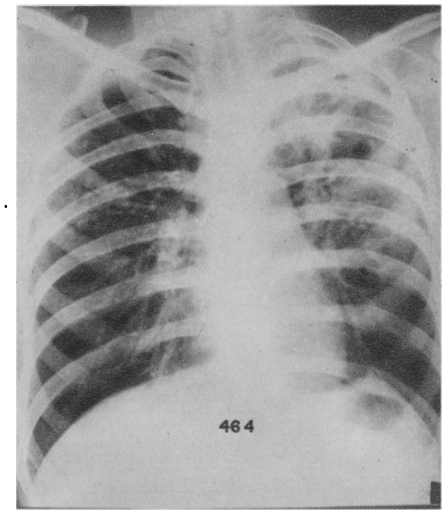

FIG. 15.—Case 46. May 23, 1947.

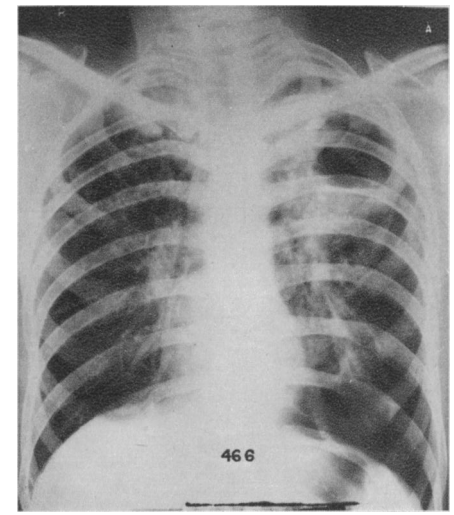

FIG. 16.—Case 46. July 21, 1947.

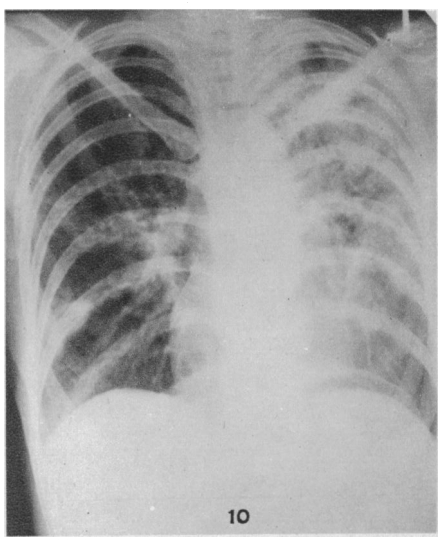

FIG. 17.—Case 1. June 2, 1947.

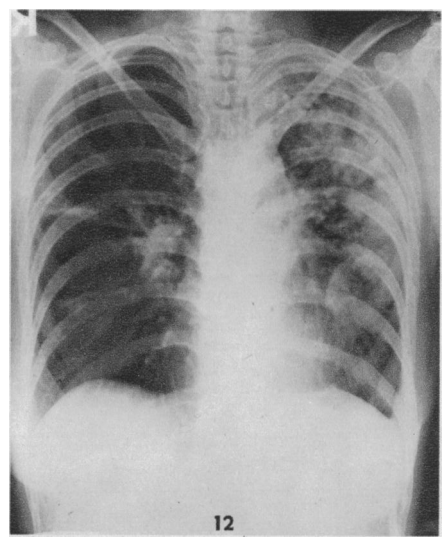

FIG. 18.—Case 1. July 25, 1947.

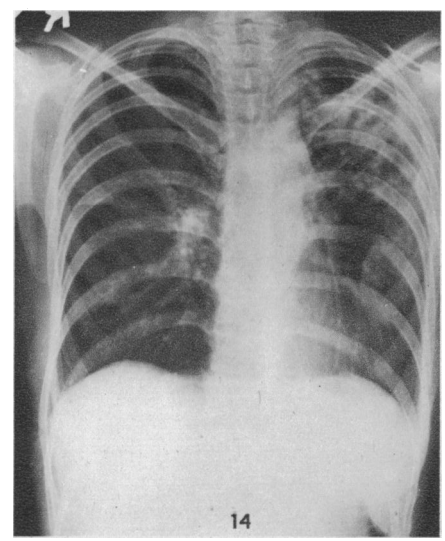

FIG. 19.—Case 1. Sept. 29, 1947.

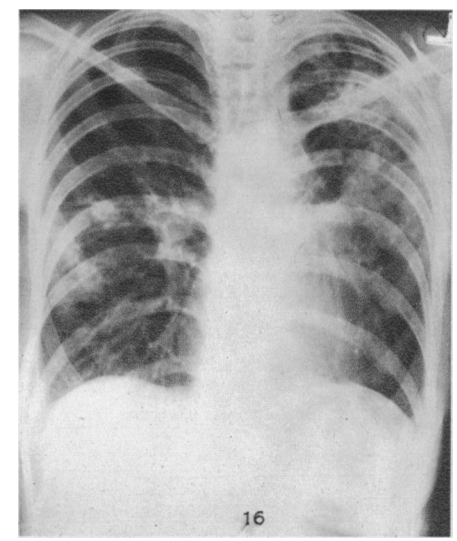

FIG. 20.—Case 1. Nov. 21, 1947.

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months. Temperature changes in the febrile patients at two months, four months, and six months after admission are shown in Table V.

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

Highest Evening Temp. During Week following Admission	Group	Total	No. of Patients whose Temperature was Normal at end of			No. of Patients Showing Temp. Fall (including Fall to Normal) at end of		
			2 Mos.	4 Mos.	6 Mos.	2 Mos.	4 Mos.	6 Mos.
101° F. (38·3° C.) or over	S	24	1	5	6	15	14	11
	C	19	0	2	3	7	6	8
99–100·9° F. (37·2–38·25° C.)	S	28	8	15	18	12	19	24
	C*	28	5	10	10	10	11	12

* Temperature for one C case not available.

The difference between S and C series at any one point of time is not statistically significant, but appears at every stage—i.e., at every stage more S patients than C patients show a temperature drop to normal or to a degree of pyrexia lower than that on admission. A common effect of streptomycin not obvious in the above simplified presentation of data is a rapid temperature drop in the first weeks of therapy, followed sometimes by a rise to a level usually lower than the level on admission. Among the less acutely febrile patients (temperature 99–100.9° F.; 37.2–38.85° C.) an increasing number of S cases show falling temperature; at six months 18 of the 28 were apyrexial and six others had temperatures lower than on admission; 10 of 28 similar C cases were apyrexial and two others had temperatures lower than on admission.

There is thus a consistent difference between S and C groups. It is important to note, however, that in 20 of 47 febrile patients treated by bed-rest without streptomycin the temperature was lower at the end of six months than on admission; in 13 of the 20 it was within normal limits. For the type of lesions selected, these results serve to emphasize both the value of prolonged bed-rest and the need of controls in an investigation of this type.

In seven of the 13 C patients with normal temperature at the end of six months an artificial pneumoperitoneum had been induced at some time during the trial, but in every case the temperature had come down to normal previous to the induction of artificial pneumoperitoneum. The temperature fall in the C patients can be attributed to the effect of bed-rest alone.

Weight (Table VI)

In the first four months 20 S patients had gained weight (5 lb.—2.27 kg.—or more), with a total weight gain between them of 253 lb. (114.76 kg.), mean 12.6 lb. (5.71 kg.). The weight gains in the C group are very similar: 20 patients gained weight, with a total gain of 255 lb. (115.67 kg.), mean 12.7 lb. (5.76 kg.). At the end of six months 24 S patients had gained weight, with a total gain of 451 lb. (204.57 kg.), mean 18.8 lb. (8.53 kg.). Eighteen C patients had gained weight, with a total gain of 313 lb. (141.97 kg.), mean 17.4 lb. (7.89 kg.).

TABLE VI.—*Weight Changes*

Weight Changes	4 Months After Admission		6 Months After Admission	
	S	C	S	C
14 lb. (6·35 kg.) or more gain	8	6	19	12
5–13 lb. (2·27–5·89 kg.) gain	12	14	5	6
Less than 5 lb. (2·27 kg.) gain or loss	15	9	12	10
5 lb. (2·27 kg.) or more loss	13	7	11	5
Deaths	0	10	4	14
Total*	48	46	51	47

* Information not available for all cases; some patients too ill to be weighed.

These facts reveal, first, that many patients with a severe form of tuberculosis gained weight on treatment by bed-rest alone; indeed, 12 at the end of six months had gained a stone (6.35 kg.) or more in weight. Secondly, the weight gains in the S group in the first four months were no greater than in the C group, and therefore do not reflect the important improvement observed in other respects; on the other hand, there was more weight gain in the last two months—i.e., after treatment had stopped. It is certain that some patients failed to gain weight, or gained little weight, during the course of streptomycin treatment, and this may be at least partly ascribed to the gastric disturbances, which were severe in a few cases and in others were mild but sufficient to reduce appetite and retard weight gain.

Menstruation

In 10 of 32 female S patients and in 12 of 31 female C patients menstruation was normal on admission and remained normal. In nine S patients and 12 C patients amenorrhoea persisted throughout. In 11 S patients and seven C patients menstruation appeared at some time during observation and remained normal subsequently; in addition two S patients had a temporary return of menstruation.

Sedimentation Rate

TABLE VII.—*Sedimentation Rate*

E.S.R.	Group	On Admission	At 2 Months	At 4 Months	At 6 Months
0–10	S	0	0	6	17
	C	0	1	2	4
11–50	S	19	31	23	17
	C	22	10	15	18
51+	S	36	24	26	15
	C	29	37	23	14
Deaths	S	—	0	0	4
	C	—	2	10	14
Total*	S	55	55	55	53
	C	51	50	50	50

* Totals do not correspond in all columns, as results were not available in all cases.

The data in Table VII show two main differences between groups S and C. If one takes into account the patients who died, in the C group the number of patients with a very high sedimentation rate (over 50) was never reduced; in the S group the number fell from 36 to 19 (including four deaths). Secondly, at six months in only four C patients had the E.S.R. fallen to within normal limits; in the S group the corresponding number was 17.

Changes in Radiological Picture During Period of Trial

After the close of the trial the chest radiographs of all patients were viewed, and changes assessed, by the three members of the radiological panel working separately. They were not told whether films were of patients from S or C series. Radiographs of each patient had been taken on admission and at monthly intervals subsequently. It was decided to make as simple an assessment as possible, reviewing progress at two-monthly intervals, each two-monthly film being compared with the film taken two months previously and with the initial film. Thus the comparisons on which report was requested were: 0 with 2 (initial film with film two months after admission), 2 with 4, 0 with 4, 4 with 6, and 0 with 6. Assessments were required to fall under one of the five headings "considerable improvement," "moderate or slight improvement," "no change," "moderate or slight deterioration," "considerable deterioration." A report "no change" might signify no appreciable change in the radiological picture or improvement in one part of the lung offset by deterioration in another.

So simple a classification invited difficulties, and these were soon evident. How should atelectasis be classified? Some films showed considerable clearing of infiltration concurrently with enlargement of cavities—radiologically they were both better and worse. The analysis in Table VIII shows the separate results of readings by the three assessors. Two most important readings have been chosen for this analysis: 0 with 4 (comparison of initial film with film four months after admission) and 4 with 6.

TABLE VIII.—*Comparison of Radiological Assessments by Three Assessors*

Interval	Group	Total Cases	Assessor	Radiological Assessment				
				Improvement		No Change	Deterioration	
				Considerable	Slight or Mod.		Slight or Mod.	Considerable
Admission to end of 4th month	S	55	X	18	24	4	5	4
			Y	27	17	3	4	4
			Z	27	15	1	6	6
	C	42	X	0	11	4	18	9
			Y	2	10	11	10	9
			Z	3	8	8	15	8
End of 4th month to end of 6th month	S	51	X	2	17	11	15	6
			Y	5	18	10	8	10
			Z	3	12	11	19	6
	C	38	X	0	11	18	7	2
			Y	2	9	19	5	3
			Z	1	10	11	14	2

It can be seen from Table VIII that there was some disagreement among the three members of the panel, but the outstanding differences between results in S and C groups remain unaffected.

Where reports were identical they were adopted as the final agreed report. Where the reports on a case by the three members fell in two adjoining columns of the classification (e.g., "considerable improvement" and "slight or moderate improvement") the majority of two was taken as the final agreed report. In all other cases there was held to be disagreement. Thus in the comparisons between radiograph on admission and radiograph at four months there was agreement in 76 cases and disagreement in 21. In the comparisons between radiographs at four months and at six months there was agreement in 75 cases and disagreement in 14.

At a final session the three members of the radiological panel met for discussion and review of films on which there had been disagreement. After a short discussion it was agreed that changes in the prognosis for the patient should be taken as the base-line of assessment. In a comparison of two radiographs of a patient the question should be, judging from these films alone, Has the outlook for the patient become better or worse? On this basis the films in question were reviewed, and agreement was reached on all of them. The analysis which follows is based on the agreed results. The overall results under the five different headings are given for each of the three assessments 0 : 2, 0 : 4, and 0 : 6 in Table IX and Chart II, and for each of the three assessments 0 : 2, 2 : 4, 4 : 6 in Table X and Charts III and IV.

It is evident that at every stage there is between the two groups a great difference in the course of the disease.

At two months 76% of S patients showed radiological improvement, and in 14% the improvement was considerable; only 6% of C patients were improved, and in none was the improvement considerable. Of C patients 4% had died and another 38% were worse than on admission; 11% of S patients were worse, and none had died.

From the end of the second month to the end of the fourth month the proportion of S patients who improved (65%) was slightly lower than in the first two months and the corresponding proportion of C patients (18%) was higher, but the difference between the two groups is still marked. Considering the overall change in the first four months, 78% of S patients were improved and only 21% of C patients; in none of the latter and in 45% of S patients the improvement was considerable. Of C patients 19% had died and another 42% were worse than on admission; no S patients had died and only 14% had deteriorated.

The proportion of S patients who improved in the fifth and sixth months was again lower than before (34% compared with 65% in the third and fourth months and 76% in the first two months); this can be seen clearly in Charts III and IV. Of S patients 7% died in that period and another 31% deteriorated (the total 38% compares with 20% in the preceding two months and 11% in the first two

TABLE IX.—*Changes in the Radiological Picture*

Interval	Group	Total	Radiological Assessment						Deaths
			Improvement			No Change	Deterioration		
			Considerable		Slight or Mod.		Slight or Mod.	Considerable	
Admission to end of 2nd month	S	55 100%	8 14%		34 62%	7 13%	5 9%	1 2%	0
	C	52 100%	0		3 6%	27 52%	14 27%	6 11%	2 4%
Admission to end of 4th month	S	55 99%	25 45%		18 33%	4 7%	4 7%	4 7%	0
	C	52 99%	0		11 21%	9 17%	14 27%	8 15%	10 19%
Admission to end of 6th month	S	55 100%	28 51%		10 18%	2 4%	5 9%	6 11%	4 7%
	C	52 100%	4 8%		13 25%	3 6%	12 23%	6 11%	14 27%

TABLE X.—*Changes in the Radiological Picture*

Interval	Group	Total	Radiological Assessment						Deaths
			Improvement			No Change	Deterioration		
			Considerable		Slight or Mod.		Slight or Mod.	Considerable	
Admission to end of 2nd month	S	55 100%	8 14%		34 62%	7 13%	5 9%	1 2%	0
	C	52 100%	0		3 6%	27 52%	14 27%	6 11%	2 4%
End of 2nd month to end of 4th month	S	55 100%	6 11%		30 54%	8 15%	8 15%	3 5%	0
	C	50 100%	0		9 18%	13 26%	16 32%	4 8%	8 16%
End of 4th month to end of 6th month	S	55 99%	3 5%		16 29%	15 27%	10 18%	7 13%	4 7%
	C	42 100%	1 2%		9 21%	17 41%	9 21%	2 5%	4 10%

months); 10% of C patients surviving at four months died and another 26% deteriorated. Despite the setback in S patients in later months, the result at six months compared with the condition on admission shows, as we saw in the preliminary analysis, a remarkable difference between the two groups.

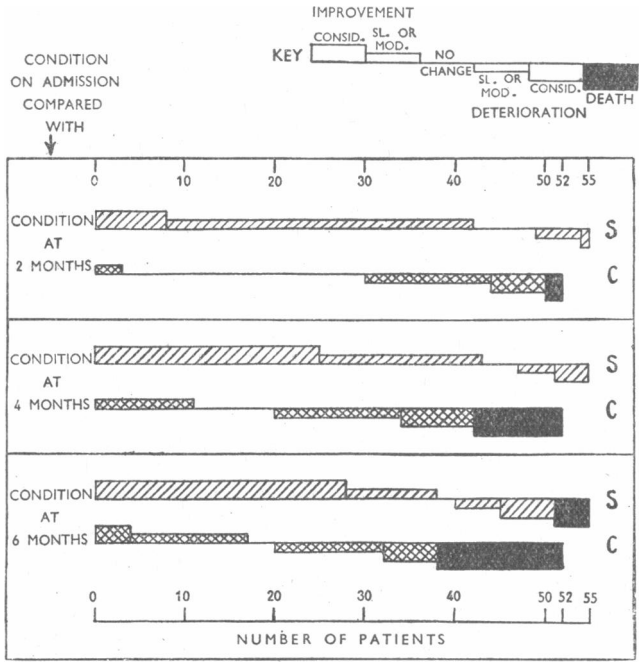

CHART II.—Condition on admission compared with condition at two, four, and six months (radiological assessment).

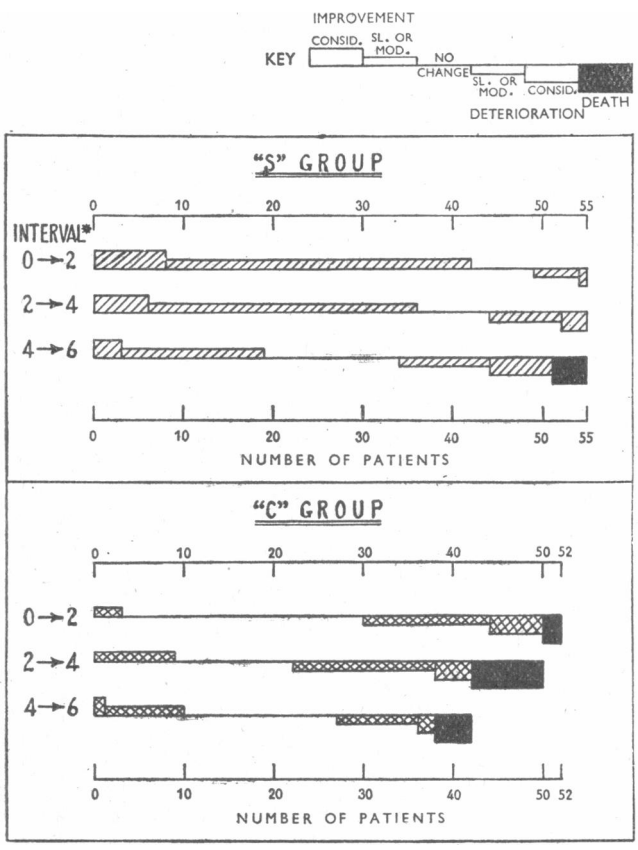

CHART III.—Changes in the radiological picture in succeeding two-monthly periods. 0→2, admission to end of second month; 2→4, end of second month to end of fourth month; 4→6, end of fourth month to end of sixth month.

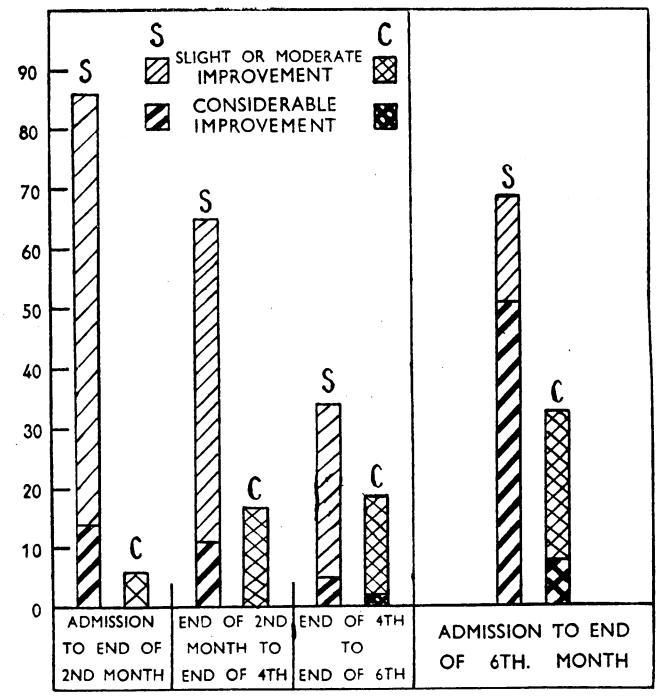

CHART IV.—Percentage of total patients admitted (*not* of survivors at beginning of each period) showing improvement in radiological picture in succeeding two-monthly periods and in six months.

It is of interest to analyse in greater detail the changes that occurred from period to period. The analysis in Tables XI and XII relates results in succeeding two-monthly periods.

TABLE XI.—*Radiological Changes in Succeeding Periods (S Cases)*

Admission to End of 2nd Month	Total	End of 2nd Month to End of 4th Month			
		Improvement	No Change	Deterioration	Deaths
Improvement ..	42	31	6	5	0
No change ..	7	4	1	2	0
Deterioration ..	6	1	1	4	0
Total ..	55	36	8	11	0
End of 2nd Month to end of 4th Month	**Total**	**End of 4th Month to End of 6th Month**			
Improvement ..	36	17	12	7*	0
No change ..	8	1	1	5†	1
Deterioration ..	11	1	2	5	3
Total ..	55	19	15	17	4

* One case had begun to deteriorate in the fourth month, though the overall assessment 2 : 4 was improvement.

† Two cases had begun to deteriorate in the fourth month, though the overall assessment 2 : 4 was no change.

Thirty-one of 42 S patients who improved in the first two months continued to improve in the third and fourth months, but less than half of those who improved in the third and fourth months made further good progress subsequently. Nearly all S patients who deteriorated in the first months continued to get worse subsequently; only one of the six in the first two months and one of the 11 in the third and fourth months improved subsequently; the improvement in the latter case began only after induction of pneumoperitoneum.

Considering now the 17 S patients who deteriorated and four who died in the fifth and sixth months, eight had been getting worse during the preceding two months, six more had shown "no change," and seven had improved in the preceding two months. These cases are analysed in detail later.

Analysis of radiological changes in the C group (Table XII) shows that here patients who improved did so much more slowly. Only three patients improved in the first two

TABLE XII.—*Radiological Changes in Succeeding Periods (C Cases)*

Admission to End of 2nd Month	Total	End of 2nd Month to End of 4th Month			
		Improvement	No Change	Deterioration	Deaths
Improvement ..	3	0	2	1	0
No change ..	27	9	9	8	1
Deterioration ..	20	0	2	11	7
Total ..	50	9	13	20	8
End of 2nd Month to end of 4th Month	Total	End of 4th Month to End of 6th Month			
Improvement ..	9	2	7	0	0
No change ..	13	5	4	4	0
Deterioration ..	20	3	6	7	4
Total ..	42	10	17	11	4

months, and they did not continue to improve subsequently. Nine patients showed improvement in the third and fourth months. In all nine the condition had been stationary in the first two months; the improvement was attributable to bed-rest alone—only one of these patients had collapse therapy, three and a half months after admission. None of the nine deteriorated in the fifth and sixth months, contrary to what was seen in the S group. On the other hand, as in the S group, nearly all patients who deteriorated in the first two months continued to deteriorate subsequently—i.e., for those who showed no response to the first two months of bed-rest and streptomycin, or bed-rest alone, the outlook was poor.

Six of the 10 C patients who improved in the fifth and sixth months received collapse therapy; in four of them the improvement was considered due to these measures.

Clinical Observations on Cases Showing Improvement

In the preceding sections various clinical and radiological changes have been analysed separately, the analysis showing for each factor differences between S and C groups. Below are additional data and some representative case histories to give a more complete picture of patients' progress under treatment.

Considerable Improvement in S Cases

Of the 28 S patients who radiologically had improved considerably at the end of six months 11 had been regarded as desperately ill on admission. All 28 improved from the first month of treatment. In none could the improvement even in later months be ascribed to collapse therapy.

(*a*) Twenty-one of the 28 improved clinically in all respects—i.e., their general condition and symptoms improved, they gained weight, temperature and E.S.R. fell, 18 were apyrexial at the end of six months, and 16 had gained more than 14 lb. (6.35 kg.) in weight. In eight cases the sputum had become negative to all examinations for tubercle bacilli.

Case 69.—A man aged 25 had been ill for four months and had been in hospital since shortly after the clinical onset. Artificial pneumothorax had been attempted, but failed; on complete bed-rest throughout the four months he continued to deteriorate. On admission to the centre he was exceedingly ill, wasted, with laryngitis, with swinging temperature 99.4–103.4° F. (37.4–39.7° C.), sedimentation rate 66, sputum heavily positive. The chest radiograph showed confluent opacities of broncho-pneumonic type throughout both upper and mid-zones, and scattered foci in the lower zones (Plate, Fig. 1). During the first two months there was slight clinical improvement: fever persisted, though at a lower level; the sedimentation rate was unchanged; the sputum was negative on direct examination and positive on culture. The chest radiograph showed little change. During the next months there was a striking turn for the better: symptoms regressed, the laryngitis improved; from the end of the fourth month he was apyrexial; he gained 42 lb. (19.05 kg.) weight from the third to the sixth month (on admission he had been too ill to weigh). The sedimentation rate had fallen to 22. Sputum was still positive, though on culture only. Radiologically there was remarkable clearing of lesions (Fig. 2).

Case 90.—A woman aged 24 had been ill for two months; her condition had been aggravated by recent parturition and post-partum haemorrhage. She was in hospital for two weeks before admission to the streptomycin centre. She was desperately ill on admission, wasted, and had a pyrexia varying from 99 to 103.4° F. (37.2–39.7° C.); sedimentation rate 150. On the chest radiograph were dense confluent opacities throughout the left lung, with some cavitation, and less extensive lesions in the right lung (Fig. 3). She remained critically ill during the first week of treatment, after which there was marked improvement in her general condition and symptoms. The evening temperature fell to 100° F. (37.8° C.) at the end of the second month, and from the end of the fourth month she was apyrexial. Weight gain was only 4 lb. (1.8 kg.). The sedimentation rate fell progressively to 20 at the end of six months. The sputum and material from gastric lavage were negative to all methods of examination for tubercle bacilli from the 59th day onwards. There was considerable radiological clearing of lesions (Fig. 4). "The result on discharge must be regarded as dramatic" (report by clinical registrar).

(*b*) Seven of the 28 patients improved clinically in most respects, but six were still pyrexial at six months, and the other, though apyrexial, remained in poor general condition, with no weight gain and a high E.S.R. (Case 39, Figs. 5 and 6).

Considerable Improvement in C Cases

Considerable improvement in the radiological picture was reported for only four C patients. None were acutely ill on admission. In none of them had the sputum become negative at the end of six months.

In Case 73 there was general clinical improvement, beginning in the first month, but the marked radiological improvement dated only from the induction of artificial pneumoperitoneum three and a half months after admission. In Case 80 also there was improvement in all respects, but only after induction of pneumoperitoneum two and a half months after admission.

In the two others, Cases 81 and 96, the improvement was attributable to bed-rest alone. Both improved clinically but retained a low pyrexia.

Case 81.—A woman aged 22 had a six-months history of illness, and had been in bed at home for six weeks. On admission she looked ill and wasted, and had a low pyrexia (97.4–99° F. (36.3–37.2° C.)) and a sedimentation rate of 110. Chest radiography showed scattered nodular shadows throughout both lungs, denser at the apices, with a large cavity in the right upper zone (Fig. 7). From the first weeks her general condition improved, and in the six months she gained 28 lb. (12.7 kg.). She retained, however, a low evening pyrexia, the sedimentation rate at the end of six months was 85, and the sputum was positive on culture. Radiologically there was considerable regression and shrinkage of lesions, and the cavity system in the right upper zone was less obvious (Fig. 8).

Slight or Moderate Improvement in S Cases

At the end of six months, of 10 S patients who showed radiologically slight or moderate improvement five were apyrexial, four had sedimentation rates not above 10, and two had gained over 14 lb. (6.35 kg.) in weight. In none of the 10 cases was the sputum negative, though in two it had been negative at some time during treatment and became positive again later.

Case 95.—A woman aged 25 was extremely ill when admitted. She had a history of symptoms for about five

months, and had been in bed at home for four weeks. On admission she had a temperature swinging between 99 and 102.4° F. (37.2 and 39.1° C.), and was very weak and wasted. The sedimentation rate was 28, the sputum heavily positive. There was extensive infiltration in the lungs, particularly in the right lung, where there were large cavities; a calcified primary complex was clearly definable on that side (Fig. 9). Clinically she made excellent progress throughout the six months, with remarkable improvement in the first two months of treatment, and she gained 28 lb. The evening temperature had fallen to 99° F. (37.2° C.) at the end of two months, and shortly after became normal and remained normal. The sedimentation rate fell to 5. The sputum was negative at four months, but subsequently was occasionally positive. Radiologically there was little change in the first two months and improvement subsequently, with clearing at the right base and cavities much less obvious at the right apex (Fig. 10).

Slight or Moderate Improvement in C Cases

Of 13 C patients who showed slight or moderate improvement radiologically at the end of six months, eight had improved clinically in all respects; three of the eight had been clinically very ill on admission. In two the sputum became negative (in one of the two after artificial pneumoperitoneum). Ten were apyrexial at six months, and six had gained over 14 lb. In most of these cases the clinical improvement was much greater than that seen in the lung radiographs.

Case 66.—A man aged 23, ill for about six weeks, had been admitted to a general hospital as a case of appendicitis one month before his admission to the centre. His general condition was fairly good, symptoms were slight, the temperature ranged from 97.6 to 100.2° F. (36.4 to 37.9° C.), the sedimentation rate was 70. There was shadowing throughout the upper and mid-zones of both lungs, particularly dense and with cavitation on the left side (Fig. 11). During the six months of observation there was slow but progressive overall improvement; he put on 24 lb. (10.88 kg.) in weight, symptoms improved, he was afebrile after the third month, three consecutive sputum specimens at the end of the fifth and sixth months were negative. Radiologically there was moderate improvement, with some shrinkage of lesions particularly on the right (Fig. 12).

Deterioration in S Cases

(*a*) In six patients there was radiological deterioration in the first two months. In two of these (Cases 87 and 99) there was no clinical response to treatment, and they continued to deteriorate until death in the fifth or sixth month. Two others (Cases 22 and 40) continued to deteriorate radiologically; clinically there was temporary improvement in the general condition, but temperature and E.S.R. remained high; one (Case 22) died in the fifth month. One (Case 16) continued to deteriorate radiologically (deterioration confined to one lung), but the temperature fell to normal limits, the patient gained weight, and felt much better until after treatment stopped; E.S.R. remained high, over 70. The sixth of these patients improved subsequently in the opinion of the radiologists' panel, but deteriorated clinically. Four of the six had gross cavitation on admission.

(*b*) In seven patients other than those just mentioned there was radiological deterioration through the third and fourth months. Five (Cases 46, 49, 60, 64, and 86) had improved radiologically in the first two months, and there had been temporary clinical improvement; in Case 60 there was marked clinical improvement until a spontaneous pneumothorax occurred three months after admission.

Case 46.—A man aged 25 had been ill for six weeks with cough, dyspnoea, lassitude, loss of weight. He had been resting in bed at home for five weeks before admission to the streptomycin centre. On admission his condition was fair, his temperature ranged from 97.6 to 102° F. (36.4 to 38.9° C.), the sedimentation rate was 40. Chest radiograph showed extensive scattered lesions in upper and mid-zones of both lungs and a large cavity in the left mid-zone. There was slight clinical improvement in the first two months of treatment, symptoms regressed, the temperature fell to a range of 97.8–99.4° F. (36.55–37.4° C.); the sedimentation rate was unchanged and weight was stationary. The clinical change was not of the same order as the change in the radiological picture, which showed considerable improvement (see Figs. 13 and 14). During the third month the clinical condition was stationary except that the temperature began to rise again, and radiologically there was extension and more cavitation of the lesions in the left lung. He then began to lose weight (7 lb.—3.18 kg.—in the fourth month), to feel tired again, and radiographs showed further deterioration with extensive cavitation; a spontaneous pneumothorax occurred in the sixth month (Figs. 15 and 16). The sputum had remained positive throughout; on the 65th day of treatment and subsequently strains of tubercle bacilli from the sputum were 8,000 times less sensitive to streptomycin than the strains isolated before treatment.

In the other two of the seven patients (Cases 54 and 105) the pulmonary condition was stationary radiologically in the first two months; one (Case 105) deteriorated clinically throughout the first months and until after induction of artificial pneumoperitoneum in the fifth month, after which there was radiological improvement also; the other was slightly better clinically in the first months of treatment, but the radiological worsening was rapidly followed by clinical deterioration, and she continued to go downhill. All seven of these cases which deteriorated radiologically for the first time in the third and fourth months had gross cavitation on admission, and five also had some atelectasis.

(*c*) Three other patients (Cases 11, 26, and 59) on whom the radiological report for the second two-month period was "no change" or "improvement" had begun to deteriorate radiologically in the fourth month—i.e., before treatment stopped. In Case 26 spontaneous pneumothorax was diagnosed in the fifth month. In Cases 26 and 59 clinical deterioration also began in the fourth month; in Case 11 only in the sixth month, after a haemoptysis. All three continued to get worse in the last months. Case 59 was the only one of these to have gross cavitation on admission.

(*d*) In nine cases radiological deterioration did not occur until the last two months. In three of these (Cases 28, 77, and 101) the radiological report for the third and fourth months was "no change"; two of them had improved in the first two months, but at the end of the fourth month all three were still febrile and had a high E.S.R. In Case 28 the temperature fell to normal in the first two months and the patient gained 11 lb. (4.98 kg.) in weight, but the temperature rose in the third month, and there was subsequently continued clinical deterioration.

Finally, radiological deterioration in the fifth and sixth months was seen in six patients who had improved radiologically to the end of the fourth month. In two of these (Cases 7 and 24) there had been little or no clinical response to streptomycin treatment; at four months they were pyrexial, had lost over a stone in weight, and had a high E.S.R.; both had gross cavitation on admission. The others (Cases 1, 4, 29, and 71) had improved clinically to the end of the fourth month, though at that date three were still pyrexial and none had an E.S.R. below 40. Only one of these four had gross cavitation on admission.

Case 1.—A woman, aged 24, had been ill for about 10 weeks, and for six weeks before admission had been in bed at home. She was very ill when admitted, pale, wasted, with severe dyspnoea and lassitude; the temperature ranged from 100 to 104.2° F. (37.8 to 40.1° C.), the sedimentation rate was 98, the sputum was strongly positive. The chest radiograph showed

extensive shadowing of bronchopneumonic type throughout both lung fields, more dense in the left lung than in the right (Fig. 17). In the first month the temperature dropped to a range of 99–101° F. (37.2–38.3° C.), and remained at this level during the rest of the four months of treatment. In the first month also there was definite improvement both in symptoms and in general appearance, and she gained 7 lb. (3.18 kg.) in weight. At the end of two months the sputum was negative to direct examination and culture, and radiologically there was some clearing of the lesions, especially on the right. In the third and fourth months she began to lose her feeling of well-being, appetite deteriorated, and she lost 5 lb. (2.27 kg.) in weight; sputum became again heavily positive (strains were 250 times less sensitive to streptomycin than strains isolated before treatment). Radiographs, however, showed further considerable clearing of lesions (Figs. 18 and 19). After treatment was stopped she felt better for a short time, but in the sixth month the condition deteriorated, symptoms were worse, the temperature rose to the same level as on admission, and radiographs at the end of the sixth month showed increased cavitation in the left lung and fresh lesions in the right (Fig. 20).

This analysis has shown that though 21 S patients deteriorated radiologically in the fifth and sixth months—i.e., at a time when no streptomycin was being given in most cases—there is much evidence of commencing deterioration or arrested improvement before the end of the fourth month. Only six of the 21 had been improving radiologically throughout the preceding two months; two of the six had lost weight, and five had remained pyrexial since admission. Moreover, it is noteworthy that in patients who received streptomycin for more than four months results were similar to those for patients treated for four months only; deterioration in the fifth and sixth months was seen in five of 13 patients treated for more than four months, compared with 16 of 42 patients treated for four months only. However, in one patient treated for five months deterioration started in the sixth month. While there is suggestive evidence in a few cases that deterioration was related to cessation of treatment, it is very probable that some factor other than this is responsible in the majority of cases that deteriorated.

Gross cavitation may be a factor in determining relapse after first improvement. Of 16 patients who deteriorated at some time after first improvement, 11 (69%) had large or multiple cavities on admission; of 30 patients who improved throughout, 14 (47%) had large or multiple cavities. The difference is not statistically significant.

Spontaneous pneumothorax occurred in four S patients. In Case 60 it occurred at three months; the patient had been much improved until then, but subsequently went downhill rapidly and died. In two other cases deterioration had begun before the pneumothorax occurred. At first the impression was that this was a particular risk in the S group, but pneumothorax occurred spontaneously also in three C cases.

Toxicity

Toxic effects of streptomycin therapy were observed in many patients, but in no single case did they necessitate cessation of treatment. For this reason and because toxic effects of this antibiotic have already been fully described by other investigators—e.g., Veterans' Administration (1947)—they will be mentioned here only briefly.

By far the most important toxic effect was the damage to the vestibular apparatus. Giddiness was a frequent first symptom; it was noticed by 36 of the 55 patients, and first appeared on sitting up in bed or turning the head suddenly. It appeared usually in the fourth or fifth week of therapy, and persisted for periods varying from one week to several months. Spontaneous nystagmus on lateral vision was another frequent sign of vestibular disturbance; blurring of vision was less common. Tests for vestibular dysfunction were not carried out in all centres with sufficient regularity and uniformity to permit analysis of grouped results, but it is possible to say that absence or reduction of caloric response was not found with the frequency reported in many American investigations, and that in some patients loss of response was temporary only. No standard functional tests at the end of treatment were performed; many patients are reported as having unsteadiness of gait, which improved gradually with visual compensation but remained a handicap in the dark. Possibly many of these patients retain a disability revealed in a dangerous ataxia on such occasions as walking downstairs in the dark, crossing a congested street, or walking in a moving train. It is highly desirable that standard tests be adopted for assessment of vestibular dysfunction.

No loss of hearing was reported, except for two cases of high-tone deafness. Many patients suffered from nausea and vomiting, symptoms which were often relieved by antihistamine therapy. Albuminuria and casts in urine, raised blood urea, pruritus and urticarial rash, eosinophilia, "yellow vision" after injection, and circumoral numbness are among other transient effects reported. All subsided spontaneously—i.e., without stopping treatment.

Bacteriology

(1) Bacterial Content of Sputum

Sputum was tested by direct-smear examination and by culture; where there was no sputum, material from laryngeal swab and/or gastric lavage was cultured. Examinations were done on admission and again at intervals of not more than one month.

In Table XIII the results in the third month and at the end of six months are related to the results on admission. Results of direct smear are recorded as "strongly positive" where one or more acid-fast bacillus per 1/12 in. (0.2 cm.) field was seen or where the result was recorded as +++ or ++; "weakly positive" includes results with less than one acid-fast bacillus per field or results recorded as +. For one hospital where only direct-smear examinations were done, and where degrees of positivity were not recorded, positive results in both groups have been tabulated in column 1, "strongly positive"; one C case and one S case (Nos. 3 and 107), positive on admission and negative to

TABLE XIII.—*Presence of Tubercle Bacilli*

Results on Admission	Total	Deaths	Results in Third Month			
			Direct Smear		Smear Negative Culture Positive	Culture Negative
			Strongly Positive	Weakly Positive		
S Cases:						
Smear strongly positive	40	0	16	12	10	2
Smear weakly positive ..	11	0	1	3	1	6
Smear negative, culture positive	3	0	1	0	0	2
C Cases:						
Smear strongly positive	29	5	19	3	1	1
Smear weakly positive ..	17	1	6	8	2	0
Smear negative, culture positive	4	0	1	1	2	0
			Results at End of 6 Months			
S Cases:						
Smear strongly positive	40	4	24	1	7	4
Smear weakly positive ..	11	0	3	3	2	3
Smear negative, culture positive	3	0	1	0	1	1
C Cases:						
Smear strongly positive	29	11	15	2	0	1
Smear weakly positive ..	17	3	4	7	3	0
Smear negative, culture positive	4	0	0	1	2	1

direct examination (no culture) at six months, have been excluded from the analysis; another (Case 62) has been excluded because no results were recorded for the third month.

Considering the results in the third month, one C case and 10 S cases were negative to all examinations for tubercle bacillus. Apart from these cases of "sputum conversion," six C cases and 23 S cases were positive at a lower level than on admission. The differences between the two series are significant. There is no doubt here of the pronounced effect of streptomycin on the tubercle bacillus.

The results at the end of six months also show a difference, though less marked, between the two groups; two C cases and eight S cases had become negative to all examinations. These final results signifying "sputum conversion" are based on repeated examinations, in most cases of sputum; the case with least satisfactory evidence had negative results from one gastric lavage and two laryngeal swabs. Besides these cases five C cases and 10 S cases were at six months positive at a lower level than on admission. Taking together cases becoming negative or positive at a lower level, the difference between the two series is significant.

In the S group the results are best in cases without gross cavitation; six of 23 became negative, compared with two of 31 cases with large or multiple cavities.

If in order to get an overall evaluation of changes we give a numerical score to each category of results (4=negative; 3=smear negative, culture positive; 2=smear weakly positive; 1=smear strongly positive; 0=death), the total in each group is as follows:

	On Admission	During Third Month	At end of Six Months
S cases ..	71	124	98
C cases ..	75	69	62

In the S group these results confirm the impression already gained of maximum improvement in the first months and subsequent deterioration.

The following numerical scores on the same basis are obtained from data for 51 of the S group analysed in greater detail (examinations for the C group were not frequent enough to provide comparable data).

Months after Admission:	0	1	2	3	4	5	6
Bact. "score"	66	111	115	127	105	104	94

This overall evaluation shows the marked improvement during the first three months, followed by a steep fall in "score" in the fourth month and further decline later.

(2) Streptomycin Sensitivity

Strains from 42 cases were tested for streptomycin sensitivity on primary isolation and during the course of treatment. Details of the technique adopted will be given in a subsequent report by the Pathological Subcommittee.

A. Degree of Sensitivity

All strains isolated before streptomycin therapy was begun showed sensitivity to the drug equivalent to that of the standard strain H37Rv (obtained from the American Depot, Trudeau Sanatorium, Saranac Lake); this was usually at a level of 0.1 to 0.5 μg. per ml., using the Tween-albumin medium.

Sensitivity after Start of Streptomycin Treatment.—(1) In one patient (Case 90) there was not full opportunity to detect streptomycin resistance, as all cultures were negative after the 59th day. (2) In six cases resistance did not emerge at a level above 10 times that of H37Rv. (3) In five cases strains were isolated which showed streptomycin resistance from 32 (one case) to 64 times (four cases) that of H37Rv. (4) In 17 cases resistance between 100 and 256 times that of H37Rv was demonstrated. (5) In 13 cases the resistance demonstrated was more than 2,000 times that of H37Rv; in four of these it was over 8,000 times.

Summarizing, strains with resistance over 10 times that of H37Rv were found in 35 of the 41 cases.

B. Time of Emergence of Streptomycin Resistance

In the majority it was not possible to detect with any great precision the date at which resistant strains could be first isolated, as specimens were not taken at frequent enough intervals. The date is taken as that midway between the date of the last sensitive culture and the date of the first resistant culture. In a few cases this interval was only a few days; in one it was 5½ months. Where it was possible to isolate strains at frequent intervals, it was seen that resistance rose rapidly to a maximum level at which it persisted subsequently with only minor fluctuations.

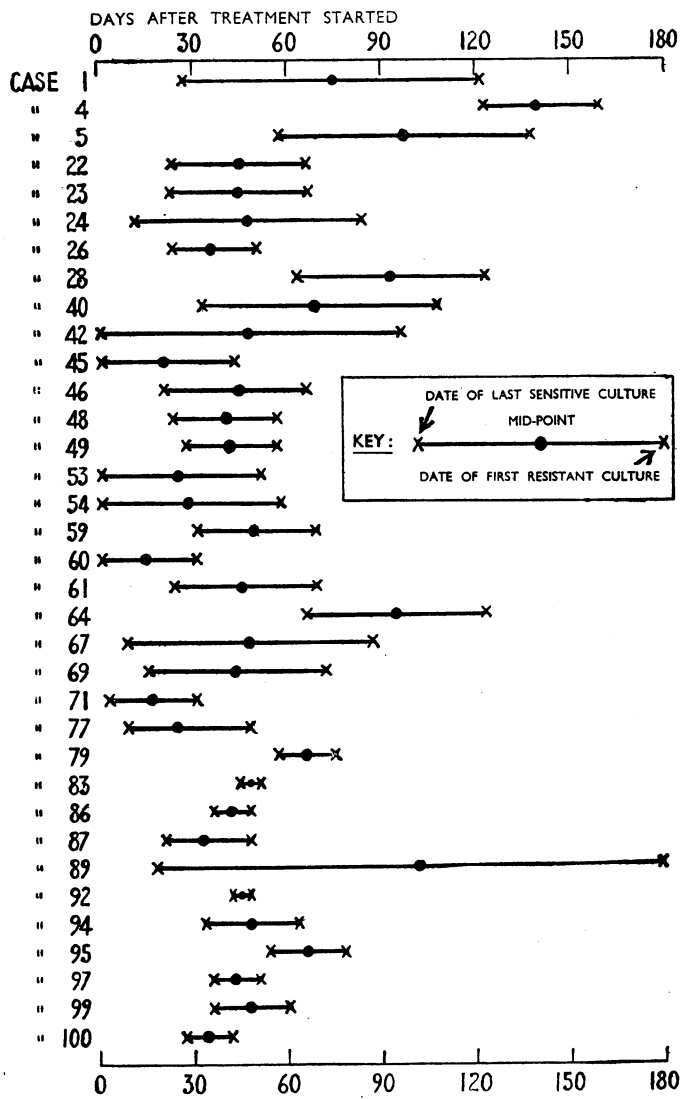

CHART V.—Showing date of emergence of streptomycin resistance (over 10 times that of H37Rv)

The results are shown in Chart V. Of 35 cases showing resistance over 10 times H37, this resistance emerged in five cases in the first month, in 21 in the second month, four in the third, four in the fourth, and one as late as the fifth month. Taking all observations, the mean date of

emergence of resistance is the 53rd day after starting streptomycin therapy. The median is the 45th day.

Results Related to Resistance Development

The results given in Chart VI raise an important point : the radiological results at six months compared with condition on admission seem to be related to the degree of

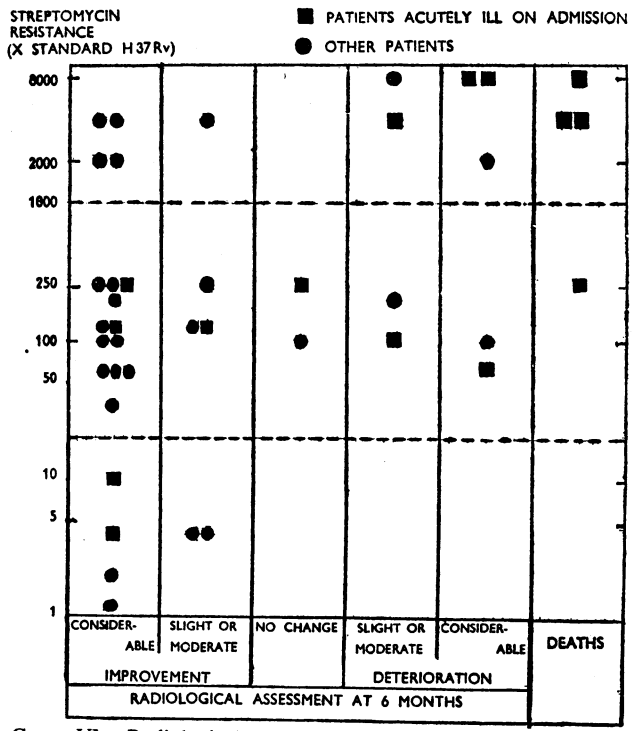

CHART VI.—Radiological assessment at six months related to degree of streptomycin resistance.

streptomycin resistance found during observation. Of six patients from whom strains isolated did not show resistance greater than 10 times that of the standard H37Rv, all had improved at six months. Twenty-two patients developed streptomycin resistance over 10 and less than 1,000 times H37Rv ; five of them, or just under 1 in 4, had deteriorated at six months (one of the five had died). Of 13 patients in whom the drug-resistance developed was over 1,000 times H37Rv, eight or over one-half had deteriorated (three of the eight had died). The differences in results in the three groups are statistically significant.

If we consider not only the result at six months but deterioration at any time during the six months, it is interesting to note that the six patients who did not develop resistance over 10 times H37Rv improved throughout, without setback at any time in the six months.

Of the 22 cases with resistance 32 to 256 times H37Rv, deterioration occurred in six in the fifth and sixth months after continuous improvement in the first four months (but only two of these were worse at the end of six months than on admission) ; in two deterioration began after two months' improvement ; one began to deteriorate in the third month, the condition having been stationary in the first two months ; one died after continuous deterioration throughout. The remainder, 12 patients, did not deteriorate at any time.

In the cases with resistance over 1,000 times H37Rv, deterioration began earlier: within the first two months in four cases, in the third and fourth months after initial improvement in three cases, and only in the final months in two cases.

Before accepting degree of streptomycin resistance as a major factor in prognosis it is important to determine if among the cases with high streptomycin resistance there is a higher proportion of initially severe cases than in the others, as if so this might account for the worse prognosis. Six of the 13 patients from whom were isolated strains over 1,000 times more resistant than H37Rv were very acutely ill on admission (had high pyrexia and large or multiple cavities), compared with nine of the 28 other patients. The difference is small. Moreover, there is both in the patients very ill on admission and in the others the trend to bad prognosis with increasing levels of streptomycin resistance. Thus in those very ill on admission the proportion deteriorating was 0/2 where resistance was not more than 10 times H37Rv, 3/7 where it was more than 10 and not more than 1,000 times (one of the three died), and 6/6 where it was above 1,000 times (three of the six died). In the other patients it was 0/5 where resistance was not more than 10 times H37Rv, 2/14 where it was more than 10 and not more than 1,000, and 2/7 where it was over 1,000 times. However, while the trend to bad prognosis with increasing levels of drug resistance is seen in both groups, the trend is greater in the patients very ill on admission than in the others ; there is a possibility of relationship between severe clinical condition and development of high degrees of streptomycin resistance. In conclusion, one can say that the results were outstandingly good in cases in which little or no drug resistance was demonstrated, but for the others it remains difficult to assess the relative importance and the interdependence of the two factors—clinical condition at start of treatment and degree of drug resistance developed during treatment.

Discussion

This planned group investigation has demonstrated both the benefit and the limitations of streptomycin therapy in pulmonary tuberculosis. The trial—the first controlled investigation of its kind to be reported—was designed to give a negative or affirmative answer to the question, Is streptomycin of value in the treatment of pulmonary tuberculosis ? It was not designed to determine in what types of pulmonary tuberculosis streptomycin could be effective, nor to determine optimal dosage or duration and rhythm of treatment.*

Analysis of the results at the end of the first six-month period has shown that the course of bilateral acute progressive disease can be halted by streptomycin therapy ; 51% of the streptomycin-treated patients showed considerable improvement radiologically when comparison was made with their chest radiographs taken on admission. That streptomycin was the agent responsible for this result is attested by the presence in this trial of the control group of patients, among whom considerable improvement was noted in only four (8%), and two of these four patients had improved only after collapse therapy. In other words streptomycin therapy was effecting what the patient's tissues alone could not do—checking the spread of the tubercle bacillus in one of its most favourable *milieux*.

Among the treated patients radiological improvement occurred most often in those who, though having extensive infection, did not have large or multiple cavitation. Nevertheless in one-third of those with gross cavitation considerable improvement also occurred, principally by resolution of recent infiltrative spread ; some cases thus became suitable for collapse therapy. Streptomycin therapy alone did not lead to closure of large cavities.

The need of a control group in trials of a new drug for pulmonary tuberculosis is underlined by the finding that

*Since this investigation was begun a number of notable publications on the effect of streptomycin in pulmonary tuberculosis have appeared. As, however, the prime objective of the Medical Research Council trial was a comparison of treated cases with controls, other investigations have not been referred to here.

impressive clinical improvement was seen in some of the patients treated by bed-rest alone: 12 gained more than 14 lb. (6.35 kg.) in weight, and in 13 of 47 febrile patients the temperature was within normal limits at the end of six months. It was to be expected that in many of these patients with gross lesions who until recently had been at work the constitutional symptoms would be temporarily improved by bed-rest, although the lesions were so advanced that bed-rest alone could not be expected to effect corresponding improvement in the radiological picture. Nevertheless it should be noted that some radiological improvement was recorded in one-third of the C patients. The improvement in these patients was mainly among those least acutely ill on admission, and it is in this group that the treated series shows the least advantage over the control series. In such cases, with little or no pyrexia, relatively low sedimentation rate, and little cavitation, the patient's natural recuperative power added to bed-rest may in itself arrest the progress of the infection, and the advisability of using streptomycin in such cases may well be doubted. The major advantage is among the acutely ill patients. Although the only deaths that occurred in the S series were in this group, it is in these patients that the striking difference between the S and C series is most clearly demonstrated.

While stressing the good results in the streptomycin group, it is important to note, first, that no clinical "cures" were effected, and that only 15% were bacteriologically negative (to direct examination and culture) at the end of six months; and, secondly, that this trial presents at the time of writing only a short-term evaluation.* The major improvement in patients treated with streptomycin was seen in the first two to three months; in the latter half of the six-month period numbers of them began to deteriorate. Thus 21 S patients deteriorated radiologically in the fifth and sixth months, and four of them died. Streptomycin therapy had been stopped at the end of four months, and it is natural to ask whether the deterioration is attributable to stoppage of treatment. This seems unlikely for the majority; most had begun to deteriorate radiologically before the end of four months; only six of the 21 had improved radiologically throughout the four months, and two of these six had deteriorated clinically.

Strains of tubercle bacilli resistant to high concentrations of streptomycin were isolated by the end of the second month of treatment from most patients whose sputum was still positive; this fact may account for at least a part of the deterioration witnessed in treated patients. Strains showing streptomycin resistance over 10 times that of the original strain or of the standard H37Rv were isolated from 35 of 41 patients for whom data are available; in 13 of the 35 cases the strains had a resistance over 2,000 times that of the control organism.

Therapeutic results appear to be related to the degree of drug resistance developed; thus the best results were seen in cases in which little or no drug resistance was demonstrated, and the worst results were in the group of 13 patients from whom were isolated strains of tubercle bacilli with a drug resistance over 2,000 times that of H37Rv; at the end of six months three of the 13 had died and five were radiologically worse than on admission. The relation between a bad prognosis and a high degree of streptomycin resistance applies particularly to patients most acutely ill at the start of treatment. The numbers involved are small, but the differences between the groups at different levels of resistance are suggestive. Probably both initial severity of clinical condition and development of drug resistance during treatment are factors responsible for deterioration, and the two factors may be interdependent. Even with the aid of a powerful chemotherapeutic agent healthy tissue reaction on the part of the host is necessary for complete destruction of the invading parasite. It is reasonable to suppose that, where a high degree of streptomycin resistance is demonstrable by the method used (which is qualitative and not quantitative), this may have occurred by rapid proliferation of resistant strains in tissues that have a poor natural defence against tuberculous infection.

*An addendum gives the results at one year after admission to the trial.

On knowledge at present available, the development or emergence of streptomycin-resistant strains of tubercle bacilli is a fundamental factor to be taken into consideration when contemplating a course of streptomycin therapy. The technique of measuring sensitivity used in this investigation is so slow as to be of little immediate use in estimating, say at the end of one or two months of therapy, whether the course can be usefully continued or not. Organized investigations will be needed to determine whether emergence of streptomycin-resistant strains can be prevented by association of streptomycin with another drug or by a special rhythm of treatment. Until such time as this problem has been solved it seems fair to assume that after two to three months of streptomycin treatment in a patient with open pulmonary tuberculosis further treatment or a repeat course later is unlikely to be effective. Moreover, the possible dangers to the public health of dissemination of streptomycin-resistant strains, with the possible subsequent production of fresh cases (including cases of miliary or meningeal tuberculosis) which would not respond to streptomycin treatment, must be borne in mind.

One must add to this disadvantage of streptomycin therapy the information on the drug's toxic effects on the vestibular apparatus. These are frequent when the dose employed in this trial, 2 g. a day, is given; recent American reports indicate reduced toxicity with a dosage of 1 g. a day, but even then the effects are far from negligible.

These considerations must dictate a full measure of caution before prescribing streptomycin for any particular patient. They must be weighed in the balance against possible advantages of streptomycin therapy, particularly when contemplating its use for tuberculous lesions likely to improve by other known forms of treatment; and they render undesirable its administration for tuberculous lesions which, by reason of their age and pathological type, are unlikely to benefit by any form of chemotherapy.

The investigation reported here has demonstrated the value of streptomycin in one not very common form of tuberculosis. The type of result obtained indicates that the drug is probably of greatest value in cases of pulmonary tuberculosis in which the lesions requiring treatment are acute and of recent development. Its use may be recommended in acute contralateral spreads after artificial pneumothorax or after thoracoplasty. It probably has a place in the treatment of rapidly advancing pulmonary tuberculosis in which immediate collapse therapy would be dangerous or impracticable; in fact its most effective use may be in preparation of such lesions for collapse therapy. It has probably little place in the treatment of the more common chronic fibro-caseous forms of the disease. These conclusions are of necessity lacking in precision; much organized work is yet required to determine the precise indications of streptomycin and the best schemes of dosage in pulmonary tuberculosis.

Addendum

Before going to press it has been possible to collect data regarding the condition of each patient one year after admission to the trial. The data are based on a general

assessment by the clinicians concerned. Radiological evaluation by a panel was not possible, and therefore, although the data give a provisional impression of the course of the disease in these patients, the figures are not comparable with those based on independent radiological assessment, for example, in Table II.

TABLE XIV.—*Condition at 12 Months Related to Condition on Admission*

Group	Total	Improvement	No Change	Deterioration	Death
S	55 *100%*	31 *56%*	4 *7%*	8 *15%*	12 *22%*
C	52 *100%*	16 *31%*	5 *10%*	7 *13%*	24 *46%*

The difference in mortality between the two groups is statistically significant.

Summary

One hundred and seven patients with acute progressive bilateral pulmonary tuberculosis, unsuitable for collapse therapy, were studied in a clinical trial of streptomycin.

The supply of streptomycin available during the investigation was limited. The type of disease selected was one considered hitherto unsuitable for any form of treatment other than bed-rest. Bed-rest accordingly was the treatment given to one group of 52 patients (C), while 55 patients were treated with bed-rest plus streptomycin (S). Patients were assigned to one or the other group by random selection, and only after acceptance as suitable for the trial.

The period of observation for each patient, under conditions laid down for the trial, was six months.

S patients received 2 g. of streptomycin intramuscularly daily in four injections at six-hourly intervals. No toxic effects necessitated stopping treatment, but vestibular disturbance was common.

At the end of six months 7% of S patients and 27% of C patients had died. Considerable improvement radiologically was noted in 51% of S cases and 8% of C cases. Slight or moderate improvement was noted in 18% of S cases and 25% of C cases. Apart from those who died, deterioration was seen in 18% of S cases and 34% of C cases.

The main difference between S and C series is among the patients clinically acutely ill on admission: thus, among patients having on admission evening temperatures of 101° F. (38.3° C.) or over, 13 of 24 S patients and two of 19 C patients showed improvement radiologically.

More S patients than C patients showed clinical improvement, but the difference between the two series is smaller than in respect of radiological changes.

Improvement in S cases was greatest in the first three months. After the end of this period many S cases began to deteriorate.

At the end of six months examinations for tubercle bacilli were negative in eight S cases and two C cases. The best results in S cases were seen in the first months of treatment.

Results of tests for streptomycin sensitivity of infecting strains are given for 41 cases. In 35 cases tests revealed *in-vitro* resistance from 32 to over 8,000 times that of the original strain or the standard H37Rv. In most cases streptomycin resistance emerged in the second month of treatment. It seems probable that streptomycin resistance is responsible for much of the deterioration seen in S cases after first improvement.

An addendum gives the results at one year after admission.

The work of this investigation fell particularly heavily on the nursing staff and laboratory technicians of the centres concerned, and grateful acknowledgment is due to them for their assistance throughout the trials.

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SUDDEN DEATH DUE TO EPENDYMOMA OF CEREBELLO-PONTINE ANGLE

REPORT OF TWO CASES

BY

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Sudden death has been described in many cases of subtentorial tumours, but such an occurrence is almost invariably preceded by symptoms of raised intracranial pressure severe enough to induce the patient to seek medical advice some months before death. In the first case described here the patient gave a history of mild illness for only two days, whilst in the second case the patient continued at work until the day before his death. The presence of an intracranial tumour was not suspected during life in either case.

Bailey, Buchanan, and Bucy (1939) point out that sudden death may occur in cases of ependymoma of the fourth ventricle, but they describe such an occurrence only after lumbar puncture or manipulations of the head. Neither of these procedures was carried out in the present cases.

Case 1

A girl aged 2 was in good health until two days before her death, when she appeared unwell and was constipated. She was taken to her doctor, who prescribed an aperient; next day she was better and able to take her food satisfactorily. On the following day, however, she suddenly had a fit, made a choking noise, and died in a few minutes.

At necropsy a firm, pale, lobulated tumour with a smooth surface and crenated edge and measuring 4.3 by 3.7 cm. was found on the inferior surface of the left lobe of the cerebellum, being related laterally to the medial surface of the left petrous bone. Superiorly the tumour reached and compressed the lower border of the pons, and inferiorly the medulla and the upper part of the cervical cord were partially encircled and thrust towards the right. The tumour reached a point 4 cm. below the lower border of the pons and 1.2 cm. to the right of the midline. The left cerebellar hemisphere was compressed.

The left eighth cranial nerve ran into the mass, whilst the left vertebral artery, which lay on its surface, was partially embedded in its substance. The whole was covered by the arachnoid mater, which could be moved freely over it. There was evidence of raised intracranial pressure, with flattening of the convolutions of the cerebrum and bulging and thinning of the infundibulum, but the lateral ventricles appeared to be normal in size. No other lesions were found post mortem.

Histologically, the tumour had the appearance of an epithelial type of ependymoma (Fig. 1). The cells composing it contained round or oval nuclei showing rather coarse chromatin granules. Many of these cells formed canals with empty lumina lined by a single layer of cuboidal or columnar epithelium with basal nuclei, whilst others were arranged in rosettes around coils of cell processes. There was a complete absence of a basement membrane separating the rosettes from the surrounding stroma. The blood vessels were thin-walled, and in some areas the tumour cells were arranged around them, their processes extending to the vascular endothelium. The stroma consisted of a fibrillary network.

Case 2

A boy aged 16 had suffered from headaches and occasional vomiting for two months but remained at work until the day before his death. He then complained of very severe headache and went to bed, where he was found dead the following day.