BRITISH MEDICAL JOURNAL

LONDON SATURDAY FEBRUARY 19 1955

VARIOUS COMBINATIONS OF ISONIAZID WITH STREPTOMYCIN OR WITH P.A.S. IN THE TREATMENT OF PULMONARY TUBERCULOSIS

SEVENTH REPORT TO THE MEDICAL RESEARCH COUNCIL BY THEIR TUBERCULOSIS CHEMOTHERAPY TRIALS COMMITTEE*

The fifth report of the Medical Research Council trial of isoniazid (isonicotinic acid hydrazide) contained a broad comparison of the effects of two combinations of drugs—streptomycin plus isoniazid compared with P.A.S. plus isoniazid—on a total of 391 patients after three months' treatment (Medical Research Council, 1953c). It was concluded that the combination P.A.S. (sodium salt) 20 g. daily plus isoniazid 200 mg. daily was of the same order of effectiveness as streptomycin 1 g. daily plus isoniazid 200 mg. daily, and as streptomycin 1 g. daily plus P.A.S. (sodium salt) 20 g. daily. There was, however, only limited information on whether the dosage of streptomycin or of P.A.S., in combination with isoniazid, could be reduced from the above levels. As a result of an increase in the total of patients to 588, it is possible in the present report to give a detailed comparison of the clinical and bacteriological effects of two dosages of streptomycin, and two dosages of P.A.S., in combination with isoniazid, after three months' treatment. These patients were admitted to the trial between September 5, 1952, and July 31, 1953, when admissions ceased. The scope of this report has been further extended by including bacteriological findings for 241 patients whose treatment was continued for six months. A list of the 51 hospitals and the names of the co-operating clinicians, bacteriologists, and pathologists are given at the end of the report. The trial was co-ordinated by the late Dr. Marc Daniels and by Dr. Wallace Fox, of the Council's Tuberculosis Research Unit; Dr. Fox and Dr. Ian Sutherland (of the Council's Statistical Research Unit) analysed the present results and prepared the report. Radiographic assessments were made by Dr. L. G. Blair. The isoniazid used throughout the trial was supplied as " nydrazid " by E. R. Squibb and Sons.

I. PLAN AND CONDUCT OF THE TRIAL

The plan and conduct of the trial are only briefly referred to here, as they have been described in detail in earlier reports (Medical Research Council, 1952, 1953a).

*Members of the Committee: Sir Geoffrey Marshall (chairman), Professor J. W. Crofton, Professor R. Cruickshank, Dr. Wallace Fox, Dr. J. E. Geddes, Professor F. R. G. Heaf, Professor A. Bradford Hill, Dr. J. V. Hurford, Dr. D. A. Mitchison, Professor W. D. M. Paton, Dr. J. G. Scadding, Dr. Norman Smith, Dr. P. D'Arcy Hart (secretary).

1. Type of Case

Certain basic requirements were laid down for all cases accepted into the trial. At the start of treatment:

(*a*) Tubercle bacilli must have been demonstrated.

(*b*) The tubercle bacilli, so far as was known, must not have been streptomycin-resistant or P.A.S.-resistant. (Any patient subsequently found to have had streptomycin-, P.A.S.-, or isoniazid-resistant organisms at the start of treatment has been excluded from the analysis: see Appendix.)

(*c*) The patient must not have had more than 15 g. streptomycin or 300 g. P.A.S. (sodium salt) within the previous three months, and not more than 3 g. isoniazid at any time.

(*d*) The patient must not have had any form of collapse therapy present on the side of the lesion requiring treatment.

Cases satisfying the above requirements were admitted to the trial in one of three main disease groups: (1) acute rapidly progressive pulmonary tuberculosis believed to be of recent origin; (2) other forms of pulmonary tuberculosis considered suitable for chemotherapy: *this group included a wide range of disease, and contained both acute and chronic cases*; (3) chronic forms of pulmonary tuberculosis expected to make only a limited response to streptomycin plus P.A.S.

2. Treatment

When a patient had been accepted for the trial, treatment was allocated by the Tuberculosis Research Unit from confidentially held prearranged lists based upon random sampling numbers.

After admission to the trial and a preliminary week of investigation, all patients were kept under observation for six months. During the first three months the prescribed treatment was followed for every patient. During the second three months patients in disease group 3 continued on the same combination of drugs. For other patients the clinician was free either to continue the original combination or to undertake any other treatment, chemotherapeutic or otherwise.

In the phase of the trial now reported, four treatments were studied concurrently—namely:

SH : Streptomycin 1 g. daily, in one intramuscular injection, plus isoniazid 200 mg. daily, in two equal doses by mouth.

S2H : Streptomycin 1 g., in one intramuscular injection, twice a week, plus isoniazid 200 mg. daily, in two equal doses by mouth.

20 PH : P.A.S. (sodium salt) 20 g. daily, in four equal doses by mouth, plus isoniazid 200 mg. daily, in two equal doses by mouth.

10 PH : P.A.S. (sodium salt) 10 g. daily, in two equal doses by mouth, plus isoniazid 200 mg. daily, in two equal doses by mouth.

In one important disease subgroup (1A—acute rapidly progressive bilateral pulmonary tuberculosis of recent origin, in patients between the ages of 15 and 30) patients were randomly allocated, for ethical reasons, only to the SH and 20 PH series. Every other patient was allocated at random to one of the four treatment series.

Prior to exclusions, 195 patients were allocated to the SH treatment, 151 to S2H, 184 to 20 PH, and 122 to 10 PH. The larger totals in the SH and 20 PH series are accounted for by the patients in subgroup 1A. The number of patients allocated to the S2H series was not intentionally larger than the number in the 10 PH series ; the difference has arisen by chance as a result of the operation of random allocation within each of the 51 hospitals. Sixty-four patients (9.8%) were excluded from the analysis of the clinical results for reasons detailed in the Appendix. Of these exclusions, 29 (4.4%) were unimportant, since the patients either did not conform to the basic requirements for entry or did not complete the week of preliminary investigation. The remaining 35 (5.4%), though relevant, are few in number and so are unlikely to have seriously distorted the results. After exclusions, the numbers remaining in the clinical analysis were 182 SH, 142 S2H, 159 20 PH, and 105 10 PH patients. The numbers in each disease group are set out in Table I. It will be noted that the numbers of group 3 patients are very small.

Since patients in subgroup 1A (acute bilateral disease in young adults) were admitted only to the SH and 20 PH treatment series, a valid comparison of the relative efficacy of all four treatments SH, S2H, 20 PH, and 10 PH can be made only after excluding the patients in this subgroup. In the first part of the tables which follow, the findings for the four treatments are presented first for all patients except those in subgroup 1A. The findings for all the SH and 20 PH patients, including those in subgroup 1A, appear in the second part of each table ; the results for patients in this important subgroup may be obtained from each table by subtraction.

II. CLINICAL PROGRESS

1. Condition on Admission

The treatment received by patients before they entered the trial was investigated. Ten patients on SH (5%), 9 on S2H (6%), 6 on 20 PH (4%), and 3 on 10 PH (3%) had already received one or more courses of chemotherapy, but not within the preceding three months. Thus 95% of the patients in the present analysis were receiving their first course of chemotherapy. Most were also newly diagnosed cases.

Table II shows the condition of patients before the start of treatment as reflected by their general condition (assessment by the clinician in charge), temperature, erythrocyte sedimentation rate (E.S.R. Westergren 200 mm. reading at

TABLE I.—*Number of Patients Admitted to the SH, S2H, 20 PH, and 10 PH Treatments after September 5, 1952, and not Subsequently Excluded*

	Treatment				All Patients
	SH Streptomycin 1 g. Daily Plus Isoniazid 200 mg. Daily	S2H Streptomycin 1 g. Twice a Week Plus Isoniazid 200 mg. Daily	20 PH P.A.S. (Sodium) 20 g. Daily Plus Isoniazid 200 mg. Daily	10 PH P.A.S. (Sodium) 10 g. Daily Plus Isoniazid 200 mg. Daily	
Group 1 : Acute rapidly progressive pulmonary tuberculosis of recent origin :					
1A. Bilateral; ages 15–30	67	—	59	—	126
1B. Bilateral; other ages } 1C. Unilateral; all ages }	42	48	29	37	156
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	68	83	62	63	276
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	5	11	9	5	30
All patients (excluding subgroup 1A)	115	142	100	105	462
All patients (including subgroup 1A)	182	142	159	105	588

TABLE II.—*Condition on Admission of Patients Treated with Isoniazid in Combination with Streptomycin or with P.A.S.*

	Treatment	Total	General Condition			Average Evening Temperature in Pre-treatment Week*				Erythrocyte Sedimentation Rate (Westergren 200 mm. Reading at 1 Hour)				Extent of Cavitation†			
			Good	Fair	Poor	Afebrile	Under 99° F.	99–99·9°F.	100° F. or More	0–10	11–20	21–50	51 or More	Nil	1-plus	2-plus	3-plus
		No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
All patients (excluding subgroup 1A)	SH	115 100	40 35	45 39	30 26	56 49	29 25	18 16	12 10	21 18	19 17	46 40	29 25	28 24	44 38	33 29	10 9
	S2H	142 100	46 32	54 38	42 30	63 44	44 31	17 12	18 13	21 15	20 14	57 40	44 31	33 23	47 33	45 32	17 12
	20 PH	100 100	24 24	43 43	33 33	42 42	31 31	18 18	9 9	16 16	18 18	39 39	27 27	29 29	29 29	30 30	12 12
	10 PH	105‡ 100	33 31	47 45	25 24	43 41	33 31	20 19	9 9	15 14	16 15	43 41	30 29	33 31	30 29	37 35	5 5
All SH and 20 PH patients (including subgroup 1A)	SH	182 100	51 28	73 40	58 32	75 41	49 27	34 19	24 13	27 15	25 14	73 40	57 31	35 19	55 30	71 39	21 12
	20 PH	159 100	31 19	67 42	61 38	53 33	54 34	29 18	23 14	17 11	21 13	67 42	54 34	34 21	40 25	58 36	27 17

* A patient was considered afebrile if *every* evening temperature in the pre-treatment week of investigation was below 99° F. (37·2° C.).
† Assessment on a single full-plate chest radiograph taken before treatment started. Tomograms were not taken into account.
‡ The sedimentation rate of one group 3 patient was not recorded.

one hour), and the extent of cavitation on a full-plate radiograph (as graded by the radiological assessor, who was unaware of the treatment series of any patient). It can be seen that, judging by the factors listed, the SH, S2H, 20 PH, and 10 PH patients had broadly similar distributions of severe and less severe illness; although the detailed figures are not presented in Table II, this applied to patients in disease groups 1 and 2 separately. When the patients in subgroup 1A were added the SH and 20 PH series still had very similar distributions of patients with severe and less severe illness.

2. Mortality

There were 7 deaths among the 588 patients (1.2%) during the three-month period of treatment—2 in SH patients, 3 in 20 PH patients, and 2 in 10 PH patients. Of these, 3 died within a week of starting treatment—a 20 PH and a 10 PH patient in group 1 and a 10 PH patient in group 2. Two others (both 20 PH, group 1) died within a month, the disease in each having pursued a steadily deteriorating course. One of these patients died after 21 days, the other after 30 days; for the latter, treatment was stopped 10 days before death because the patient was too ill to swallow. The remaining 2 deaths (both SH, group 1) occurred after 5 and 12 weeks. All the deaths were due to pulmonary tuberculosis except for the last patient, who died from renal failure secondary to acute nephritis, confirmed at post-mortem examination. This patient had slight clinical and radiographic deterioration at one month and showed further clinical and radiographic deterioration at the end of two months. The nephritis was diagnosed in the third month. A specimen taken from the lung at post-mortem examination yielded a strain on culture which was sensitive both to streptomycin and to isoniazid.

3. Toxicity

There is nothing further to add to previous reports (Medical Research Council, 1952, 1953c) of the absence of severe toxicity to isoniazid, in the dosage used, over a three-month period. There were also no noteworthy toxic manifestations in patients who continued to receive the drug for the whole six months. Treatment was stopped in 6 patients because of severe toxic reactions attributed to P.A.S., and in 1 patient with a severe toxic reaction attributed to streptomycin (see Appendix). Toxicity to P.A.S. must therefore be considered a disadvantage of treatment with the combination P.A.S. plus isoniazid.

4. The Comparison Between the SH, S2H, 20 PH, and 10 PH Treatments

Radiographic Changes in the First Three Months.—Table III sets out the radiographic changes at the end of three months' treatment. The assessments were made at a reading of full-plate chest radiographs by the radiologist, who was unaware of the treatment of any patient. In assessing improvement or deterioration three degrees were

TABLE III.—*Changes in Radiographic Appearances in the First Three Months*

	Treatment	Total		Improvement						No Change		Deterioration						Death	
				3-plus		2-plus		1-plus*				1-minus		2-minus		3-minus			
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Subgroups 1B and 1C: Acute rapidly progressive pulmonary tuberculosis of recent origin (excluding bilateral disease, ages 15–30)	SH	42	*101*	10	*24*	15	*36*	15	*36*	0	*0*	0	*0*	0	*0*	0	*0*	2	*5*
	S2H	48	*100*	7	*15*	19	*40*	16	*33*	3	*6*	1	*2*	2	*4*	0	*0*	0	*0*
	20 PH	29	*99*	3	*10*	5	*17*	14	*48*	5	*17*	0	*0*	0	*0*	0	*0*	2	*7*
	10 PH	37	*100*	5	*14*	14	*38*	9	*24*	6	*16*	2	*5*	0	*0*	0	*0*	1	*3*
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SH	68	*99*	15	*22*	18	*26*	20	*29*	15	*22*	0	*0*	0	*0*	0	*0*	0	*0*
	S2H	83	*99*	11	*13*	25	*30*	23	*28*	21	*25*	1	*1*	2	*2*	0	*0*	0	*0*
	20 PH	62	*101*	11	*18*	14	*23*	25	*40*	11	*18*	1	*2*	0	*0*	0	*0*	0	*0*
	10 PH	63	*101*	7	*11*	13	*21*	29	*46*	11	*17*	1	*2*	1	*2*	0	*0*	1	*2*
All patients (excluding subgroup 1A)	SH	115	*100*	26	*23*	36	*31*	35	*30*	16	*14*	0	*0*	0	*0*	0	*0*	2	*2*
	S2H	142	*100*	18	*13*	44	*31*	45	*32*	29	*20*	2	*1*	4	*3*	0	*0*	0	*0*
	20 PH	100	*100*	14	*14*	19	*19*	43	*43*	20	*20*	2	*2*	0	*0*	0	*0*	2	*2*
	10 PH	105	*100*	12	*11*	28	*27*	40	*38*	19	*18*	3	*3*	1	*1*	0	*0*	2	*2*
All SH and 20 PH patients (including subgroup 1A)	SH	182	*101*	38	*21*	59	*32*	56	*31*	25	*14*	1	*1*	1	*1*	0	*0*	2	*1*
	20 PH	159	*100*	19	*12*	42	*26*	64	*40*	28	*18*	3	*2*	0	*0*	0	*0*	3	*2*

* The assessments for one SH and one 10 PH patient were made by the clinician in charge. The radiographs were subsequently lost.

TABLE IV.—*Summary of Comparisons of Isoniazid in Combination with Streptomycin or with P.A.S. at the End of Three Months' Treatment*

	All Patients (Excluding Subgroup 1A)								All SH and 20 PH Patients (Including Subgroup 1A)			
	SH Streptomycin 1 g. Daily Plus Isoniazid 200 mg. Daily		S2H Streptomycin 1 g. Twice a Week Plus Isoniazid 200 mg. Daily		20 PH P.A.S. 20 g. Daily Plus Isoniazid 200 mg. Daily		10 PH P.A.S. 10 g. Daily Plus Isoniazid 200 mg. Daily		SH Streptomycin 1 g. Daily Plus Isoniazid 200 mg. Daily		20 PH P.A.S. (sodium) 20 g. Daily Plus Isoniazid 200 mg. Daily	
	No.	%	No.	%	No.	%	No.	%	No.	%	No	%
General condition:	(115)*		(142)		(100)		(105)		(182)		(159)	
Improvement 2-plus		*29*		*32*		*34*		*35*		*35*		*36*
" 1-plus		*59*		*58*		*50*		*57*		*55*		*51*
No change		*10*		*9*		*14*		*6*		*9*		*11*
Deterioration		*0*		*1*		*0*		*0*		*0*		*0*
Death		*2*		*0*		*2*		*2*		*1*		*2*
Weight:	(111)		(139)		(95)		(102)		(179)		(152)	
Gain 14 lb. (6·4 kg.) or more		*38*		*58*		*41*		*48*		*42*		*40*
" 7–13 lb. (3·2–6·3 kg.)		*36*		*28*		*28*		*31*		*35*		*29*
" less than 7 lb., or no change		*23*		*12*		*24*		*19*		*20*		*24*
Loss		*4*		*2*		*6*		*2*		*3*		*7*
Average gain in weight (lb.)	11·3		14·8		11·3		13·9		12·4		11·2	
Temperature:	(57)		(78)		(56)		(60)		(105)		(103)	
Afebrile at 3 months (febrile at start)		*79*		*72*		*82*		*73*		*75*		*83*
Sedimentation rate:	(72)		(100)		(64)		(72)		(127)		(118)	
Fall to 10 or less from 21 or more, in 3 months		*38*		*41*		*48*		*39*		*35*		*42*

* The figures in parentheses indicate the total numbers of patients upon which the percentages are based.

allowed in each—namely, 1-plus, 2-plus, and 3-plus, and 1-minus, 2-minus, and 3-minus. Of 115 SH patients, 84% improved radiographically compared with 75% of 142 S2H patients, 76% of 100 20 PH patients, and 76% of 105 10 PH patients. Two-plus and 3-plus improvement also was more frequent under the SH treatment (54%) than under the other treatments (S2H 44%, 20 PH 33%, and 10 PH 38%). The differences between this percentage for the SH treatment and those for the 20 PH and 10 PH treatments attain statistical significance—that is, at the 5% level. There were no radiographic deteriorations and 2 deaths in the SH series, 6 deteriorations and no deaths in the S2H series, 2 deteriorations and 2 deaths in the 20 PH series, and 4 deteriorations and 2 deaths in the 10 PH series.

Changes in the other Clinical Assessments.—In Table IV are set out for the four treatment series the changes in the general condition and in the weight, and the resolution of pyrexia and the lowering of the sedimentation rate in the three-month period. Apart from weight changes the responses of the patients in the four treatment series were very similar. In the SH series, 38% of patients gained 14 lb. (6.4 kg.) or more, compared with 58% for the S2H series, 41% for the 20 PH series, and 48% for the 10 PH series. The average weight gains were 11.3 lb. (5.1 kg.) for the SH and 14.8 lb. (6.7 kg.) for the S2H patients, the difference being statistically significant. This difference may be related to disturbances associated with streptomycin injections in a proportion of patients (Riches, 1954). The corresponding averages were 11.3 lb. (5.1 kg.) for the 20 PH patients, and 13.9 lb. (6.3 kg.) for the 10 PH patients, the difference again being statistically significant. This difference is likely to be a result of greater gastro-intestinal disturbance to patients receiving the higher dosage of P.A.S.

The SH treatment was thus radiographically superior to any of the other three treatments. Otherwise the differences appear to be of little importance.

5. The Comparison Between all the SH and 20 PH Treated Patients

Radiographic Changes in the First Three Months.—The percentages of patients showing radiographic improvement were 84% for the 182 SH patients and 79% for the 159 20 PH patients (Table III). The proportion of patients showing 2-plus and 3-plus radiographic improvement was higher for the SH series (53%) than for the 20 PH series (38%), a difference that is statistically highly significant—that is, at the 1% level.

Changes in the other Clinical Assessments.—The changes in the general condition and in the weight, and the resolution of pyrexia and the lowering of the sedimentation rate, are set out in Table IV. There is a close similarity in the responses of patients on the two treatments.

The SH treatment is thus clearly superior to the 20 PH treatment on the radiographic assessment, but in other respects the differences are small.

III. BACTERIOLOGY DURING THE FIRST THREE MONTHS

The bacteriological findings for three months were analysed for those patients whose clinical progress has been reported above. The bacterial content of the sputum was determined after one, two, and three months of treatment, and the development of bacterial resistance after two and three months. Sensitivity to isoniazid was tested for patients under each of the four treatments, to streptomycin for SH and for S2H patients, and to P.A.S. for 20 PH and for 10 PH patients.

The procedure for taking specimens, the technique for sensitivity tests to each of the three drugs, and the definitions of resistance and sensitivity have been described in detail in previous reports (Medical Research Council, 1953a, 1953b). The examinations of bacteriological specimens and the sensitivity tests to isoniazid and to streptomycin were made in the co-operating laboratories. The P.A.S.-sensitivity tests were all made in the reference laboratory (see Acknowledgments).

The result of a bacteriological examination, or of a sensitivity test, for a given month was accepted only if it was performed on a specimen collected not more than seven days before or after the appropriate date. When more than one such result was available, the one referring to a specimen taken on or nearest to the appropriate date was selected to avoid bias. Thus in all the bacteriological tables each item represents a number of patients for each of whom a single test was selected, and not a total of all the tests performed on a smaller number of patients.

1. Exclusions

In addition to the patients already excluded from the clinical analysis, a further 5 patients (3 SH, 1 S2H, 1 10 PH) have been excluded from the bacteriological analysis. No tubercle bacilli were seen or isolated from pre-treatment specimens for any of these patients, and although there was

TABLE V.—*Presence of Tubercle Bacilli at Single Examinations made at Monthly Intervals*

Disease Group	Months after Entry to Trial	Treatment	Total Patients Examined		"Positive" Direct Examination*		"Scanty Positive" Direct Examination*†		Direct Examination Negative and Culture Positive or Laryngeal Swab Positive		Direct Examination and Culture Negative; or Laryngeal Swab Negative	
			No.	%	No.	%	No.	%	No.	%	No.	%
All patients (excluding subgroup 1A)	1	SH	107	*101*	37	*35*	6	*6*	21	*20*	43	*40*
		S2H	135	*100*	41	*30*	15	*11*	35	*26*	44	*33*
		20 PH	95	*100*	25	*26*	12	*13*	26	*27*	32	*34*
		10 PH	99	*99*	27	*27*	7	*7*	31	*31*	34	*34*
	2	SH	102	*101*	15	*15*	6	*6*	25	*25*	56	*55*
		S2H	131	*101*	27	*21*	10	*8*	25	*19*	69	*53*
		20 PH	95	*99*	19	*20*	5	*5*	24	*25*	47	*49*
		10 PH	96	*100*	15	*16*	6	*6*	24	*25*	51	*53*
	3	SH	105	*100*	8	*8*	4	*4*	14	*13*	79	*75*
		S2H	132	*100*	18	*14*	1	*1*	15	*11*	98	*74*
		20 PH	92	*100*	11	*12*	3	*3*	11	*12*	67	*73*
		10 PH	97	*99*	8	*8*	1	*1*	15	*15*	73	*75*
All SH and 20 PH patients (including subgroup 1A)	1	SH	171	*100*	58	*34*	11	*6*	48	*28*	54	*32*
		20 PH	150	*100*	44	*29*	15	*10*	51	*34*	40	*27*
	2	SH	163	*99*	30	*18*	12	*7*	41	*25*	80	*49*
		20 PH	150	*99*	35	*23*	8	*5*	39	*26*	68	*45*
	3	SH	166	*100*	18	*11*	5	*3*	30	*18*	113	*68*
		20 PH	147	*100*	19	*13*	3	*2*	25	*17*	100	*68*

All patients were bacteriologically positive before treatment—that is, at least one pre-treatment specimen showed bacilli on direct examination or was positive on culture.

* Even if culture-negative.

† Defined as follows: only a few clumps of acid-fast bacilli found after five minutes' search.

no doubt of the diagnosis they did not conform to the bacteriological requirements on entry to the trial. Eleven patients have already been excluded (see Appendix) because they were found to have had bacilli resistant to at least one of the drugs on entry to the trial. The bacteriological as well as the clinical analysis is thus confined to patients whose organisms were sensitive at the start of the trial to both of the drugs they were receiving.

2. Bacterial Content of Sputum

The results at one, two, and three months of the selected single examinations of the sputum for tubercle bacilli are set out in Table V. The incidence of negative cultures increased each month, and the proportions were very similar for all four treatments. At one month 40% of the SH patients, 33% of the S2H, 34% of the 20 PH, and 34% of the 10 PH patients yielded specimens negative both on direct examination and on culture. The corresponding percentages at two months were 55%, 53%, 49%, and 53%, and by three months the percentages had increased to 75%, 74%, 73%, and 75% respectively. The findings for acute disease (group 1) and for the other lesions, both acute and chronic, considered suitable for chemotherapy (group 2) were very similar, and have not been tabulated separately.

When the progress of all the SH and all the 20 PH patients was compared there was again a close similarity in the responses of the two series; 68% of 166 SH patients and 68% of 147 20 PH patients yielded specimens negative both on direct examination and on culture at three months.

3. Sensitivity Tests

Isoniazid Sensitivity.—The results of the isoniazid-sensitivity tests are set out in Table VI. Comparing the four treatments, it can be seen that at three months 2 resistant strains were obtained from 22 patients with positive cultures on SH, 12 resistant strains from 30 similar patients on S2H, none from 24 patients on 20 PH, and 2 from 25 patients on 10 PH. The results for the SH, 20 PH, and 10 PH patients were alike, and satisfactory. The figures for the S2H series were less satisfactory, since the resistant cultures at three months represented 40% of all positive cultures, compared with 9% for the SH series, 0% for the 20 PH series, and 8% for the 10 PH series. When expressed as percentages of all the patients for whom cultures were undertaken, resistant strains were isolated from 9% of 132 S2H patients compared with 2% of 105 SH patients, 0% of 92 20 PH patients, and 2% of 97 10 PH patients. At two months the results for the S2H series were already inferior to those of the other series, for 6 resistant strains were obtained from 59 positive cultures (10%), whereas no resistant strains were isolated from any of the patients on the other three treatments. The inferiority of the S2H series compared with the other three treatments at three months is statistically significant.

In the second part of Table VI are set out the results for all the SH and 20 PH patients. At three months there were 3 resistant strains among 52 positive cultures from 166 SH patients. In the 20 PH series there were no resistant strains among 44 positive cultures from 147 patients. Each treatment therefore proved effective in preventing the emergence of isoniazid-resistant organisms over a period of three months.

Streptomycin Sensitivity.—The first part of Table VII compares the results of streptomycin-sensitivity tests in the SH and S2H patients. At three months there were no resistant strains among 22 positive cultures from 105 patients in the SH series, compared with 3 resistant strains among 31 positive cultures from 132 S2H patients.

TABLE VI.—*Results of Isoniazid-sensitivity Tests in SH, S2H, 20 PH, and 10 PH Patients (excluding those found to have organisms resistant to any drug on entry to trial)*

	Months after Entry to Trial	Treatment	Total Patients with Culture Examined (a)	Culture-Negative (No Sensitivity Test Possible)	Culture-Positive but No Sensitivity Result Available	Patients Culture-positive with Sensitivity Tests: Total Results Available (b)	Sensitive: No Growth on 0·2 μg. per ml.	Doubtful: Growth on 0·2 μg. per ml. Not on 1	Resistant: Growth on 1 μg. per ml. Not on 5	Resistant: Growth on 5 μg. per ml. Not on 10	Resistant: Growth on 10 μg. per ml. Not on 50	Resistant: Growth on 50 μg. per ml.	Total Resistant: No. (c)	Total Resistant: (c) as % of (b)	Total Resistant: (c) as % of (a)
All patients (excluding subgroup 1A)	2	SH	102	57	2	43	37	6	0	0	0	0	0	*0*	*0*
		S2H	131	70	2	59	48	5	1	3†	1	1	6	*10*	*5*
		20 PH	95	52	2	41	35	6	0	0	0	0	0	*0*	*0*
		10 PH	96	56	0	40	39	1	0	0	0	0	0	*0*	*0*
	3	SH	105	83	0	22	20	0	0	2†	0	0	2	*(9)**	*2*
		S2H	132	100	2	30	14	4	6	3	0	3	12	*40*	*9*
		20 PH	92	67	1	24	20	4	0	0	0	0	0	*(0)*	*0*
		10 PH	97	71	1	25	21	2	1	0	0	1	2	*8*	*2*
All SH and 20 PH patients (including subgroup 1A)	2	SH	163	78	3	82	73	8	1	0	0	0	1	*1*	*1*
		20 PH	150	75	3	72	65	7	0	0	0	0	0	*0*	*0*
	3	SH	166	114	0	52	47	2	0	2†	0	1	3	*6*	*2*
		20 PH	147	102	1	44	40	4	0	0	0	0	0	*0*	*0*

* Percentages based upon fewer than 25 observations are enclosed in parentheses as an indication of the small totals.
† One of these cultures showed growth on 5 μg. per ml., but was not tested on higher concentrations.

TABLE VII.—*Results of Streptomycin-sensitivity Tests in SH and S2H Patients (excluding those found to have organisms resistant to any drug on entry to trial)*

	Months after Entry to Trial	Treatment	Total Patients with Culture Examined (a)	Culture-Negative (No Sensitivity Test Possible)	Culture-Positive but No Sensitivity Result Available	Patients Culture-positive with Sensitivity Tests: Total Results Available (b)	Sensitive	Moderately Resistant (Ratio 8 to 99)	Strongly Resistant (Ratio 100 or More)	Total Resistant: No. (c)	Total Resistant: (c) as % of (b)	Total Resistant: (c) as % of (a)
All patients (excluding subgroup 1A)	2	SH	102	57	2	43	42	1	0	1	*2*	*1*
		S2H	131	70	2	59	57	2	0	2	*3*	*2*
	3	SH	105	83	0	22	22	0	0	0	*(0)**	*0*
		S2H	132	100	1	31	28	2	1	3	*10*	*2*
All SH patients (including subgroup 1A)	2	SH	163	78	4	81	80	1	0	1	*1*	*1*
	3	SH	166	114	1	51	50	1	0	1	*2*	*1*

* Percentages based upon fewer than 25 observations are enclosed in parentheses as an indication of the small totals.

Full information on the ability of the SH combination to prevent the emergence of streptomycin-resistant strains is obtained when the results for the patients in subgroup 1A are included. At three months there was only 1 resistant strain among 51 cultures from a total of 166 SH patients.

P.A.S. Sensitivity.—The first part of Table VIII compares the results of P.A.S.-sensitivity tests in the 20 PH and 10 PH series. At three months 1 resistant strain was obtained from 22 positive cultures from 92 patients on 20 PH compared with 1 resistant strain from 23 positive cultures from 97 patients on 10 PH. Each combination is thus effective in preventing the emergence of bacilli resistant to P.A.S. over a three-month period.

When the results for the patients in subgroup 1A are included, there were 2 resistant strains among 75 positive cultures in the 20 PH patients at two months, and 1 resistant strain among the 40 positive cultures from 147 patients at three months.

IV. SENSITIVITY TESTS AT FOUR, FIVE, AND SIX MONTHS

During the second three months the original combination of drugs was continued for the few patients in disease group 3, and for other patients selected by the clinician. A total of 67 SH, 78 S2H, 58 20 PH, and 38 10 PH patients continued on their original drug combination, the majority doing so for the whole of the second three months. There were, however, some changes of dosage. In 29 of the 67 SH patients the dosage of streptomycin was reduced (to 1 g. three times or to 1 g. twice a week), and in 9 of the 78 S2H patients it was increased. In 3 of the 58 20 PH patients the dosage of P.A.S. was reduced, and in 2 of the 38 10 PH patients it was increased. Collapse therapy, usually a pneumoperitoneum, was induced in the second three months for 45% of the SH patients, 33% of the S2H patients, 28% of the 20 PH patients, and 32% of the 10 PH patients.

The results of sensitivity tests for these patients have been used to study the subsequent course of the pattern of resistance which emerged for each combination of drugs in the first three months. Because the groups of patients who continued on their original combination were not drawn at random, they may not be representative samples from the four treatment series. Analyses were therefore undertaken to investigate this point. The clinical condition of the patients on admission to the trial is set out in Table IX. A comparison of this Table with Table II shows that the subgroups of S2H, 20 PH, and 10 PH patients who continued on their original drug combination had an initial distribution of severe and less severe illness which was similar to that of the groups from which they were respectively drawn. The subgroup of SH patients who continued on the combination was initially more ill than its parent group, notably in extent of cavitation; this slight disadvantage may have biased the results towards the emergence of bacterial resistance (Medical Research Council, 1948, 1952, 1954; Howlett *et al.*, 1949; Tucker, 1949; Bignall *et al.*, 1950; Lotte and Poussier, 1953).

The results of sensitivity tests at three, four, five, and six months for the four subgroups of patients are given in Tables X–XII. By comparing the three-month results for the patients who continued on the prescribed combination with the three-month results for the full series of patients in Tables VI–VIII respectively, it can be seen that the proportion of resistant strains isolated from each subgroup is similar at three months to the proportion in the parent group. As a consequence of the similarity in initial clinical

TABLE VIII.—*Results of P.A.S.-sensitivity Tests in 20 PH and 10 PH Patients (excluding those found to have organisms resistant to any drug on entry to trial)*

	Months after Entry to Trial	Treatment	Total Patients with Culture Examined (*a*)	Culture-negative (No Sensitivity Test Possible)	Culture-positive but No Sensitivity Result Available	Patients Culture-positive with Sensitivity Tests: Total Results Available (*b*)	Sensitive	Moderately Resistant (Ratio 8 to 99)	Strongly Resistant (Ratio 100 or More)	Total Resistant: No. (*c*)	(*c*) as % of (*b*)	(*c*) as % of (*a*)
All patients (excluding subgroup 1A)	2	20 PH	95	52	0	43	41	2	0	2	*5*	*2*
		10 PH	96	56	3	37	37	0	0	0	*0*	*0*
	3	20 PH	92	67	3	22	21	0	1	1	*(5)**	*1*
		10 PH	97	71	3	23	22	1	0	1	*(4)*	*1*
All 20 PH patients (including subgroup 1A)	2	20 PH	150	75	0	75	73	2	0	2	*3*	*1*
	3	20 PH	147	102	5	40	39	0	1	1	*3*	*1*

* Percentages based upon fewer than 25 observations are enclosed in parentheses as an indication of the small totals.

TABLE IX.—*Condition on Admission of those Patients who Continued on the Prescribed Combination of Drugs beyond Three Months*

	Treatment	Total	General Condition			Average Evening Temperature in Pre-treatment Week*				Erythrocyte Sedimentation Rate (Westergren 200 mm. Reading at 1 Hour)				Extent of Cavitation†			
			Good	Fair	Poor	Afebrile	99° F.	99–99·9° F.	100° F. or More	0–10	11–20	21–50	51 or More	Nil	1-plus	2-plus	3-plus
		No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
All patients (excluding subgroup 1A)	SH	44 *100*	10 *23*	17 *39*	17 *39*	17 *39*	8 *18*	11 *25*	8 *18*	4 *9*	5 *11*	20 *45*	15 *34*	8 *18*	13 *30*	18 *41*	5 *11*
	S2H	78 *100*	22 *28*	31 *40*	25 *32*	36 *46*	24 *31*	7 *9*	11 *14*	9 *12*	15 *19*	31 *40*	23 *29*	17 *22*	26 *33*	27 *35*	8 *10*
	20 PH	39 *100*	8 *21*	15 *38*	16 *41*	16 *41*	11 *28*	7 *18*	5 *13*	6 *15*	6 *15*	17 *44*	10 *26*	11 *28*	10 *26*	12 *31*	6 *15*
	10 PH	38‡ *100*	18 *47*	13 *34*	7 *18*	16 *42*	13 *34*	8 *21*	1 *3*	8 *21*	8 *21*	13 *34*	8 *21*	17 *45*	7 *18*	14 *37*	0 *0*
All SH and 20 PH patients (including subgroup 1A)	SH	67 *100*	15 *22*	24 *36*	28 *42*	20 *30*	18 *27*	16 *24*	13 *19*	6 *9*	7 *10*	29 *43*	25 *37*	9 *13*	17 *25*	34 *51*	7 *10*
	20 PH	58 *100*	10 *17*	23 *40*	25 *43*	18 *31*	19 *33*	11 *19*	10 *17*	7 *12*	6 *10*	26 *45*	19 *33*	14 *24*	13 *22*	19 *33*	12 *21*

* A patient was considered afebrile if *every* evening temperature in the pre-treatment week of investigation was below 99° F. (37·2° C.).
† Assessment on a single full-plate chest radiograph taken before treatment started. Tomograms were not taken into account.
‡ The sedimentation rate of one group 3 patient was not recorded.

condition, and the similarity in the results of sensitivity tests at three months, the analyses from four to six months have been regarded as continuations of the analyses for the first three months in the earlier tables. However, because the patients who continued on their original combination were not chosen at random at the end of the three months, the reliance which may be placed upon the conclusions for the second three months cannot be quite so firm as in the first three months.

For the patients in each series who stopped or changed chemotherapy before six months, the results are given for as long as the patient received the prescribed combination. The patients in disease subgroup 1A have been included in the Tables to increase the numbers.

Isoniazid Sensitivity.—Table X shows that at four, five, and six months very small numbers of positive cultures were obtained from patients on any of the four treatments and that only an occasional isoniazid-resistant strain was

TABLE X.—*Results of Isoniazid-sensitivity Tests in Patients Treated with Streptomycin Plus Isoniazid or P.A.S. Plus Isoniazid for a Period of up to Six Months (excluding those found to have organisms resistant to any drug on entry to trial)*

	Months after Entry to Trial	Total Patients with Culture Examined (*a*)	Culture-negative (No Sensitivity Test Possible)	Culture-positive but No Sensitivity Result Available	Patients Culture-positive with Sensitivity Tests: Total Results Available (*b*)	Sensitive: No Growth on 0·2 μg. per ml.	Doubtful: Growth on 0·2 μg. per ml. Not on 1	Resistant: Growth on 1 μg. per ml. Not on 5	Resistant: Growth on 5 μg. per ml. Not on 10	Resistant: Growth on 10 μg. per ml. Not on 50	Resistant: Growth on 50 μg. per ml.	Total Resistant: No. (*c*)	Total Resistant: (*c*) as % of (*b*)	Total Resistant: (*c*) as % of (*a*)
All patients on streptomycin 1 g. daily plus isoniazid (SH) for three months, and continuing on streptomycin plus isoniazid	3	65	46	0	19	18	0	0	0	0	1	1†	(5)*	2
	4	60	53	0	7	6	0	0	0	0	1	1†	(14)	2
	5	57	54	0	3	2	0	0	1	0	0	1†	(33)	2
	6	60	58	0	2	2	0	0	0	0	0	0	(0)	0
All patients on streptomycin 1 g. twice weekly plus isoniazid (S2H) for three months, and continuing on streptomycin plus isoniazid	3	76	58	1	17	8	1	3	3	0	2	8§	(47)	11
	4	70	55	0	15	6	0	2	2	0	5	9‡	(60)	13
	5	62	53	0	9	1	3	2	2	0	1	5	(56)	8
	6	64	55	0	9	1	0	2	2	4	0	8‡	(89)	13
All patients on P.A.S. 20 g. daily plus isoniazid (20 PH) for three months, and continuing on P.A.S. plus isoniazid	3	56	38	1	17	15	2	0	0	0	0	0	(0)*	0
	4	49	41	1	7	6	0	1	0	0	0	1†	(14)	2
	5	46	44	0	2	1	0	0	1	0	0	1†	(50)	2
	6	47	47	0	0	0	0	0	0	0	0	0	(0)	0
All patients on P.A.S. 10 g. daily plus isoniazid (10 PH) for three months, and continuing on P.A.S. plus isoniazid	3	36	30	0	6	5	0	1	0	0	0	1†	(17)	3
	4	33	31	0	2	1	1	0	0	0	0	0	(0)	0
	5	25	23	0	2	2	0	0	0	0	0	0	(0)	0
	6	27	25	0	2	2	0	0	0	0	0	0	(0)	0

* Percentages based upon fewer than 25 observations are enclosed in parentheses as an indication of the small totals.
† This was the first isoniazid-resistant strain to be isolated from this patient.
‡ Including 3 patients for whom this was the first isoniazid-resistant strain to be isolated.
§ Including 5 patients for whom this was the first isoniazid-resistant strain to be isolated.

TABLE XI.—*Results of Streptomycin-sensitivity Tests in Patients Treated with Streptomycin Plus Isoniazid for a Period of up to Six Months (excluding those found to have organisms resistant to any drug on entry to trial)*

	Months after Entry to Trial	Total Patients with Culture Examined (*a*)	Culture-negative (No Sensitivity Test Possible)	Culture-positive but No Sensitivity Result Available	Patients Culture-positive with Sensitivity Tests: Total Results Available (*b*)	Sensitive	Moderately Resistant (Ratio 8 to 99)	Strongly Resistant (Ratio 100 or More)	Total Resistant: No. (*c*)	Total Resistant: (*c*) as % of (*b*)	Total Resistant: (*c*) as % of (*a*)
All patients on streptomycin 1 g. daily plus isoniazid (SH) for three months, and continuing on streptomycin plus isoniazid	3	65	46	0	19	19	0	0	0	(0)*	0
	4	60	53	0	7	6	0	1	1†	(14)	2
	5	57	54	0	3	3	0	0	0	(0)	0
	6	60	58	0	2	2	0	0	0	(0)	0
All patients on streptomycin 1 g. twice weekly plus isoniazid (S2H) for three months, and continuing on streptomycin plus isoniazid	3	76	58	0	18	17	0	1	1	(6)	1
	4	70	55	1	14	13	0	1	1	(7)	1
	5	62	53	0	9	6	2	1	3‡	(33)	5
	6	64	55	0	9	6	1	2	3	(33)	5

* Percentages based upon fewer than 25 observations are enclosed in parentheses as an indication of the small totals.
† This was the first streptomycin-resistant strain to be isolated from this patient.
‡ Including 2 patients for whom this was the first streptomycin-resistant strain to be isolated.

TABLE XII.—*Results of P.A.S.-sensitivity Tests in Patients Treated with P.A.S. Plus Isoniazid for a Period of up to Six Months (excluding those found to have organisms resistant to any drug on entry to trial)*

	Months after Entry to Trial	Total Patients with Culture Examined (*a*)	Culture-negative (No Sensitivity Test Possible)	Culture-positive but No Sensitivity Result Available	Patients Culture-positive with Sensitivity Tests: Total Results Available (*b*)	Sensitive	Moderately Resistant (Ratio 8 to 99)	Strongly Resistant (Ratio 100 or More)	Total Resistant: No. (*c*)	Total Resistant: (*c*) as % of (*b*)	Total Resistant: (*c*) as % of (*a*)
All patients on P.A.S. 20 g. daily plus isoniazid (20 PH) for three months, and continuing on P.A.S. plus isoniazid	3	56	38	2	16	16	0	0	0	(0)*	0
	4	49	41	1	7	7	0	0	0	(0)	0
	5	46	44	1	1	1	0	0	0	(0)	0
	6	47	47	0	0	0	0	0	0	(0)	0
All patients on P.A.S. 10 g. daily plus isoniazid (10 PH) for three months, and continuing on P.A.S. plus isoniazid	3	36	30	0	6	6	0	0	0	(0)	0
	4	33	31	0	2	2	0	0	0	(0)	0
	5	25	23	0	2	2	0	0	0	(0)	0
	6	27	25	0	2	2	0	0	0	(0)	0

* Percentages based upon fewer than 25 observations are enclosed in parentheses as an indication of the small totals.

isolated from the SH, 20 PH, and 10 PH patients. The experience of the S2H series was not so satisfactory; at four months 15 positive cultures were obtained from 70 patients, and 9 of these were resistant to isoniazid. At five months 5 of 9 positive cultures obtained from 62 patients were resistant, and at six months 8 of 9 positive cultures from 64 patients were resistant. It may be concluded that this further study of isoniazid sensitivity under the four treatments has yielded very few positive results for sensitivity studies, an observation which is in itself of considerable importance. But, in addition, such sensitivity results as are available confirm the unsatisfactory nature of the S2H treatment in that it fails to prevent the emergence of isoniazid-resistant organisms to the same extent as the other three combinations of drugs.

Streptomycin Sensitivity.—The results of the streptomycin-sensitivity tests at three, four, five, and six months for patients in the SH and S2H series are given in Table XI. The SH patients fared very well. There was 1 streptomycin-resistant strain among 7 cultures at four months, none among 3 cultures at five months, and none among 2 cultures from 60 patients at six months. The results for the S2H patients were not quite so satisfactory. At five months 3 strains resistant to streptomycin were found among 9 positive cultures. At six months 3 streptomycin-resistant strains were again isolated from 9 positive cultures from 64 patients.

P.A.S. Sensitivity.—The results of the P.A.S.-sensitivity tests at three, four, five, and six months for patients in the 20 PH and 10 PH series are given in Table XII. Very few positive cultures were obtained after the third month in either series and none of the strains was resistant to P.A.S.

The Relationship of Resistance to Streptomycin and to Isoniazid in the S2H Series.—A further study was made of the 21 patients in the S2H series in whom resistance to streptomycin or to isoniazid emerged while the patient was receiving the combination. In 2 of these patients isoniazid and streptomycin resistance emerged simultaneously. In 1 patient streptomycin resistance alone emerged and there was no subsequent information. In the remaining 18 patients strains which were isoniazid-resistant but streptomycin-sensitive were obtained. No subsequent information was available for 8 of the patients. In the other 10 the strains were known to be sensitive to streptomycin in 3 patients one month later, in 1 patient two months later, and in 3 patients three months later; strains resistant to streptomycin emerged in 2 patients two months after, and in 1 patient three months after, the isoniazid-resistant strain.

The numbers of resistant strains with the other three treatments were too small for useful analysis.

V. ISONIAZID-SENSITIVITY TESTS IN PATIENTS WITH INITIALLY P.A.S.-RESISTANT STRAINS

Six patients, who were admitted, observed, and treated according to the requirements of the trial, were excluded from the above analysis because they were later found to have had bacilli resistant to P.A.S. on entry to the trial. Four received the 20 PH and 2 the 10 PH treatment for a period of at least three months. At two months there were 3 positive cultures, 1 of which was resistant to isoniazid. At three months 5 cultures were examined; 3 were positive and 1 of these was isoniazid-resistant. The 2 patients with isoniazid-sensitive strains at three months continued on the 20 PH treatment for two and for three more months respectively. At six months the former was culture-negative and the latter had an isoniazid-resistant strain. In all, 3 of the 6 patients yielded isoniazid-resistant strains while receiving P.A.S. plus isoniazid, at two, at three, and at six months respectively. In view of the association between the emergence of isoniazid resistance and the extent of initial cavitation (Medical Research Council, 1952, 1954; Lotte and Poussier, 1953), it is of interest to note that none of the 6 patients had extensive (3-plus) cavitation on admission to the trial. The result thus compares very unfavourably with the total of 4 patients in whom isoniazid resistance emerged among the 264 20 PH and 10 PH patients with initially P.A.S.-sensitive organisms.

VI. DISCUSSION

In the fifth report of this trial (Medical Research Council, 1953c) a clinical and bacteriological comparison of streptomycin 1 g. daily plus isoniazid 200 mg. daily (SH) and P.A.S. (sodium salt) 20 g. daily plus isoniazid 200 mg. daily (20 PH) was presented for a period of three months. Larger groups of patients receiving these two treatments have now been studied, and it has been found that the treatments are of comparable efficacy in improving the general condition, in fostering weight gain, in resolving pyrexia, in lowering the sedimentation rate (Table IV), and in suppressing tubercle bacilli in the sputum (Table V). Both treatments are also very effective for three months in preventing the emergence of bacterial resistance to the drugs used (Tables VI–VIII). These findings confirm those in the fifth report. But it has now also been shown that the SH treatment is superior in the important radiographic assessment, 53% of the 182 patients showing substantial (2-plus or 3-plus) radiographic improvement, compared with 38% of the 159 20 PH patients, a statistically highly significant difference (Table III).

For 67 of the 182 SH patients and 58 of the 159 20 PH patients the clinician elected to continue the same drug combination beyond three months. For reasons given, the analysis of bacterial sensitivity for these patients during the second three months may be regarded as a continuation of the analysis in the first three months. At six months only 2 positive cultures, and these sensitive to both drugs, were obtained from 60 SH patients and there were no positive cultures from 47 20 PH patients. Combining the figures at four, five, and six months, a total of 12 positive cultures was isolated from the SH patients; one culture was resistant both to isoniazid and to streptomycin and another to isoniazid only; there were 2 isoniazid-resistant strains and no P.A.S.-resistant strains among the corresponding total of 9 positive cultures from 20 PH patients. Thus the bacteriological effectiveness of each combination was maintained for six months. The findings on isoniazid sensitivity for the subgroup of SH patients are particularly worthy of note, since the dosage of streptomycin in nearly half these patients was reduced at three months either to 1 g. three times or to 1 g. twice a week, and neither of the resistant strains occurred among these patients. Moreover, the SH patients who continued were in worse clinical condition on entry to the trial—particularly as regards extent of cavitation—than those in whom treatment was changed at three months.

In the phase of the trial reported here two other combinations were also studied, involving lower dosages of streptomycin or of P.A.S. These were streptomycin 1 g. twice a week plus isoniazid 200 mg. daily (S2H) and P.A.S. (sodium salt) 10 g. daily plus isoniazid 200 mg. daily (10 PH). A three-month clinical and bacteriological comparison of these two treatments, and of the SH and 20 PH patients admitted concurrently with them, is presented. For this comparison the patients in disease subgroup 1A (acute bilateral disease in young adults) have been excluded, since they were allocated only to the SH and 20 PH series. The analysis, which is based on 115 SH, 142 S2H, 100 20 PH, and 105 10 PH patients, shows that over a three-month period the four treatments were of similar efficacy, both clinically and in suppressing tubercle bacilli in the sputum, but the SH combination was radiographically superior to any of the other three treatments.

Judging from the results of bacterial sensitivity tests over a three-month period, the 10 PH treatment was of the same high order of effectiveness as the 20 PH treatment in preventing the emergence of strains resistant to either drug. There were no isoniazid-resistant strains among 24 positive cultures from 92 20 PH patients, although there were 2 among 25 cultures from 97 10 PH patients; each combination yielded 1 P.A.S.-resistant strain. (In view of the possible relevance of the dosage rhythm of P.A.S. to the

emergence of bacterial resistance to isoniazid, it should be noted that in both treatments each dose of P.A.S. consisted of 5 g. of the sodium salt.) On the other hand, at three months there were 12 isoniazid-resistant strains among 30 positive cultures from 132 S2H patients but only 2 among 22 cultures from 105 SH patients. The S2H treatment is thus much less satisfactory in preventing isoniazid resistance than any of the other three combinations, the differences being statistically significant. Moreover, streptomycin-resistant strains were found among 3 of the S2H patients and in none of the SH patients.

An analysis of sensitivity results for the 78 S2H and 38 10 PH patients who continued on their original drug combination beyond three months confirms these bacteriological trends. At four, five, and six months a total of 6 positive cultures was obtained from the 10 PH patients; none was resistant to either drug. The S2H treatment remained unsatisfactory; 9 of 15 positive cultures were isoniazid-resistant at four months, 5 of 9 at five months, and 8 of 9 at six months. There was 1 streptomycin-resistant strain at four months, 3 at five months, and 3 at six months.

There have been a number of other studies of streptomycin plus isoniazid, notably by the U.S. Public Health Service (Mount *et al.*, 1953; U.S. Public Health Service, 1953; Mount and Ferebee, 1954), by the U.S. Veterans Administration (1953, 1954), and by Pitts *et al.* (1953), in the main using streptomycin 1 g. twice a week. There is general agreement on the clinical effectiveness of the combination for periods of study of up to eight months. Bacteriologically, however, streptomycin 1 g. twice a week with daily isoniazid appears from these studies to be inadequate to prevent the emergence of resistance to isoniazid. The present trial gives the only information so far available on a comparison of daily streptomycin plus isoniazid and intermittent streptomycin plus isoniazid, in which the treatments were allocated concurrently and at random. The daily treatment is clearly superior when assessed bacteriologically for six months, and shows some radiographic superiority at three months.

Turning to the combination P.A.S. plus isoniazid, most other studies agree with the present report on its clinical value over a three-month period. Over a longer period of time there are differences of opinion. Favourable reports come from the U.S. Public Health Service (Mount and Ferebee, 1954) based on 303 patients treated for thirty-two weeks, from the U.S. Veterans Administration (1954), based on 75 patients treated for five to eight months, and from Thoren and Hinshaw (1952), based on 15 patients treated for six months. On the other hand, Ford (1953) reported initial improvement in 22 patients, "most of whom had reached the end of their therapeutic road," but the majority relapsed clinically during the second three months. However, 19 of the patients had received previous chemotherapy which included P.A.S., and no pre-treatment bacterial sensitivity tests were performed. Unfavourable reports also came from Joiner *et al.* (1954), based on 15 patients with chronic disease, but the authors state that the radiological assessments were inconclusive. It is reasonable to conclude, from the larger of these studies, that the clinical effectiveness of the combination P.A.S. plus isoniazid continues for many months.

There are also differences between the reports on bacterial sensitivity for patients on the combination P.A.S. plus isoniazid. The findings in the present study for a wide range of acute and chronic disease, in patients 95% of whom had received no previous chemotherapy and all of whom had sensitive organisms at the start of treatment, have been very satisfactory over a period of six months. They are in sharp contrast to the present findings for 6 patients with P.A.S.-resistant organisms initially, in 3 of whom isoniazid resistance subsequently emerged under treatment with P.A.S. plus isoniazid. The U.S. Veterans Administration (1954) also reported favourably on the combination for a period of five to eight months. As in the present study, there was a lower incidence of isoniazid resistance with P.A.S. plus isoniazid than with streptomycin 1 g. twice a week plus isoniazid. Thoren and Hinshaw (1952), Ford (1953), and Joiner *et al.* (1954) gave unfavourable reports. However, neither of the first two studies presented pre-treatment sensitivity findings to P.A.S., so that it is difficult to appraise the unfavourable results of the isoniazid-sensitivity tests. Thoren and Hinshaw (1952) gave no information on the previous chemotherapy received by their cases, but 19 of the 22 patients in Ford's (1953) series had previously received chemotherapy which included P.A.S. Ten of the 15 patients treated by Joiner *et al.* (1954) had received previous chemotherapy, although all the strains were sensitive both to isoniazid and to P.A.S. at the start of the study. It may be concluded from the findings of the larger inquiries that the combination is satisfactory, both clinically and bacteriologically, for six or more months, at least in patients receiving their first course of chemotherapy.

This survey of the literature indicates the difficulty of assessing the value of a combination of drugs from studies of patients who have received previous courses of chemotherapy. Such patients are selected to some extent by virtue of failure to respond adequately to the earlier courses, and their response is thus likely to be prejudiced. Newly diagnosed cases of pulmonary tuberculosis are a much more suitable group for the study of the relative merits of chemotherapeutic combinations. First, whereas previously treated cases may have resistant organisms, there is at present a high degree of assurance that the organisms of newly diagnosed cases will be sensitive to any prescribed combination (though this must still be confirmed by sensitivity tests on pre-treatment specimens—Medical Research Council, 1953a; Thomas *et al.*, 1954). Secondly, newly diagnosed cases provide a wider variety of disease for study, ranging from minimal to far-advanced lesions, and from hyperacute to very chronic disease. Thirdly, they respond better to chemotherapy, and so will indicate the relative efficacy of different treatments more readily than cases in which chemotherapy has previously been used.

In conclusion, streptomycin 1 g. daily plus isoniazid 200 mg. daily is radiographically the most effective of the four treatments over a three-month period, though otherwise there is little to choose between them clinically. The treatment is also superior, but not greatly superior, to streptomycin 1 g. daily plus P.A.S. (sodium salt) 20 g. daily (Medical Research Council, 1953b). It thus represents the most effective combination studied at any stage of the trial.

On the other hand, treatment with streptomycin 1 g. twice a week plus isoniazid 200 mg. daily has proved less satisfactory in preventing the emergence of isoniazid-resistant organisms and, because of this, its use cannot be recommended as a primary chemotherapeutic measure. There is, however, evidence that it is bacteriologically effective as a continuation of a three-month course of daily streptomycin plus isoniazid.

The present report confirms the earlier finding (Medical Research Council, 1953c) that P.A.S. plus isoniazid is an effective combination, although it is not quite so powerful as daily streptomycin plus isoniazid. Further, there is little to choose between 20 g. and 10 g. P.A.S. (sodium salt) daily in combination with isoniazid 200 mg. daily, whether assessed clinically over a three-month period, or bacteriologically over a six-month period. Either combination of P.A.S. with isoniazid can therefore be considered a valuable form of combined chemotherapy in the treatment of pulmonary tuberculosis, and each has the great advantage that it can be administered entirely by mouth.

VII. SUMMARY

In the final stage of a clinical trial of isoniazid (isonicotinic acid hydrazide) in the treatment of pulmonary tuberculosis, 588 patients were studied in 51 hospitals: 182 were treated with streptomycin 1 g. daily plus iso-

niazid 100 mg. twice a day (SH); 142 with streptomycin 1 g. twice a week plus isoniazid 100 mg. twice a day (S2H); 159 with P.A.S., sodium salt, 5 g. four times a day plus isoniazid 100 mg. twice a day (20 PH); and 105 with P.A.S., sodium salt, 5 g. twice a day plus isoniazid 100 mg. twice a day (10 PH). When submitting a case the physician did not know which treatment the patient would receive, this being determined by random allocation. The present report analyses clinical and bacteriological results at the end of three months' treatment. Bacteriological results are also studied for 241 patients over a six-month treatment period.

The types of disease studied ranged from acute rapidly progressive disease to very chronic disease. Most of the cases were newly diagnosed; less than 5% had received previous courses of chemotherapy. All patients included in the analysis had organisms sensitive at the start of treatment to both of the drugs they were receiving.

Cases in an important subgroup (acute rapidly progressive bilateral disease of recent origin, in patients aged 15–30) were allocated only to treatment with SH (67 patients) or with 20 PH (59 patients). The report contains a comparison of the SH, S2H, 20 PH, and 10 PH treatments, excluding the patients in this subgroup, and a further comparison of the SH and 20 PH treatments, including these patients.

On admission, the four treatment series had similar distributions of patients with severe and less severe illness. At the end of three months' treatment the majority of patients had improved. In terms of general clinical condition, resolution of pyrexia, and improvement in the sedimentation rate, the differences between the four treatment series were small. The average weight gains were 11.3 lb. (5.1 kg.) for the SH, 14.8 lb. (6.7 kg.) for the S2H, 11.3 lb. (5.1 kg.) for the 20 PH, and 13.9 lb. (6.3 kg.) for the 10 PH patients.

Changes in radiographic appearances were independently assessed by a radiologist unaware of the treatment of any patient. Two-plus or three-plus improvement was seen in 54% of SH, 44% of S2H, 33% of 20 PH, and 38% of 10 PH patients. The differences between this result for the SH treatment and those for the 20 PH and 10 PH treatments attain statistical significance. There were no radiographic deteriorations and 2 deaths in the SH series, 6 deteriorations and no deaths in the S2H series, 2 deteriorations and 2 deaths in the 20 PH series, and 4 deteriorations and 2 deaths in the 10 PH series.

The proportions of patients bacteriologically negative, both on direct examination and on culture, at a single examination at three months were 75% in the SH, 74% in the S2H, 73% in the 20 PH, and 75% in the 10 PH series.

At three months bacillary resistance to isoniazid was found in 2 of 22 culture-positive SH patients, compared with 12 of 30 similar S2H patients, 0 of 24 20 PH patients, and 2 of 25 10 PH patients. Bacillary resistance to streptomycin was found at three months in 0 of 22 culture-positive SH patients and 3 of 31 S2H patients, and to P.A.S. in 1 of 22 culture-positive 20 PH patients and 1 of 23 10 PH patients.

The addition to the SH and 20 PH series of the results for the young adults with acute bilateral disease confirms both the radiographic superiority of the SH treatment and also the close similarity of the results with the SH and 20 PH treatments in other respects.

It is concluded, *judging solely from the results at three months,* that streptomycin 1 g. daily plus isoniazid 200 mg. daily is not only the most effective of the four treatments but also represents the most effective drug combination studied at any stage of the trial. Streptomycin 1 g. twice a week plus isoniazid 200 mg. daily is less satisfactory in preventing the emergence of isoniazid-resistant organisms, and its use as a primary chemotherapeutic measure cannot be recommended. P.A.S. plus isoniazid has proved itself a very effective combination of drugs, although it is not quite so powerful as daily streptomycin plus isoniazid. There is little to choose between the clinical and bacteriological efficacy of 20 g. and of 10 g. P.A.S. (sodium salt) daily plus isoniazid 200 mg. daily. Either combination of P.A.S. with isoniazid is a most valuable oral form of combined chemotherapy in the treatment of pulmonary tuberculosis.

A proportion of patients in each of the four treatment series continued on the same combination of drugs beyond three months. For reasons given the analysis of bacterial sensitivity for these patients during the second three months may be regarded as a continuation of the analysis in the first three months. The analysis, based on a total of 241 patients, confirms, *for a period of six months,* the adequacy of the SH, 20 PH, and 10 PH treatments, and the inadequacy of the S2H treatment, in preventing the development of bacterial resistance to isoniazid. Combining the figures at four, five, and six months, 2 of 12 positive cultures from SH patients, 2 of 9 from 20 PH patients, and 0 of 6 from 10 PH patients were found to be isoniazid-resistant. On the other hand, 9 of 15 strains from S2H patients were resistant to isoniazid at four months, 5 of 9 at five months, and 8 of 9 at six months.

A small group of patients with P.A.S.-resistant organisms on entry to the trial was not protected from the risk of development of isoniazid resistance during treatment with P.A.S. plus isoniazid.

APPENDIX

Exclusions from the Clinical Analysis

Nine patients were excluded before treatment was started:

2 died before the start of treatment (1 20 PH, 1 10 PH);
2 were too ill to be moved to hospital (1 SH, 1 S2H);
2 discharged themselves against medical advice (2 20 PH);
2 refused to go to hospital (2 SH);
1, although admitted, did not start treatment, because no positive sputum was obtained (SH).

Fifty-five patients were excluded after treatment had begun:

2 were found not to have had pulmonary tuberculosis (1 S2H, 1 20 PH);
4 were found to have had organisms resistant to streptomycin at the start of treatment (2 SH, 2 S2H);
6 were found to have had organisms resistant to P.A.S. at the start of treatment (4 20 PH, 2 10 PH);
1 was found to have had organisms resistant to isoniazid at the start of treatment (10 PH) (no check-test was performed in the reference laboratory);
7 were found to have had excessive recent chemotherapy (1 SH, 1 S2H, 4 20 PH, 1 10 PH);
5 were given the wrong treatment (1 SH, 2 S2H, 2 20 PH);
14 discharged themselves against medical advice—6 in the first, 7 in the second, and 1 in the third month (2 SH, 2 S2H, 3 20 PH, 7 10 PH);
2 were transferred to other hospitals in the first month for investigations of non-pulmonary complaints (1 20 PH, 1 10 PH);

1 was transferred to a mental hospital with a psychosis, in the second month (10 PH);

6 had severe toxic reactions attributed to P.A.S. (4 20 PH, 2 10 PH);

1 had a severe toxic reaction attributed to streptomycin (SH);

2 stopped treatment in the second month—one because of acute nephritis, the other because of persistent haemoptysis believed to be related to treatment (2 SH);

2 had a change of treatment in the first month: for one 10 PH patient streptomycin was added after eight days, and the dosage of P.A.S. was doubled, because of the serious clinical condition: for one 20 PH patient streptomycin was added after 18 days because of radiographic deterioration; this patient had 1-minus deterioration at one month, and the deterioration at three months was still classed as 1-minus;

2 had a change of treatment in the second month (2 20 PH): one patient had deteriorated both clinically and radiographically and the treatment was changed to SH at six weeks; at ten weeks a radiograph showed 1-plus improvement compared with the condition on admission: the other patient deteriorated radiographically and streptomycin was added at six weeks, but there was 2-minus deterioration at three months.

ACKNOWLEDGMENTS

The hospitals and the doctors co-operating in the phase of the trial reported here are as follows:

Hospitals.—Aberdeen City Hospital; Aintree Hospital; Ashludie Hospital, Monifieth; Ayrshire Central Hospital, Irvine; Bangour Hospital, West Lothian; Black Notley Hospital, Braintree; Brierton Hospital, West Hartlepool; British Legion Sanatorium, Nayland; Brompton Hospital; Broomfield Hospital, Chelmsford; Canadian Red Cross Memorial Hospital, Taplow; Clare Hall Hospital, Herts; Connaught Military Hospital; Cumberland Hospital, Surrey; Dumfries and Galloway Sanatorium; East Fortune Hospital, East Lothian; Edgware General Hospital; Edinburgh City Hospital; Foxhall Hospital, Ipswich; Glenafton Hospital, Ayrshire; Hammersmith Hospital; Heathcote Hospital, Leamington Spa; Heathfield Hospital, Ayrshire; Hillingdon Hospital; Holywood Hall Hospital, Bishop Auckland; Inverurie Hospital, Aberdeen; Kettlewell Hospital, Kent; King Edward VII Sanatorium, Midhurst; King George V Hospital, Godalming; King George's Sanatorium for Sailors, Hants; Lenham Sanatorium, Kent; Llangwyfan Hospital, Denbigh; Mearnskirk Hospital, Renfrewshire; Mount Pleasant Hospital, Middlesex; Newcastle General Hospital; North Middlesex Hospital; Poole Sanatorium, Middlesbrough; Robroyston Hospital, Glasgow; Romsley Hill Hospital, Worcestershire; Royal Victoria Hospital, Edinburgh; St. Albans City Hospital; St. Helen's Hospital, Ipswich; St. Helier Hospital, Surrey; St. Wulstan's Hospital, Worcestershire; Seaham Hall Sanatorium, Sunderland; Southfield Hospital, Edinburgh; Westcliff Hospital; West Heath Hospital, Birmingham; Woodend Hospital, Aberdeen; Wooley Sanatorium, Northumberland; Yardley Green Hospital, Birmingham.

Physicians.—Drs. P. G. Arblaster, M. Barry, D. Bell, W. Biagi, W. M. Borthwick, J. T. Boyd, L. E. Burkeman, L. W. Carstairs, K. M. Chalmers, J. A. Chamberlin, C. W. Clayson, J. B. Cochran, R. C. Cohen, A. H. C. Couch, Professor J. W. Crofton, Drs. R. Cunningham, V. Davies, V. F. Dawkins, M. K. Dhole, J. W. Duerden, T. A. Watkin Edwards, I. Elmslie, W. J. Ferraby, P. Forgacs, M. A. Foulis, R. Fraser, M. A. Gallagher, J. E. Geddes, I. W. B. Grant, J. S. B. Greenfield, L. A. Hardie, W. C. Harris, H. F. Harwood, M. Hemming, E. V. Hess, J. A. Hill, F. Hodgkiss, N. W. Horne, J. V. Hurford, G. Hurrell, J. E. M. Hutchinson, Lieutenant G. J. Jones, Drs. G. Penrhyn Jones, R. Sinclair Kennedy, G. M. Lewis, G. M. Little, T. W. Lloyd, L. C. Lum, E. G. Sita Lumsden, G. R. W. N. Luntz, Lieutenant-Colonel J. Mackay-Dick, Drs. W. MacDermid, N. MacFarlane, D. G. McIntosh, G. R. McNab, A. T. Mason, W. T. Miller, K. Murray, W. A. Murray, P. J. O'Rooney, J. P. Parkinson (the late), Hayden J Partington, W. C. Pinkney, A. C. P. Ritchie, J. B. Robinson, J. T. Nicol Roe, Hector J. T. Ross, I. D. Ross, J. D. Ross, J. B. M. Runciman, F. A. H. Simmonds, D. H. Smith, J. Morrison Smith, J. Stevenson, C. J. Stewart, P. Stradling, G. J. Summers, J. Sumner, J. O. Taubman, D. Teare, H. E. Thomas, O. F. Thomas, B. C. Thompson, H. R. Thomson, Sir Geoffrey S. Todd, Drs. H. J. Trenchard, F. W. A. Turnbull, M. Walton, W. F. Wheeler, A. B. White, F. L. Wollaston, W. L. Yell, D. van Zwanenberg, and the consultant staff of Brompton Hospital (registrars, R. N. Johnston and K. Citron).

Bacteriologists and Pathologists.—Drs. C. S. Anderson, D. F. Barrowcliff, R. Blowers, D. M. H. Cogman, R. T. Cooke, J. E. Craik, P. B. Crone, J. C. Dick, Professor A. W. Downie, Drs. J. M. Dunbar, W. J. Godden, T. E. W. Goodier, W. I. Gordon, J. Harper, J. F. Heggie, E. D. Hoare, Captain C. H. Jones, Drs. E. R. Jones, P. Kidd, M. Laidlaw, G. Laws, J. T. A. Lloyd, A. Macdonald, J. Marks, P. H. Martin, A. Messer, D. A. Mitchison, Squadron-Leader A. D. Moore, Captain H. D. S. Morgan, Drs. E. Nassau, J. W. Nicholas, W. H. A. Picton, R. Pilsworth, Squadron-Leader J. S. Porterfield, Drs. A. I. D. Prentice, I. A. Purdie, K. Rafinski, R. W. Riddell, J. M. Robertson, B. R. Sandiford, F. E. T. Scott, A. G. Signy, T. Skeoch, J. Smith, P. J. Taylor, W. K. Taylor, A. T. Wallace, R. F. Welch, W. Whitelaw. The bacteriologists and pathologists formed a laboratory subcommittee under the chairmanship of Professor R. Cruickshank.

Dr. E. H. Bailey, Southern Group Laboratory, supplied culture medium where desired. Dr. D. A. Mitchison's laboratory, Postgraduate Medical School of London, served as reference laboratory for drug-resistance tests.

The above cannot be a comprehensive list of all the doctors who contributed to the results reported here, nor has it been possible to name the many laboratory technicians who did detailed and valuable work. The Tuberculosis Chemotherapy Trials Committee expresses its thanks to all members of hospital staffs who assisted in the investigation.

The Research Committee of the Tuberculosis Society of Scotland was of considerable assistance in initiating the trial in Scotland. The Edinburgh team was in receipt of a research grant from the Royal Victoria Hospital Tuberculosis Trust.

REFERENCES

Bignall, J. R., Clegg, J. W., Crofton, J. W., Smith, B. J. D., Holt, H. D., Mitchison, D. A., and Armitage, P. (1950). *British Medical Journal*, **1**, 1224.
Ford, R. M. (1953). *Med. J. Aust.*, **2**, 366.
Howlett, K. S., jun., O'Connor, J. B., Sadusk, J. F., jun., Swift, W. E., jun., and Beardsley, F. A. (1949). *Amer. Rev. Tuberc.*, **59**, 402.
Joiner, C. L., MacLean, K. S., Carroll, J. D., Marsh, K., Collard, P., and Knox, R. (1954). *Lancet*, **2**, 663.
Lotte, A., and Poussier, J. (1953). *Rev. Tuberc.*, **17**, 1.
Medical Research Council (1948). *British Medical Journal*, **2**, 769.
—— (1952). Ibid., **2**, 735.
—— (1953a). Ibid., **1**, 521.
—— (1953b). *Lancet*, **2**, 213.
—— (1953c). *British Medical Journal*, **2**, 1005.
—— (1954). *Thorax*, **9**, 254.
Mount, F. W., and Ferebee, S. H. (1954). *Amer. Rev. Tuberc.*, **70**, 521.
—— Jenkins, B. E., and Ferebee, S. H. (1953). Ibid., **68**, 264.
Pitts, F. W., Tempel, C. W., Miller, F. L., Sands, J. H., Fitzpatrick, M. J., and Weiser, O. (1953). *J. Amer. med. Ass.*, **152**, 886.
Riches, H. R. C. (1954). *Brit. J. Tuberc.*, **48**, 298.
Thomas, O. F., Borthwick, W. M., Horne, N. W., and Crofton, J. W. (1954). *Lancet*, **1**, 1308.
Thoren, M., and Hinshaw, H. C. (1952). *Stanford med. Bull.*, **10**, 316.
Tucker, W. B. (1949). Minutes of the Eighth Streptomycin Conference held on November 10 to 13, Atlanta, Georgia, p. 254. Veterans Administration, Washington.
U.S. Public Health Service (1953). *Amer. Rev. Tuberc.*, **67**, 553.
U.S. Veterans Administration (1953). Transactions of the Twelfth Conference on the Chemotherapy of Tuberculosis, held on February 9 to 12, 1953, Atlanta, Georgia. Veterans Administration, Atlanta and Washington.
—— (1954). Transactions of the Thirteenth Conference on the Chemotherapy of Tuberculosis, held on February 8 to 11, 1954, St. Louis, Missouri. Veterans Administration, St. Louis and Washington.

RESULTS OF SURGICAL TREATMENT OF CARCINOMA OF THE LUNG*

BY

T. HOLMES SELLORS, D.M., M.Ch., F.R.C.S.

Thoracic Surgeon, Middlesex, London Chest, and Harefield Hospitals

In the treatment of cancer of the lung it is generally accepted that surgery alone offers any real hope of success. Up to the present time radiotherapy has played a part that is largely palliative, and the experiences gained by the combined use of radiotherapy and surgery are too limited to be of value. There are now large enough numbers of surgically treated cases on which a rough estimate of long-term results can be based, and in this article an analysis of personal cases operated on between the years 1940 and 1950 is made. The follow-up was carried out up to the end of 1953, which gives a five-year survival figure for cases operated on prior to 1948 and three-year survival figures for those treated in the subsequent two years.

Excision of a tumour of the lung is a practicable proposition so long as the mass can be actually removed and so long as the patient can sustain the inevitable loss of lung tissue. Pneumonectomy is regarded as the standard operation in the treatment of pulmonary cancer, though a more limited resection in the form of lobectomy can be carried out in certain circumstances. Improvements in all branches of thoracic medicine and surgery have been responsible for making lung resection a relatively safe technical procedure and in reducing the post-operative mortality and complications to reasonable limits. The lapse of time has now been long enough to permit evaluation of the results of operation.

Incidence

The steady annual ascent of the recorded death rate in relation to carcinoma of the lung is indicated by the Registrar-General's figures given in Table I, and, even allowing for a much greater awareness of the disease and for

*Based on a paper given at the Sectional Meeting of the American College of Surgeons, London, May, 1954.