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

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

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

Summary

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

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

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

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

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

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

CHEMOTHERAPY OF PULMONARY TUBERCULOSIS IN YOUNG ADULTS

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

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

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

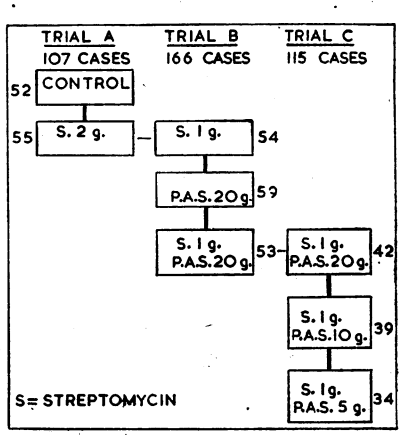

FIG. 1.—Diagram showing groups involved in the three trials.

made according to a plan previously agreed by all concerned; and, finally, the results of each trial were analysed by the Tuberculosis Research Unit of the Medical Research Council.

The groups involved in the three trials are shown in Fig. 1. There were 107 cases in Trial A, 166 in Trial B, 115 in Trial C: a total of 388 cases. An important feature of each study was that the groups on different treatments were observed concurrently. On the other hand, although the three trials took place at different points of time, a comparison between the non-concurrent groups is justifiable, since the methods of study were so similar and the type of case, as defined, remained the same. Also a link between the successive trials was deliberately introduced: Trial A and Trial B each had a group treated with streptomycin only (though in the first the daily dose was 2 g. and in the second 1 g.); Trials B and C each had a group treated with streptomycin, 1 g., and P.A.S., 20 g., daily. This "overlap" of a similarly treated group from one trial to the next should reveal whether it is fair to make comparisons between differently treated patients in the different trials.

Larger numbers are made available by bringing the three trials together. The main objects of this analysis are therefore: (1) to compare the clinical results of the different treatments employed in the three trials; (2) to analyse the effect of different treatments on streptomycin sensitivity; and (3) to assess the clinical significance of streptomycin resistance.

Comparability of Cases in the Three Trials

In Table I are given data, for each of the three trials, concerning the condition of patients before treatment started. The results are shown diagrammatically in Fig. 2. The analysis shows that the groups are very similar, though there is a suggestion that the cases admitted were somewhat less acute in successive trials. The proportion with average evening temperature of 100° F. (37.8° C.) or more in the pre-treatment observation week was 28% in Trial A, 27% in Trial B, 18% in Trial C; 7% were afebrile in Trial A, 10% in Trial B, and 17% in Trial C. The figures for sedimentation rate show a similar trend. Gross cavitation was found in 58% of patients in Trial A, compared with 52% in Trial B and 53% in Trial C. These differences are small enough to justify comparisons of results, but the question of initial condition will be referred to in respect of certain analyses.

TABLE I.—*Condition Before Treatment Started. Comparison of Patients in Three Trials*

Condition on Admission to Trial		Trial A		Trial B		Trial C	
		No.	%	No	%	No.	%
Total cases		107	100	166	100	115	100
Average evening temperature in first week	Afebrile	7	7	16	10	19	17
	Less than 90° F. (37·2° C.)	31	29	50	30	30	26
	99–99·9° F. (37·2–37·75° C.)	39	36	55	33	45	39
	100° F. + (37·8° C.+)	30	28	45	27	21	18
Sedimentation rate (Westergren)	0–10	0*	0	3*	2	2	2
	11–20	5	5	6	4	8	7
	21–50	36	34	67	41	50	43
	51+	65	61	89	54	55	48
X-ray: gross cavitation		62	58	87	52	61	53

* Examination not done in one case.

Results: Radiological Assessment

The most important measure of clinical results for each of the trials is the radiological assessment of changes between the condition just before treatment started and the condition six months later. The data for each of the eight groups are brought together in Table II. In Table III and Fig. 3 the two groups treated with streptomycin only (A2 and B1) have been combined; so also have the two groups receiving streptomycin plus 20 g. of P.A.S. (B3 and C1), and the groups receiving streptomycin plus 5 or 10 g. of P.A.S. (C2 and C3). Table II reveals, it is important to note, that in each of the pairs thus grouped together the results were strikingly similar. In other words, there is good evidence of a constancy of conditions in these three trials—ample justification, therefore, for adding groups together and for making cross-comparisons between the trials.

The results given in Table III show clearly a gradation in the frequency of improvement, from 33% for the cases treated by rest in bed only (the original comparative group) to 56% for those treated by P.A.S. alone, 71% for those treated by streptomycin alone, and, finally, nearly

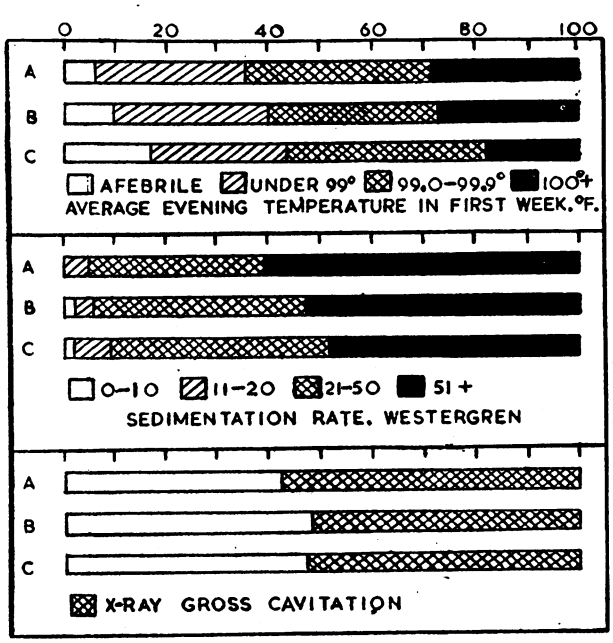

FIG. 2.—Condition before treatment started. Comparison of patients in three trials.

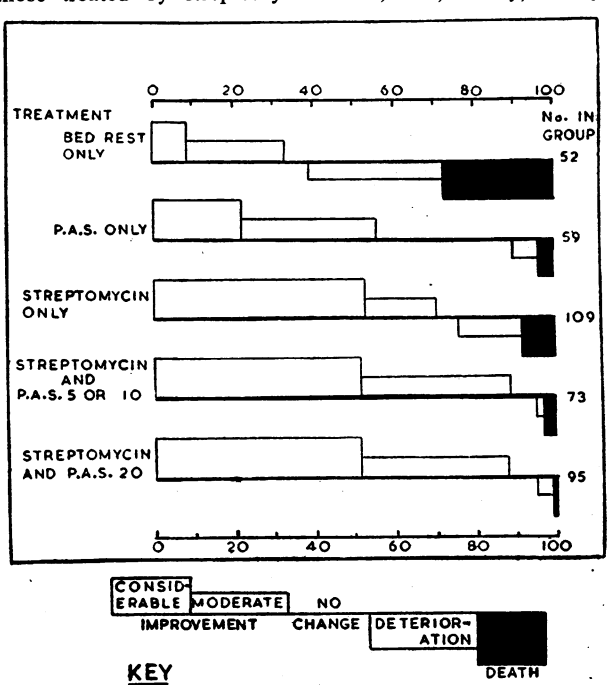

FIG. 3.—*X*-ray assessment at six months. Combined results of three trials.

TABLE II.—*Radiological Assessment at Six Months: Results in Three Trials*

Trial Group	Treatment (Daily Dose)		Total		Improvement				No Change		Deterioration		Death	
					Considerable		Moderate							
	Streptomycin	P.A.S.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
A1	Nil	Nil	52	*100*	4	*8*	13	*25*	3	*6*	18	*34*	14	*27*
A2	2 g.	Nil	55	*100*	28	*51*	10	*18*	2	*4*	11	*20*	4	*7*
B1	1 g.	Nil	54	*100*	30	*56*	10	*18*	3	*6*	6	*11*	5	*9*
B2	Nil	20 g.	59	*100*	13	*22*	20	*34*	20.	*34*	4	*7*	2	*3*
B3	1 g.	20 g.	53	*101*	27	*51*	19	*36*	3	*6*	3	*6*	1	*2*
C1	1 g.	20 g.	41*	*100*	22	*54*	14	*34*	4	*10*	1	*2*	0	*0*
C2	1 g.	10 g.	39	*100*	19	*49*	15	*38*	4	*10*	1	*3*	0	*0*
C3	1 g.	5 g.	34	*100*	19	*56*	11	*32*	2	*6*	0	*0*	2	*6*

* *X*-ray films of one patient not available.

TABLE III.—*Radiological Assessment at Six Months: Results in Three Trials*

Trial Group	Treatment (Daily Dose)		Total		Improvement				No Change		Deterioration		Death	
					Considerable		Moderate							
	Streptomycin	P.A.S.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
A1	Nil	Nil	52	*100*	4	*8*	13	*25*	3	*6*	18	*34*	14	*27*
B2	Nil	20 g.	59	*100*	13	*22*	20	*34*	20	*34*	4	*7*	2	*3*
A2 B1	1 or 2 g.	Nil	109	*100*	58	*53*	20	*18*	5	*5*	17	*16*	9	*8*
C2 C3	1 g.	5 or 10 g.	73	*101*	38	*52*	26	*36*	6	*8*	1	*2*	2	*3*
B3 C1	1 g.	20 g.	94*	*99*	49	*52*	33	*35*	7	*7*	4	*4*	1	*1*

* *X*-ray films of one patient not available.

TABLE IV.—*Radiological Assessment at Six Months Related to Clinical Condition on Entry*

Condition on Entry	Treatment	Total		Improvement				No Change		Deterioration		Death	
				Considerable		Moderate							
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Acutely febrile	S only	34	*100*	11	*32*	6	*18*	2	*6*	6	*18*	9	*26*
	S + P.A.S.	34	*100*	12	*35*	12	*35*	3	*9*	4	*12*	3	*9*
Not acutely febrile but but with gross cavitation	S only	39	*100*	18	*46*	11	*28*	3	*8*	7	*18*	0	*0*
	S + P.A.S.	65	*100*	32	*49*	26	*40*	6	*9*	1	*2*	0	*0*
Others	S only	36	*99*	29	*80*	3	*8*	0	*0*	4	*11*	0	*0*
	S + P.A.S.	68	*100*	43	*63*	21	*31*	4	*6*	0	*0*	0	*0*

S = Streptomycin.

90% for those on combined treatment with streptomycin and P.A.S.

Clearly, all groups receiving either P.A.S. or streptomycin, or both, showed results very much better than the groups treated by rest in bed alone.

All groups receiving streptomycin had similar numbers showing considerable improvement (52–53%), results very much better than for the group given P.A.S. alone (22%).

The groups treated with streptomycin and P.A.S. had significantly greater numbers improving and significantly less deteriorating than those treated with streptomycin only. Deterioration (including those with a fatal ending) occurred in only 5% of those on combined therapy, against 24% in patients on streptomycin alone. In view, however, of the indication in Table I that cases were rather less severe in the later trials than in the earlier, the comparison between groups on combined therapy and those on streptomycin alone has been related to the condition before treatment started; the data are set out in Table IV. It is clear that the differences already observed apply regardless of initial condition.

It will also be seen that among the groups on combined chemotherapy the radiological results are almost identically the same whether they received 5, 10, or 20 g. of P.A.S. (see Tables II and III).

TABLE V.—*Radiological Assessment at Six Months: Men and Women*

	Total		Improvement				No Change		Deterioration		Death	
			Considerable		Moderate							
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
All cases:												
Men ..	175*	*99*	69	*39*	51	*29*	21	*12*	18	*10*	16	*9*
Women ..	212	*100*	93	*44*	61	*29*	20	*9*	26	*12*	12	*6*
All cases on chemotherapy:												
Men ..	154*	*99*	68	*44*	45	*29*	20	*13*	13	*8*	8	*5*
Women ..	181	*100*	90	*50*	54	*30*	18	*10*	13	*7*	6	*3*

* *X*-ray films of one patient not available.

Results in Men and Women.—Of male patients, 12% were in the early group treated by rest in bed only, 17% were on P.A.S. alone, 24% on streptomycin alone, and 47% on streptomycin plus P.A.S. Of the corresponding female patients 15% were on rest in bed, 14% on P.A.S. alone, 32% on streptomycin alone, and 40% on combined therapy. These proportions are fairly similar. The results for men and women separately, for all groups, and for all groups on chemotherapy—that is, excluding the control group—are shown in Table V. The small difference in favour of the women is not statistically significant.

Results of Sputum Examination

After radiological assessment the effect of chemotherapy on bacterial content of sputum is one of the most important measures of efficacy. The results for five groups are set out in Table VI. They show the same gradation of results

TABLE VI.—*Sputum Examination: Results From Three Trials*

Treatment Group	Total Cases in Trial	Cases Sputum-Negative Throughout 3rd Month		Cases Sputum-Negative Throughout 6th Month	
		No.	%	No.	%
Rest in bed only	52	1	*2*	2	*4*
P.A.S only	59	5	*8*	4	*7*
Streptomycin only ..	109	16	*15*	17	*16*
Streptomycin +P.A.S. 5 or 10 g.	73	16	*22*	18	*25*
Streptomycin + P.A.S. 20 g.	95	27	*28*	22	*23*

as did the *x*-ray examinations, and again there is no significant difference between the groups on combined therapy but with different amounts of P.A.S.

Streptomycin Sensitivity Related to Treatment

For the purpose of the analysis of streptomycin sensitivity the results have been set out in four groups:

S2: The group in Trial A, treated with streptomycin only, 2 g. daily (55 patients).

S1: The group in Trial B, treated with streptomycin only, 1 g. daily (54 patients).

SP 5/10: Groups in Trial C, treated with streptomycin 1 g. daily plus P.A.S. 5 or 10 g. (73 patients).

SP 20: Group in Trials B and C treated with streptomycin 1 g. daily plus P.A.S. 20 g. (95 patients).

The grouped data are shown in Table VII and represented graphically in Fig. 4. In each successive month there is a clear gradation in results, from the highest percentage resistant in the S2 group to the lowest in SP 20. The differences are very striking, especially in respect of the proportion with strongly resistant strains (R.R. 100+); in the second month the proportion was 35% in the S2 group, 16% in the S1, 2% in the SP 5 or 10, and *nil* in the SP 20 group. In the fourth month it was 78% in the S2 group, 45% in the S1, 21% in the SP 5 or 10, and 4% in the SP 20.

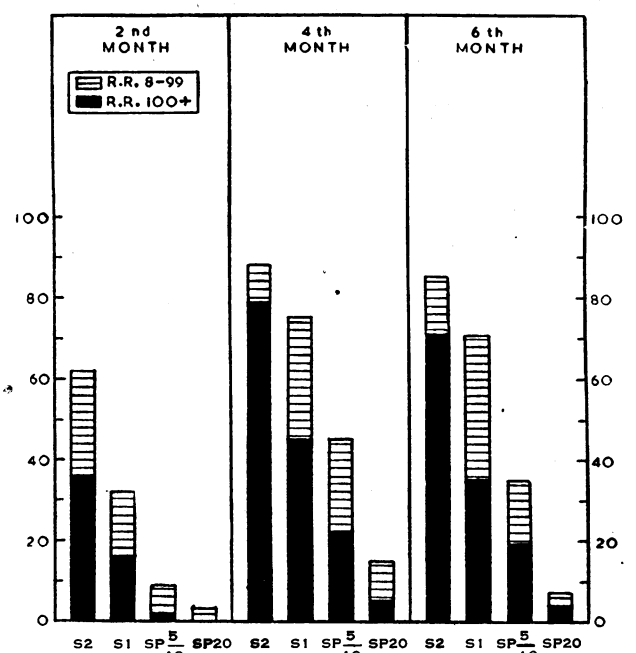

FIG. 4.—Percentage of cases with streptomycin-resistant strains in second, fourth, and sixth months after treatment started. Results from three trials. S2=Daily streptomycin 2 g. S1=Daily streptomycin 1 g. SP5/10=Daily streptomycin 1 g.+P.A.S. 5 or 10 g. SP20=Daily streptomycin 1 g.+P.A.S. 20 g.

The great difference between those receiving streptomycin only and those receiving streptomycin plus 20 g. of P.A.S. has been previously noted and discussed. So also has the difference between those receiving low doses of P.A.S. (5 or 10 g.) and those receiving 20 g. of P.A.S. daily. It is important, however, to note from the present analysis that, though the effect of 5 or 10 g. of P.A.S. is less than that of 20 g. in preventing emergence of streptomycin resistance, it is nevertheless quite considerable. Among those who received 5 or 10 g. of P.A.S. in addition to 1 g. of streptomycin

TABLE VII.—*Streptomycin Resistance in Successive Months after Start of Treatment: Results from Three Trials*

Month After Treatment Started	Treatment Group	Total Cases with Positive Cultures Examined for Sensitivity		Streptomycin-resistance Ratio* (Highest Recorded During the Month)					
				Less than 8 (Sensitive)		8–99 (Mod. Resistant)		100+ (Strongly Resistant)	
		No.	%	No.	%	No.	%	No.	%
First ..	S2	24	*100*	24	*100*	0	*0*	0	*0*
	S1	44	*100*	41	*93*	3	*7*	0	*0*
	SP 5 or 10	59	*100*	57	*97*	2	*3*	0	*0*
	SP 20	77	*100*	76	*99*	1	*1*	0	*0*
Second ..	S2	26	*100*	10	*38*	7	*27*	9	*35*
	S1	43	*99*	29	*67*	7	*16*	7	*16*
	SP 5 or 10	53	*100*	49	*92*	3	*6*	1	*2*
	SP 20	75	*100*	73	*97*	2	*3*	0	*0*
Third ..	S2	28	*101*	8	*29*	5	*18*	15	*54*
	S1	47	*100*	15	*32*	15	*32*	17	*36*
	SP 5 or 10	43	*100*	35	*81*	5	*12*	3	*7*
	SP 20	55	*100*	51	*93*	3	*5*	1	*2*
Fourth ..	S2	23	*100*	3	*13*	2	*9*	18	*78*
	S1	40	*100*	10	*25*	12	*30*	18	*45*
	SP 5 or 10	38	*100*	21	*55*	9	*24*	8	*21*
	SP 20	52	*100*	45	*86*	5	*10*	2	*4*
Fifth ..	S2	26	*101*	3	*12*	2	*8*	21	*81*
	S1	40	*100*	11	*27*	13	*33*	16	*40*
	SP 5 or 10	47	*100*	31	*66*	9	*19*	7	*15*
	SP 20	60	*100*	54	*90*	3	*5*	3	*5*
Sixth ..	S2	21	*99*	3	*14*	3	*14*	15	*71*
	S1	34	*99*	10	*29*	12	*35*	12	*35*
	SP 5 or 10	45	*101*	30	*67*	7	*16*	8	*18*
	SP 20	58	*99*	54	*93*	2	*3*	2	*3*

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

daily, the proportion producing strongly resistant strains by the fourth to sixth month was only half that in the group receiving 1 g. of streptomycin without P.A.S. It is also noteworthy that in those receiving P.A.S. resistance developed at a somewhat later date.

Another important finding was the more frequent reduction of drug resistance in cases on combined therapy than in cases on streptomycin alone. In 5 of the 12 patients (42%) receiving streptomycin plus 20 g. of P.A.S. daily from whom resistant strains were isolated, the final cultures obtained in the six months were sensitive. Corresponding figures for the SP 5 and SP 10 groups are 13 out of 30 (43%), while in the group receiving 1 g. of streptomycin daily without P.A.S. only 4 out of 39 cases (10%) had subsequently sensitive cultures.

Clinical Significance of Streptomycin Resistance

In each of the trials it was found that the clinical results were least good in the cases with streptomycin-resistant strains. It was, however, difficult to dissociate this from the fact that streptomycin resistance was observed most frequently in patients most severely ill on admission. There was some indication, nevertheless, that streptomycin resistance was of some importance in determining the course of the disease. The amalgamation of data from the three trials makes it possible now to analyse this problem more effectively.

For the analysis set out in Table VIII, the results of streptomycin-sensitivity tests have been combined for 163 cases from four groups: those receiving streptomycin only and those receiving streptomycin plus P.A.S., 5 or 10 g. The percentage with resistant strains is so low in the groups receiving 20 g. of P.A.S. that their inclusion would weight the figures excessively with those for sensitive strains.

Of the 44 patients who were acutely febrile on admission, 27, or 61%, later produced strongly resistant strains, compared with 40% of the 63 not acutely febrile but with gross cavitation, and 21% of the 56 others.

Looking first at the results for all cases it is obvious that results were worst in those who produced strongly resistant strains at any time: 16% of them died, and no deaths occurred in the others; 36% died or deteriorated, against only 2–5% of the others; 55% improved, compared with 88–95% of the others. There is little difference between those with sensitive strains and those with moderately resistant strains, though the results slightly favour the former.

To assess the effect of initial condition in relation to the sensitivity results, the cases have been divided into three groups according to clinical condition on entry, and the results then related to sensitivity tests within each of those groups.

High fever has been taken as the main indicator of a severe condition on admission. The 10 deaths that occurred were all in the group of 44 patients who were acutely febrile before treatment started. But it will be noted that these deaths were all in those 27 who produced strongly resistant strains—a fatality rate of 37%; furthermore, only 11 of the 27 in this group improved, against 13 of the 17 others. The results were less good in those with moderately resistant strains than in those remaining sensitive: three of ten in the former group showed considerable improvement, compared with six of the seven in the latter. The difference is significant.

Among patients not acutely febrile on admission, but having gross cavitation, the only deterioration observed was in those with strongly resistant strains. Improvement was seen in 60% of these, compared with 94–96% of the others. There is no difference between those remaining sensitive and those with moderately resistant strains.

Among patients who were neither acutely febrile nor had gross cavitation, again the only deterioration observed was in those with strongly resistant strains, and in this group improvement was seen in 75%, compared with 94–97% of the others. Here again there is no difference between those remaining sensitive and those with moderately resistant strains.

Summarizing this analysis, it can be said that the relatively poor results in those who became strongly drug-resistant were not due solely to their initial severe condition. Among those acutely ill at the start of treatment the results were markedly worse in those who became strongly drug-resistant than in the others. In other clinical groups also the worst results were in the group with strongly resistant strains; 9 out of 37 deteriorated, and none of the 82 others, but the difference is less great than in those acutely febrile. Moderate drug resistance appears to be of much less clinical significance than resistance at higher levels.

Discussion

The discovery of streptomycin six years ago, and later of other specific drugs for tuberculosis, has changed radically many concepts of treatment and prognosis of this disease. To evaluate these drugs and determine how they can be used most effectively has been the task of many workers since that time. A series of chemotherapy trials organized by the Medical Research Council has contributed to that end. It

TABLE VIII.—*X-ray Assessment at Six Months Related to Clinical Condition on Entry and Streptomycin Resistance. Combined Results (from Three Trials) for Patients who Received Streptomycin Alone or Streptomycin Plus 5 or 10 g. P.A.S., and for whom Sensitivity Results are Available from Specimens Taken after the First Month of Treatment*

Condition on Entry	Streptomycin-resistance Ratio*	Total		Improvement				No Change		Deterioration		Death	
				Considerable		Moderate							
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Acutely febrile (average evening temperature 100° F. (37·8° C.) or over during first week)	Less than 8	7	*100*	6	*86*	0	*0*	0	*0*	1	*14*	0	*0*
	8–99	10	*100*	3	*30*	4	*40*	1	*10*	2	*20*	0	*0*
	100+	27	*100*	5	*19*	6	*22*	2	*7*	4	*15*	10	*37*
	Total	44	*101*	14	*32*	10	*23*	3	*7*	7	*16*	10	*23*
Not acutely febrile but with gross cavitation	Less than 8	23	*100*	11	*48*	11	*48*	1	*4*	0	*0*	0	*0*
	8–99	15	*101*	7	*47*	7	*47*	1	*7*	0	*0*	0	*0*
	100+	25	*100*	11	*44*	4	*16*	4	*16*	6	*24*	0	*0*
	Total	63	*101*	29	*46*	22	*35*	6	*10*	6	*10*	0	*0*
Others	Less than 8	27	*101*	21	*78*	5	*19*	1	*4*	0	*0*	0	*0*
	8–99	17	*100*	12	*70*	4	*24*	1	*6*	0	*0*	0	*0*
	100+	12	*100*	8	*67*	1	*8*	0	*0*	3	*25*	0	*0*
	Total	56	*100*	41	*73*	10	*18*	2	*4*	3	*5*	0	*0*
All cases	Less than 8	57	*101*	38	*67*	16	*28*	2	*4*	1	*2*	0	*0*
	8–99	42	*100*	22	*52*	15	*36*	3	*7*	2	*5*	0	*0*
	100+	64	*100*	24	*38*	11	*17*	6	*9*	13	*20*	10	*16*
	Total	163	*101*	84	*52*	42	*26*	11	*7*	16	*10*	10	*6*

* Highest recorded during the 6 months.

is appropriate, at a time when claims are being made for other newly discovered drugs (Robitzek and Selikoff, 1952), to look back over the series of Medical Research Council trials and to attempt, by amalgamating the results, to define the potentialities and limitations of the two drugs investigated. Evaluation of new drugs in the future can the more profitably be set against the background of established knowledge.

The three main trials undertaken were concerned with the effect of streptomycin and then of P.A.S. in pulmonary tuberculosis. All three were based on comparison of concurrently observed treatment groups, the placing of each case in one or another treatment group having been made by random allocation. In the first trial the value of streptomycin was compared with that of treatment by bed rest alone; in the second, P.A.S. was assessed by comparing it with streptomycin alone and in combination with that drug; the third was designed to determine the smallest dose of P.A.S. which, in association with streptomycin, would delay or prevent emergence of streptomycin resistance. A well-defined form of pulmonary tuberculosis was chosen for these investigations and served throughout the trials, giving them a uniformity which has made possible the present review of the combined results. Analysis of the condition on admission of the 388 patients in these trials shows that the various treatment groups are very similar in this respect. and the overlap of similarly treated groups from each trial to the next provides further justification for considering as one whole these three investigations, which took place at different points of time.

Radiologically all groups treated with streptomycin or P.A.S., or both, fared much better than the group treated by bed rest alone. Of the groups on chemotherapy, those treated with P.A.S. alone fared least well; results were much better in all groups treated with streptomycin, and best in those receiving P.A.S. in addition to streptomycin. Among the latter, the radiological results were the same whether the daily dose was 5, 10, or 20 g. of sodium P.A.S. Similar results apply to sputum conversion in the various treatment groups. It is clear that, on this assessment alone, the best chance of getting quickly effective action with streptomycin in pulmonary tuberculosis lies in its use with P.A.S.

Analysis of the levels of drug sensitivity adds weight to these findings. Streptomycin resistance developed more rapidly and more frequently in patients receiving streptomycin alone than in those treated with streptomycin plus P.A.S. In the fourth month after the start of treatment the proportion of cases with highly resistant organisms was 78% in the group treated with 2 g. of streptomycin daily, 45% in those on 1 g. of streptomycin daily, 21% in those treated with 1 g. of streptomycin plus 5 or 10 g. of P.A.S., and only 4% in those receiving 20 g. of P.A.S. with 1 g. of streptomycin. Further, reversion to drug sensitivity was seen frequently in cases on combined therapy, but relatively rarely in those treated with streptomycin only.

Though since 1946 much information has been obtained concerning emergence of streptomycin-resistant strains—and this has generally been assumed to worsen the prognosis—assessment of the clinical significance of bacterial drug resistance has been difficult. Certainly the best results were seen in patients who did not develop resistant strains, but on the whole these patients were at the start of treatment less ill than those from whom resistant organisms were later isolated. Many patients with streptomycin-resistant strains continue nevertheless to improve—whether under the influence of continued treatment or by their own resources is not clear. It is known also that drug-resistant organisms may be excreted into the bronchi from one lesion while other lesions in the same lung harbour streptomycin-sensitive bacilli (Canetti and Rocher, 1950). Because of the many complexities it has been difficult in relatively small investigations to judge the weight of this factor in prognosis. The present analysis has made it possible to disentangle some of the elements.

The relatively unfavourable prognosis in patients with highly resistant organisms was found to be due only in part to the fact that on admission they were very acutely ill; the clinical results were better in patients equally ill but who did not develop resistant strains. The analysis shows that, regardless of the initial clinical condition, the prognosis is, on the average, adversely affected by the emergence of strongly resistant organisms; moderate drug resistance seems to be of much less significance. Similar conclusions have been reached in a statement by the American Trudeau Society (1952).

It is true that in the groups on combined therapy there was no measurable difference in clinical results between those on 20 g. of P.A.S. and those on smaller doses, though drug resistance emerged in a greater proportion of the latter. However, the results in all groups on combined therapy were so good (87–88% showing radiological improvement) that differences are unlikely to show in groups of the size available. The one death that occurred in the 95 patients on 20 g. of P.A.S. and the two deaths in the 73 patients on lower doses were all three in cases from which strongly resistant strains were isolated. In view of the outstanding results in all groups on combined chemotherapy, and of the finding that even small doses of P.A.S. reduce appreciably the risk of drug resistance (compared with streptomycin alone), it is not possible to lay down absolute recommendations on dosage. The clinician must in each case weigh the lessened risk of drug resistance when high doses of P.A.S. are used against the greater digestive discomfort these doses may produce in the patient. The best working rule is probably to continue to give the maximum dose of 20 g. of sodium P.A.S. unless it is not tolerated by the patient.

The findings reported here relate to short-term results only (it is proposed later to analyse the results in the same cases at two years after the start of treatment), but they will help, it is believed, to determine the direction of work in connexion with new antibacterial agents in tuberculosis and possibly with drugs which may affect the host's reaction to the organism (Hart, Long, and Rees, 1952). Of the need of such scientific assessment as that produced by these trials there is no doubt: after each new advance assessment becomes the more difficult since each new drug must be measured against higher standards. The analysis of the results here presented has been made possible by the uniformity of the relatively small investigations from which they were derived, and by methods of planning which, now well proved, can be rapidly set in motion for the assessment of any new drugs.

Summary

The results of three Medical Research Council trials of chemotherapy in pulmonary tuberculosis have been amalgamated to provide material for a detailed analysis. 388 patients with similar forms of acute progressive bilateral pulmonary tuberculosis have been studied in these trials: 52 were treated by rest in bed only, 109 by streptomycin alone, 59 by P.A.S. alone, 73 by streptomycin plus 5 or 10 g. of P.A.S. daily, and 95 by streptomycin plus 20 g. of P.A.S. daily.

The results at six months after the start of treatment were much better in all groups on chemotherapy than in the group on rest in bed alone. They were much better in groups receiving streptomycin than in the group having P.A.S. only, and better in groups on combined therapy than in those on streptomycin alone. There was no apparent difference between the groups having different daily doses of P.A.S. plus 1 g. of streptomycin daily. There was no difference between the results in men and those in women.

The percentage of patients developing streptomycin-resistant strains was much higher in patients treated with

streptomycin only than in those on combined therapy; among the latter it was higher in those patients for whom the daily dose of P.A.S. was 5 or 10 g. than in those receiving 20 g. daily. The clinical significance of streptomycin resistance is discussed. In patients with a similar initial condition the results were worst in those who developed high degrees of drug resistance. Moderate drug resistance seems to be of less clinical significance.

This report is based on the work of clinical investigations directed first by the Medical Research Council Streptomycin in Tuberculosis Trials Committee, and then by a Joint Subcommittee composed of members from the parent committee and from the Research Committee of the British Tuberculosis Association. In these trials a large number of clinicians and pathologists have taken part. Their names appear in the report of each trial. To them the gratitude of the medical profession is due; only by their constant adherence to a centrally devised scheme and by a most remarkable team spirit on a large scale have these investigations been possible.

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KERNICTERUS WITHOUT PREMATURITY OR BLOOD-GROUP INCOMPATIBILITY

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Blood-group incompatibility was formerly believed to be a necessary precursor of kernicterus (Wiener and Brody, 1946; Claireaux, 1950). However, Aidin, Corner, and Tovey (1950), and also Zuelzer and Mudgett (1950) established the occurrence of kernicterus in premature infants without blood-group incompatibility. Zuelzer and Mudgett (1950) described a number of cases in which serologically compatible premature babies died of kernicterus, and also eight cases in which babies with birth weights of over 5½ lb. (2.5 kg.) showed presumptive evidence that no blood-group incompatibility existed, although none were first pregnancies. In only one of these eight instances does evidence for serological normality seem conclusive, in that direct Coombs tests were negative on the infants' cells, ABO groups were compatible, and no abnormal antibody was present in the maternal serum, either before or after delivery. Aidin, Corner, and Tovey (1950), although they included one baby whose birth weight was over 5½ lb. (2.5 kg.) in their group of kernicteric infants without blood incompatibility, gave no serological data for this case.

Thus, although the occurrence of kernicterus in the absence of blood-group incompatibility seems established in premature babies; only one unequivocal instance of this lesion occurring without either blood incompatibility or prematurity has yet been published. For this reason the following case is presented in which kernicterus occurred in a first-born infant, weighing 6 lb. 6 oz. (2.9 kg.) at birth, in whom blood-group incompatibility is believed to have been excluded, so far as is possible at the present day, by serological testing.

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Case History

The patient was a first baby, born in the Obstetric Hospital at University College Hospital on July 2, 1951. The mother was a primipara aged 21. Her Wassermann reaction was negative, and there were no previous abortions or stillbirths, blood transfusions or other injections of blood or serum. The antenatal period was normal. Spontaneous labour occurred at 39 weeks and 1 day, followed by a normal vertex delivery. The first stage occupied three hours and the second stage 15 minutes. There was no foetal distress. The infant was a girl whose birth weight was 6 lb. 6 oz. (2.9 kg.). She was cyanosed at birth and remained so for several hours, but cried lustily at once and breathed normally within one minute. At the age of 3 hours the infant became restless, with an anxious facies and a high-pitched irritable cry. There was also pronounced inspiratory recession of the lower ribs with poor air entry at both bases. A diagnosis of intracranial irritation and atelectasis was made, due probably to a precipitate second stage of labour. The baby was transferred immediately to the resuscitation unit, where she was nursed in 50% oxygen and treated prophylactically with intramuscular penicillin, 100,000 units twice daily.

She remained irritable for the first 24 hours, but then her general condition improved, the cyanosis disappeared, and she began to suck. Oral feeding was started at 24 hours with expressed breast milk given three-hourly. At 36 hours jaundice first became apparent and deepened progressively for the next eight days, the spleen being just palpable from the third day onwards, when a peripheral blood count at 72 hours showed: red cells, 5,480,000; Hb, 110%; white cells, 12,800 (P. 63%, L. 27%, M. 7.5%, E. 2.5%). There were 1.5 normoblasts per 100 white cells. In view of the early onset of a deepening jaundice, with a negative direct Coombs test on the infant's cells (see Serology), a careful search was made for infection, but this revealed only a transient seropurulent umbilical discharge on the sixth day which disappeared 24 hours later but grew on culture *Bact. coli* and a penicillin-resistant *Streptococcus faecalis*. A course of oral sulphadimidine (total 4.5 g.) and chloramphenicol (total 1.7 g.) was therefore given for the next few days. The urine contained on one occasion 0.5 g. of albumin per litre, with occasional pus cells and three red blood cells per 1/6 microscopical field, with numerous epithelial and some granular casts. A transient apical systolic murmur was heard on the fifth and sixth days.

On the morning of the fifth day her general condition deteriorated rapidly with onset of head retraction and drowsiness, punctuated at intervals by athetoid movements of the limbs and occasional myoclonic twitchings. The anterior fontanelle was not full, but tone appeared to be increased in the limbs. A lumbar puncture produced only a small quantity of xanthochromic fluid, insufficient for chemical estimation, but with no excess of white blood cells or organisms in the Gram-stained centrifuged deposit. The baby became increasingly lethargic and refused to suck; intravenous fluids were given on the fifth day for 24 hours in the form of half-strength Hartmann's solution with 5% glucose. In view of the deepening jaundice, amino-acid supplements in the form of "pronutrin," 10 g., and choline chloride, 250 mg., were given daily by stomach tube, together with "becosym," 0.5 ml., and "synkavit," 10 mg. intramuscularly. By the sixth day the infant became febrile—101° F. (38.3° C.)—and was in a stage of opisthotonos and had two small generalized convulsions. All feeds had to be given by tube and were followed frequently by respiratory distress and cyanotic attacks, while large quantities of