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THE CLINICAL SIGNIFICANCE OF POSITIVE CULTURES AND OF ISONIAZID-RESISTANT TUBERCLE BACILLI DURING THE TREATMENT OF PULMONARY TUBERCULOSIS

REPORT TO THE TUBERCULOSIS CHEMOTHERAPY TRIALS COMMITTEE OF THE MEDICAL RESEARCH COUNCIL

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Within a few months of the introduction of isoniazid (isonicotinic acid hydrazide) in the treatment of pulmonary tuberculosis, reports appeared of the frequent and rapid emergence of isoniazid-resistant bacteria when the drug was used alone (Medical Research Council, 1952; Ferebee and Long, 1953; Lotte and Poussier, 1953; U.S. Veterans Administration, 1953). In view of earlier experience with streptomycin (Medical Research Council, 1948; Ferebee and Appel, 1951), this was regarded as an undesirable feature of isoniazid therapy. First it was presumed that a patient yielding resistant organisms would derive no further, or at best reduced, benefit from continued treatment with the drug. Secondly there was a risk that contacts might be infected with isoniazid-resistant organisms. In Great Britain, as a consequence, the widespread use of isoniazid alone stopped, and research was directed to the prevention of isoniazid resistance by the use of other anti-tuberculosis drugs in combination with isoniazid. Various combinations have since been shown to reduce considerably the incidence of isoniazid resistance (Medical Research Council, 1953c, 1955; Pitts, Tempel, Miller, Sands, Fitzpatrick, and Weiser, 1953; U.S. Public Health Service, 1953; U.S. Veterans Administration, 1953, 1954).

It has been suggested that bacterial resistance to isoniazid may in some patients be transitory (Ashino, 1953; Petit, 1953a and b; Ogilvie, 1954). Other data, however, show little evidence of a general reversion of resistant strains towards sensitivity over a period of at least six months after stopping treatment with isoniazid (Medical Research Council, 1954). It has also been shown that organisms which are highly resistant to isoniazid may be of low pathogenicity in some animal species (Barnett, Bushby, and Mitchison, 1953; Barry, Conalty, and Gaffney, 1953; Middlebrook and Cohn, 1953; Meissner, 1954; Mitchison, 1954), but it is not known whether this applies in man. Because the strains do not rapidly return to sensitivity and because their pathogenicity may have altered, it is important to examine the clinical progress of patients in whom isoniazid-resistant organisms have emerged.

A preliminary study of the clinical significance of isoniazid resistance was made in the first report of the Medical Research Council isoniazid trial (1952), but the bacteriological information was then far from complete. A full study over a three-month period, derived from the complete information for all patients who received isoniazid alone in that trial, is now presented. The essence of this study has been to divide the patients into groups based upon the results of cultures and sensitivity tests after two months' treatment in the trial, and to compare the clinical progress of the groups over the three-month period.

Details of the organization of the isoniazid trial were given in the first two reports (Medical Research Council, 1952, 1953a); the list of hospitals, and the names of the clinicians, bacteriologists, and pathologists on whose observations the present report is based, were given at the end of the second report.

Patients were admitted in one of three main disease groups:

GROUP 1.—Acute rapidly progressive pulmonary tuberculosis believed to be of recent origin.

GROUP 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.

GROUP 3.—Chronic forms of pulmonary tuberculosis expected to make only a limited response to streptomycin plus P.A.S.

Direct examinations of the sputum, cultures, and sensitivity tests were routinely performed on entry to the trial, and at monthly intervals thereafter, using standardized techniques (Medical Research Council, 1953b).

One series of patients, chosen at random from those who entered the trial, was allocated treatment with isoniazid alone (100 mg. twice daily). This treatment was prescribed for three months for patients in disease groups 1 and 2, and for six months for patients in group 3.

Bacteriological results for 264 of these patients were studied in an earlier report of the trial (Medical Research Council, 1953c). In the present report 30 patients had to be excluded because of incomplete information or departure from the prescribed treatment: no culture result was available at two months for 22 patients; a culture, but no sensitivity result, was available for four patients; two patients were discharged against medical advice in the third month, and two patients changed treatment during the third month because of clinical deterioration.

Only one patient received any collapse therapy during the three months; this was a pneumoperitoneum induced after 11 weeks' treatment. The patient has been retained in the analysis.

There remain 234 patients in the analysis. At the start of treatment all had organisms sensitive to isoniazid. At the end of two months, 91 of the patients had a negative culture. The other 143 were culture-positive; when divided according to the result of the sensitivity test at two months, 44 of the cultures were sensitive, 30 were doubtfully resistant, 31 were moderately resistant (cultures growing on 1 or on 5 μg. of isoniazid per ml.) and 38 were strongly resistant (cultures growing on 10 or on 50 μg. of isoniazid per ml.). It has been established that during treatment a doubtfully resistant result, using the Medical Research Council technique, is sometimes indicative of a resistant and sometimes of a sensitive strain (Medical

TABLE I

RESULTS OF CULTURES AND ISONIAZID-SENSITIVITY TESTS IN PATIENTS AFTER TWO MONTHS' TREATMENT WITH ISONIAZID ALONE ACCORDING TO INITIAL CLINICAL CONDITION

Clinical Condition at Start of Treatment	Results of Cultures						Results of Sensitivity Tests						Level of Resistance					
	Total Patients		Negative		Positive		Total Positive Cultures		Sensitive		Resistant		Total Resistant Cultures		Moderately Resistant		Strongly Resistant*	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
General condition:																		
Good	50	*100*	32	*64*	18	*36*	18	*100*	7	*39*	11	*61*	11	*100*	5	*45*	6	*55*
Fair	116	*100*	38	*33*	78	*67*	78	*100*	31	*40*	47	*60*	47	*100*	27	*57*	20	*43*
Poor	68	*100*	21	*31*	47	*69*	47	*100*	20	*43*	27	*57*	27	*100*	15	*56*	12	*44*
Extent of cavitation†:																		
Nil	45	*100*	27	*60*	18	*40*	18	*100*	14	*78*	4	*22*	4	*100*	3	*43*	1	*57*
1-plus	57	*100*	32	*56*	25	*44*	25	*100*	15	*60*	10	*40*	10		3		7	
2- „	89	*100*	27	*30*	62	*70*	62	*100*	24	*39*	38	*61*	38	*100*	25	*66*	13	*34*
3- „	43	*100*	5	*12*	38	*88*	38	*100*	5	*13*	33	*87*	33	*100*	16	*48*	17	*52*
Erythrocyte sedimentation rate (Westergren 200 mm. reading at 1 hour):																		
0–10 mm.	17	*100*	12	*71*	5	*29*	5	*100*	3	*52*	2	*48*	2	*100*	1	*40*	1	*60*
11–20 „	35	*100*	19	*54*	16	*46*	16		8		8		8		3		5	
21–50 „	89	*100*	38	*43*	51	*57*	51	*100*	15	*29*	36	*71*	36	*100*	18	*50*	18	*50*
51 mm. or more	93	*100*	22	*24*	71	*76*	71	*100*	32	*45*	39	*55*	39	*100*	25	*64*	14	*36*
Average evening temperature in week of preliminary investigation‡:																		
Afebrile	101	*100*	47	*47*	54	*53*	54	*100*	19	*35*	35	*65*	35	*100*	16	*46*	19	*54*
Under 99° F.	72	*100*	27	*38*	45	*62*	45	*100*	21	*47*	24	*53*	24	*100*	15	*62*	9	*38*
99–99·9° F.	38	*100*	11	*29*	27	*71*	27	*100*	13	*48*	14	*52*	14	*100*	8	*57*	6	*43*
100° F. or more	23	*100*	6	*26*	17	*74*	17	*100*	5	*29*	12	*71*	12	*100*	8	*67*	4	*33*
Disease group (see text):																		
1	87	*100*	31	*36*	56	*64*	56	*100*	24	*43*	32	*57*	32	*100*	18	*56*	14	*44*
2	106	*100*	46	*43*	60	*57*	60	*100*	26	*43*	34	*57*	34	*100*	17	*50*	17	*50*
3	41	*100*	14	*34*	27	*66*	27	*100*	8	*30*	19	*70*	19	*100*	12	*63*	7	*37*
Total	234	*100*	91	*39*	143	*61*	143	*100*	58	*41*	85	*59*	85	*100*	47	*55*	38	*45*

* Strongly resistant: Growth of 20 or more colonies on 10 or on 50 μg. isoniazid per ml. (Medical Research Council, 1953b).
† Assessment on a single full-plate chest radiograph taken before treatment started. Tomograms were not taken into account.
‡ A patient was considered afebrile if every evening temperature in the pre-treatment week was below 99° F. (37·2° C.).

Research Council, 1953b). On the basis of later observations, at three and, if necessary, four months (see Appendix), the 30 doubtfully resistant results at two months were divided into 14 which were " probably sensitive " and 16 which were " probably resistant," and the patients with these strains were added to the sensitive and moderately resistant groups respectively. There is no evidence that the division of the doubtfully resistant group in this way has altered the conclusions to be drawn from the ensuing analysis. As a result of this re-grouping the analysis is based upon 91 patients with negative cultures, 58 with sensitive strains, 47 with moderately resistant strains, and 38 with strongly resistant strains at two months.

Bacteriological Results at the End of Two Months Related to Clinical Condition at the Start of Treatment

For two reasons it was necessary to study the results of the cultures and sensitivity tests at the end of two months in relation to the clinical condition of the patients at the start of treatment. First, to discover which factors in the initial clinical condition might influence the bacteriological course of the disease when treated with isoniazid alone. Secondly, to make any necessary allowances for these initial clinical characteristics in analysing the three-month clinical progress of patients in the various culture and sensitivity groups. The results are given in Table I and are arranged in such a way that it is possible to study successively, in relation to initial clinical condition, the frequency of negative cultures, the development of isoniazid resistance among those who remained culture-positive, and finally the level of isoniazid resistance.

It can be seen, first, that patients with favourable clinical characteristics at the start of treatment were more frequently culture-negative at the end of two months than those with unfavourable clinical findings. For example, 64% of the 50 patients in good general condition on admission were culture-negative at two months, compared with 31% of the 68 in poor general condition; similarly, 60% of 45 patients with no cavitation on admission were culture-negative at two months, compared with only 12% of 43 patients with 3-plus cavitation. The culture results were also related to the erythrocyte sedimentation rate and, to a less extent, to the average evening temperature at the start of treatment. On the other hand they were apparently unrelated to the acuteness or chronicity of the disease, as indicated by the disease group.

Secondly, when the patients with positive cultures were divided into those with sensitive and those with resistant organisms at two months, little or no association was found between the emergence of resistant organisms and the initial clinical observations, except in respect of cavitation. Whereas only 22% of positive cultures from 18 patients without cavitation on admission were resistant at two months, the proportion rose to 87% for the 38 patients with 3-plus cavitation. Again it should be noted that the type of disease was not an important factor. At two months, 57% of 56 positive cultures from patients in disease group 1 (acute disease) were resistant, compared with 57% of 60 cultures from patients in group 2 (acute and chronic disease) and 70% of 27 cultures from patients in group 3 (chronic disease). The differences between these percentages are not statistically significant.

Finally, when the patients with resistant strains at two months were divided into those with moderately and those with strongly resistant strains, no important association was apparent between any of the initial clinical characteristics and the level of resistance. There was, if anything, a slight tendency for the strongly resistant strains to emerge more frequently in patients with favourable clinical characteristics at the start of treatment.

Thus the culture results at two months were related to all the initial clinical factors studied, except for the disease group; patients with favourable clinical signs more frequently became culture-negative. On the other hand, among patients who had positive cultures at two months, isoniazid-resistant organisms emerged more readily in those with extensive cavitation initially than in those with little or no cavitation; but the other clinical factors studied were unimportant. For this reason, the clinical progress of patients with sensitive and resistant organisms cannot be validly compared unless the patients are first grouped according to extent of initial cavitation, and this has been done below.

Since, as with streptomycin (Steenken, 1949), the size of the bacterial population may be relevant to the emergence of isoniazid-resistant strains, it would have been desirable, in addition, to investigate the bacteriological results at the end of two months in relation to the bacterial content of the sputum at the start of treatment. This was not possible because the pre-treatment bacteriological result which was submitted for each patient was usually the most positive result of a series of tests and so did not indicate the average bacterial content of the sputum. It may be, however, that the size of

the bacterial population is related to the extent of initial cavitation, in which case it will have been in part allowed for in the following study of clinical progress.

Radiographic Assessments in the Three-month Period Related to Bacteriological Results at the End of Two Months

In investigating clinical progress at the end of three months' treatment with isoniazid alone, changes in radiographic appearances, sedimentation rate, temperature, and bacterial content of the sputum have all been studied. The major index of progress which has been adopted is the independent radiographic assessment. This was made by a radiologist who had no knowledge of the bacteriological status of the patients after the start of treatment; although he knew that all the trial patients had received chemotherapy, he did not know which had received isoniazid alone. Table II presents the assessments of radiographic change in the three-month period, related both to the extent of cavitation at the start of treatment and to the bacteriological findings at the end of two months. The table is arranged in such a way that it is possible to compare successively the radiographic progress of patients with negative and with positive cultures, of those with sensitive and with resistant organisms, and finally of those with moderately and with strongly resistant organisms.

Comparison of Culture-negative and Culture-positive Patients.—For each category of cavitation, the patients who had a negative culture at two months fared substantially better than those who had a positive culture. For example, 93% of the 27 culture-negative patients with 2-plus cavitation had improved radiographically compared with 48% of the 62 who were culture-positive. When allowance is made (by the statistical procedure of indirect standardization) for differences in the extent of initial cavitation of patients in the various bacteriological groups, the standardized percentage of all patients with negative cultures who improved radiographically was 75%, compared with 50% for those with positive cultures. The corresponding figures for patients who deteriorated were 2% for the negative group and 8% for the positive group.

Table II

CHANGES IN RADIOGRAPHIC APPEARANCES IN THE THREE-MONTH PERIOD RELATED TO THE EXTENT OF CAVITATION AT START OF TREATMENT AND THE RESULTS OF CULTURES AND ISONIAZID-SENSITIVITY TESTS AT THE END OF TWO MONTHS

Extent of Initial Cavitation	Bacteriological Result at Two Months	Total	Improvement			No Change	Deterioration			Percentage Improved	Percentage Deteriorated
			3-plus	2-plus	1-plus		1-minus	2-minus	3-minus		
3-plus ..	Negative	5	0	0	2	3	0	0	0	*40*	*0*
	Positive	38	0	0	9	20	7	1	1	*24*	*24*
2- ,, ..	Negative	27	2	15	8	1	1	0	0	*93*	*4*
	Positive	62	1	8	21	29	3	0	0	*48*	*5*
1- ,, ..	Negative	32	3	13	11	5	0	0	0	*84*	*0*
	Positive	25	1	4	13	6	0	1	0	*72*	*4*
Nil ..	Negative	27	4	10	8	5	0	0	0	*81*	*0*
	Positive	18	0	5	4	8	1	0	0	*50*	*6*
All degrees	Negative	91	9	38	29	14	1	0	0	*75**	*2**
	Positive	143	2	17	47	63	11	2	1	*50**	*8**
3-plus ..	Sensitive	5	0	0	1	4	0	0	0	*20*	*0*
	Resistant	33	0	0	8	16	7	1	1	*24*	*27*
2- ,, ..	Sensitive	24	1	4	9	10	0	0	0	*58*	*0*
	Resistant	38	0	4	12	19	3	0	0	*42*	*8*
1- ,, ..	Sensitive	15	0	3	8	4	0	0	0	*73*	*0*
	Resistant	10	1	1	5	2	0	1	0	*70*	*10*
Nil ..	Sensitive	14	0	4	4	6	0	0	0	*57*	*0*
	Resistant	4	0	1	0	2	1	0	0	*25*	*25*
All degrees	Sensitive	58	1	11	22	24	0	0	0	*55**	*0**
	Resistant	85	1	6	25	39	11	2	1	*46**	*10**
3-plus ..	Moderately resistant	16	0	0	4	8	4	0	0	*25*	*25*
	Strongly ,,	17	0	0	4	8	3	1	1†	*24*	*29*
2- ,, ..	Moderately ,,	25	0	3	8	12	2	0	0	*44*	*8*
	Strongly ,,	13	0	1	4	7	1	0	0	*38*	*8*
1- ,, ..	Moderately ,,	3	1	1	0	1	0	0	0	*67*	*0*
	Strongly ,,	7	0	0	5	1	0	1	0	*71*	*14*
Nil ..	Moderately ,,	3	0	1	0	1	1	0	0	*33*	*33*
	Strongly ,,	1	0	0	0	1	0	0	0	*0*	*0*
All degrees	Moderately ,,	47	1	5	12	22	7	0	0	*46**	*10**
	Strongly ,,	38	0	1	13	17	4	2	1	*46**	*10**

* Standardized for differences in extent of initial cavitation between patients in the various bacteriological categories.
† This patient had 2-minus deterioration at two months, was too ill to have a radiograph at three months, and died the following day.

Since only the effect of initial cavitation was taken into consideration in this analysis, it was possible that this difference in radiographic progress between patients with a negative and those with a positive culture at two months might be in part due to the lesser initial severity of the disease in the negative group in respects other than cavitation. A further analysis was therefore undertaken, standardizing not only for initial cavitation but also for the general condition, the sedimentation rate, and the average evening temperature at the start of treatment. The standardized percentages of patients with radiographic improvement were practically unaltered, being 74% for the negative group and 50% for the positive group.

COMPARISON OF PATIENTS WITH SENSITIVE AND WITH RESISTANT CULTURES.—Radiographic improvement was shown by the positive-sensitive group more often than by the positive-resistant group. For example, of the 24 patients in the sensitive group who had 2-plus cavitation, 58% improved compared with 42% of the 38 patients in the resistant group. The standardized percentages of patients who showed radiographic improvement were 55% for the sensitive group as a whole compared with 46% for the resistant group. The corresponding figures for patients who deteriorated were 0% for the sensitive group and 10% for the resistant group. The differences just attain statistical significance at the 5% level. The patients with resistant cultures have thus fared worse on the average than those with sensitive cultures, but the contrast is not so great as that between the progress of the positive and the negative groups of patients.

COMPARISON OF PATIENTS WITH MODERATELY AND WITH STRONGLY RESISTANT CULTURES.—Little difference can be observed between the radiographic progress of patients with moderately and with strongly resistant strains. In each group the standardized percentage of patients who improved was 46% and of those who deteriorated was 10% (Table II). On the other hand there is a slight suggestion in each cavitation category that substantial (2-plus or 3-plus) improvement was more frequent in the moderately resistant group, and substantial deterioration more frequent in the strongly resistant group.

To summarize, this study of radiographic changes has demonstrated differences between the three-month progress of the patients when grouped according to the bacteriological results at the end of two months. Thus, the standardized percentages showing radiographic improvement were 75% for the negative group, 55% for the positive-sensitive group, and 46% for the positive-resistant group. The negative group, in other words, fared substantially better than the patients with positive cultures, whether the strains were sensitive or resistant. To appraise the clinical significance of the emergence of isoniazid-resistant organisms a detailed comparison is made in the following sections of the clinical progress of the patients in the positive-sensitive and positive-resistant groups. Although it is probable that the negative group consists largely of patients with sensitive strains, this group cannot fairly be included in the comparison because of the likelihood that the patients will have smaller bacterial populations, on the average, than the patients with positive cultures at two months. It is relevant to note that of the patients with negative cultures at two months (26%) yielded a positive result on direct examination at one month, and only 9% at three months, compared with 61% and 54% respectively of those with positive cultures at two months.

TIMING OF RADIOGRAPHIC CHANGES IN PATIENTS WITH SENSITIVE AND WITH RESISTANT CULTURES.—When the independent radiographic assessment for the three-month period was undertaken, three radiographs were used, namely on entry to the trial, at the end of two, and at the end of three months. An assessment was first made over the whole three months and was then apportioned between the first two months and the third month. It is thus possible to investigate when during the three-month period the radiographic changes occurred in the resistant and in the sensitive group of patients. The results of this investigation are presented in Table III, which shows that in each period radiographic improvement occurred less frequently in the resistant group of patients. For example, of 24 patients in the sensitive group with 2-plus cavitation initially, 58% improved in the first two months and 42% in the third month. The corresponding figures for the 38 patients in the resistant group were 34% and 26%. This pattern is confirmed by the standardized percentages showing improvement, which are in each period less for the resistant than for the sensitive group. In each period, too, a larger proportion of patients deteriorated in the resistant than in the sensitive group. It will be observed, further, that in the third month, when a greater disadvantage might have been expected from the development of isoniazid resistance, the contrast between the resistant and sensitive groups was very similar to that in the first two months. It may be concluded that the disadvantage to the resistant group of patients applied in each period separately.

Since it has been stated that patients frequently deteriorate at the time of, or soon after, the detection

TABLE III

CHANGES IN RADIOGRAPHIC APPEARANCES IN THE THREE-MONTH PERIOD APPORTIONED TO THE FIRST TWO MONTHS AND TO THE THIRD MONTH RELATED TO EXTENT OF CAVITATION AT START OF TREATMENT AND RESULTS OF ISONIAZID-SENSITIVITY TESTS AT THE END OF TWO MONTHS

Extent of Initial Cavitation	Bacteriological Result at Two Months	Total	Changes in First Two Months						Changes in Third Month					
			Improvement		No Change		Deterioration		Improvement		No Change		Deterioration	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
3-plus ..	Sensitive	5	1	*20*	4	*80*	0	*0*	1	*20*	4	*80*	0	*0*
	Resistant	33	6	*18*	19	*58*	8	*24*	4	*12*	26	*79*	3	*9*
2- ,, ..	Sensitive	24	14	*58*	8	*33*	2	*8*	10	*42*	13	*54*	1	*4*
	Resistant	38	13	*34*	23	*61*	2	*5*	10	*26*	25	*66*	3	*8*
1- ,, ..	Sensitive	15	6	*40*	8	*53*	1	*7*	10	*67*	5	*33*	0	*0*
	Resistant	10	6	*60*	3	*30*	1	*10*	5	*50*	5	*50*	0	*0*
None ..	Sensitive	14	7	*50*	7	*50*	0	*0*	7	*50*	7	*50*	0	*0*
	Resistant	4	0	*0*	4	*100*	0	*0*	1	*25*	2	*50*	1	*25*
All degrees	Sensitive	58	28	*43**	27	*49**	3	*8**	28	*40**	29	*58**	1	*2**
	Resistant	85	25	*32**	49	*57**	11	*11**	20	*28**	58	*65**	7	*7**

* Standardized for differences in extent of initial cavitation between patients in the resistant and sensitive groups.

TABLE IV

CHANGES IN RADIOGRAPHIC APPEARANCES IN THREE-MONTH PERIOD RELATED TO RESULTS OF CULTURES AND ISONIAZID-SENSITIVITY TESTS AT END OF TWO MONTHS FOR THOSE PATIENTS WHO DETERIORATED RADIOGRAPHICALLY IN FIRST TWO MONTHS, IN THIRD MONTH, OR IN BOTH PERIODS

	Total	Deterioration 0–2 m. Deterioration 2–3 m.	Deterioration 0–2 m. No Change 2–3 m.	Deterioration 0–2 m. Improvement 2–3 m.	No change 0–2 m. Deterioration 2–3 m.	Improvement 0–2 m. Deterioration 2–3 m.
Negative ..	3	0	1	0	0	2
Sensitive ..	4	0	0	3	0	1
Resistant ..	16	2	7	2	4	1

TABLE V

CHANGES IN ERYTHROCYTE SEDIMENTATION RATE IN THREE-MONTH PERIOD RELATED TO EXTENT OF CAVITATION AT START OF TREATMENT AND RESULTS OF CULTURES AND ISONIAZID-SENSITIVITY TESTS AT END OF TWO MONTHS

Extent of Initial Cavitation	Bacteriological Result at Two Months	Sedimentation Rate in Pre-treatment Week						All Cases with Initial Sedimentation Rate of 21 or More		
		11–20 mm.		21–50 mm.		51 mm. or More			E.S.R. of 0–10 mm. at 3 Months	
		Total	No. with E.S.R. 0–10 at 3 Months	Total	No. with E.S.R. 0–10 at 3 Months	Total	No. with E.S.R. 0–10 at 3 Months	Total	No.	%
3-plus ..	Negative	1	1	1	0	3	0	4	0	*0*
	Positive	2	1	13	1	22	0	35	1	*3*
2- ,, ..	Negative	4	4	14	8	9	2	23	10	*43*
	Positive	6	0	21	6	30	3	51	9	*18*
1- ,, ..	Negative	8	5	16	8	4	2	20	10	*50*
	Positive	3	2	10	3	11	2	21	5	*24*
Nil ..	Negative	6	4	7	4	6	2	13	6	*46*
	Positive	5	2	6	2	7	3	13	5	*38*
All degrees	Negative	19	14	38	20	22	6	60	26	*35**
	Positive	16	5	50	12	70	8	120	20	*19**
3-plus ..	Sensitive	1	0	1	0	3	0	4	0	*0*
	Resistant	1	1	12	1	19	0	31	1	*3*
2- ,, ..	Sensitive	3	0	4	1	14	2	18	3	*17*
	Resistant	3	0	17	5	16	1	33	6	*18*
1- ,, ..	Sensitive	1	0	6	2	8	2	14	4	*29*
	Resistant	2	2	4	1	3	0	7	1	*14*
Nil ..	Sensitive	3	2	4	2	7	3	11	5	*45*
	Resistant	2	0	2	0	0	0	2	0	*0*
All degrees	Sensitive	8	2	15	5	32	7	47	12	*21**
	Resistant	8	3	35	7	38	1	73	8	*16**
,,	Moderately resistant	3	0	18	3	25	1	43	4	*13**
	Strongly ,,	5	3	17	4	13	0	30	4	*22**

* Standardized for differences in extent of initial cavitation between patients in the various sensitivity categories.

of isoniazid resistance (Joiner, MacLean, Pritchard, Anderson, Collard, King, and Knox, 1952; Coates, Meade, Steenken, Wolinsky, and Brinkman, 1953; Gernez-Rieux, 1953), a more detailed study has been made of the records of all the 23 patients who showed radiographic deterioration in the first two months, in the third month, or in both periods; three were culture-negative at two months, four were in the sensitive group, and 16 were in the resistant group (Table IV). Of the 11 patients in the resistant group who showed radiographic deterioration in the first two months, two deteriorated further in the third month, but seven showed no change and two actually improved. The remaining five of the 16 patients in the resistant group deteriorated only in the third month; however, so did three of the seven patients with sensitive or negative results at two months. These figures do not show that the deteriorations in the resistant group occurred principally in the third month, as might have been expected if deterioration was the direct result of a loss of chemotherapeutic effectiveness due to the development of bacterial resistance. Bearing in mind that the first period is twice as long as the second, the deteriorations—11 against 7—appear to be fairly evenly divided between them.

Although there was no independent assessment of radiographic change in the first month, the monthly progress reports from the clinicians in charge of the patients provide further information on the timing of the deteriorations. Among the 11 patients in the resistant group for whom deterioration was reported by the assessor at two months, radiographic deterioration was reported by the clinician in the first month for four, in the second month for one, and in both months for two patients. The timing of these changes also provides no evidence that radiographic deterioration was a consequence of the emergence of isoniazid resistance.

In summary, this study of the radiographic assessments during the three-month period indicates that, when allowance is made for the extent of cavitation present at the start of treatment, the patients who yielded resistant organisms at the end of two months had not responded so well as those with sensitive organisms. There is, however, no evidence from the timing of the radiographic changes that the emergence of isoniazid-resistant strains was responsible for the difference. It is possible that in the resistant group the less satisfactory radiographic progress and the development of isoniazid resistance are both characteristics of patients with a particular host response or type of disease, perhaps associated with a large bacterial population.

Changes in Sedimentation Rate and in Temperature in the Three-month Period Related to Bacteriological Results at the End of Two Months

The changes in the sedimentation rate during the three months of isoniazid therapy were also examined according to the extent of cavitation at the start of treatment and the bacteriological findings at the end of two months. The results are summarized in Table V. Among patients with a sedimentation rate of 21 mm. or more initially, the standardized percentages with a normal sedimentation rate (0–10 mm.) at the end of three months were 35% for the negative and 19% for the positive group, showing a substantial, and statistically significant, benefit to the negative group. (When these percentages were standardized in addition for the general condition, the sedimentation rate and the average evening temperature at the start of treatment, they were essentially unaltered, being 32% and 20% respectively.) In contrast there was only slight evidence that the patients with sensitive cultures at two months had responded better than those with resistant cultures, the percentages being 21% and 16% respectively. The unimportance of this difference is emphasized by the results for the patients with strongly resistant organisms, who showed as favourable a response (22%) as the sensitive group (21%). Study of the few patients in whom the sedimentation rate had risen by the end of three months, and a detailed investigation of the changes month by month, showed no evidence that the development of bacterial resistance influenced the sedimentation rate.

Corresponding studies of temperature offered no evidence of a relation between the development of bacterial resistance and temperature response.

Bacterial Content of Sputum in the Three-month Period Related to Results of Sensitivity Tests at the End of Two Months

A further study of the progress of the groups of patients with sensitive and with resistant strains at the end of two months was made by investigating the bacterial content of the sputum at one, two, and three months. The results after three months are shown in Table VI. The proportion of results which were positive on direct examination has been used to give an approximate indication of the numbers of tubercle bacilli being excreted by a group of patients. Considering the standardized percentages, 27% of the patients with sensitive strains at two months had a positive result on direct examination at three months, compared with 65%

TABLE VI

PRESENCE OF TUBERCLE BACILLI AT END OF THREE MONTHS RELATED TO EXTENT OF CAVITATION AT START OF TREATMENT AND RESULTS OF ISONIAZID-SENSITIVITY TESTS AT END OF TWO MONTHS

Extent of Initial Cavitation	Bacteriological Result at Two Months	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	Percentage "Positive" or "Scanty Positive" on Direct Examination
3-plus ..	Sensitive	4	2	1	1	0	*75*
	Resistant	31	21	5	5	0	*84*
2- ,, ..	Sensitive	24	3	2	9	10	*21*
	Resistant	37	21	5	9	2	*70*
1- ,, ..	Sensitive	15	2	0	7	6	*13*
	Resistant	10	5	2	1	2	*70*
Nil ..	Sensitive	14	2	2	3	7	*29*
	Resistant	4	1	1	1	1	*50*
All degrees	Sensitive	57	9	5	20	23	*27‡*
	Resistant	82	48	13	16	5	*65‡*
,,	Moderately resistant	46	28	5	10	3	*64‡*
	Strongly ,,	36	20	8	6	2	*66‡*

* Even if culture-negative.
† Defined as follows: only a few clumps of acid-fast bacilli found after five minutes' search.
‡ Standardized for differences in extent of initial cavitation between patients in the various sensitivity categories.

of those with resistant strains. Thus the bacteriological responses of the sensitive and resistant groups differed substantially at the end of three months' treatment, the difference being apparent for each degree of initial cavitation. It will be noted, however, that the responses of the patients with moderately and with strongly resistant strains were very similar.

Because of these differences between the sensitive and resistant groups at three months, it was important to undertake corresponding investigations of the bacterial content of the sputum at one month and at two months to see when the difference emerged. (It was not possible to compare the findings during treatment with those at the start, because the pre-treatment bacteriological result which was submitted for each patient was usually the most positive result from a series of tests, and so was not representative.) The results at one, two, and three months are summarized in the upper part of Table VII. In the sensitive group, the standardized percentages of patients with a positive direct examination were 61% at one month, 30% at two months, and 27% at three months. In the resistant group the corresponding figures were 71%, 62%, and 65%. At one month there was thus no great difference between the results in the two groups. By two months the sensitive group had shown a substantial fall in the frequency of positivity, whereas in the resistant group the percentages at two and three months remained nearly as high as at one month. A further study was therefore undertaken of this difference between the resistant and sensitive groups.

First, considering the 85 patients with a resistant result at two months, the group contained 24 patients who had already given a resistant result at one month (13 yielded resistant and 11 doubtful, probably resistant, results), and 48 patients with a sensitive result at one month. (Of the remaining 13 patients, nine had a negative culture and four no test at one month.) The bacteriological results for these two subgroups of patients at one, two, and three months are summarized in the lower part of

TABLE VII

PERCENTAGES OF PATIENTS POSITIVE ON DIRECT EXAMINATION AT END OF ONE, TWO, AND THREE MONTHS IN VARIOUS SENSITIVITY CATEGORIES (STANDARDIZED FOR DIFFERENCES IN EXTENT OF INITIAL CAVITATION)

Results of Isoniazid-sensitivity Tests			Total Number of Patients*	Standardized Percentage "Positive" or "Scanty Positive" on Direct Examination		
1 Month	2 Months	3 Months		1 Month	2 Months	3 Months
—	Sensitive	—	58	*61*	*30*	*27*
—	Resistant	—	85	*71*	*62*	*65*
—	Sensitive	Sensitive	24	*63*	*51*	*47*
—	,,	Resistant	10	*100*	*30*	*40*
Sensitive	Resistant	—	48	*69*	*61*	*66*
Resistant	,,	—	24	*81*	*67*	*60*

* Results of sputum examinations were not available for a few of these patients at one and at three months.

Table VII. For the small subgroup of 24 patients in whom resistant strains emerged during the first month, the percentage of patients with a positive result on direct examination showed a fall from 81% at one month to 67% at two months, and to 60% at three months. For the subgroup of 48 patients in whom resistant strains emerged during the second month, the corresponding figures were almost unchanged over the period, being 69%, 61%, and 66%. It will be noted that the percentages in the two subgroups were very similar at two and at three months. The figures do not suggest that the time of emergence of resistant strains has had an important influence on the subsequent bacteriological progress of these patients, and they do not yield evidence of the " fall and rise " phenomenon (a decrease in the bacterial content of the sputum while cultures remain sensitive, followed by an increase when resistant strains emerge).

Turning to the 58 patients with a sensitive result at two months, the group contained 10 patients who gave a resistant result at three months (eight yielded resistant and two doubtful, probably resistant, results) and 24 patients still with a sensitive result at three months. (Of the remaining 24 patients, 22 had a negative culture and two no test at three months.) The bacteriological results for these two subgroups of patients at one, two, and three months are also summarized in the lower part of Table VII. Although the number of patients in each subgroup is small, there is no evidence that the results were more favourable in the patients with sensitive organisms at the end of three months than in those in whom resistant strains emerged in the third month.

The pattern of these findings within the two main groups of patients with resistant and with sensitive organisms at two months is not easy to interpret. In the first place they do not yield evidence of changes in the size of bacterial populations, occurring as a consequence of the emergence of isoniazid-resistant organisms in the sputum. Nevertheless, the frequency of specimens positive on direct examination in patients with resistant organisms at two months was high throughout the period, whereas it fell for those in whom the strains remained sensitive. This again suggests the possibility that patients with a particular host response or type of disease at the start of treatment may tend both to retain a heavily infected sputum and to develop bacterial resistance.

Discussion

Following the introduction of isoniazid, it was soon found that among patients with positive cultures after three months' treatment with isoniazid alone, approximately two-thirds had organisms resistant to the drug (Medical Research Council, 1952; Ferebee and Long, 1953). It is therefore important to establish whether the emergence of isoniazid-resistant bacteria is accompanied by a loss of clinical effectiveness of the drug. A preliminary analysis of the data from the Medical Research Council isoniazid trial indicated that, as with streptomycin (Medical Research Council, 1948), resistance to isoniazid developed more readily in patients acutely ill at the start of treatment. When the progress of patients with similar pre-treatment characteristics was studied for a period of three months, it was found that those with drug-resistant organisms had fared, as a group, less well than those not known to have drug-resistant organisms. The bacteriological information in that report (Medical Research Council, 1952) was, however, far from complete.

The present report is based upon the complete information for 234 patients in that trial who received isoniazid alone for a period of three months, and consists of two main studies. In the first part of the report the results of culture examinations and of sensitivity tests at the end of two months have been related to the clinical condition at the start of treatment. As would be expected, patients in poor general condition, or with high degrees of pyrexia, high sedimentation rates, or extensive cavitation at the start of treatment, were more frequently culture-positive at the end of two months than those with more favourable initial clinical characteristics. In contrast, the development of bacterial resistance in the patients whose cultures remained positive was related only to the extent of initial cavitation; patients with extensive cavitation more frequently yielded resistant cultures. As a consequence of this close relationship between the extent of cavitation and the subsequent emergence of resistant organisms, it is essential, when studying the clinical significance of isoniazid resistance, to restrict comparisons to patients with the same degree of initial cavitation. It should be noted that neither the frequency of positive cultures nor the development of bacterial resistance was related to the type of disease, as indicated by the disease group. Finally, the level of resistance did not seem to depend upon any of the initial clinical findings.

The second part of the present report contains a study of the clinical progress of patients during the three-month treatment period in relation to the results of the culture examinations and sensitivity tests at the end of two months. It shows that there was a notable difference between the clinical progress of patients who were culture-negative at

two months and those who were culture-positive. After three months' treatment the responses in radiographic appearances and also in the sedimentation rate were better for the negative group. These differences persisted when allowance was made for the initial clinical differences between the groups.

Further study of the group with positive cultures at two months shows that, when allowance was made for the extent of initial cavitation, patients with isoniazid-resistant organisms were radiographically at a disadvantage at the end of three months' treatment compared with those with sensitive organisms. The difference just attains statistical significance. The data suggest, however, that this difference may not be a direct consequence of the development of bacterial resistance. If the relationship were causal it would have been expected that the lack of radiographic improvement in the resistant group would have been apparent towards the end of the three months rather than earlier, and this was not so. The available evidence also suggests that the radiographic deteriorations were evenly divided among the three months. It thus remains uncertain whether the radiographic disadvantage shown by the patients who had developed resistant organisms at the end of two months is a direct consequence of the emergence of resistant strains or whether poor radiographic progress and the development of resistance to isoniazid (used alone) are both characteristics of patients with a particular host response or type of disease. Cohen (1954), in an editorial article based upon unpublished data of the U.S. Public Health Service Cooperative Investigation, has reached a similar conclusion.

Changes in the sedimentation rate and in the temperature in the resistant and sensitive groups were similarly studied. There is little evidence that the course of either was affected by the development of bacterial resistance.

When the resistant group was subdivided, there was no evidence that the three-month radiographic or clinical progress of the patients with strongly resistant organisms at the end of two months had differed from that of patients with moderately resistant organisms.

The apparent discrepancy between these inconclusive findings concerning isoniazid resistance and those in the interim report of the isoniazid trial (Medical Research Council, 1952) is readily resolved. Owing to the comparatively small number of sensitivity results which were available when the interim report was prepared, the progress of the patients known to have resistant cultures at the end of two months was compared with that shown by all the remaining patients; but many of these were later found to be culture-negative at two months. The results of the present more complete analysis indicate that the differences which emerged in the earlier report were essentially differences between patients with positive and with negative cultures, not between patients with resistant and with sensitive cultures.

In the present report the results of the monthly sputum examinations have also been studied in relation to the development of resistance. Although the percentage of patients with specimens positive on direct examination at three months was much higher in the resistant than in the sensitive group, a study of the figures month by month showed no evidence of changes in bacterial content of the sputum, associated with the development of bacterial resistance. It is possible that an initial difference between the resistant and sensitive groups, either in the size or the character of the bacterial population, may be the explanation of the differences during the three-month period. Because of the nature of the available bacteriological data, no direct comparison of the bacterial content of the sputum in the resistant and sensitive groups was possible at the start of treatment. There may also have been some difference in host resistance in the two groups at the start of treatment.

There have been a number of reports of clinical, bacteriological, or radiographic deterioration, or of failure to improve, associated with the emergence of isoniazid-resistant strains (Joiner and others, 1952; Berg, Herholz, and Meissner, 1953; Berg and Meissner, 1953; Coates and others, 1953; Gernez-Rieux, 1953; Lotte and Poussier, 1953). However, none has presented adequate evidence that the patients relapsed as a consequence of the emergence of the isoniazid-resistant organisms. Lotte and Poussier (1953) demonstrated the association between initial clinical condition and the subsequent development of resistance, and recognized the consequent limitations of their data.

The present analysis has shown clearly that a study of the clinical significance of the emergence of organisms resistant to a drug in the treatment of pulmonary tuberculosis presents many problems, and these will now be discussed.

It has often been demonstrated (Medical Research Council, 1948, 1952; Howlett, O'Connor, Sadusk, Swift, and Beardsley, 1949; Steenken, 1949; Tucker, 1949; Lotte and Poussier, 1953) that there is a definite, and direct, relationship between initial clinical condition, particularly with regard to the extent of cavitation, and the subsequent emergence of resistant organisms. Comparisons which do not

take account of this relationship will tend to exaggerate any clinical significance there may be in the emergence of drug-resistant organisms. Because patients with extensive cavitation usually develop drug resistance, whereas those with little or no cavitation tend to retain sensitive cultures, it is difficult, even in a large-scale trial of a drug which is being given alone, to assemble numbers which are adequate to compare patients with resistant and with sensitive organisms in each cavitation category. Again, a large proportion of patients receiving anti-tuberculosis chemotherapy begin to yield negative cultures soon after the start of treatment, thus further reducing the numbers available for a comparison of equally ill patients with resistant and with sensitive cultures.

In the present report, the absence of any clear disadvantage resulting from the development of isoniazid resistance may also be due to the short period of observation. For the majority of patients it was, however, undesirable on ethical grounds to stipulate a long period of treatment with a single relatively untried drug without allowing the clinician to change chemotherapy or to undertake collapse measures or resection when necessary for the patient. These essential provisos illustrate a practical difficulty in assessing the efficacy of any prescribed treatment over a protracted period. Changes of regime occur for a wide variety of reasons, ranging from very satisfactory progress to a most disappointing response which demands further measures. The patients who remain on their original prescribed treatment become a progressively more and more selected group.

Although in the present trial the period of observation was short, it was long enough to allow a study of the suggestion of a number of other investigators (Joiner and others, 1952; Coates and others, 1953; Gernez-Rieux, 1953) that there are immediate adverse clinical and bacteriological responses to the emergence of isoniazid-resistant organisms. If, in the present trial, such responses had occurred in a large proportion of the patients who developed resistance, the analyses of the timing of the clinical and bacteriological changes should have revealed them, even within the available period of observation.

The " fall and rise " phenomenon, namely a decrease in the bacterial population while cultures remain sensitive, followed by an increase after the emergence of drug-resistant strains, was studied for streptomycin by Mitchison (1950). The reports of Joiner and others (1952), Coates and others (1953), Wallace, Stewart, Turnbull, and Crofton (1954), and Widelock and Robins (1954) suggest that the development of isoniazid resistance is similarly associated in some patients with a diminution in the suppressive effect of the drug on bacterial multiplication. It is thus of particular interest that the present data have not yielded evidence that the " fall and rise " phenomenon occurs frequently. However, it is possible that the basis of assessment of the bacterial content of the sputum in the present trial was not sufficiently sensitive to detect any such effect.

The type of disease studied may also introduce a difficulty in investigations of the clinical significance of bacterial resistance. In the first controlled trial of streptomycin in pulmonary tuberculosis, which was restricted to a very acute, extensive form of the disease, there was a clear contrast between the early radiographic improvement shown by most of the patients on streptomycin and rest in bed and the early radiographic deterioration shown by most of those treated only with rest in bed (Medical Research Council, 1948). These conditions offered a good opportunity to observe whether bacterial resistance was of clinical significance, because patients on ineffective treatment tended to deteriorate. If, however, less acute disease is studied, as in the present trial, a considerable proportion of patients would be expected to improve if treated with bed-rest alone. They would also be expected to improve when receiving bed-rest plus chemotherapy which was no longer effective due to bacterial resistance. Any differences between such a group of patients and a group receiving effective chemotherapy would be much less easy to demonstrate, because the comparison would be in terms of degrees of improvement rather than in terms of a contrast between improvement and deterioration. It will be appreciated that, with less acute disease, further improvement in a patient on chemotherapy after the development of bacterial resistance to the drug is not necessarily evidence of its continued clinical effectiveness. Thus, although the present report provides no adequate evidence that the development of isoniazid resistance in itself leads to a loss of clinical effectiveness of the drug, this may be due in part to the difficulties which have just been discussed and which are inherent in the analysis of these data. While, therefore, it would be wrong to conclude that the drug has necessarily remained fully effective, the analysis fails to show any substantial early loss in clinical effectiveness of isoniazid, due directly to the development of bacterial resistance.

There are, in addition, other considerations in assessing the clinical significance of the emergence of isoniazid-resistant strains. There is evidence

that patients with streptomycin-resistant organisms are not protected against the development of isoniazid resistance by treatment with streptomycin plus isoniazid (Medical Research Council, 1953a) and that patients with P.A.S.-resistant organisms are not protected against the development of streptomycin resistance by treatment with streptomycin plus P.A.S. (Medical Research Council, 1953c) nor against the development of isoniazid resistance by treatment with isoniazid plus P.A.S. (Medical Research Council, 1955). It would be of value to know whether, in patients with isoniazid-resistant organisms, isoniazid in combination with another drug, for example, streptomycin or P.A.S., would no longer prevent the emergence of strains resistant to the second drug. This would indicate the relevance of the development of isoniazid resistance to the chemotherapy which the individual patient might need at a later date.

Bacilli highly resistant to isoniazid often have a lowered pathogenicity to guinea-pigs and sometimes to mice (Barnett and others, 1953; Barry and others, 1953; Middlebrook and Cohn, 1953; Meissner, 1954; Mitchison, 1954). If a proportion of resistant organisms was of lowered pathogenicity in man, then the development of resistance might result in a tendency towards clinical improvement, even though the isoniazid was no longer effective in killing or suppressing the growth of the resistant bacilli. However, definite information on the pathogenicity of resistant strains in man is still lacking. If, as has been the case with streptomycin-resistant strains (Tinne and Henderson, 1950; Harold, 1951; Medical Research Council, 1953a; Thomas, Borthwick, Horne, and Crofton, 1954), and with P.A.S.-resistant strains (Medical Research Council, 1953b; Thomas and others, 1954), reports appear of patients newly infected with strains highly resistant to isoniazid, then the retention of some pathogenicity by such strains in man, and, as a consequence, their importance to public health will be established. Katz, Storey, and McCormick (1954) have reported a case of tuberculous pneumonia apparently due to infection with a strain resistant to streptomycin, isoniazid, and P.A.S., and fully pathogenic to the guinea-pig.

It must be remembered finally that throughout the present report the development of isoniazid resistance has been identified with the appearance of a resistant result to a sensitivity test undertaken at two months, using the Medical Research Council technique (1953b). Pyle (1947) and Colwell, Pitner, and Moravec (1951) have shown for streptomycin, and Stewart (1954) has shown for isoniazid, that even though a test has given a resistant result, the resistant organisms may be in a minority in the tested specimen. Also, even when resistant organisms are present in the sputum, portions of the lungs which do not communicate with the bronchus may contain sensitive strains (Canetti and Saenz, 1951). Thus over a three-month period any loss of effectiveness of the drug or any alteration in bacterial pathogenicity may in some patients relate to only a small proportion of the bacterial population and so be clinically inapparent in these patients.

In conclusion, this analysis has shown an important association between the favourable progress of patients under treatment with isoniazid alone and the early disappearance of tubercle bacilli from the sputum; patients who continue to have positive cultures are relatively at a disadvantage, whether the strains are sensitive or resistant to isoniazid. There is much less difference between the progress of patients with sensitive and with resistant strains, when account has been taken of the influence of the extent of initial cavitation upon the development of resistance.

It should be emphasized that, although the clinical consequences of the emergence of isoniazid-resistant organisms remain uncertain, the development of isoniazid resistance must be regarded as an important event. By virtue of the association between resistance and clinical progress, it provides evidence that the patient is suffering from a form of the disease which is not responding well to treatment with isoniazid alone. Thus the development of bacterial resistance to isoniazid is a sign of prognostic value.

This report illustrates the complexities inherent in assessing the clinical significance of bacterial resistance. As it is possible that the development of isoniazid resistance is a direct disadvantage to the patient in some way which has not been demonstrated by this analysis, it would be wise to continue to regard the development of isoniazid resistance as indicating some loss of clinical effectiveness of the drug, and also as constituting a potential risk to public health. Isoniazid should therefore be used only with other anti-tuberculosis drugs in combinations which are effective both in suppressing tubercle bacilli in the sputum and in preventing the emergence of isoniazid-resistant strains.

Summary and Conclusions

To investigate the clinical significance of the development of bacterial resistance to isoniazid, a study has been made of the progress of 234 patients with pulmonary tuberculosis, who were treated with isoniazid alone (100 mg. twice daily) for

three months. The patients were classified, from the bacteriological findings at the end of two months, into groups of 91 with negative cultures, 58 with strains sensitive to isoniazid, 47 with moderately resistant strains, and 38 with strongly resistant strains.

These bacteriological findings were first related to the clinical characteristics of the patients at the start of treatment. Patients in poor general condition, or with high degrees of pyrexia, high sedimentation rates, or extensive cavitation were culture-positive at the end of two months more frequently than those with more favourable clinical characteristics at the start of treatment. In contrast, the emergence of isoniazid-resistant organisms was related only to the extensiveness of initial cavitation. These findings make it essential, when studying the clinical significance of isoniazid resistance, to restrict comparisons to patients with the same degree of initial cavitation.

Patients who had negative cultures at the end of two months showed on the average greater clinical progress after three months' treatment than patients with positive cultures at two months. Thus, when standardized for differences in extent of initial cavitation, the percentages with radiographic improvement at the end of three months were 75% for the negative group and 50% for the positive group. The corresponding figures for patients whose sedimentation rates fell to normal (10 mm. or less) from a level of 21 mm. or more at the start of treatment were 35% and 19%.

There was much less difference in clinical progress at the end of three months between the patients with sensitive and the patients with resistant strains. The standardized percentages showing radiographic improvement were 55% for the sensitive and 46% for the resistant group. The corresponding figures for the lowering of the sedimentation rate were 21% and 16%. Further investigation suggests that even these differences may not be a direct consequence of the development of bacterial resistance, since the radiographic improvements and deteriorations were evenly distributed throughout the three-month period. It is therefore possible that relatively poor clinical progress and the development of bacterial resistance are both characteristics of patients with a particular host response or type of disease.

Similar studies of the bacterial content of the sputum show a considerable benefit at three months to the sensitive group, 27% having specimens positive on direct examination compared with 65% for the resistant group. Again further analyses yield no evidence that this difference arose from changes consequent upon the development of resistance.

The complex problems involved in studying the clinical significance of drug resistance are discussed, and the limitations inherent in the data, even when obtained from large numbers of patients, are stressed.

It is concluded that the early disappearance of tubercle bacilli from the sputum is an important sign of favourable progress of patients treated with isoniazid alone. The study of possible clinical disadvantages due directly to the development of isoniazid resistance is inconclusive. Nevertheless, because isoniazid resistance tends to occur in disease which is pursuing a relatively unfavourable course, its development is an adverse prognostic sign.

As it is possible that isoniazid resistance is a direct disadvantage to the patient in some way which has not been demonstrated in this study, it would be wise to continue to regard the development of isoniazid resistance as indicating some loss of clinical effectiveness of the drug, and also as constituting a potential risk to public health. Isoniazid should therefore be given only in combination with suitable dosages of other drugs.

APPENDIX

The following procedure was adopted for assigning doubtfully resistant results of isoniazid-sensitivity tests at two months to "probably resistant" and "probably sensitive" categories on the basis of the bacteriological findings at three and, if necessary, four months.

Result of Culture and Sensitivity Test at Three Months	Result of Culture and Sensitivity Test at Four Months	Decision on Doubtfully Resistant Result at Two Months
Resistant	—	Probably resistant
Doubtfully resistant	Resistant	
Negative	,,	
Sensitive	—	,, sensitive
Doubtfully resistant	Sensitive	
	Doubtfully resistant or negative	
Negative	Sensitive	
	Doubtfully resistant or negative	

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