



THE PUBLIC HEALTH SIGNIFICANCE OF DRUG RESISTANCE
(Review of data)

Development of events

The importance of epidemiological and clinical understanding of the problem of drug resistance in tuberculosis is growing together with the extension of mass chemotherapy.

The WHO Informal Meeting of Advisers on Laboratory Methods for the Drug Sensitivity/Resistance Determination of Mycobacteria, Geneva, December 1961,¹ proposed the definition of the terms "sensitive" and "resistant" strains of Mycobacterium tuberculosis as follows:

"Sensitive" strains are those that have never been exposed to the main antituberculosis drugs ("wild" strains) and that respond to these drugs, generally in a remarkably uniform manner.

"Resistant" strains are those that differ from sensitive strains in their capacity to grow in the presence of higher concentrations of a drug.

This definition of resistance is based on the laboratory response; strains that are resistant in this sense do not necessarily fail to respond to the usual doses of the drug in the lesions of the patient. However, a diminished clinical response has been shown to occur whenever resistance is demonstrated in the laboratory, even though the extent or degree of that resistance is small.

In the course of the last decade, there have been different evaluations of the clinical significance of drug resistance.

Already in 1956, a review of the opinions of chest physicians in different countries revealed divergencies.²

¹ Canetti, G. et al. (1963) Bull. Wld Hlth Org., 29, 565.

² Bull. int. Un. Tuberc., 1956, 26, 149.

Most participants in a symposium on the clinical significance of bacterial resistance tests (1957) thought that these were very important for the success of treatment, but there were wide differences of opinion as to what constituted a clinically significant level of resistance.¹

Partly as a result of this discussion, and probably after the publication of a survey in England, Wales, and Scotland, on the prevalence of primary drug resistance, the first of its kind - the two committees of the International Union Against Tuberculosis (IUAT) (Committee on Laboratory Methods and Committee on Antibiotics and Chemotherapy) decided to obtain an idea of the proportion of patients admitted to hospitals or sanatoria with strains resistant to the standard antituberculosis drugs. Table 1 presents some of the data collected.

On the basis of the analysed results from 72 hospitals or sanatoria in 17 different countries, it was concluded that the amount of drug resistance presented a formidable problem to the clinician, and that the majority of the techniques in current use did not permit precise quantitative tests.

¹ Bull. int. Un. Tuberc., 1957, 27, 223.

² Fox, W. et al. (1957) Tubercle (Lond.), 38, 71.

³ Bull. int. Un. Tuberc., 1960, 30, 2.

TABLE 1. PRIMARY RESISTANCE IN UNTREATED PATIENTS WITH ORGANISMS TESTED FOR RESISTANCE TO AT LEAST ONE DRUG

(Includes both those who had had no treatment and who had had less than eight days)

Country	Streptomycin		PNC		Isoniazid	
	No. tested	% resistant	No. tested	% resistant	No. tested	% resistant
Austria	29	3.4	29	14	29	0
Belgium	53	2.9	68	0	68	4.4
Canada	165	1.5	156	0.75	163	3.0
Czechoslovakia	103	2.0	104	4.0	103	4.0
France	137	3.6	182	0.5	182	4.3
Germany	254	0.7	254	0.3	254	1.5
Japan	38	5.2	38	5.2	38	16
Netherlands	123	2.4	105	0	128	0
Poland	69	5.7	7	0	77	5.1
Romania	12	0	12	0	12	(8.3)
Switzerland	98	2.0	98	2.0	92	3.0
United Kingdom	263	2.2	263	1.8	266	1.5
United States of America	256	3.3	266	3.0	266	5.2
Yugoslavia	29	10	28	7.0	29	3.4
Total	1 668		1 628		1 718	
Percentage	100	4.0	100	1.8	100	3.3

Percentages based on a total of less than 20 cases are given in parenthesis.

The two IUAT Committees considered that it would be useful to check the value of the different methods by an exchange of cultures and a comparison of the tests made on the same strains in different laboratories.

The replies to a questionnaire, sent out to several laboratories in different countries, in which these laboratories were asked to indicate their criteria for considering a strain to be sensitive or resistant to each of the three major drugs, revealed extraordinary differences in these criteria for each of the drugs.¹ The confusion, marked in this field some years ago,² has not lessened since then.

Canetti (1960) emphasized the disadvantages of such a state of affairs in two fields: statistical - the impossibility of making a comparative analysis of the data from different countries regarding the frequency of resistant strains; and therapeutic a possible failure of treatment in a large number of patients. He proposed that a working plan for the study of the drug resistance problem by an international committee should be organized.³

Although the WHO Expert Committee on Tuberculosis in its Seventh Report⁴ noted that resistance to drugs, especially to isoniazid, had not proved to be the public health problem originally feared, at the same time the pressing need for international standards for the definition and determination of drug resistance was stressed.

Evidence of the need for such standards was demonstrated by the symposium on treatment of pulmonary tuberculosis in patients harbouring bacilli resistant to the three major drugs, held in Paris in September 1960,⁵ in confirming, by brief survey of the situation in some countries (United Kingdom, France, Japan, United States of America, Poland, and Czechoslovakia - see Table 2), the seriousness of the drug resistance problem.

¹ Bull. int. Un. Tuberc., 1964, 30, 15.

² Canetti, G. (1955) Bull. int. Un. Tuberc., 25, 157.

³ Canetti, G. (1960) Bull. int. Un. Tuberc., 30, 48.

⁴ WHO Expert Committee on Tuberculosis (1960) Seventh report, Wld Hlth Org. te Rep. Ser., 125.

⁵ Bull. int. Un. Tuberc., 1961, 31, 3.

TABLE 2.¹ RESISTANCE IN PATIENTS ALREADY TREATED AND WHOSE ORGANISMS WERE TESTED FOR RESISTANCE TO ALL THREE DRUGS

Country	No. tested to all 3 drugs	Per cent. resistant to:		
		At least one drug	At least two drugs	All three drugs
Austria	374	7	19	2.9
Belgium	204	11	30	11
Brazil	33	54	58	9.0
Canada	30	17	47	13
Czechoslovakia	585	23	4.8	0.8
France	441	35	14	1.1
Germany	541	45	11	1.2
India	305	52	26	4.5
Japan	318	58	34	11
Netherlands	120	13	7.5	1.6
Poland	53	32	3.8	0
Romania	67	54	16	2.2
Switzerland	47	45	23	8.5
United Kingdom	414	32	19	9.6
United States of America	598	43	22	10
Yugoslavia	191	58	29	13
Total	4 341			
Percentage	100	42	18.5	5.5

¹ Bull. int. Un. Tuberc., 1961, 31, 7.

According to Dr Hobby's report on the Toronto Conference (1961),¹ no analysis of therapeutic results has been attempted yet so as to establish clearly the threshold level of drug resistance. No laboratory study in itself can establish this threshold. This is of the utmost importance, for any consideration of the epidemiological and clinical significance of drug resistant mycobacterial strains must be based on prevalence rates established by the use of arbitrarily-selected criteria of microbial resistance.

Thus, a uniform method of determining resistance in vitro has become a first requisite for evaluating mycobacterial drug resistance. Such a standard procedure should satisfy at one and the same time clinician, bacteriologist, and epidemiologist.

In December 1961, WHO took the first step towards standardization in the definition and determination of drug resistance by convening in Geneva an Informal Meeting of Advisers on Laboratory Methods for Drug Sensitivity/Resistance Determination of Mycobacteria.²

An attempt was made to formulate prerequisites for reliable sensitivity tests and to specify the technical procedures for them.

Laboratory tests of the sensitivity of tubercle bacilli to chemotherapeutic drugs serve three main purposes:

1. They can be used as a guidance in the choice of the first course of chemotherapy to be given to the patient.
2. They may be of value in confirming that drug resistance has emerged, and may guide the choice of a further course of treatment with different drugs.
3. They may be employed to estimate the prevalence of primary and acquired resistance in a community.

For each of these purposes, it is very important to use a reliable technique in performing the tests.

¹ Hobby, G. (1962) Bull. Int. Un. Tuberc., 32, 52.

² Canetti, G. et al. (1963) Bull. Wild Health Org., 29, 565.

In searching for a test that will be accurate, reproducible, economical, and rapid, the participants in the above-mentioned meeting considered only the three main antituberculosis drugs (isoniazid, streptomycin, and FAS), although accurate tests for resistance to the minor drugs are also of considerable importance.

Three different tests for determining drug sensitivity - the absolute-concentration method, the resistance-ratio method,¹ and the proportion method^{2,3} - are generally considered to give reasonably accurate results.

Further research is necessary on rapid methods of sensitivity testing, since the direct tests mentioned require a period of four weeks before the result is available.

A simple test for resistance to isoniazid was recommended for further trial, and it was recommended also that a comparison be made between different carefully selected methods in each of several laboratories. The methods themselves must be strictly adhered to in each laboratory.

Studies to be carried out in different territories on the prevalence of infections due to drug-resistant organisms in patients who claim not to have received previous chemotherapy were suggested.

WHO-assisted studies on the lines proposed are under way.⁴

Primary drug resistance

Meanwhile, the problem of primary resistance is emerging. This comparatively new problem is attracting more and more attention, particularly in respect of its potential epidemiological significance.

Previously untreated patients who harbour resistant organisms are referred to as having primary resistance, to distinguish them from those patients who have resistance as a result of previous treatment (secondary or acquired resistance).

¹ Selkon, J. B. & Mitchison, D. A. (1958) In: Veterans Administration - Armed Forces, Transactions of the 17th Conference on the Chemotherapy of Tuberculosis, Memphis, Tennessee, p. 258.

² Canetti, G., Rist, N. & Grosset, J. (1963) Rev. Tuberc. (Paris), 27, 217.

³ Augier, J., Schoepff, G. & Polaska, R. (1964) Acta phthisiol., 63, 2.

⁴ Document WHO/TB/Techn.Information/7 Rev.1, 4 February 1964.

It is from those with secondary resistance that most patients with primary resistance have acquired their infection.

Experience has shown that it is not nearly as simple to determine the prevalence of primary drug resistance as had been anticipated.

In some surveys, it has taken a fantastic amount of checking on the possibility of previous, but unreported, treatment, to really come down to a fairly pure, untreated group (C. Palmer (1963) - personal communication).

According to A. S. Moodie (personal communication, 1963), in Hong Kong, in a group selected for a drug trial, who on three separate occasions had denied previous treatment, 22 out of 42 cases found to be isoniazid-resistant admitted on a fourth questioning to having had treatment previously.

At the Tuberculosis Chemotherapy Centre, Madras, some patients disclosed their previous treatment only after a long period of association with the Centre, when an atmosphere of confidence and friendship had developed between them and the staff (P. R. J. Gangadharam (1963) - personal communication).

Whatever may be the reason, the fact remains that the separation of primary from acquired resistance is very difficult. This was not unexpected. It is already well known that, soon after the discovery of streptomycin and its introduction as a drug effective in the treatment of tuberculosis, a small number of drug-resistant organisms were constantly being found among a large number of streptomycin-susceptible bacilli of any population of mycobacteria. These drug-resistant bacilli were capable of dominating the microbial population rapidly and disturbing the beneficial effects of streptomycin.¹

Soon after the introduction of isoniazid, in 1952, significant numbers of bacilli resistant to isoniazid were detected in most, if not all, strains of tubercle bacilli prior to their contact with the drug.²

¹ Hobby, G. (1962) Bull. int. Un. Tuberc., 32, 52.

² Hobby, G. & Lenert, T. E. (1952) Amer. Rev. Tuberc., 65, 771.

There is still no satisfactory explanation for this phenomenon, but the circumstances are very confusing, particularly since evidence has been obtained that even low degrees of resistance have clinical significance (Crofton, 1954;¹ Mitchison, 1954²).

A review of the literature shows that there is a lack of uniformity in the methods of performing sensitivity tests, in interpreting such tests, and in compiling data derived from them.

Table 3 shows the results of the first studies on the prevalence of primary resistance in different countries. It can be seen that the prevalence varied widely from one country to another.

In 1957, at a Panel held in Paris, interesting figures indicating the proportions of patients who appeared to have been infected with resistant organisms were discussed and these seemed to lie between one and five per cent. in different centres.³ The situation has since been complicated by the conception of changed pathogenicity of isoniazid-resistant strains and its eventual implications for epidemiology (use of isoniazid therapy alone, etc.).

The divergency of the views expressed makes it clear that much more evidence needs to be found in order to clarify the situation.

¹ Crofton, J. (1954) Brit. med. Bull., 10, 125.

² Mitchison, D. A. (1954) Brit. med. Bull., 10, 115.

³ Bull. int. Un. Tuberc., 1957, 27, 223.

At the Sixteenth International Tuberculosis Conference (Toronto, 10-14 September 1961), the discussion of the bacteriological, therapeutic, and epidemiological aspects of primary drug resistance began with the definition of primary resistance: the term "primary resistance" applies to resistant tubercle bacilli cultured before any chemotherapy in fresh cases.

A strain is called "primarily resistant" when there is resistance to the same concentration as in the secondary resistance referred to in treated patients. This means that any strain that is not sensitive must be regarded as resistant.¹

Compared with the average incidence of 6.5 per cent. shown by Rist & Crofton, there have been very few primarily resistant cases in some countries: e.g., Hungary (two per cent.), Germany (2.9 per cent. according to Lydtin, 2.7 per cent. according to Meissner, 4.5 per cent. according to Bartmann). Thibier & Canetti indicated 14 per cent. for selected groups; slightly lower figures of this type were found by Pepys and by Dissman & Iglauer. A medium-to-high percentage has been found in England, Sweden, and France (5-6 per cent.) (Table 4).

¹ Meissner, G. (1962) Bull. int. Un. Tuberc., 32, 15.

TABLE 4. PRIMARILY RESISTANT TUBERCLE BACILLI IN ADULTS

Investigator(s)	Year	% Resistance to:				No. of strains	% Resistance
		Isoniazid	Strepto- mycin	PAS	Two drugs		
Bogen	1947/58	2.2	3.3	2.9	-	17 000	?
Veterans	1956/57	6	5	8	8	1 833	ca 11
Rist-Crofton	1957/58	1.8	2.5	0.8	1.5	1 415	6.5
Pepys Africa	1953/58	11	-	7.5	-	721	10.5
Chaves USA	1953/55	6.8	6.5	-	-	1 016	13.3
Dissmann Austria	1955/59	6.2	2.4	0.1	0.8	703	8.04
Fox et al. England	1955/56	0.7	2.3	2.2	-	1 404	5.1
Bernard Paris	1954/57	2	3.6	1.6	1.6	707	5.1
Lind Göteborg	1957/59	1.1	1.1	2.3	1.1	179	5.6
Bartmann Berlin	1957	4.7	0	0.8	0.8	129	4.7
Lydttin Munich	1957/58	0.7	1.5	0.7	-	137	2.9
Meissner Borstel	1956/59	0.7	1.1	0.5	0.5	1 233	2.7
Kertey Hungary	1956/57	0.4	1.2	0.4	-	1 274	2
Koehler u. Fr. Leipzig	1954/59	2.7	5.1	1.4	0.3	294	9
Thibier-Canetti Paris	1958/59	9	9	0.7	5	123	14
Reiss a. T. Florida	1956	10				322	-
Wu a. Chang China	1958	4.8					
Taquet a. V. Lille	1958?	0.7-1.3					

An analysis of the data collected has shown that the degree of primary resistance has varied and that there have been considerable differences in the increase in such resistance.

The conclusion reached was that the epidemiological situation as regards primarily resistant strains is equivocal.

In some countries, the situation is regarded as serious, whereas other countries have as yet no epidemiological problem in this respect. Attempts have been made to eliminate from such surveys those patients who had had previous chemotherapy. In some studies, however, certain patients might have received chemotherapy for a short period. One cannot ignore, insisted Hobby (1962),¹ the possible significance of even short courses of chemotherapy. Even one to two weeks could conceivably alter the proportion of susceptible to resistant bacilli in a patient.

Moreover, the qualitative nature of the test employed for determining drug resistance is of significance. The action of any antimicrobial agent is influenced to a large extent by the number of micro-organisms present, by the drug concentration, and by the time during which that drug and the microbe remain in contact. The minimum inhibitory concentration of any antimicrobial agent depends largely upon the number of organisms present. Yet in none of the studies described has inoculum size been more than qualitatively controlled. Although Hobby's deduction concerned only investigations in the United States of America, one could conclude the same about most of the studies presented at the Sixteenth Tuberculosis Conference.

Adding to the confusion are the wide variations in drug concentrations used by the various laboratories, the large differences between drug concentrations employed in any single laboratory, and the varying criteria of drug resistance.²

There was also the possibility that some drug-resistant strains referred to as strains of Mycobacterium tuberculosis may have been strains of "unclassified" mycobacteria, which are generally drug-resistant.

The differentiation of these strains was not undertaken in any of the studies reported at Toronto.

¹ Hobby, G. (1962) Bull. int. Un. Tuberc., 32, 52.

² Hobby, G. (1962) Bull. int. Un. Tuberc., 32, 52.

The following measures were proposed by the Sixteenth International Tuberculosis Conference.

1. In all countries, a survey of primary resistance must be made as soon as possible.
2. Correct chemotherapy as the best prophylaxis against primary resistance must be used.
3. Measures must be taken to prevent the free sale or unsupervised distribution of antituberculosis drugs to patients.
4. Other prophylactic measures against the development of primary resistance, such as the prevention of contagion, the provision of better bacteriological supervision, etc.

The methods of performing sensitivity tests require more attention.

The two surveys carried out by the United States Public Health Service and the Veterans Administration have demonstrated the importance of identifying drug-resistant mycobacteria as Mycobacterium tuberculosis var. hominis, and the necessity of obtaining an accurate history of previous treatment, in order to obtain valid rates.

The former survey deals with the results in 2400 strains isolated from untreated adults in whom active pulmonary tuberculosis had been newly diagnosed and who had been admitted to 22 state and city hospitals. These patients participated in a study made between September 1961 and July 1962, and a comparison was made with tests performed in the same laboratory for similar patients admitted to the same hospitals between 1952 and 1960.¹

The Public Health Service did not detect an increase in the incidence of "primary drug resistance" between 1952 and the time of the 1961-62 study. Of the strains for 1961-1962 admissions, 1.6 per cent. were resistant to isoniazid, 2.8 per cent. resistant to streptomycin, and 0.8 per cent. were resistant to PAS. Rates at least as high were found for each drug between 1952 and 1960.

¹ United States Public Health Service Cooperative Investigation (1963) Reveals a Decrease in Resistance to Isoniazid, Streptomycin, and PAS, Am. Rev. Resp. Dis., 88, 38

Resistance to more than one drug was uncommon (0.5 per cent. to both Isoniazid and streptomycin).

The significance of this report is that, in a series extending over a decade in which the same laboratory used the same methods to determine resistance in strains from similar patients from the same hospitals, the frequency of primary drug resistance has remained unchanged.

The frequency of resistant strains was not associated with age, race, sex, extent of disease, or presence of cavitation.

Of special interest in the survey in a veteran population in the United States¹ was an attempt to estimate the results obtained in one sub-survey, (the study consists of two surveys, still in progress: the Special Research Laboratory Direct Test, initiated in December 1960, and the Special Research Laboratory Indirect Test on patients admitted to VA hospitals between September 1962 and September 1963), by the criteria of three other investigators (Table 5):

TABLE 5

Drug	By the criteria of:			
	Hobby	Castelli	British Medical Research Council	Chaves (Significant resistance)
	3	Estimated	Estimated	Estimated
Streptomycin	4.7	3.1	2.1	3.6
PAS	3.7	27.0	3.1	6.1
Isoniazid	5.3	5.7	1.8	6.0

* Evaluating at 1 to 4 µg of PAS, rather than at 0.5 µg per ml of medium, this figure fell to 3.1 per cent.

An important conclusion was reached: differences in criteria of drug resistance probably do not account for the marked differences in the prevalence of primary drug resistance reported in various laboratories and geographical areas.

¹ Hobby, G. et al. (1964) A continuing study of primary drug resistance in tuberculosis in a veteran population within the United States. I. Amer. Rev. resp. Dis. 89: 337

It should be noted, however, that the methods used in this direct test survey did not permit a precise interpretation of results by the criteria of the investigator cited.

The next important point of this paper is that, quite probably, the speed with which resistant cells may increase in number (and become predominant) is more significant than the existence of small numbers of resistant cells within the total population prior to contact with the drug in question.

The investigation gives grounds for proposing as significant levels of resistance - in vitro at least - mycobacterial growth with less than 2 µg of streptomycin, more than 4 µg of PAS, and more than 0.5 µg of isoniazid per ml of medium. These threshold levels were based on the assumption that it is justifiable to accept not less than 20 colonies as evidence of growth.

Using different laboratory techniques but essentially equivalent criteria for the definition of significant drug resistance in both surveys, the investigators confirmed previously reported observations (Hobby, 1961, 1963; Chaves et al. 1956; Meissner, 1957) that the present level of "primary drug resistance" in the United States of America remains low (five per cent. or less to each of the three major drugs).

It has been argued that these surveys offer no justification for complacency, since (1) patients admitted to a selected group of hospitals, and (2) a veteran population, may not be the most representative in the United States, and (3) the survey failed to include children under the age of thirteen who belong to the group probably giving the most sensitive index of primary drug resistance.¹

Different data (on selected groups) confirm this opinion: for instance, there has been no change in the incidence of primary drug resistance of tubercle bacilli among patients seen at the Mayo Clinic during the past eight years (approximately 1.9 per cent.).²

¹ Amer. Rev. resp. Dis., 1964, 89, No. 3 (editorial).

² Hershfield, E. S. et al. (1963) Proc. Mayo Clin., 38, 22.

Primary resistance to one or more of the standard drugs is seen in only one per cent. of cases in the Netherlands, while acquired resistance has been found in 110 out of 2204 cases over the past eight years.

On the other hand, evidence has been produced of the rising incidence of primary drug resistance of Mycob. tuberculosis in East Africa, as summarized by Pepys, Mitchison & Kinsley (1960).¹ The investigation made by Short (1961) provided further confirmation of the high level of resistance to Isoniazid found in Uganda.²

Data about the isoniazid resistance rate from some countries using the same criteria in resistance determination have shown an increase in the prevalence of primary Isoniazid resistance: United States of America, New York (Chaves et al.) 1955:³ 1%, 1960: 2.5%;⁴ National Survey in Japan, 1957: 11.9%, 1958: 15.8%; India, 1956-57: 3.6%, 1957-58: 5.3%; Hungary (Lanyi), 1955: 0.44% (1956: 1.28%, 1957: 0.96%, 1958: 0.61%), 1960: 1.26%.

Mitchison (1964)⁵ also noticed the low prevalence of true primary drug resistance, even in countries where much inefficient treatment is given.

WHO-assisted prevalence surveys in Africa have shown, in general, very good agreement between drug resistance and information on previous treatment.⁶

In preparing this review on the drug resistance problem and in an attempt to obtain as much reliable information on this subject as possible, the Tuberculosis unit, WHO, asked all the members of the WHO Expert Advisory Panel on Tuberculosis

¹ Pepys, J. et al. (1960) Tubercle (Lond.), 41, 32.

² Short, G. M. (1961) Tubercle (Lond.), 42, 308.

³ Chaves, A. D. et al. (1955) Amer. Rev. Tuberc., 72, 143.

⁴ Chaves, A. D. et al. (1951) Amer. Rev. Resp. Dis., 64, 647.

⁵ Mitchison, D. A. (1964) The hard road to tuberculosis control, The New Scientist, 4 April.

⁶ Roesgaard, E., Iversen, E. & Bløcher, C. (1964) Bull. Wld Hlth Org., 30, No. 4 (In press).

about their personal experience and views on the present prevalence of primary and acquired resistance to the three main tuberculosis drugs in their country or region, and about its trend over the last five to 10 years.

Only a few of the replies received show the present situation in the respective countries (Table 6). Many of the answers are based on the results of studying a selected group of patients (Carlo Forlanini Institute, Hôpital Laennec, Tuberculosis Institute of the Russian Federation, different sanatoria, etc.); some of the members have referred to published literature; in some countries there simply are no such data.

In short, adequate information on the present prevalence of primary drug resistance is still not available.

Among 23 replies to the question on the trend of primary resistance over the last five to 10 years, 10 noticed an increase, five no change and two a decrease, while six found that the present data do not allow for an answer to this question.

Conclusion

As the review of the literature and other available data has shown, it has not been proved yet that primary drug resistance has become a serious public health problem (in newly discovered, untreated, patients).

Increasing experience in the chemotherapy of tuberculosis shows that the therapeutic value of a drug and its value as an agent in combined therapy are defined by its ability to act on the sensitive part of the bacilli strain and on the mutants that are resistant to another antibiotic administered simultaneously. It is known that the percentage of mutant bacilli resistant to the major drugs (isoniazid, streptomycin, and PAS) in normal strains is very small. The same, however, is not true for all drugs. Thus, pretreatment drug resistance to thiacetazone appears to be common in some areas: a prevalence of 20 per cent. to 50 per cent. or even higher depending on the definitions adopted in Madras and in Hong Kong (Fox, 1964),¹ in

¹ Fox, W. (1964) Realistic chemotherapeutic policies for tuberculosis in the developing countries (Mimeographed document TRU.64/C.57, 19 May 1964).

Tunisia,¹ even when thiacetazone has not been used on any scale in the past. Because of the operational and economic advantages of thiacetazone as a companion drug to isoniazid, the relationship of such pretreatment resistance to therapeutic efficacy of thiacetazone needs further clarification.

Acquired resistance

If primary drug resistance does not appear to be a public health problem of serious significance yet, acquired drug resistance is already such a problem in many countries. It is important in so far as the prevalence of drug-resistant tubercle bacilli is a measure of the efficacy of past treatment and the extent of future tasks. To be more exact, the prevalence of acquired drug resistance is a guide for future methods of tuberculosis control: (a) the reduction in therapeutic effectiveness of the drugs given to an individual patient, and (b) the epidemiological implications of drug-resistant infections in a community.

If the drugs for tuberculosis chemotherapy are correctly employed, drug-resistant organisms should emerge rarely, if at all, irrespective of the degree of severity of the disease.

In practice, however, the use of multiple-drug therapy, though definitely beneficial, is not an absolute guarantee against the occurrence of drug-resistant infections: for some patients with moderately advanced or far advanced cavitary tuberculosis, chemotherapy with the main drugs (isoniazid, streptomycin, and PAS) fails and resistance develops (McDermott, 1960).

Bernard stated that, in 1954, 30.9 per cent. of patients admitted to hospital were "resistant" to one or more of the main drugs; in 1955, there were 22.5 per cent; in 1956, 32 per cent.² Lydtin found the percentage of "resistant" patients to be 30.9 in 1954; 22.5 in 1955; and 32 per cent. in 1956.³ At the Central Dispensary of Warsaw during the period 1954-1956, 35 per cent. out of 5821 strains examined were found to be streptomycin-resistant; 30 per cent. of 1281 strains isoniazid-resistant (Misiewicz, 1957).⁴

¹ Unpublished data.

² Bernard, E. (1957) Bull. int. Un. Tuberc., 27, 262.

³ Lydtin, K. (1957) Bull. int. Un. Tuberc., 27, 256.

⁴ Misiewicz, J. (1957) Bull. int. Un. Tuberc., 27, 255.

TABLE 7. RESISTANCE IN PATIENTS ALREADY TREATED AND WHOSE ORGANISMS WERE TESTED FOR RESISTANCE TO AT LEAST ONE DRUG

Country	Streptomycin		PAS		Isoniazid	
	No. tested	% resistant	No. tested	% resistant	No. tested	% resistant
Austria	377	20	376	8.2	378	40
Belgium	204	38	204	14	204	40
Brazil	41	75	33	9.0	40	60
Canada	52	69	30	23	52	65
Czechoslovakia	587	5.1	585	8.5	586	17.5
France	443	22	397	2.2	398	29
Germany	542	15	543	4.0	542	38
India	305	25	305	11	305	46
Japan	318	43	319	33	319	27
Netherlands	123	3.2	121	8.2	124	13
Poland	528	41	53	1.8	568	48
Romania	134	47	87	1.1	135	46
Spain	77	43	0	-	77	71
Switzerland	37	43	37	16	37	38
United Kingdom	414	20	414	16	414	25
United States of America	625	23	601	18	624	34
Yugoslavia	192	27	191	28	192	41
Total	4 999		4 296		4 995	
Percentage	100	25	100	12.5	100	35

The inquiry of the International Union Against Tuberculosis, which took 1957 as the sample year, demonstrated that, among patients who had had previous treatment and required admission to hospital for a relapse or because of failure of initial treatment, over 40 per cent. had organisms resistant to at least one drug and nearly 20 per cent. to two drugs (Table 7).¹

It need hardly be repeated that the criteria of resistance adopted by the different centres vary considerably.

The first accurate estimate of the size of the problem of secondary resistance was carried out in the United Kingdom. A random sample of 38 chest clinics provided a single sputum specimen from each of 514 patients with pulmonary tuberculosis who had had a positive sputum at the time of the survey (October 1960 to April 1961) and also twelve months or more previously. Eighty-one per cent. of the cultures were resistant to one or more of the three main drugs, 15 per cent. being resistant to one drug, 26 per cent. to two, and 41 per cent. to all three. It was possible to estimate the number of treated patients throughout the country who in 1960 were excreting resistant bacilli. There appear to have been at least 3500 with cultures resistant to at least one drug and 1800 resistant to all three. The survey showed that, in about half the patients excreting resistant bacilli, tuberculosis was first diagnosed during the period 1950-55. In only six of the 335 had it been diagnosed in 1959 or 1960. This suggests, perhaps, that the efficacy of treatment during the past decade has been considerably improved.²

At several recent symposia the value of correct combined chemotherapy from the outset of treatment, as a means of avoiding the emergence of drug resistance, was discussed repeatedly.^{3,4,5,6}

¹ Bull. int. Un. Tuberc., 1960, 30, 2.

² British Tuberculosis Association (1963) Tubercle (Lond.), 44, 1.

³ Bull. int. Un. Tuberc., 1961, 31, 3.

⁴ Bull. int. Un. Tuberc., 1962, 32, 133.

⁵ Bull. int. Un. Tuberc., 1963, 33, 122.

⁶ Abstracts of IIIrd International Congress of Chemotherapy, Stuttgart, 1963.

As in the case of primary drug resistance, the members of the WHO Expert Advisory Panel on Tuberculosis were asked by the Tuberculosis unit about the present prevalence of acquired resistance and its trend over the last five to 10 years.

The figures received confirm that the situation is very complicated (Table 8).

As to the trend of acquired drug resistance over the last five to 10 years, nine members of the Expert Panel definitely noticed an increase, three supposed a decrease, and 10 found that the present data are not sufficient to permit an answer to this question.

Conclusion

Information on prevalence of acquired drug resistance is difficult to obtain because no scientifically accurate data are available.

No data, therefore, are available to establish a trend in the development of acquired resistance over the past five to 10 years.

Infectivity and pathogenicity of resistant strains

Among other consequences of drug resistance, it is considered that an evaluation of the infectivity and pathogenicity of strains from cases with primary or acquired resistance would be rewarding.

Experimental data and clinical observations (Youmans & Karlson, 1947;¹ Wolinsky et al., 1948;² McCoy, 1950;³ Harold, 1951;⁴ Canetti et al., 1951;⁵ Debré et al., 1952,⁶ etc.) do not reveal any difference between tubercle bacilli sensitive and

¹ Youmans, G. P. & Karlson, A. G. (1947) Amer. Rev. Tuberc., 55, 529

² Wolinsky, E., Reginster, A. & Steenken, W. (1948) Amer. Rev. Tuberc., 58, 335

³ McCoy, H. J. (1950) Amer. Rev. Tuberc., 62, 227

⁴ Harold, J. T. (1951) Lancet, 2, 658

⁵ Canetti, G. et al. (1951) Rev. Tuberc. (Paris), 15, 128

⁶ Debré, R., Erissaud, H. E. & Noufflard, H. (1952) Sem. Hôp. Paris, 28, 1676

resistant to streptomycin and PAS. On the other hand, the development of isoniazid resistance has been found to be closely associated with a decrease of virulence of Myco. tuberculosis for certain laboratory animals (Barnett et al., 1953;¹ Barry et al., 1953;² Middlebrook & Cohn, 1953;³ Middlebrook, 1954;⁴ Rist, 1956;⁵ Zitrin & Lincoln, 1961,⁶ etc.).

The problem, however, is whether or not this loss of virulence is paralleled by a loss of virulence for man. Information is lacking, both microbiological and clinical, to answer this question, although the relationship between isoniazid resistance and the pathogenicity of such strains for man has been discussed for about 10 years. One of the discussions of the subject was at a symposium held in Paris (20 September 1957) on the Clinical Significance of Bacterial Resistance.⁷ While participants in this symposium stressed the fact that isoniazid-resistant tubercle bacilli cannot be considered to be avirulent even though they fail to kill guinea-pigs (N. Rist); that there is not a direct relationship between the level of catalase activity and pathogenicity (B. Kreis); that the appearance of isoniazid resistance is undesirable (E. Tanner); and that the prognosis in patients with isoniazid-resistant bacilli is much more uncertain than that in those with sensitive bacilli (M. Lucchesi), others thought that, where the bacilli cannot be eliminated completely from the patient's system, treatment should aim at turning them all isoniazid resistant (E. Freerksen).

¹ Barnett, M., Bushby, S. & Mitchison, D. A. (1953) Erit. J. exp. Path., 34, 568

² Barry, V. C., Conalty, M. L. & Gaffney, E. G. (1953) Lancet, 1, 979

³ Middlebrook, G. & Cohn, M. L. (1953) Science, 118, 297

⁴ Middlebrook, G. (1954) Amer. Rev. Tuberc., 69, 471

⁵ Rist, N. (1956) Amer. Rev. Tuberc., 74, Supplement, 75

⁶ Zitrin, Ch. M. & Lincoln, E. M. (1961) J. Pediat., 58, 219

⁷ Bull. int. Un. Tuberc., 1957, 27, 212

In D. A. Mitchison's opinion, isoniazid-resistant strains are always more virulent than BCG and are capable of producing widespread progressive forms of tuberculosis in guinea-pigs. Therefore, treatment should aim at eliminating bacilli rather than at making them resistant. W. McDermott agreed basically and admitted that isoniazid-resistant bacilli could be a danger for human beings.

It must be emphasized that isoniazid-monotherapy in developing countries (with a few exceptions) was not the consequence of a policy of "isoniazid alone", but of the lack of a satisfactory treatment organization. The literature on this point is voluminous and cannot be detailed here. The current lack of knowledge is reflected in the following opinions of members of the WHO Expert Advisory Panel on Tuberculosis in reply to a questionnaire sent to them by the WHO Tuberculosis unit about the present conception of the infectivity and pathogenicity of strains from cases with primary or acquired resistance.

Isoniazid-resistant tubercle bacilli are considerably different in their biological properties and in their ability to form the enzyme catalase, and the loss of infectivity or pathogenicity is closely correlated with this biological property (B. Papanicolaou). At the same time, in experiments, the virulence of isoniazid-resistant strains was lower than that of strains resistant to other drugs (M. Lucchesi et al.). The latter strains are able to multiply in the body of a tuberculosis patient and cause death. The tuberculosis caused by strains primarily isoniazid-resistant has not the clinical characteristics of the disease provoked by sensitive strains (E. Bernard). There is no evidence (H. Walkup) to demonstrate that primarily resistant organisms cause other than the typical human infection in man, with no attenuation of virulence, although evidence of attenuated virulence has been observed in laboratory animals infected with isoniazid-resistant organisms. It is often explained that this is because strains with lost catalase activity, i.e., catalase negative, do not show the same pathogenicity in experimental animals, but once they have produced disease in man, it takes the same course as it would with other organisms (N. L. Bordia) or even worse (Ph. V. Šebanov). The Madras study has shown that isoniazid-resistant, catalase-negative organisms probably do not produce

disease as fast as normal virulent tubercle bacilli (unpublished data from the Madras Chemotherapy Centre). The lower infectivity of isoniazid-resistant strains is based on the fact that the proportion of such strains is much smaller in primary resistance than in acquired resistance (A. L. Cochrane).

From the special study on pathogenicity of isoniazid-resistant strains of Mycob. tuberculosis, the conclusion was drawn that almost 50 per cent. of the 76 strains tested showed no pathogenic effect in guinea-pigs, about 25 per cent. showed a slight effect, and 25 could not be considered as pathogenic (O. Garcia-Rosell).

In summary, the general impression is that tubercle bacilli that are both resistant to isoniazid and catalase-positive are virulent. Catalase-negative organisms do not show the same pathogenicity in experimental animals, but no such difference has yet been established in man.

The possibility of increasing isoniazid resistance to a maximum by means of the long-term application of isoniazid, consequently decreasing the epidemiological significance of isoniazid-resistant strains, did not prove to be correct (L. Šula).

There is a group of cases in which infection by resistant strains is particularly dramatic: cases of tuberculous meningitis. It is hoped that useful information may be obtained by matching the drug resistance pattern in tuberculous meningitis in children under five years of age with the general resistance pattern.

Conclusion

A certain parallelism has been described between sensitivity to drugs (particularly isoniazid), and pathogenicity. This has been demonstrated on animals, but there seems to be disagreement between the results of the animal experiments and of the clinical experience.

Available information is very scanty as very little work has been done on this subject. Further observations and research are required before a final conclusion can be reached.

In vitro resistance and clinical prognosis

In reviewing problems related to drug-resistant Myco. tuberculosis, it would be difficult not to touch on the relationship between the results of in vitro resistance determination and the clinical results of treatment with homologous and heterologous drugs. Analysis of the replies received from the Tuberculosis Expert Advisory Panel members to this question might point out areas of agreement and areas for possible further investigations.

The relationship between resistance and the results of treatment depends on the quality of resistance determination. The fact that, in many statistics, chronic patients who do not respond to treatment have been evaluated as excretors of sensitive bacilli shows that the level of resistance generally adopted is too high (E. Bernard). Under the conditions where 0.2 µg/ml for isoniazid and 4 µg/ml for streptomycin are significant, the relationship between the determination of resistance and the clinical results was satisfactory.

In many patients there is a mixture of drug-resistant and drug-susceptible strains. In their treatment, a clinical effect is obtained through the action of drugs on the susceptible strains of mycobacteria (Ph. V. Šebanov).

Some of the Panel members have a more definite point of view. J. Frimodt-Møller affirmed that it has been established beyond doubt that the prevalence of resistance to a certain drug renders it useless for further treatment; he added, however, that this is not always supported by sensitivity tests.

In any case, the definite correlation between in vitro resistance determination and the clinical results of treatment with drugs is very impressive (N. K. Menon). There is a clear difference between the results of treatment in patients with drug-sensitive and drug-resistant mycobacteria, particularly in cases with resistance to two or three drugs (A. Omodei Zorini, G. L'Eltore, A. S. Moodie, etc.).

As to the homologous preparations, significant or total resistance to one of the primary antituberculosis agents (streptomycin and isoniazid in particular) will adversely affect the clinical response of an individual to the drug in question (H. Walkup). In other words, homologous drugs are mainly unsuccessful in such patients (Sir Harry Wunderly).

Heterologous drugs are very much more satisfactory. Largely owing to the greater tolerance of the inhabitants of Hong Kong, the failure rate in treatment with heterologous drugs was not more than two per cent. (A. S. Moodie).

Though the occurrence of mutants resistant to two drugs is infrequent, and of those resistant to three, rare, the clinical response, other factors being equal, will depend on the relative effectiveness of the secondary drug in question. Favourable results have been reported from a variety of combinations of drugs (H. Walkup).

When previously isoniazid- or streptomycin-resistant cases became sensitive, in spite of continuous administration of the drugs, parallelism between clinical improvement and lessening or disappearance of resistance was found. When resistance to two or three drugs was present, this parallelism was noted less frequently (O. Garcia-Rosell). Some authors, however, repeat the well-known concept of W. McDermott¹ that the history of previous treatment has a greater bearing on the clinical results than in vitro resistance results (B. K. Sikand).

The decision whether to stop or to continue treatment with drugs to which mycobacteria have begun to show resistance must be based to a greater degree on clinical rather than on laboratory data (Ph. V. Šebanov).

Previously untreated "resistant" patients appear to respond, to some extent, to treatment with the same drug, as if the organisms were sensitive (N. L. Bordia). Previously treated resistant patients respond very poorly to standard therapeutics (B. A. Dormer). That is: patients with acquired resistance do not respond to treatment with drugs to which they are resistant (N. L. Bordia).

Conclusion

To sum up, a relationship clearly exists between the results of in vitro resistance determination and the clinical results of treatment with homologous and heterologous drugs. Drug resistance undeniably has an unfavourable influence on the clinical effect of the corresponding drug.

¹ McDermott, W. (1958) In: Veterans Administration - Armed Forces, Transactions of the 17th Conference on the Chemotherapy of Tuberculosis, Memphis, Tennessee, p. 262

Recommended research on drug resistance

What type of research could be carried out quickly, leading to an understanding of the drug resistance problem in tuberculosis control programmes in different countries?

With the object of finding a way to solve this problem, the Expert Advisory Panel members were asked for their advice.

They nearly all suggested that arrangements should be put in hand in all countries to follow up the prevalence of drug resistance and its pattern as long-term longitudinal studies.

These must be related to the standardization and improvement of laboratory methods. In particular, there should be a uniform method of drug sensitivity/resistance testing with universal standards to delineate between "partial" and "significant" resistance to the standard tuberculosis drugs. Reference laboratories should be organized in as many countries as possible.

These proposals are rational and, if approved, could lead to advances in future tuberculosis control.

The purpose of the WHO/TB/Techn.Information series of documents is to acquaint WHO staff and interested individual research and public health workers with the progress of tuberculosis research and control by means of:

- (1) summaries of some relevant problems;
- (2) field reports and other communications which are of particular interest but which would not normally be printed in any WHO publications;
- (3) papers that may eventually appear in print but which, on account of their immediate interest or importance, deserve to be made known without delay.

The issue of a paper in this series does not, therefore, constitute formal publication, and a paper so issued may, with the agreement of the author and WHO, be published in a WHO periodical or elsewhere.

Authors alone are responsible for views expressed in signed articles. The mention of manufacturing companies or of their proprietary products does not imply that they are recommended or endorsed by the World Health Organization.

TABLE 3. PRIMARY RESISTANCE

Author(s)	Year	% Resistance to:			No. of strains	% Resistance	Source
		Isoniazid	Streptomycin	PAS			
Furtos, N. C. & Doane, E. A., <u>USA</u>	1949	-	1 (case)	-	385 pat.	-	<u>J. Amer. med. Ass.</u> , 1949, <u>140</u> , 1274
Brennan, A. I. & Wickelhausen, R. H., <u>USA</u>	1949	-	1 (case)	-	-	-	<u>J. Amer. med. Ass.</u> , 1949, <u>140</u> , 1275
Baudot, J., Delaude, A. & Gay, <u>France</u>	1951	-	23	-	52	23	<u>Rev. Tuberc. (Paris)</u> , 1952, <u>16</u> , 61
Wilking, V. N., Nemir, R. L., Lincoln, E. M., Martin, J. D., <u>USA</u>	1952	-	4.6	-	187	4.6	<u>Amer. Rev. Tuberc.</u> , 1952, <u>66</u> , 63*
Thomas, O. F., Horne, N. W., Borthwick, W. M., Crofton, J. W., <u>UK</u>	1954	-	4 (cases)	4 (cases)	-	-	<u>Lancet</u> , 1954, <u>1</u> , 1308
Cummings, M. M. & Livings, D. C., <u>USA</u>	May-December 1952	-	2.6	-	1 166	-	<u>Amer. Rev. Tuberc.</u> , 1954, <u>70</u> , 637
Frapplier, A., Desjardins, R., Panisset, M., <u>Canada</u>	1953-1954	0.6 Rimifon 41.1 (Marsilid)**	10.8	0.6	686	-	<u>Canad. med. Ass. J.</u> , 1957, <u>76</u> , 653
Katz, S., Storey, P. B., McCormick, G. F., <u>USA</u>	1954	2.3	1.6	-	385	-	<u>Amer. Rev. Tuberc.</u> , 1954, <u>70</u> , 887
Chaves, A. D. et al., <u>N.Y.</u>	July 1953-January 1955	2.3	1.6	-	385	-	<u>Amer. Rev. Tuberc.</u> , 1955, <u>72</u> , 143
Chaves, A. D. et al., <u>N.Y.</u>	1955	1.0	0.5	-	390	-	<u>Amer. Rev. Tuberc.</u> , 1956, <u>74</u> , 293
Meissner, G., <u>Germany</u>	1954	6 (cases)	-	-	-	12.0	<u>G. ital. Chemioter.</u> , 1954, <u>1</u> , 320

* This study concerned children only.

** According to the author, the very high resistance to the isopropyl form of isoniazid (Marsilid) is attributed to a natural rather than an acquired resistance of the strains of tubercle bacilli tested.

TABLE 3. PRIMARY RESISTANCE (continued)

Author(s)	Year	% Resistance to:			No. of strains	% Resistance	Source
		Isoniazid	Streptomycin	PAS			
Beck, F., USA	1955 (five-year study)	-	1.6	-	600	-	<u>Amer. Rev. Tuberc.</u> , 1955, <u>72</u> , 1
Fox, W., Wiener, A., Mitchison, D. A., Selkon, J. R., Sutherland, I., UK	1955-1956	0.7	2.3	2.2	1 404	-	<u>Tubercle</u> , 1957, <u>38</u> , 71
British Tuberculosis Association, UK	1959-1960	-	-	-	-	4.5	<u>Tubercle</u> , 1963, <u>44</u> , 1
Madras Chemotherapy Centre	1956-1957	3.6	2.2	2.6	192	-	
Bell, W. & Brown, P. B. (1960) Ashanti, Ghana	1958	9.1	8.5	5.5	343	15.4	<u>Tubercle</u> , 1960, <u>41</u> , 277
Bell, W. & Brown, P. B. (1961)	1960	18.4	8.8	4.8	125	23.2	<u>Amer. Rev. Tuberc.</u> , 1961, <u>84</u> , 1
Chaves, A. D. Dangler, G., Abeles, H., Robins, A. B., & Widelock, D.	1960	4.1	3.5	2.1	428	(16.4)	<u>Tubercle (Lond.)</u> , 1960, <u>41</u> , 32
Pepys, J., Mitchison, D. A., Kinsley, B. I., Uganda JH/PH	III 1953- II 1955	-	-	-	56	-	
Sulfone	III-X 1956	7.9	-	2.9	-	-	
Kenya	1956-1959	6.8	-	-	191	-	
TB1-Pilot	I-IV 1957	3.75	-	-	40	-	
Isoniazid	V-XII 1957	12.6	-	10.7	-	-	
TB1/DPT	VIII 1958- II 1959	16	-	12.9	-	-	
		9.9	-	4.1	-	-	
WHO TB Chemotherapy Centre, Nairobi, Kenya-4	1958-1961	-	-	-	32	6	Report from 29 November 1961
Dissmann, E. & Iglauer, E., Klagenfurt	1955	3	-	-	190	-	<u>Tuberk.-Arzt</u> , 1961, <u>14</u> , 1-9
	1956	4	-	-	166	-	
	1957	7	-	-	190	-	
	1958	9	-	-	157	-	
Short, G. M., Uganda	1959-1960	8.7	2.1	1.1	242	-	<u>Tubercle (Lond.)</u> , 1961, <u>42</u> , 51
Public Health Laboratory Service, England & Wales	1960	-	-	-	1 371	3.1	<u>Tubercle (Lond.)</u> , 1961, <u>42</u> , 31
Hershfield, E. S., Karlson,	1955-1962	2c	2c	3c	372	1.9	Proceedings of the Staff Meet: of the Mayo Clinic, 1963, <u>31</u>

TABLE 1. PRIMARY RESISTANCE

Author	Country/ Territory	Year	Resistance to:			No. of strains	% Resistance	Remarks
			Isoniazid	Streptomycin	PAS			
A. S. Moodie	Hong Kong	1958-1962					12	No less than 12% of positive cases who have strongly denied previous treatment
A. Omodei Zorini	Italy	1960-1961	4	4			11-12	Data from Istituto C. Forlanini
G. L'Eltore	Italy	1960	4	4			12	Data from Istituto C. Forlanini
Et. Bernard	France	until 1957	2.0	3.6	1.6	707	5.1	Hôpital Laennec
		1961-1962 1963					3-5 10	Hôpital Laennec Centre d'Etude de la Resistance (prévu pour tout le pays)
R. Neubauer	Yugoslavia	1958-1960 1958 1959 1960 last years				1 501	10.6 11 10.2 10.3 5	B. Fortic Slovenia Goldman, Kamanicu
B. A. Dormer	Union of S. Africa		1/2 (5 gamma)					Previously untreated admissions to King George V Hospital
Chaves et al.	USA	1955	1					Different criteria were used
US Public Health Service	USA	IX 1960- XII 1962	1.6	2.8	0.8	2 400	4.0	To at least one of three drugs
Cummings & Livings	USA (Vet. Admin.)	1952 1956-1957						No significant increase
N. L. Bordia	India (Mysore State)			2-3	1		12	Tumkur Survey

TABLE 6. PRIMARY RESISTANCE (continued)

Author	Country/ Territory	Year	% Resistance to:			No. of strains	% Resistance	Remarks
			Isoniazid	Streptomycin	PAS			
I. Macgregor	UK	1955-1956	0.7	2.3	2.2	1 000	4.5	Too few patients to be truly representative
Med. Res. Council Brit. Tub. Assoc.	UK	1959-1960				171	11.1	
Pub. Health Lab. Service	England and Wales	1960				1 300	3.1	
Thomas	England (Birmingham)	1963					2.5	
Sir Harry Wunderly	Australia						uncommon	5 Australian States and Papua, New Guinea
Ph. V. Šebanov	USSR						6.6-8.2	of all new cases
K. Styblo	Czechoslovakia						4-5	
A. L. Cochrane	Wales		1.0	2.1	1.0			No change over last 5-10 years
O. Garcia-Rosell	Peru	1959 IX 1960- VIII 1961					29.3 26.09	Thorax Hospital Orbegozo Dispensary
L. Šula	Czechoslovakia	1961, 1962, 1963				78	7.8	Bohemia and Moravia (children & adolescents)
		1961, 1962, 1963				230	2.5 3.5	Adults in Kolín
Sauter	Switzerland	1963					12.5	Provisional data
T. I. Gökçe	Turkey	1960, 1961, 1962, 1963	7.6-30.7	7.6-23.1		13		Sanatorium d'Erenköy
		1953-1955	4	8		400	12)	Sanatorium
		1955-1962	4.2	3.1		1 300	7.3)	Atatürk
		1958-1963				124	12	Sanatorium Valdebag
		1960					20.4)	TB Clinic of University
		1961					20.8)	of Istanbul
		1962					23.5)	
		1956-1960	17 (5 gamma) 15 (3 gamma)	18 (10 gamma) 30 (5 gamma)		100		Sanatorium Heybeliada

TABLE 6. PRIMARY RESISTANCE (continued)

Author	Country/ Territory	Year	% Resistance to:			No. of strains	% Resistance	Remarks
			Isoniazid	Streptomycin	PAS			
K. N. Rao	India						1.3-14 1-4	
P. K. Sen	India (Calcutta)						0.5-5	
Raj Narain	" (NTI, Bangalore)						8.3	
K. T. Jesudian	" (Madanapalle)	1956-1962	1.3	1.2	3.7	441		
N. K. Menon	" (Hyderabad)	1959-1960	15	4			17	
B. K. Sikand	" (New Delhi, TB Centre)	1961 1962	14 14			451 550		
H. E. Dingley	" (Mehrauli TB Hospital)					150	17.34	
J. Frimodt-Møller	" (Madanapalle)	1959	6	6				
Madras Chemotherapy Centre	" (Madras)	1956-1962	4.7	3.1		838 829		

TABLE 8. ACQUIRED RESISTANCE

Author(s)	Country/ Territory	Year	% Resistance to:		No. of strains	% Resistance	Remarks
			Isoniazid	Streptomycin			
A. S. Moodie	Hong Kong	1958 1962	37* 82	74* 58	?		1/3 of positive cases attending the public clinic
A. Onodei-Zorini	Italy	1960-1961	39.1	38.6	6.4	55	Data from Istituto C. Forlanini
G. L'Eltore	Italy	1960-1961	39.1	38.6	6.4	55	Data from Istituto C. Forlanini
Et. Bernard	France	1955 1956 1957 1958 1959 1960 1961				47) 45) 68.5) 56) 57.8) 54) 57.8)	Hôpital Laennec
R. Neubauer	Yugoslavia				31	18 pat.	Simeonov, Sarajevo
American National Tuberculosis Association	USA				All ad- missions of US Admin.	40	Tucker
	USA					ov. 40	United States Public Health Service
I. Macgregor	UK				410	82	British Tuberculosis Association
Sir Harry Wunderly	Australia					7-10	5 Australian States & Papua, N. Guinea
Ph. V. Šebanov	USSR					42-65	of treated and re-admitted patients
K. Styblo	Czechoslovakia (Kolín)				63	22.2	In-patients with relapse

* Of all resistant cases

TABLE 8. ACQUIRED RESISTANCE (continued)

Author(s)	Country/ Territory	Year	% Resistance to:			No. of strains	% Resistance	Remarks
			Isoniazid	Streptomycin	PAS			
Sauter	Switzerland	1963	26.52	19.53	3.65	1 071	32	
T. J. Gökçe	Turkey	1960-1962	50.4	56.3	13.6	220)		Sanatorium D'Erenköy
		1963	55.8	57.8	16.9	242)		
		Last 10 years	31.12	34.05	3.23			Sanatorium Atatürk
		1958-1963				124	20	Sanatorium Valdebag
		1957				117	58.1)	
		1958				146	58.2)	
		1959				217	53.9)	TB Clinic, University of Istanbul
		1960				158	43)	
		1961				172	47.1)	
		1962				173	46.8)	
						983	Total 50.9	
			(5 µg)	(10 µg)				
		1955	23.5	38.2		387)		
		1956	25.6	53.6		407)		
		1957	27.1	48.6		432)		
		1958	20.1	38.3		529)		Sanatorium Heybeliada
		1959	24.9	39.3		539)		
		1960	23.3	49.9		685)		
		1961	23.3	53.5		842)		
		1962	27.6	58		910)		
		1963	28.1	58.7		925)		
K. N. Rao	India	Last 5- 10 years	10-48	5-27				
P. K. Sen	India (Calcutta)						2-15	
H. N. Sengal	India (Kasauli)	1956-1959				123	24	
		1959-1963				303	80	
K. T. Jesudian	" (UMT Sana- torium, Madanapalle)	1956-1962				1 489	14.3	
N. K. Menon	" (Hyderabad)	1959-1960					52	
B. K. Sikand	" (New Delhi TB Centre)	1961	48			451		
		1962	44			550		
H. B. Dingley	" (Mehrauli TB Hospital)					150	37.35	
J. Frimodt-Møller	" (Madanapalle)	1959					20-25	Sample survey in 12 towns
		1959-1960				283	61	Discharged from UMT Sanatorium
B. C. Roy	" (Research TB Institute)					166	55	