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Drug Resistance in Patients with Pulmonary Tuberculosis

PRESENTING FOR TREATMENT AT THE INFECTIOUS DISEASES HOSPITAL, SALISBURY

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The problems of the treatment of patients harbouring resistant tubercle bacilli, and the prevention of the emergence of resistant organisms in patients under treatment, have exercised the minds of all those concerned with the prevention and eradication of tuberculosis for a considerable number of years.

The gravity of the problem has been emphasised recently by the Canadian Tuberculosis Association who, in their March Bulletin (1961), refer to "A Cloud Bigger than a Man's Hand"; and by Dr. James W. Raleigh (1961), Medical Director of the American Thoracic Society, who is of the opinion that "Only the above-water portion of the 'iceberg' of drug resistance is now visible."

Workers in the Federation have been aware of the existence of this problem for some years, but have been seriously handicapped in their efforts to combat the problem by the fact that, in the Federation, there exists no tuberculosis laboratory specially equipped to carry out full bacteriological examinations of specimens of bronchial secretions, including drug sensitivity tests. The pressure of general pathological and bacteriological work which existing laboratories are called upon to perform is so great that their staff have not the necessary time to devote to the time-consuming procedures necessary for a full bacteriological examination of bronchial secretions.

Dr. A. J. Walker Wilkins, Medical Officer of Health, arranged in January, 1961, for the W.H.O./U.N.I.C.E.F. assisted specialist tuberculosis laboratory in Nairobi to examine specimens of bronchial secretions which are flown to them each week in refrigerated containers. Specimens are sent from patients in the infectious diseases hospitals and from patients (African, European, Asian and Coloured) attending the municipal chest clinics. The majority of specimens are from patients in the African infectious diseases hospital, and the results of the examination of these specimens form the basis of this interim report on the prevalence of drug resistance in Salisbury.

Materials and Methods

Specimens of bronchial secretions were collected in plastic screw-top containers and kept in a refrigerator prior to despatch by air in a refrigerated container. The plastic containers were subsequently found to leak and were discarded in favour of "universal containers." Priority was given in the early days to "new admissions" and to patients who were suspected, on clinical grounds, of harbouring resistant bacilli. At first it was only possible to send one specimen from each patient for examination, but subsequently we were able to introduce a routine procedure of sending three specimens from each patient.

The W.H.O. laboratory report first on the microscopic examination of direct smears, then on the results of culture, and finally on the sensitivity of the bacilli to the three major drugs: streptomycin (S.M.), Isoniazid (INAH) and para-aminosalicylic acid (P.A.S.).

The criteria for resistance to each of the drugs adopted by the W.H.O. laboratory are as follows:

I.N.A.H.—Growth is defined as growth of 20 or more colonies.
Sensitive.—No growth on 0.2 mcg/ml.
Resistant.—Growth on 1 mcg/ml.
Doubtful Resistant.—Growth on 0.2 mcg/ml. If growth is repeated on 0.2 mcg/ml. or more, the bacilli are classified as resistant.
P.A.S. and S.M.—In these two drugs the degree of resistance is expressed as the ratio:

$$\frac{\text{Lowest concentration of drug inhibiting test organisms}}{\text{Lowest concentration of drug inhibiting H. 37 Rv.}}$$

Sensitive.—A resistance ratio of two or less.
Resistant.—A resistance ratio of eight or more.
Doubtful Resistant.—A resistance ratio of four. If, however, on a repeat test a resistance ratio of four or more is obtained, the bacilli are classified as resistant.

Results

P.A.S. Sensitivity.—The criteria for reporting strains as resistant to P.A.S. set out above have produced results which suggest that the value of P.A.S. sensitivity tests on African strains are as uncertain as they have been proved to be on Indian strains (Selkon *et al.*, 1960).

In our study no less than 15 of 24 patients, whose strains were examined and found resistant before chemotherapy was commenced, were resistant to P.A.S. alone, while only two of 26 patients whose strains were examined and found resistant after they had received chemotherapy were reported as resistant to P.A.S. alone.

It is to be hoped that further work will result in a more reliable P.A.S. sensitivity test, as P.A.S. is used extensively, combined with I.N.H., in the treatment of outpatients. It is obviously of great importance to the physician to know whether the strains are sensitive to both drugs.

Similar difficulties have not been encountered with S.M. and I.N.H. sensitivity tests and the results of these tests are discussed below.

Six hundred and fifty-three specimens of bronchial secretions from 506 patients in the African infectious diseases hospital between January and December, 1961, were examined. Sensitivity tests were completed on 200 sputum positive cases, excluding the 17 patients reported as resistant to P.A.S. alone.

Table I

Bacterial Resistance in 200 Positive Cases

	Patients	Percentage
Sensitive bacilli	168	84
Resistant bacilli	32	16
S.M. resistant	6	3
I.N.H. resistant	13	6.5
S.M. and I.N.H. resistant	2	1
S.M. and I.N.H. and P.A.S. resistant	11	5.5

The results are further analysed to show the prevalence of resistant strains in patients prior to the start of treatment (Primary Resistance, Table II) and in patients under treatment (Secondary Resistance, Table III).

Discussion

The fact that 32 out of 200 patients with pulmonary tuberculosis with positive sputums admitted to our hospital during 1961 for treatment or re-treatment were carriers of tubercle bacilli resistant to one or more of our three main drugs confirms the necessity of carrying out sensitivity tests on all patients as soon after admission to hospital as possible. The value of these tests is greatest in the case of patients, newly admitted to hospital, who give no history of previous antituberculosis chemotherapy. In these patients we have no grounds for suspecting that the infecting bacilli may be resistant to our drugs, and by the time drug resistance is suspected the bacilli may have become resistant to two or more of our drugs. One of the most notable features of our results is that all our patients with primary resistant strains were resistant to one drug only, whereas in patients known to have had chemotherapy prior to the sensitivity tests being carried out, more than half were resistant to two or three drugs.

Patients resistant to one drug only have a far better prognosis than the true therapeutic failures who are resistant to all three main drugs, as they can be treated with a combination of two "front line" drugs supplemented, if necessary, by one of the "second line" or "salvage" drugs. The patient who is resistant to all three drugs must rely for his treatment on a series of "second line" drugs whose tuberculous activity is relatively weak and whose

Table II

Primary Drug Resistance

Number of patients	Resistant Strains					
	Total	%	S.M.	%	I.N.H.	%
84	9	10.7	5	5.9	4	4.7

Table III

Secondary Drug Resistance

Number of patients	Total	%	S.M.	%	I.N.H.	%	S.M. & I.N.H.	%	S.M. & I.N.H. & P.A.S.	%
116	23	20.7	1	0.9	9	7.7	2	2.6	11	9.5

capacity for producing undesirable side effects is formidable.

The physician must rely on the results of sensitivity tests alone for his diagnosis of primary drug resistance, and it is thus important that more than one specimen of bronchial secretions be submitted to the laboratory, as the results of a single test may be fallacious.

The prevalence of primary resistance in Salisbury is much higher than the rate reported in Britain of 3.1 per cent. (Public Health Laboratory Service Report, 1961), but is not so alarming as that reported in East Africa for primary Isoniazid resistance of 16 per cent. (Pepys *et al.*, 1960). The rate in Salisbury is, in fact, very similar to that reported in Madras, where the tuberculosis chemotherapy centre (1960) found a prevalence rate of 9.2 per cent.—5.9 per cent. Isoniazid resistant and 3.3 per cent. streptomycin resistant.

Primary drug resistance is generally accepted as arising from infection by bacilli which are already resistant to one or more of the standard drugs. There is, however, a large reservoir of P.A.S. and I.N.H. in tablet form readily available for uncontrolled distribution to the public by outpatients who are themselves on treatment. It is thus possible that some of our patients who on admission deny previous chemotherapy may, in fact, have been given P.A.S. or I.N.H. by well-meaning friends or relatives prior to admission.

The emergence of drug-resistant bacilli is, without a doubt, the fault of either the physician or the patient or both. The physician is often guilty of accepting sputum conversion and marked radiological improvement as indicating cure after only a short course of chemotherapy. Keers (1962), amongst others, has stressed the following basic principles governing the employment of the three standard drugs, which have been established and universally accepted:

(1) At least two of the standard drugs require to be administered simultaneously if the emergence of a strain of drug-resistant organisms is to be prevented.

(2) The full dose of each drug must be taken with unfailing regularity. Inadequate dosage or irregular administration is not only therapeutically ineffective, but will lead to the development of drug resistance.

(3) Treatment must be prolonged. A minimum daily treatment for 18 months is necessary for the average case; the more severe case, with much tissue destruction, should remain on daily chemotherapy for two to three years.

Probably the most difficult problem confronting those physicians responsible for the treatment of tuberculosis to-day is in providing adequate facilities and staff to enable outpatients to be kept under close surveillance and to ensure that the prescribed chemotherapy is taken in adequate dosage regularly and for adequate periods.

The two drugs most frequently used for the treatment of outpatients are Isoniazid and P.A.S. In the Federation these drugs are given separately with the danger that one of the drugs may be omitted, thus increasing the risk of the emergence of drug resistance to the other. It is common practice in Britain and other developed countries to supply this combination of drugs in preparations containing a mixture of the two drugs, and only when so issued can the combination be regarded as adequate.

The efficacy of domiciliary treatment of pulmonary tuberculosis, providing there is adequate surveillance, has been demonstrated in Madras (Tuberculosis Chemotherapy Centre, 1960), in Tanganyika (Gordon, 1961) and in Kenya (Turner, 1962). There should never be any question of issuing a month's supply of drugs to the patient and piously hoping that he will take the drugs regularly as prescribed. The patient requires to be seen frequently so that not only may manifestations of drug toxicity or hypersensitivity be promptly detected, but the opportunity can be taken to check in detail the exact quantity of drugs taken each day. The protracted nature of the treatment makes considerable demands on the patient's endurance and an atmosphere of enthusiastic interest must be maintained throughout the many months of his treatment. Frequent visits, of not less than one per week, further reduce the amount of drugs available for uncontrolled distribution to the community. There is no practical alternative to long-term outpatient chemotherapy, and the sooner this fact is accepted and funds allocated to improve this service, the sooner will tuberculosis cease to be a serious public health problem in our country.

Summary

(1) The prevalence of bacterial resistance to the three main antituberculosis drugs confirms the necessity for carrying out drug sensitivity tests on patients on admission to hospital.

(2) The basic principles governing the employment of the three standard drugs are discussed.

(3) The combination of P.A.S. and Isoniazid for the treatment of outpatients can only be regarded as adequate when the combination is supplied in preparations containing a mixture of the two drugs.

(4) Frequent visits by a health visitor to the patient or frequent visits by the patient to the chest clinic are necessary to ensure that the prescribed chemotherapy is taken in adequate dosage, regularly and for adequate periods.

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