Drug-resistant tuberculosis in Waltham Forest, 1953-68

A clinical and epidemiological study

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A study of acquired and primary drug resistance in pulmonary tuberculosis has been made in the London Borough of Waltham Forest over the 15-year period 1953-68. Aetiology, clinical and bacteriological features, treatment, and prognosis are examined and contrasted for both groups of patients. The incidence of both types of resistance is compared with the national incidence and is considered in relation to Commonwealth immigration into the borough. Reasons are suggested for the decline of the acquired and the rise in the primary type of resistance. National surveys of drug-resistant tuberculosis have served a valuable purpose in focussing epidemiological attention on the many problems raised by this potentially dangerous form of the disease.

Although the prognosis of tuberculosis has improved remarkably in recent years, infection with drug-resistant organisms may frustrate the physician's intention to secure the best possible treatment for his patient. The necessity to initiate treatment weeks or months before the sensitivities of the bacillus can possibly be known involves the calculated risk that the drugs chosen may not be appropriate to the particular case. The use of a combination of drugs, which includes one or more to which the bacillus is resistant, may lead to the development of resistance to the companion drug, or drugs, a risk which is enhanced by any failure on the patient's part to adhere rigidly to the prescribed regimen. It is not an exaggeration to state that a patient's life may depend on the care with which chemotherapy is initially prescribed, and on the extent to which the physician can secure his active co-operation in a prolonged, irksome, and sometimes dangerous course of treatment.

Tuberculous patients may harbour resistant bacilli for two main reasons. When a newly diagnosed case is found to have resistant bacilli these are said to exhibit 'primary resistance,' which is presumed to be due to infection from a source case excreting resistant bacilli. 'Acquired resistance' occurs when a patient excreting initially sensitive strains of bacilli begins to excrete resistant bacilli as a result of inappropriate treatment. The amount of resistant disease in a community is thus a measure of the effectiveness with which

antituberculosis chemotherapy has been deployed, and a high level of such resistance is evidence of bad treatment.

PRIMARY RESISTANCE

The Medical Research Council has estimated the prevalence of primary resistance to one or more of the three 'standard' drugs (streptomycin, para-aminosalicylic acid, and isoniazid) in the United Kingdom on two separate occasions. In 1955-6 the figure was 4.5% of newly diagnosed cases (Fox *et al.*, 1957) and in 1963 it was 4.1% for the nation as a whole, but 2.1% in London and south-east England (Miller *et al.*, 1966). These figures provided reassuring evidence that the problem was being contained, although other evidence has suggested that the position is less favourable in many overseas countries.

ACQUIRED RESISTANCE

The British Tuberculosis Association (1963a) estimated the level of acquired resistance in the United Kingdom in 1960-1 in a survey of patients from 38 chest clinics, whose sputum had remained positive for a year or more. The results suggested that there were 6.22 patients excreting bacilli resistant to one or more of the 'standard' drugs per 100,000 of population. At least 3,500 such patients in the United Kingdom were thought to have bacilli resistant to one drug and at least 1,800

to have bacilli resistant to three drugs. As in the case of primary resistance, other evidence shows that the problem is much greater elsewhere.

As far as the United Kingdom is concerned, the problem is probably a diminishing one. In Birmingham, Thomas (1963) demonstrated a falling incidence of acquired resistance following a peak in 1957, pointing out the considerable weighting of the drug-resistance register by patients notified in 1952-4, when the deployment of chemotherapy was comparatively unsophisticated. The mortality in these patients was high; up to half of those with multiple resistance were dead in five years. The scale of the problem was further reduced by successful treatment in most of the remainder, so that the public health danger diminished rather than increased, subsequent improvements in the standards of chemotherapy ensuring against its recurrence on a large scale. Experience in Wolverhampton (Aspin and Cross, 1962) confirmed the combined effect of mortality, further therapy, and normal healing in gradually eroding the problem of the resistant infecter pool.

CLINICAL ASPECTS

The successful treatment of resistant tuberculosis calls for considerable experience and determination on the physician's part, since the affected patients are frequently unco-operative, truculent, unmotivated towards recovery, and unconvinced of the value of the treatment. Among the best reported results are those of Somner and Brace (1966) who, in a dedicated and tenacious enterprise, obtained sputum conversion in 22 out of 26 chronic cases by two years' continuous treatment using the reserve drugs, ethionamide, cycloserine, and pyrazinamide. Comparable results have also been reported by Zierski (1964) in Poland, Jančík, Zelenka, Toušek, and Máková (1963) in Czechoslovakia, and Pines (1965) in this country; but the daunting nature of such undertakings was shown in a co-operative study by the British Tuberculosis Association (1963b) when, out of 117 patients, only 14 persisted with the prescribed year's course, nearly half having been withdrawn by their doctors because of toxic effects of the drugs used and over one-third having refused treatment or discharged themselves. The general results of treatment in this country are reflected in the report of the Chief Medical Officer of the Ministry of Health (1968). Of 4,057 resistant cases registered between 1962 and December 1966, 31% had died and only 33% had converted to negative sputum.

THE PROBLEM IN WALTHAM FOREST, 1953-68

In 1962 the chest services in the Essex boroughs of Walthamstow, Chingford, and Leyton were reorganized and centred in the new Whipps Cross Hospital Chest Clinic, and in 1965 these three boroughs were conveniently unified to become the London Borough of Waltham Forest (population 247,000). Waltham Forest is an urban area of mixed industrial and residential character in north-east London, bounded on the north and east by Epping Forest and on the west by the valley of the river Lea.

During the 16 years under review (1953-68) 1,809 cases of respiratory tuberculosis were notified, among which records show 12 (0.7%) cases of primary and 38 (2.1%) cases of acquired drug resistance. This report analyses these 50 cases to determine the causes of resistance and describes the treatment and outcome.

ACQUIRED DRUG RESISTANCE These 38 patients were originally diagnosed as suffering from tuberculosis at dates ranging from 1931 to 1966, and Table I shows how the dates of diagnosis were spread over the period.

TABLE I
DATE OF ORIGINAL DIAGNOSIS OF TUBERCULOSIS

Year of Diagnosis	No. of Cases
Before 1950	14
1950-59	16
1960-66	8
Total	38

Of the 38 cases, 27 were men and 11 women. Table II shows that at the time when tuberculosis was originally diagnosed the men were considerably older than the women and that nine years elapsed on average between diagnosis and the positive identification of bacterial resistance.

TABLE II
AVERAGE AGE (YEARS) AT DIAGNOSIS

Average Age when:	Men	Women	All Patients
Tuberculosis first diagnosed	46	29	41
Diagnosed 'resistant'	54	40	50
Interval (yr)	8	11	9

Without exception, the patients all suffered from an advanced form of the disease with positive sputum. Cavitation was present at some time in every case, bilaterally in 28 cases out of 38. Many

patients had persistent cavitation with positive sputum for years on end. Table III shows that two-thirds of the patients had three or more zones involved (as seen on the chest radiograph) out of a total of six.

TABLE III
EXTENT OF PULMONARY DISEASE

Zones Involved	No. of Patients
1-2	13
3	10
4-6	15
Total	38

The 38 cases were found on scrutiny to fall into three groups:

Group 1 23 patients whose chemotherapy was prescribed in a manner which made resistance a likely outcome;

Group 2 10 patients who were unable to muster the determination to overcome distaste for treatment which was correctly prescribed and which usually led to much initial improvement;

Group 3 5 patients in whom no definite cause could be found.

Group 1—Faulty treatment This was the largest group. In all but three cases, chemotherapy was first prescribed after the year 1950, when published co-operative studies were demonstrating the supreme importance of double or triple therapy and the critical nature of both dosage and duration of treatment. Nevertheless, the records show that single or untried mixtures of drugs were employed in what seems to have been a haphazard fashion intermittently over several years in many of the patients, and mostly on a domiciliary basis. In at least 9 of these 23 patients, chemotherapy had begun at the patient's home.

When the responsibility for the care of these patients passed to the newly formed Whipps Cross Hospital Chest Clinic, a serious attempt was made to establish their re-treatment on a rational basis. Many of them, however, proved refractory to the suggestion of a new approach, and several had difficult personalities engendered by years of ill health and the ineffectual treatment which must be regarded as the prime cause of the problem.

The case histories of this group showed that several patients had had genuine side effects which rendered treatment irksome; one had a severe isoniazid neuropathy and three probably suffered from mental changes due to isoniazid and cycloserine, but in no case could bacterial resist-

ance be ascribed directly to side effects on the one hand or to hypersensitivity reactions on the other.

Among this group, many were finally persuaded to accept a new chemotherapy regimen, and in 9 out of 23 the disease was 'arrested' at the 1969 review. Eleven had died—mostly due directly to active tuberculosis—one had a positively discharging chest-wall sinus but healed pulmonary disease, and in two patients the disease was currently 'quiescent' under the influence of reserve chemotherapy. Further details are given in Table IV.

Group 2—Unco-operative patient This group comprised 10 patients who appear to have been unco-operative from the start, this being the main cause of their drug-resistant infection. They were mainly recalcitrant people of the type known to every chest physician, disgruntled habitual defaulters or self-dischargers with defects of character amounting sometimes to frankly psychopathic states. Five discharged themselves against advice, three refused readmission, and three were admitted to mental hospitals, one having attempted suicide possibly due to isoniazid effects. One was mentally retarded and another was a likeable old miner with massive fibrosis and a casual attitude to his disease. In all of these patients, chemotherapy was first prescribed after 1952, and in most after 1956. All received initial treatment in hospital, correctly prescribed as triple (4 cases) or double (6 cases) chemotherapy. Nevertheless, most (7) of this group failed to achieve negative sputum at first treatment, and it is likely that their failure to take drugs as prescribed dated from their first hospital admissions.

The mortality of this group was high, 7 out of 10 dying with active tuberculosis. Of the three survivors, one is a permanently hospitalized schizophrenic who was persuaded to have a thoracoplasty, and two have accepted reserve chemotherapy which has recently effected sputum conversion. Further details are shown in Table IV.

Group 3—No obvious cause In five cases resistance emerged for no apparent reason, the most likely explanation being undetected failure on the patients' part to take drugs as prescribed, although there is no reason to believe that they were unco-operative as a group. Only one patient in this group died of tuberculosis without the benefit of reserve chemotherapy; four were treated with reserve drugs, which arrested the disease in three cases and have led to sputum conversion in the fourth (see Table IV).

Re-treatment and outcome In the 1950s the number and effectiveness of reserve drugs were very limited, so that several of the earlier patients in this series did not have reserve treatment of such a high standard as those who came later.

Of the 19 patients who died, 15 had been prescribed regimens of reserve drugs but all failed to take them as prescribed. Several died at a time when the choice of reserve drugs was very limited.

Of the 19 patients who survived, 12 achieved arrest of disease by reserve drugs prescribed from 1960 onwards, usually in combinations of three or more, standard drugs also being used where sensitivities and expediency permitted. Ethionamide, cycloserine, and pyrazinamide were used in nearly all cases, and viomycin, tetracycline, thiacetazone, kanamycin, ethambutol, and capreomycin occasionally. In the successful cases, sputum conversion occurred mostly within a few months of starting re-treatment, which was usually continued for two years or more. Five further patients achieved negative bacteriology on reserve treatment but at the time of review cannot yet be considered to have arrested disease.

Only one patient continues to excrete resistant bacilli from a chest-wall sinus despite re-treatment. This is a case of empyema following an old thoracoplasty.

The status of all 38 patients in 1969 is given in Table IV, classified according to the aetiology of drug resistance. The best prognosis was in the group of patients in whom no obvious cause could be found, only one death occurring out of five patients. Next came the group whose initial treatment had been faulty, 11 dying out of 23. The

unco-operative group fared worst, mainly because they would not accept re-treatment, and in this group 7 out of 10 died.

As might be expected from the data in Table II and the chronic nature of the disease, most of the deaths occurred between the ages of 50 and 70, the youngest being a Pakistani woman aged 25 with far advanced disease and multiple drug resistance acquired before entry to this country. Ten patients survived up to five years, and six up to 10 years after the diagnosis of drug resistance.

In this group of patients there was a tendency in individual cases for resistance to become multiple as time went on but occasionally the reverse happened. In two chronic isoniazid-resistant cases the bacilli became fully sensitive after an interval of two years or more during which none of the standard drugs had been prescribed. In Table V the number of standard drugs, for which resistance is quoted, is taken as the highest number recorded for each patient at any time. Several patients also had bacilli resistant to some of the reserve drugs. Single drug resistance was usually to isoniazid. When two drugs were involved, they were more often isoniazid and streptomycin in that order. Isoniazid was more often involved in drug resistance (34 cases) than streptomycin (28 cases) or para-aminosalicylic acid (25 cases).

Table V also shows the difference in prognosis between single and multiple drug resistance. Single drug resistance was followed by death in only one case—a massive relapse which proved fatal before reserve treatment could be instituted. Multiple resistance, on the other hand, carried a mortality of well over 50%.

TABLE IV

ACQUIRED DRUG-RESISTANT TUBERCULOSIS: STATUS OF ALL PATIENTS IN 1969

Cause of Resistance	No.	Dead	Active Disease	Quiescent	Arrested
Faulty treatment	23	11	1	2	9
Unco-operative patient	10	7	—	2	1
Unknown	5	1	—	1	3
Total	38	19	1	5	13

PRIMARY DRUG RESISTANCE During the period under review (1953-68 inclusive) the first two reports of primary drug resistance appeared in 1960 and 1962, both in United Kingdom citizens. From 1964 to 1968, 10 more cases appeared, two being U.K. citizens and eight Asians from Pakistan (5 cases), India (2 cases), and Kenya (1 case). The four U.K. citizens were men of average age 53; of the Asians four were men of average

TABLE V

ACQUIRED DRUG RESISTANCE: DETAILS OF DRUGS INVOLVED

Resistant to	No. of Patients	Resistant to			Deaths	
		S (1)	P (2)	H (4)	No.	%
1 drug	7	S + P (1)	S + H (8)	H + P (4)	1	14
2 drugs	13	S + P + H (18)			7	54
3 drugs	18				11	61
Total	38	S (28)	P (25)	H (34)	19	

S=streptomycin; P=para-aminosalicylic acid; H=isoniazid

TABLE VI

PRIMARY RESISTANCE: DETAILS OF DRUGS INVOLVED

Resistant to	No. of Patients	Resistant to			No. of Relapses
1 drug	8	S (1)	P (3)	H (4)	0
2 drugs	3		P+H (1)	S-H (2)	2
3 drugs	1	S+P+H (1)			1
Total	12	S (2)	P (4)	H (6)	3

S=streptomycin; P=para-aminosalicylic acid; H=isoniazid

age 34 and four were women of average age 25. Although many of the patients had acute toxæmic disease, lung involvement tended to be less extensive than in patients with acquired resistance; thus eight had one to two zones and four had three zones involved. All were co-operative and anxious to be cured except for one elderly Indian with kala-azar. In eight patients the bacilli were resistant to a single drug, in three they were resistant to two drugs, and only one patient showed triple resistance, details being shown in Table VI.

With the exception of the Indian with kala-azar (see later), all 12 patients were treated initially with standard triple chemotherapy, the intention being to continue daily streptomycin, PAS, and isoniazid for three months after which streptomycin would be discontinued and treatment completed with the other two drugs, for a total period of not less than 18 months. The receipt of sensitivity reports revealing resistance called for modifications of treatment. These are described according to the number of drugs involved, and the results are given.

Resistance to one drug (8 cases) A report of resistance to one drug was not specially disturbing, since reliance could be placed on the combined effectiveness to date of the remaining pair. Nevertheless, an alternative was usually prescribed in place of the ineffective drug, and this revised triple therapy was continued with a subsequently reduced weekly total of streptomycin, into the fifth or sixth month, when the streptomycin was finally discontinued. Progress at this stage was satisfactory in all eight patients and treatment was completed with two (occasionally three) oral preparations. More problems arose, in fact, out of hypersensitivity, toxic reaction, and intolerance to the drugs on the patients' part, than from drug resistance in the infecting bacilli; only three patients were free from such side effects, and many changes of treatment had to be made in the remainder. One only patient—a Pakistani child—had a streptomycin-resistant infection, reported when she had already converted to negative

sputum. In this case, duple therapy with PAS and isoniazid was continued as elective treatment. Satisfactory progress and follow-up were observed in all eight patients (2 to 7 years).

Resistance to two drugs (3 cases) Primary resistance to two drugs raised much more serious problems, and two of these three patients suffered a clinical relapse. The case histories are instructive and are briefly described:

(1) J. M., a white man aged 40, developed acute disease in 1962 which regressed clinically and radiographically on initial triple therapy but his sputum remained positive and in the twelfth week of treatment the laboratory reported resistance to PAS and isoniazid (and also to cycloserine). Treatment was consequently changed to ethionamide, pyrazinamide, and viomycin. Coincidentally the patient suffered a clinical relapse associated with fever and a large pleural effusion. On the revised regimen, however, he gradually improved and his subsequent progress and five-year follow-up were unexceptional.

(2) R. C., an Indian man aged 27, presented in 1966 with acute pneumonic disease. He made good clinical and radiographic progress on standard triple therapy, including sputum conversion within the first month. Sensitivity reports showed resistance to streptomycin and isoniazid and so treatment was changed to ethionamide, pyrazinamide, PAS, and viomycin. Intolerance of ethionamide led to its substitution by cycloserine, which was in turn abandoned because of peripheral neuropathy; a rise of SGPT led to the discarding of pyrazinamide in favour of thiacetazone, and this, with PAS, became the final treatment which was completed in one and a half years. A year later the patient suffered an acute relapse and was treated with capreomycin, rifampicin, and ethambutol. Again the bacillus proved resistant to streptomycin and possibly also to isoniazid; ethambutol had to be given up on ophthalmic advice and treatment was continued with prothionamide and rifampicin. The patient responded well and will shortly have completed two years' re-treatment.

(3) S. W., an Indian man aged 65 with kala-azar, was admitted in 1967 with prolonged, recurring attacks of *Bacillus coli* septicaemia and adrenal insufficiency. He was treated with several antibiotics together with antimony and steroids. His lungs were

initially clear but while in hospital he developed (possibly as a 'fortuitous' infection) acute pulmonary tuberculosis which was initially treated with isoniazid, ethionamide, and PAS (streptomycin was not given because of his age and dehydrated state). Nausea, vomiting, and psychiatric changes dictated a change of treatment to pyrazinamide, thiacetazone, and cycloserine but major fits followed and cycloserine was substituted by ethambutol. At this stage, sputum cultures revealed *Mycobacterium tuberculosis* resistant to streptomycin and isoniazid but the bacilli were otherwise sensitive and his treatment had been theoretically adequate. The tuberculosis regressed on continued treatment despite many accompanying clinical problems such as a large staphylococcal lung abscess which in turn resolved completely on antibiotics and physiotherapy. The patient finally died after prolonged refusal of food and medicines. Necropsy revealed evidence of kala azar but no active tuberculosis and it was concluded that, although his resistance to infection had been undermined by kala-azar and steroid therapy, he had overcome an active tuberculous lesion with a doubly resistant organism, by means of a fortunate initial choice of drugs.

Resistance to three drugs Only one patient had primary resistance to three drugs. Relapse also occurred in this case, which is briefly described.

A. B., a white man aged 59, had extensive disease with a giant cavity, diagnosed in 1960. Impressive radiographic improvement followed three months' treatment with three standard drugs, and perhaps for this reason a report suggesting resistance to all three drugs was not acted upon. A catastrophic relapse later led to further tests confirming resistance; reserve drugs were substituted but led to side effects (including convulsions thought to be due to cycloserine) and the disease remained active till lobectomy eliminated the large cavitated lesion; reserve drugs were continued for a further year and the patient remains well eight years later.

Thus of the 12 cases of primary resistance, eight were resistant to one drug only. In all eight, dropping of the ineffective drug was dictated by laboratory rather than clinical considerations. A third drug was prescribed for a period in most cases: all made good progress and none relapsed. The four cases of multiple drug resistance, however, proved a more taxing problem; relapse occurred in three of these, prior warning having been received in the form of the sensitivity reports in each case. The warning was acted upon in two cases but, in spite of apparently correct treatment and good early progress, one had a late relapse. The warning was ignored in the third case; disastrous relapse followed, requiring surgical intervention to save life. Although the fourth case made an impressive early recovery from tubercu-

losis on 'correct' treatment, the follow-up period was cut short by early death from kala-azar.

Clearly, single-drug resistance is noteworthy, and calls for modifications in treatment but has a favourable prognosis if triple therapy is prescribed initially. In contrast, resistance to two or more drugs requires urgent and radical reconsideration of treatment, and relapse is likely.

DISCUSSION

The number of resistant cases recorded prior to 1960 almost certainly represents an underestimate, since epidemiological interest in the problem was not specially aroused at that time. By 1960, however, the problem had claimed attention, and at the time of the British Tuberculosis Association's national survey of acquired resistance of 1960-1 there were 19 such patients living in Waltham Forest, an incidence of about 8 per 100,000, which compares with the survey's current estimate of 6.2 per 100,000 for the country as a whole.

In the years following 1960, special attention was paid to the problem and the number of patients developing acquired resistance became progressively fewer, so that in the five-year period, 1964-8 inclusive, only eight further cases of acquired resistance came to light, five of which had been notified as tuberculous at least two years previously.

Turning to primary resistance, there is again a rough correlation between the figure presented here for Waltham Forest and that established for London and south-east England in the Medical Research Council's survey of 1963. In Waltham Forest only 12 cases were recorded between 1960 and 1968 inclusive out of 760 new cases of the disease, an incidence of 1.6% as against a regional figure of 2.1% in the M.R.C. survey. Only for the years 1964-8 inclusive do the local figures approximate to the national, when 10 primarily resistant cases were recorded out of a total of 379 new cases, an incidence of 3.8% as against 4.1% recorded nationally by the M.R.C. for 1963. The explanation for the rising incidence from 1964 onwards is found in the big increase in notifications of Commonwealth immigrants which occurred at that time (Table VII).

In fact the bulk of primarily resistant cases was derived from Commonwealth immigrants who were estimated by 1968 to constitute 8.5% of the borough's population (Wright, 1969). Table VIII shows the big difference between the incidence of such cases in immigrants (9%) and patients originating in Britain (0.7%).

TABLE VII
PULMONARY TUBERCULOSIS NOTIFICATION, WALTHAM FOREST 1961-8

	1961	1962	1963	1964	1965	1966	1967	1968
British	87	89	105	70	77	46	47	50
Immigrant	2	2	1	16	17	19	20	17
Total	89	91	106	86	94	65	67	67

TABLE VIII
PRIMARY DRUG RESISTANCE, PULMONARY TUBERCULOSIS, WALTHAM FOREST, 1964-8 INCLUSIVE

Notifications of Pulmonary Tuberculosis		Primary Resistance	
Origin	No.	No.	%
Immigrant	89	8	9 (7)
British	290	2	0.7 (3)
Total	379	10	3.79

Equivalent figures taken from M.R.C. Survey of 1963 are given in parenthesis.

All eight resistant cases in the immigrant group occurred among the 70 notified cases originating in Pakistan and India, so that the incidence of primary resistance among those from the Indian sub-continent was as high as 11.4%, a figure which corresponds with that of 10% (5 out of 49 cases) in the M.R.C. survey of 1963. The figure of 0.7% for patients born in Britain is much lower than the corresponding figure of 3% derived from the M.R.C. survey for the nation as a whole (although the figure for London and south-east England—not given—was presumably lower). Taken in conjunction with the figure of 0.5% for British-born patients notified in the years 1960-3 inclusive, it reflects a low incidence of primary drug resistance in natives of Waltham Forest.

This survey underlines the big differences between patients with acquired as opposed to primary drug resistance. The former represent a very considerable therapeutic challenge to the physician; they are usually older, have more extensive and chronic disease, and are apt to be personally recalcitrant and disenchanted with treatment. Patients with primary resistance, on the other hand, are younger, likely to be recently arrived from Pakistan or India, to have less extensive if more acute disease, and to be co-operative and anxious to be cured. The prognosis in acquired resistance is bad unless the patient is strongly motivated towards recovery, and this in turn demands constant bolstering of the doctor-patient relationship; in primary resistance, provided only one drug is involved, the prognosis is good if the physician is vigilant and supported by reliable bacteriology. Where the infection is resistant to

two or more drugs, however, relapse is probable and an urgent review of treatment is called for.

The management of drug-resistant tuberculosis calls for early detection by routine sensitivity tests on diagnosis, repeated if the sputum fails to convert by the sixth month or if the direct smear shows persisting high bacterial counts. Apparently good clinical and radiographic progress can and does occur in the early months of treatment in such cases, and should not deter the physician from taking firm action on the basis of the laboratory report. In any case of tuberculosis previously treated and now presenting with relapse, acquired resistance should be suspected. A careful review should be made of the prescribing and acceptance of previous treatment, and those drugs already used should not be relied on again until sensitivity reports are to hand, sufficient second-line drugs now being available to start re-treatment with triple chemotherapy. Primary resistance must be expected in a proportion of Asian immigrants, who are best treated initially in hospital where they can be impressed with the importance of regular medication; on discharge their peripatetic habits must be borne in mind and forwarding addresses obtained for transfer of the case to the next chest clinic.

Single-drug resistance is a contingency already catered for in the policy of initial triple therapy but substitution of the ineffective drug is a wise precaution. Resistance to two or more drugs calls for a complete change of regimen to three alternative drugs irrespective of favourable clinical progress to date. Further identification of the bacillus together with repeated sensitivity tests should be carried out to include the whole range of available antimycobacterial drugs and a close control exercised over the remaining period of treatment which should be of two years' duration. In the face of continued deterioration, surgical treatment may be considered but the availability of newer, potent antimycobacterial agents renders this choice less mandatory now than hitherto.

Both types of resistant tuberculosis require experienced management and follow-up. A successful outcome depends on the availability of a

sufficient range of reserve drugs, preferably well tolerated and non-toxic. Treatment of such patients should not be undertaken without full chest clinic facilities which must include the services of health visitors and a social worker.

The problem of acquired resistance is a diminishing one. The older patients are either being cured or dying off, and fewer young patients are acquiring resistance because of higher therapeutic standards, greater awareness of the dangers of inadequate treatment, and a wider choice of effective chemotherapy. On the other hand, primary drug resistance appears to be increasing and largely associated with immigration; and the possibility should be borne in mind with every new case of tuberculosis among the immigrant community.

The surveys of primary and acquired resistance carried out by the Medical Research Council and the British Tuberculosis Association have served a valuable purpose in focussing attention on a potentially dangerous epidemiological situation; they have also resulted in improved clinical and bacteriological standards. The central register of drug-resistant cases set up in 1960 provided a monitoring service for resistant mycobacteria at the Tuberculosis Reference Laboratory, whose work revealed uneven standards of sensitivity testing at routine hospital laboratories (Marks, 1965), work which has since come to be concentrated in specialized laboratories.

CONCLUSIONS

A survey of drug-resistant pulmonary tuberculosis in Waltham Forest shows that acquired drug resistance is found in older patients with chronic disease. When this is due to an unco-operative patient the prognosis is bad; when due to previous faulty treatment it is better; and when no cause can be ascribed it is good. The local incidence of this type of case has been average for the nation and is now falling. The incidence of primary drug resistance in Waltham Forest has been lower than the national average; it has risen due to the influx of Commonwealth immigrants since 1964, and can be expected to continue to rise. Such patients are younger and are anxious to be cured; they present few major problems in treatment, provided resistance is to one drug only. Those with infections

resistant to more than one drug, however, require careful appraisal and are likely to relapse. Both types of resistance call for experienced management (which is discussed) together with full chest clinic facilities.

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