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The nature of mycobacterial disease in south east England, 1977–84

MALCOLM D YATES, JOHN M GRANGE, AND CHRISTOPHER H COLLINS

From the Public Health Laboratory, Dulwich Hospital, London SE22 8QF and Cardiothoracic Institute, University of London, Fulham Road, London SW3 6HP.

SUMMARY The nature and incidence of bacteriologically confirmed mycobacterial disease in south east England over the eight year period 1977–84 has been determined by a study of cultures received by the PHLS Regional Centre for Tuberculosis Bacteriology at Dulwich. The number of cases of tuberculosis in the ethnic European population has shown a decline, more so among males than females, but there has not been a significant decline in cases among ethnic Asians. Most tuberculosis is due to the classical human tubercle bacillus but cases due to the Asian human type, the bovine type *(M. bovis)*, and the African types *(M. africanum)* also occur. The number of cases of disease due to 'atypical' mycobacteria has doubled over the eight year period, and these now account for about 5% of bacteriologically diagnosed mycobacterial disease in this region. The continuing role of reference facilities for the surveillance of tuberculosis and the diagnosis and management of the growing numbers of other mycobacterial infections is stressed.

Although the incidence of tuberculosis has declined dramatically in Great Britain since John Bunyan termed it 'the Captain of all of these men of Death', it is far from extinct. Horne[1] has commented that the decline in tuberculosis, though most welcome, has generated problems of its own—not least of which is a loss of clinical interest leading to delayed or missed diagnosis. A similar lack of interest and motivation could well adversely affect the standard of tuberculosis bacteriology, a branch of microbiology requiring considerable expertise and organisation.[2] Although bacteriological services are crucial to the effective control of tuberculosis in high prevalence areas, they are no less important in low prevalence regions where the aim should be eradication rather than mere control.

The incidence of tuberculosis in a community may be assessed by a notification system or by returns from reference laboratories. Neither is ideal, as a significant proportion of cases escape notification while others are diagnosed in the absence of bacteriological confirmation. From available notification rates[3 4] and bacteriological data, it may be estimated that, in the present decade, around eight to ten thousand new cases occur annually in England and Wales.

At the present time, about 8000 strains of mycobacteria are cultured annually in Great Britain, though not all of these are *Mycobacterium tuberculosis*. Over 95% of these cultures are submitted to the Public Health Laboratory Service (PHLS) for identification and sensitivity testing:[3] about 3500 annually to the Mycobacterium Reference Unit in Cardiff; 2500 to the Regional Centre for Tuberculosis Bacteriology at Dulwich; and the remainder to five smaller centres at Birmingham, Leeds, Liverpool, Manchester, and Newcastle.[5]

In this paper we review the contribution made by bacteriological studies to an understanding of the nature and behaviour of mycobacterial disease in south east England—the region served by the PHLS Centre for Tuberculosis Bacteriology at Dulwich—during the last eight years.

Some problems posed by mycobacterial disease

When the authors began their cooperative studies in 1977, there was considerable concern over the high incidence of tuberculosis among Asian immigrants from India, Pakistan, and East Africa and in the fact that many of the patients presented with non-pulmonary manifestations of the disease, notably cervical lymphadenitis. The question was raised as to whether the unusual pattern of disease was due to different variants of the tubercle bacillus.

Improvements in bacteriological technique made it easier to identify the bovine type of tubercle bacillus *(Mycobacterium bovis)* and it became evident that a small but significant proportion of cases of

tuberculosis in man were due to this variant.[6] In view of its association with disease in cattle its behaviour and transmission demands careful surveillance.

As a result of a number of international cooperative studies, the role of other species of mycobacteria in disease in man and animals became much more apparent. It is perhaps with respect to the growing problem posed by this group of diseases that the services of the specialist tuberculosis laboratories will prove of particular value in the future.

Variants of the tubercle bacillus

In view of the differing behaviour of tuberculosis in various ethnic groups, there was a clear need for tests that could reliably subdivide tubercle bacilli for epidemiological purposes. Initially, bacteriophage typing was used[7] and, although only three major types were delineated, their distribution among Asian and indigenous European patients differed markedly. One phage type, frequently found in the Asian group, was found to correspond to a variant known to be common in South India. This so-called Asian or South Indian type is susceptible to killing by hydrogen peroxide and, in common with bovine strains, it is usually sensitive to thiophen-2-carboxylic acid hydrazide (TCH), a compound closely related to the antituberculous drug isoniazid.[8 9] Phage typing and TCH susceptibility testing revealed that about 20% of strains from Asian immigrants and only 5% of those from indigenous European patients were of this South Indian type.[7 10 11] This, together with other phage typing and drug resistance patterns, indicated that the two ethnic groups were infected with different populations of bacilli although it was not possible to determine how many patients had arrived infected and how many had become infected after arrival. It was clear, however, that there was no relationship between the type of bacillus and the presenting feature of the disease. Thus the percentage of cases of non-pulmonary disease among ethnic Asians infected with the TCH-resistant and -sensitive strains were 49% and 51% respectively, an insignificant difference. Furthermore, there were no associations between the type of bacillus and the site of the non-pulmonary lesion.[10] Thus other causes must be sought for the high incidence of lymphadenitis and other non-pulmonary manifestations of tuberculosis occurring in the ethnic Asian community in this country.

Since 1977, the Dulwich Centre has used four simple and reliable tests to subdivide isolates of tubercle bacilli, namely, TCH susceptibility, oxygen preference, nitratase activity, and pyrazinamide resistance.[12 13] A fifth test, cycloserine sensitivity, is included to identify BCG. Using this system, five types of virulent tubercle bacilli isolated from human clinical material have been delineated: the classical and Asian (or South Indian) human types already mentioned, the classical bovine type (often referred to as *Mycobacterium bovis)*, and two additional types termed African I and African II. The latter correspond to two major variants of a heterogeneous group of tubercle bacilli isolated from man in equatorial Africa and known as *M. africanum*.[14] The African I type corresponds with strains of *M. africanum* occurring mainly in West Africa while African II strains resemble those predominant in East Africa. Strains of this type have also been termed 'Afro-Asian bovine' tubercle bacilli[15] although there is no evidence that they infect cattle. In fact they appear to bridge the gap between the human and bovine types: East African strains share properties with the former, and Western African strains have more in common with the latter.

During the eight year study period 184 strains of the African type were identified, ie, about 23 annually, of which most, but not all, were isolated from Asian or African immigrants from Africa (table 1).

A similar number of cases of tuberculosis in the region (ie, about 20 new cases annually) are caused by bovine strains. About half the cases are of cervical lymphadenopathy in elderly individuals, probably due to reactivation of old milk-borne infections, and half are pulmonary and other lesions which often occur in younger patients.[6 16] As the latter tend to be town dwellers who consume pasteurised milk, infection could well be the result of person-to-person transmission.[17] If this is so, man must be added to the list of animals that are a reservoir for this strain and therefore a threat to cattle.

By far the majority of tuberculosis in Great Britain, however, is due to human strains. In general, tuberculosis is declining in this country, although the rate of decline varies according to the ethnic groups and is more evident among males than females.[18] The decline in the number of cases of tuberculosis registered at Dulwich is shown in tables 2 and 3. The overall annual decline rates among males and females were 3·5% and 2·2% respectively. These figures

Table 1 *Number of strains of the five types of* Mycobacterium tuberculosis *isolated from patients of European, Asian, and African ethnic origin, 1977–84**

Variant	*Ethnic group*			*Total*
	European	*Asian*	*African*	
Classical human	6743	3389	116	10248
Asian human	693	765	34	1492
Bovine	140	23	3	166
African I	31	63	35	129
African II	10	25	20	55
Total	7617	4265	208	12090

*Other ethnic groups are excluded, thus the total is less than that in table 3.

Table 2 *New cases of tuberculosis and 'atypical' mycobacterial infections, 1977–84*

Year	Total cases	Tuberculosis	'Atypical' infections	% 'atypical' disease of total
1977	1707	1666	41	2·4
1978	1909	1872	37	1·9
1979	1767	1725	42	2·4
1980	1935	1859	76	3·9
1981	1836	1768	68	3·7
1982	1641	1548	93	5·7
1983	1675	1597	78	4·7
1984	1475	1377	98	6·6

Table 3 *Total number of isolates of tubercle bacilli and 'atypical' mycobacteria received, 1977–84*

Year	Total	Tubercle bacilli	'Atypicals'	% 'atypicals' of total
1977	2387	2124	263	11·0
1978	2655	2334	321	12·1
1979	2575	2244	331	12·9
1980	2730	2286	444	16·3
1981	2576	2160	416	16·1
1982	2462	1919	543	22·1
1983	2549	1979	570	22·4
1984	2251	1729	512	22·8

correspond closely to those for England and Wales reported by Springett and his colleagues[18] for the period 1971–78/9. The annual decline rates of ethnic European and Asian patients were 3·7% and 0·96% respectively. These decline rates were less than those calculated for England and Wales between 1978/9 and 1983 on the basis of notification.[4] Interestingly, although the number of cases among ethnic Europeans due to classical strains is declining, cases in this ethnic group due to the Asian strain increased fairly steadily from 66 to 107 annually over the study period. Drug resistance patterns (see below), however, indicate that the Asian strains isolated from European patients are distinct from those infecting Asian patients. Hence it is unlikely that this increase is due to disease being transmitted from the Asian community.

Drug resistance patterns

At present it is the practice at Dulwich to test all isolates of tubercle bacilli for sensitivity to the current first line drugs, namely, isoniazid, rifampicin, ethambutol, pyrazinamide, and, occasionally, streptomycin. If resistance to two or more of these drugs is encountered, or if there is a specific request from the referring laboratory, isolates are sent to the PHLS Mycobacterium Reference Unit at Cardiff to be tested against ethionamide, cycloserine, and capreomycin. During the seven years 1977–83, 2·7% of isolates from Europeans and 8·3% of those from Asians were resistant to one or more drugs.[10] As shown in table 4, the percentage of resistant strains isolated from ethnic Asian patients showed a much greater annual variation than those from ethnic European patients. The percentage of resistant strains from Asian patients in the years 1979 and 1983 (7·8% and 11·2% respectively) closely correspond to the figures from the MRC notification surveys of 1978/9 and 1983[3,4] (7·5% and 12·8% respectively). Despite this fluctuation, there were no significant changing trends in the incidence or pattern of drug resistance over this period. As mentioned above, the incidence of resistance within each ethnic group was unrelated to the type of bacillus (classical or Asian type). This suggests that cross infection between the two ethnic groups had not occurred to a significant degree.

Of particular relevance is the number of strains that are resistant to the present regimen advocated by the British Thoracic Society, namely, isoniazid, rifampicin, ethambutol, and pyrazinamide daily for two months and the first two drugs only for a further four months. Among European patients, 1·8% of isolates were resistant to one of these drugs (usually isoniazid) and only 12 (0·18%) were resistant to two, one drug always being isoniazid. Two isolates were resistant to all except pyrazinamide but none was resistant to all four. Among isolates from Asians, 5·5% and 0·49% were resistant to one and two drugs respectively. Again, isoniazid was the principal drug to which resistance occurred. Three strains from Asians were resistant to three drugs and one was resistant to all four drugs. Consequently, with rare exceptions, modern antituberculous chemotherapy should prove highly effective. Nevertheless, in view of the predominant isoniazid resistance, a number of patients would, in the absence of the results of sensitivity testing, effectively be receiving rifampicin monotherapy in the four month continuation phase which may result, and in some cases has resulted, in the emergence of resistance to this drug. It is to avoid this occurrence that the PHLS undertakes sensitivity testing on all isolates and advises that no drug is stopped until the results are known. Additional strains (2·8% and 0·9% of those from ethnic Asians and Europeans respectively) were resistant to streptomycin and/or one or more of the second line drugs. In this context it is important to note that all bovine strains are naturally resistant to pyrazinamide.

Table 4 *Annual percentage of drug resistant strains of human tubercle bacilli isolated from ethnic European and Asian patients, 1977–83*

	1977	1978	1979	1980	1981	1982	1983
European	3·1	3·0	2·9	1·5	2·7	2·7	2·7
Asian	6·8	10·4	7·8	6·7	9·1	5·8	11·2

The 'atypical' mycobacteria

The variants of the tubercle bacillus described above are not the only members of the genus *Mycobacterium* causing disease in this country. A number of other species that usually live freely in the environment may, when given an opportunity, also be pathogenic. Infections due to these species, which are usually termed 'atypical mycobacteria', can only be distinguished from tuberculosis by isolation and identification of the causative organism. Such infections are reviewed in detail elsewhere.[19] In brief, they usually cause lesions that mimic the pulmonary and non-pulmonary manifestations of tuberculosis, including disseminated infections, particularly in patients with conditions associated with immunosuppression, including AIDS. Some species also cause post-injection abscesses and infections of accidental or surgical wounds.

'Atypical' mycobacterial disease is rarely transmitted from person to person: its incidence is thus unrelated to that of tuberculosis and is unaffected by tuberculosis control measures. Furthermore, in contrast to tuberculosis, its incidence shows no racial predilection but is related to the presence and distribution of strains in the environment. Accordingly the predominant causative species varies from region to region.

Being unaffected by tuberculosis control measures the incidence of infection due to 'atypical' mycobacteria is rising relative to that of tuberculosis in those regions where that disease is in decline. There has also been an absolute increase in reports of such disease in Great Britain and other industrially developed nations. Although this may in part be due to an increase in interest and awareness, and advances in bacteriological technique, there also seems to have been a real increase in the number of cases. As shown in tables 2 and 3, the number of new cases recorded and the number of isolates received each year, at Dulwich, has more than doubled over the last eight years, and they now account for over 5% of cases of bacteriologically confirmed mycobacterial disease in south east England. This trend is worrying as such infections are often life-threatening and pose serious therapeutic challenges especially when they occur, as often happens, in immunocompromised patients. The problem is exacerbated by the lack of firm guidelines on therapy: there is often a discrepancy between drug sensitivity *in vitro* and the clinical response. Experience has shown that the interests of the patient with such an infection are best served by frequent consultations between the clinician, the microbiologist, and the reference laboratory.

It is important to note that, whereas all clinical isolations of *M. tuberculosis* imply disease in the patient (provided, of course, that there has been no cross-contamination or labelling error), the 'atypical' mycobacteria abound in the environment, including piped water supplies,[20] and therefore frequently occur as transient commensals in the upper respiratory tract and intestine and on the skin. They also frequently contaminate specimens, during either collection or laboratory processing. For these reasons, and because diagnosis of 'atypical' mycobacterial disease is usually based on multiple isolations, the number of cultures received by the reference laboratory far exceeds the number of patients with disease. Indeed, almost a quarter of all cultures currently received are species other than *M. tuberculosis*, and the extra identification procedures required adds to the workload of the laboratory.

In Great Britain the predominant species overall is *M. kansasii*, but in south east England it is *M. xenopi*: indeed, we probably see the world's highest prevalence of disease due to this species. Next comes *M. kansasii*,

Table 5 *Total number of isolates of 'atypical' mycobacteria received annually, 1977–84*

Species	1977	1978	1979	1980	1981	1982	1983	1984	*Total*
M. xenopi	86	115	125	166	173	233	168	183	1249
M. kansasii	54	58	63	72	67	93	104	92	603
MAIS	31	24	31	41	36	38	62	47	310
M. fortuitum	28	38	20	23	23	28	39	43	367
M. chelonei			7	35	13	24	28	18	
M. malmoense	—	2	—	1	3	4	4	21	35
M. marinum	1	2	1	4	3	2	6	2	21
M. szulgai	1	—	2	—	—	4	—	5	12
M. terrae group	NI	NI	2	—	—	4	2	25	10
M. ulcerans	—	—	—	—	1	—	—	—	1
Scotochromogens	46	71	65	74	90	103	140	87	676
Non-chromogens	9	4	14	20	5	7	9	7	75
Rapid growers	7	7	1	8	2	3	8	5	41

MAIS = *M. avium-intracellulare-scrofulaceum* complex
M. terrae group includes *M. terrae*, *M. triviale*, and *M. nonchromogenicum*
NI = not identified as such at that time.

Table 6 *Number of new cases of disease due to 'atypical' mycobacteria registered annually.*

Species	1977	1978	1979	1980	1981	1982	1983	1984	*Total*
M. xenopi	13	15	12	29	29	38	22	34	192
M. kansasii	12	14	11	19	20	21	24	26	147
MAIS	9	5	12	14	10	18	20	13	101
M. fortuitum / *M. chelonei*	4	—	3 / 1	1 / 9	1 / 2	4 / 2	— / 5	5 / 4	41
M. malmoense	—	—	—	—	1	1	2	6	10
M. marinum	1	2	1	3	3	2	5	2	19
M. szulgai	—	—	1	—	—	2	—	1	4
M. terrae group	NI	NI	—	—	—	2	—	—	2
M. ulcerans	—	—	—	—	1	—	—	—	1
Other	2	1	1	1	1	2	—	7	15

MAIS = *M. avium-intracellulare-scrofulaceum* complex
M. terrae group includes *M. terrae*, *M. triviale*, and *M. nonchromogenicum*
NI = not identified as such at that time.

then the so-called MAIS group (ie, the *M. avium-intracellulare-scrofulaceum* group). The annual number of isolates received, and new cases of disease registered, are shown in tables 5 and 6. The behaviour of *M. malmoense* is of particular interest and concern as the incidence of proven disease due to this species in Great Britain has, for unknown reasons, increased very significantly during the past five years.[20 21]

Conclusions

Bacteriological studies still have an important role to play in the surveillance of tuberculosis in a low prevalence area such as south east England where emphasis should now be on eradication rather than mere control. Disease due to the 'atypical' mycobacteria, although relatively uncommon, may pose serious problems in management, and in this field assistance and advice from the reference laboratory may prove particularly valuable. As tuberculosis declines, interest is shifting to the other mycobacterial infections, but, at the present rate of decline, the former disease is likely to remain the predominant source of concern for quite some time.

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