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Subdivision of *Mycobacterium tuberculosis* for epidemiological purposes: a seven year study of the 'Classical' and 'Asian' types of the human tubercle bacillus in South-East England

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SUMMARY

Human strains of *Mycobacterium tuberculosis* were divided into the 'Classical' and 'Asian' types according to their sensitivity to thiophen-2-carboxylic acid hydrazide. The isolation of these two types in South-East England was studied during a seven-year period (1977–1983). The 'Asian' type was more prevalent among ethnic Asian patients than among ethnic Europeans. Among Europeans there was a decline in the isolation rate of 'Classical' strains and a small but significant increase in 'Asian' strains during the study period, so that the proportion of the latter type in this group is increasing. The type of bacillus was unrelated to the site of isolation except that the incidence of lymphadenitis due to the 'Asian' type among European females was significantly higher than expected. In general, European patients tended to be older than Asian patients, and the differences in age distribution according to site of isolation and type of bacillus in each ethnic group were small. A notable exception occurred with European females infected with the 'Asian' type, whose age distribution was similar to the Asians.

In view of the differences in behaviour of the two types of human tubercle bacilli in this country there is a need to continue a bacteriological surveillance and also to determine whether the nature of the host–pathogen interaction varies according to the type of bacillus.

INTRODUCTION

The mammalian tubercle bacilli are conventionally divided into three main types – human, bovine and vole. Some workers regard these as variants of the single species *Mycobacterium tuberculosis* while others, for reasons of convenience, prefer to use three separate species designations, *M. tuberculosis*, *M. bovis* and *M. microti* respectively, and add a fourth, *M. africanum*, to include a somewhat heterogeneous group of tubercle bacilli isolated from man in some parts of Africa.

The human type is clearly differentiated from the other types in being a strict aerobe, showing a luxuriant or eugonic growth on glycerol–egg media, reducing nitrate to nitrite and usually being sensitive to pyrazinamide (Collins & Lyne, 1984).

The human type is usually virulent for the guinea-pig although some isoniazid-resistant mutants are attenuated for this animal. Studies in South India, however, showed that a high proportion of the isoniazid-sensitive human strains in this region were also attenuated in the guinea-pig (Dhayagude & Shah, 1948) and differed from the virulent type in being relatively susceptible to the cidal effect of hydrogen peroxide *in vitro* (Mitchison, Selkon & Lloyd, 1963). Further investigations revealed that strains of this 'South Indian' or 'Asian' variant contained a characteristic cell wall lipid termed the Attenuation-Indicator Lipid (Goren, Brokl & Schaefer, 1974), and that they were usually of a characteristic bacteriophage type (type I: Grange *et al.* 1978; Goren *et al.* 1982). Thiophen-2-carboxylic acid hydrazide (TCH) has been used to differentiate human strains, which are resistant to it, from bovine strains which are sensitive (Bönicke, 1958). It was found, however, that the majority of the 'Asian' strains were also sensitive to TCH, although not quite as sensitive as the bovine type (Grange *et al.* 1977, 1978). The latter property has been used to distinguish between these two variants for epidemiological purposes (Collins, Yates & Grange, 1982, 1984).

In addition to being found in India and adjacent countries, the 'Asian' strains have been isolated from patients of Asian ethnic origin in Great Britain (Grange *et al.* 1977; Yates & Collins, 1979; Yates, Collins & Grange, 1982). The incidence of tuberculosis is higher among this ethnic group than among Europeans and there is also a relatively high incidence of extrathoracic manifestations of the disease, especially cervical lymphadenitis, in the ethnic Asian group (British Thoracic Association, 1978; Medical Research Council, 1980; Grange, Collins & Yates, 1982). The reason for the differences in the behaviour of the disease in the two ethnic groups is unknown: in a previous study of 6638 cases, no association between the type of bacillus and the pattern of disease was found (Yates, Collins & Grange, 1982).

Since 1977 all human strains of *M. tuberculosis* received by the P.H.L.S. Regional Centre for Tuberculosis Bacteriology, Dulwich, have been divided into the 'Classical' and 'Asian' types according to their susceptibility to TCH.

In this study we present the results of a seven-year study of the epidemiological behaviour of these two types in South-East England.

MATERIALS AND METHODS

The P.H.L.S. Regional Centre for Tuberculosis Bacteriology at Dulwich receives cultures of mycobacteria from about 80 referring laboratories, and this number has not altered significantly during the past seven years.

The strains included in this study were those from ethnic European and Asian (Bangladeshi, Indian and Pakistani) patients. The latter included individuals who had immigrated directly from Asia, those previously resident in East Africa and those born to Asian parents in this country. Strains from other ethnic groups (African, Arabic, Chinese, etc.) were relatively small in number and were excluded.

The strains were identified as the human type and were subdivided into the 'Classical' and 'Asian' types according to their susceptibility to 5 mg/l thiophen-2-carboxylic acid hydrazide (TCH) as described previously (Collins, Yates & Grange, 1982).

The resistance of strains to antituberculous drugs were determined by the resistance-ratio method (Collins & Lyne, 1984). For the purpose of this study four categories of drug resistance were used: isoniazid (INH); streptomycin (SM); both INH and SM; other drugs.

The age, sex and ethnic origin of each patient, the year in which the culture was received and the site from which the bacilli were isolated, were recorded. Extrathoracic isolates were placed in the following categories: lymph node; bone, joint and soft tissue; urinary tract; male genital; female genital; meninges and central nervous system; abdominal (excluding lymphatic and renal) and others (principally pericardial and bone marrow). The data were analysed by the chi-squared, Mann–Whitney and Kolmogorov–Smirnov tests and by time-series analysis where appropriate.

RESULTS

During the period 1977 to 1983 inclusive, 10700 strains of the human type of *Mycobacterium tuberculosis* from the two ethnic groups, as defined above, were received by the Dulwich laboratory; 6850 of these were from the European group and 3850 were from the Asian group. Nine per cent (616) of the European isolates were TCH-sensitive while among the Asians 663 (17·2 %) were of this type; a highly significant difference ($P < 0{\cdot}001$). In the European group the TCH-sensitive strains were more prevalent among females (10 %) than among males (8·5 %, $P < 0{\cdot}05$), while in the Asian group there was little difference in the sex distribution of these strains (16·8 % and 17·4 % respectively).

Table 1 shows the annual number of the two types of strains according to ethnic origin and sex of the patients and whether the strain was isolated from the lung or from an extrapulmonary site. In both groups there were more male than female patients although there were relatively more females in the Asian group (46·7 %) than in the European group (32·4 %; $P < 0{\cdot}001$). The percentage of isolates from extrapulmonary sites was much higher in the Asian group (49·5 %) than in the European group (21·4 %; $P < 0{\cdot}001$) and within each group there were relatively more extrapulmonary isolations from females than from males (33·9 % and 15·3 % respectively in the European group, $P < 0{\cdot}001$; 54·8 % and 44·8 % respectively in the Asian group, $P < 0{\cdot}001$).

Among the European males, Asian males and Asian females, isolates from extrapulmonary sites showed a slight, but not significant, tendency to be of the TCH-sensitive type. Among the European females the tendency for extrapulmonary isolates to be of this type was significant ($\chi^2 = 5{\cdot}14$, $P = 0{\cdot}022$). This association was limited to bacilli isolated from lymph nodes ($\chi^2 = 14{\cdot}04$, $P < 0{\cdot}001$); bacilli from other organs showed no such association ($\chi^2 = 1{\cdot}56$, $P = 0{\cdot}20$).

During the seven-year period there was no significant change in the ratio of pulmonary to extrapulmonary isolations, except in the Asian females infected by TCH-resistant strains in whom the percentage of extrapulmonary isolates declined

Table 1. *Annual numbers of strains received according to ethnic group, sex, type of bacillus and site of isolation**

Sex	Sensitivity to TCH†	Site of isolation	Year of isolation 1977	1978	1979	1980	1981	1982	1983	Total
			Europeans							
Male	Resistant	Pulmonary	583	598	570	536	471	428	406	3592
Male	Resistant	Extrapulmonary	104	113	102	96	77	78	71	641
Male	Sensitive	Pulmonary	33	50	48	57	28	52	57	325
Male	Sensitive	Extrapulmonary	7	11	10	11	8	13	8	68
Female	Resistant	Pulmonary	224	214	173	195	183	167	180	1336
Female	Resistant	Extrapulmonary	103	114	101	89	85	91	80	663
Female	Sensitive	Pulmonary	13	12	17	25	17	16	32	132
Female	Sensitive	Extrapulmonary	13	9	13	19	12	15	10	91
			Asians							
Male	Resistant	Pulmonary	106	137	146	157	152	105	103	906
Male	Resistant	Extrapulmonary	106	121	92	119	114	87	80	719
Male	Sensitive	Pulmonary	21	22	33	23	31	31	30	191
Male	Sensitive	Extrapulmonary	23	19	22	26	25	31	26	172
Female	Resistant	Pulmonary	60	103	84	120	104	90	95	656
Female	Resistant	Extrapulmonary	109	151	111	144	118	79	80	792
Female	Sensitive	Pulmonary	16	12	18	20	24	23	17	130
Female	Sensitive	Extrapulmonary	19	24	21	23	28	22	25	162

* These numbers are less than the total number of strains received as, in a few cases, the sex of the patient was not recorded.

† Thiophen-2-carboxylic acid, 5 mg/l.

Table 2. *The number of strains isolated from the various extrapulmonary sites*

Site of lesion	European patients				Asian patients			
	TCH-resistant		TCH-sensitive		TCH-resistant		TCH-sensitive	
	(No.)	(%)	(No.)	(%)	(No.)	(%)	(No.)	(%)
Lymph node	382	29·1	64	40·3	880	55·8	185	54·9
Bone, joint, soft tissue	253	19·3	34	21·4	377	23·9	96	28·5
Urinary tract	486	37·1	41	25·8	99	6·3	23	6·8
Male genital	25	1·9	0	—	7	0·4	2	0·6
Female genital	33	2·5	3	1·9	18	1·1	2	0·6
Central nervous system	69	5·3	6	3·8	74	4·7	8	2·4
Abdominal	54	4·1	8	5·0	110	7·0	20	6·0
Other	9	0·7	3	1·9	12	0·8	1	0·3
Total	1311		159		1577		337	

steadily from 64·5 % in 1977 to 45·7 % in 1983 (96·8 % of the variance was accounted for by this trend, $P < 0{\cdot}001$). This decline was due to the drop in the percentage of cases of lymphadenitis: there was no decline in the incidence of isolates from other extrapulmonary sites. There was no other significant change in the pattern of extrapulmonary disease during the seven years.

Table 2 shows the numbers, and percentages, of the TCH-resistant and -sensitive strains isolated from the various extrapulmonary sites in the two ethnic groups. Among the Europeans there was a significant tendency for lymph node disease to be caused by TCH-sensitive strains (this tendency, as described above, was only significant among the females). No other significant relationship between site of isolation and type of bacillus was found in either ethnic group. The percentages of isolates from lymph nodes, bone, joints and soft tissues, central nervous system and the abdomen were significantly higher in the Asian group ($P < 0{\cdot}001$ in each case) but the percentage of isolates from the urinary tract was higher in the European group ($P < 0{\cdot}001$).

Fig. 1 shows the annual numbers of isolates according to type and ethnic origin of the patient. Since 1978 there has been a fairly steady and significant decline in the numbers of TCH-resistant strains isolated from Europeans. During this period the number of such isolates from European males and females decreased by 32·9 % and 20·7 % respectively. The isolation rate of TCH-sensitive strains from this group did not likewise decrease but showed a slight yet significant tendency to increase. The annual isolation rate of TCH-resistant strains from the Asians showed a greater degree of fluctuation than that from the Europeans, but there has been a significant decline since 1980. No significant change in the isolation rate of the TCH-sensitive type was observed in this group. As a result there has been an overall decline in the isolation rate of the TCH-resistant types but not of the TCH-sensitive types, so that the latter have shown an increase from 9·4 % of the total in 1977 to 15·6 % of the total in 1983.

There was no significant change in the age distributions of the patients within either ethnic group or according to site of isolation during the seven-year period. Thus changes, where they occurred, affected all age groups. Figs 2 and 3 show the

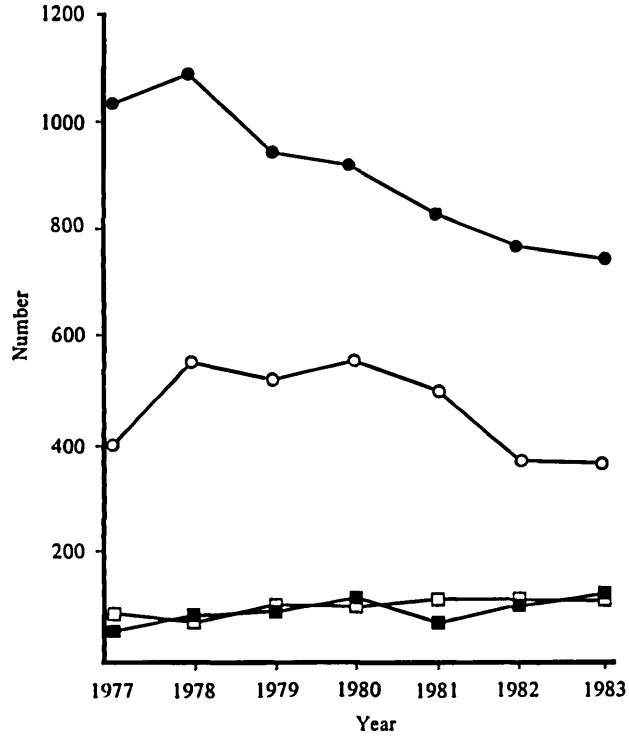

Fig. 1. The annual isolation rate of strains of *Mycobacterium tuberculosis* according to the ethnic origin of the patient and the susceptibility of the strains to TCH. ●——●, European, TCH-resistant; ■——■, European, TCH-sensitive; ○——○, Asian, TCH-resistant; □——□, Asian, TCH-sensitive.

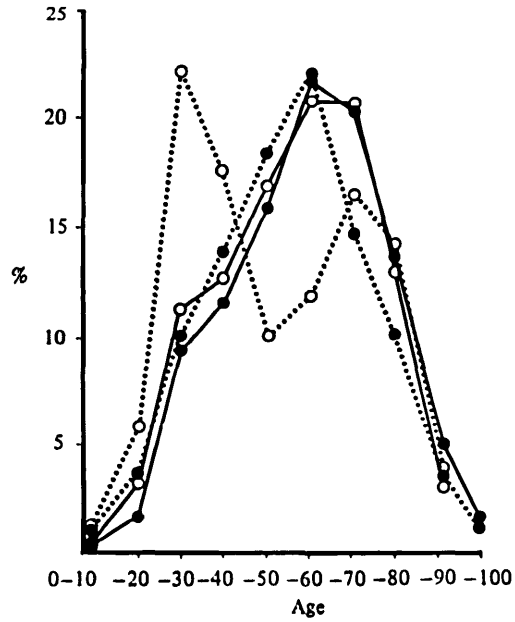

Fig. 2. The age distribution of ethnic European male patients according to bacillary type and site of isolation. ●——●, TCH-resistant pulmonary isolate; ●·····●, TCH-resistant extrapulmonary isolate; ○——○, TCH-sensitive pulmonary isolate; ○·····○, TCH-sensitive extrapulmonary isolate.

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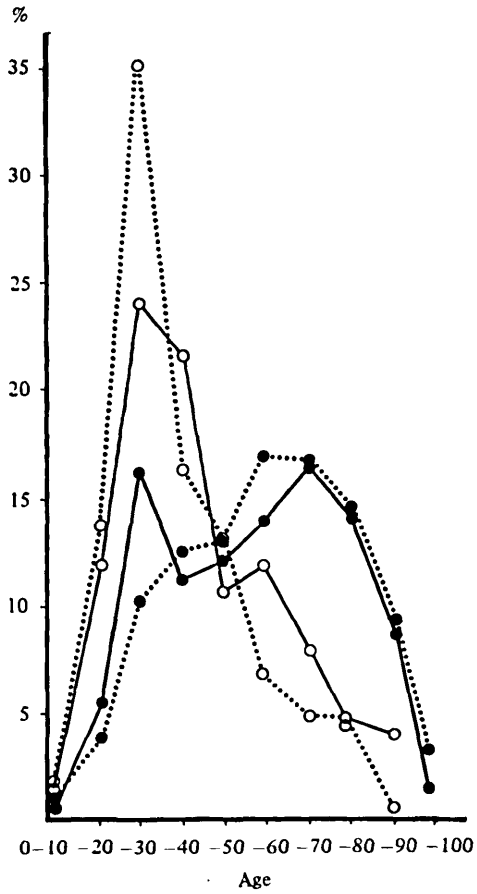

Fig. 3. The age distribution of ethnic European female patients according to bacillary type and site of isolation. Key as in Fig. 2.

age distribution of the European male and female patients respectively according to type of organism and site of disease. Figs 4 and 5 show the corresponding distributions of the Asian patients. Among European males the age distributions of the pulmonary cases caused by TCH-sensitive bacilli, and both pulmonary and extrapulmonary lesions caused by TCH-resistant strains are very similar but extrapulmonary cases caused by TCH-sensitive bacilli show a bimodal distribution with peaks in the 20–30 and the 60–70 year age groups. There is a very significant difference in the age distribution of the two types of organism among the European females, but within each distribution the difference in ages between those with pulmonary and extrapulmonary disease is small. The age distributions of the European females are all significantly different from those of the males and the age distribution of females infected with the TCH-sensitive strains approximates to those of the Asians. Among the Asians the effect of sex, type of bacillus and site of disease on the age distribution is less than among the Europeans. The age distributions of Asian males with pulmonary disease due to the two types of

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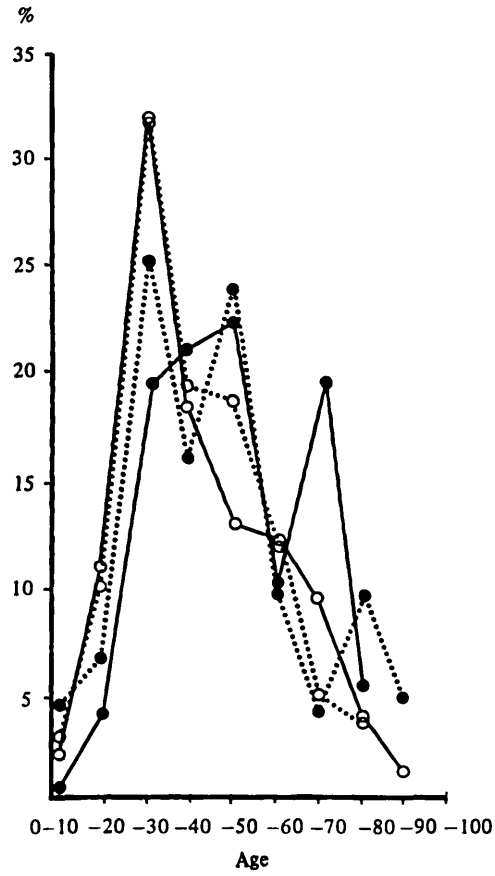

Fig. 4. The age distribution of ethnic Asian male patients according to bacillary type and site of isolation. Key as in Fig. 2.

bacillus differ significantly ($P < 0{\cdot}005$), but the other age distributions in the Asian group are not significantly different.

Table 3 shows the incidence of strains resistant to INH, SM, both INH and SM, and other drugs (mainly PAS, thiacetazone and pyrazinamide). The percentage of resistant strains was lower in the European group than in the Asian group. In the former group the incidence of drug resistance was similar in the TCH-sensitive and -resistant strains. In the latter group, drug resistance was more frequent among the TCH-resistant strains ($\chi^2 = 4{\cdot}95$, $P < 0{\cdot}025$), more so in those from pulmonary sites (10·4%) than from extrapulmonary sites (6·3%; $\chi^2 = 20{\cdot}1$, $P < 0{\cdot}001$). There was no sex-related difference in the incidence of drug resistance in either ethnic group. The patterns of resistance in the two groups differed very significantly ($\chi^2 = 45{\cdot}0$, $P < 0{\cdot}0001$); in the Asian group, strains resistant to INH, or INH with SM, were relatively more frequent. Within each ethnic group there was no obvious difference in the patterns of drug resistance between the TCH-sensitive and -resistant strains, although the number of drug-resistant TCH-sensitive strains was too low to permit meaningful statistical comparisons.

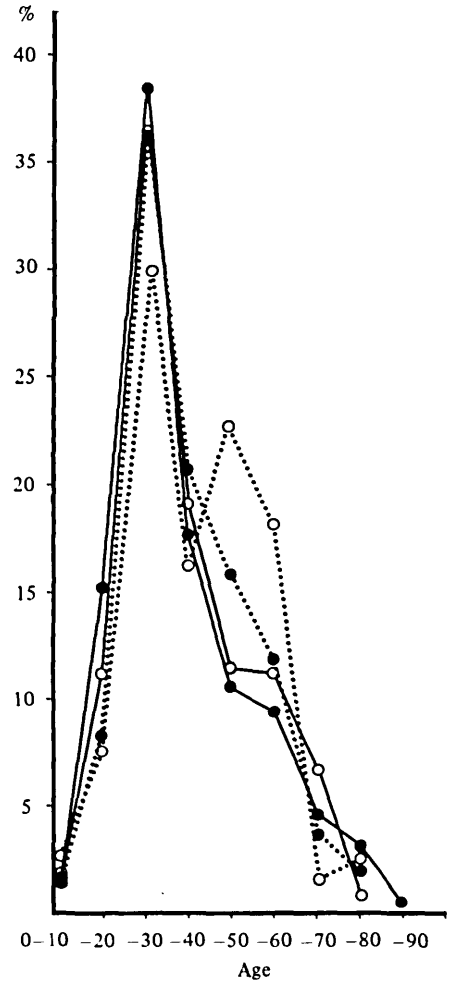

Fig. 5. The age distribution of ethnic Asian female patients according to bacillary type and site of isolation. Key as in Fig. 2.

Table 3. *The occurrence of drug-resistant strains in the two ethnic groups*

TCH susceptibility	Drug resistance				Total resistant	Percentage of isolations
	INH	SM	INH/SM	Other		
			European			
Resistant	42	83	30	12	167	2·69
Sensitive	5	5	2	1	13	2·11
Total	47	88	32	13	180	2·64
			Asians			
Resistant	116	59	96	9	280	8·75
Sensitive	16	12	9	4	41	6·18
Total	132	71	105	13	321	8·31

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DISCUSSION

The Asian or South Indian variant of the human tubercle bacillus is characterized by its attenuation in the guinea-pig, its susceptibility to hydrogen peroxide, its sensitivity to TCH, its phage type and its possession of the Attenuation Indicator (AI) lipid. The *in vitro* characteristics, however, do not show a complete correlation. Detection of the AI lipid appears to be the most reliable means of identifying this variant (Goren *et al.* 1982) but the technique is too time-consuming to be used in a routine laboratory faced with a large work load. Accordingly, for epidemiological purposes, this variant is defined as a human type showing sensitivity to TCH (Collins, Yates & Grange, 1982). This classification is applicable to both INH-sensitive and -resistant strains as, although cross-resistance to these agents occurs *in vitro*, it appears to be a rare event *in vivo* (Yates, Grange & Collins, 1984).

Although termed the Asian type on account of its prevalence in India and adjacent countries, it cannot be assumed that all strains of this type originated in Asia. Neither can it be assumed that Europeans infected by this type acquired the infection from Asian patients. Unfortunately we have no knowledge of the prevalence of this type in Great Britain before 1977. A phage typing study of 85 strains of *M. tuberculosis* collected in this country before 1966 showed that four were of phage type I, but the ethnic origin of these patients was not stated (Bates & Mitchison, 1969). It is likely, therefore, that the Asian strains isolated from the European patients have been present in this country for many years and represent a bacteriological population different from that present in the ethnic Asian community in this country. Indeed, they may have been brought to this country by members of the British colonial power in India prior to that country's independence. This view is supported, to some extent, by the differences in the incidence and pattern of drug resistance between the two types of bacillus in each ethnic group.

Information on the incidence and distribution of tuberculosis in a community or nation may be gained through systems of compulsory notification or by examination of the records of reference centres for tuberculosis bacteriology. Neither method is perfect as, in practice, not all cases are notified and a considerable number of cases are diagnosed clinically but not confirmed bacteriologically. Ideally both epidemiological methods should be considered together, and modern information technology should render this easy. Bacteriological surveys, however, have the advantage that the behaviour of different types of bacillus can be monitored.

The success of notification surveys depends on the constancy of returns made by the various practitioners, clinics and hospitals. Likewise, bacteriological surveys depend on the constancy of referrals of cultures to the reference centre. This study is based on cultures referred to the P.H.L.S. Regional Centre for Tuberculosis Bacteriology at Dulwich – a laboratory that receives about 95% of all strains of tubercle bacilli isolated in London and South-East England. The number of referring laboratories, and the hospitals and clinics that they serve, has not changed substantially during the seven-year period, so that valid studies on the changing trends in referrals may be undertaken. In this study disease is divided

into 'pulmonary' and 'extrapulmonary' on the basis of the site of isolation of the bacillus; although it is likely that some of the patients thus classified as 'pulmonary' cases also had extrapulmonary lesions that were not examined bacteriologically.

During the study period there was an overall decline in the isolation rate of tubercle bacilli and there has been a similar decline in the notification rate of tuberculosis throughout the country (Sutherland, Springett & Nunn, 1984). Both the notifications and the bacteriological studies showed that the incidence of the disease clearly declined among the Europeans, but that in the Asian group the annual isolation (or notification) rate was much more erratic and no significant overall trend was evident. The latter group is, however, subject to several variables including the rate of immigration into this country, relocation within the country and the changing ratio of immigrants to individuals born of Asian parents in this country. The notification and bacteriological surveys also both showed that the overall decline of disease was more evident among males than females.

As reported previously (Grange *et al.* 1977; Yates, Collins & Grange, 1982) the Asian strains are found among both European and Asian ethnic groups in Great Britain, but relatively more frequently among the latter. During the seven-year period the annual isolation rate of this strain was very constant in both ethnic groups. Accordingly, in view of the significant decline in the isolation rate of the TCH-resistant strains from European patients, the ratio of the latter to the former strains increased significantly in this group during the study period.

Although the differences in age distribution between males and females and between the two ethnic groups are probably influenced by overall differences in age distribution, some differences are not explainable in this manner. The most striking difference in age distribution was that between European females infected with TCH-sensitive and -resistant strains. Indeed the age distribution of European females infected with the former approximated closely to that of the Asian females. There was a slight tendency for patients with extrapulmonary disease to be younger than those with pulmonary disease, but this tendency was not enough to account for the high incidence of extrapulmonary disease among the Asian patients.

The general patterns of disease, other than the declines referred to above, remained very similar during the seven years. Thus the age distribution in each group and the types of extrapulmonary disease, and their incidence relative to pulmonary disease, did not alter significantly. An exception to this principle was the decline in the proportion of cases of tuberculous lymphadenopathy among Asian females.

Among European males and Asians of both sexes there was a slight but not statistically significant tendency for the Asian strains to be associated with extrapulmonary disease. This tendency was too small to account for the high incidence of such disease among the Asian patients. Among the European females, however, there was a significant association between the Asian strain and lymphadenitis, but not other extrapulmonary manifestations. As mentioned above, European females infected by this strain were considerably younger than those infected with TCH-resistant strains. It is unlikely, however, that this age

difference accounts for the association between lymphadenitis and the type of bacillus, as patients with such disease showed a very similar age distribution to those with other extrapulmonary and pulmonary infections caused by this type.

This study has shown that the division of the human tubercle bacillus into two types according to its sensitivity to TCH reveals epidemiological trends that are of interest and importance. In particular, the relative increase in the number of Asian to Classical strains in the ethnic European population is of interest. The genetic basis of the difference between Classical and Asian strains remain unknown. The latter may represent a distinct subspecies that evolved in Asia or they may arise regularly from the former by mutation in all parts of the world but become dominant only in certain regions where undefined host factors permit. Thus it is possible that such factors that once led to the selection of this type in South India now exist in Great Britain.

The higher than expected incidence of lymphadenitis due to this type in European females, and the similarity of age distribution of this type among European and Asian females is, in this respect, noteworthy. It appears necessary and desirable, therefore, to maintain an active interest in the behaviour of the various types of *M. tuberculosis* in this country despite an overall decline in the incidence and prevalence of tuberculosis.

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