The epidemiology of primary biliary cirrhosis: A survey of mortality in England and Wales

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SUMMARY Primary biliary cirrhosis is a rare disease in the general population. Estimates of its true incidence are difficult but since survival time is unaffected by treatment, mortality may reflect important regional and other variations. One hundred and sixty-five death certificates collected in England and Wales over the five-year period 1967-1971 were inspected and confirmed an overwhelming predilection for females. Deaths rose sharply at ages 50-54 in the latter with a peak of $4.1 \text{ million}^{-1} \text{ year}^{-1}$, with perhaps a secondary peak at ages 70-74. No relation of mortality with climate, altitude, soil type, annual temperature range, or occupation was found, although outside the UK a broad correlation exists with total cirrhosis deaths. There was a suggestive excess of deaths among married women. The greater frequency of deaths in the London area, a rise in mortality from country to urban areas, a fall-off in deaths from primary biliary cirrhosis in old age, and predominance for social class I suggest a simple relationship with standards of medical care or diagnosis. An 'epidemic' of deaths in 1971 is attributed to greater availability of the mitochondrial antibody test in the regions. The importance of familial primary biliary cirrhosis and various models of pathogenesis are discussed. Both constitutional and environmental factors producing the disease must be widely distributed in the population of this country.

Primary biliary cirrhosis is a very rare disease. Little is known of its aetiology, although drugs (Read, Harrison, and Sherlock, 1961), toxins (Goldfarb, Singer, and Popper, 1962), viral hepatitis (Jones and Tisdale, 1963), and ulcerative colitis (Holdsworth, Hall, Dawson, and Sherlock, 1965) may be associated with a similar clinical and histopathological picture, autoaggressive pathology is now favoured (Peronetto, 1970).

It has long been known that there are peculiarities in the distribution of primary biliary cirrhosis, with a predilection for both the European race and for middle-aged females. We thought that a survey of incidence in this country would throw light upon geographical and environmental factors important in producing the disease. However, there are problems of sampling in a retrospective survey of this nature. This is a disease of insidious onset and relatively low in the consciousness of most doctors, so that notification at first presentation might be unnaturally biased towards teaching hospitals and other large clinical centres.

Primary biliary cirrhosis is, unfortunately, almost uniformly fatal and no treatment now exists to modify its course. These facts provide an answer, for

the death rate as judged from relatively large samples, larger than that can be collected even at specialist centres, will closely reflect incidence in the general population. Despite the difficulties of diagnostic validation we felt that a mortality survey would provide an unbiased estimate of incidence of the disease in the general population.

Method

Death certificate draft entries for England and Wales over the five-year period 1967-1971 were searched for any mention of primary biliary cirrhosis as a cause of death. Those retrieved were examined for: (1) sex, (2) age at death, (3) permanent address, (4) occupation, (5) place of birth. Figures were obtained for the age and sex composition of the English-Welsh population (Jones and Tisdale, 1963) and used to calculate standardized mortality (as deaths per million or deaths per 100 000 living) and standardized mortality ratios (deaths observed/deaths expected $\times 100$). Differences were tested using Mantel's modification of chi-square (Gilliam and MacMahon, 1960). Comparisons were made between age groups and the Registrar General's (Office of Population Censuses and Surveys, 1971) nine

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Fig 1 Mean annual death rates for primary biliary cirrhosis per million living by age (females) for England and Wales 1967-71.

standard regions, socio-economic classes, and occupational categories of the deceased and expressed in the usual way.

Results

Over the five-year period 1967-1971 deaths from primary biliary cirrhosis amounted to 165. This corresponds to a crude death rate of 1.2 million⁻¹ year⁻¹ for females or 0.6 million⁻¹ year⁻¹ for both sexes. Cirrhosis (all forms) itself accounts for approximately 2.5% of deaths from all causes and primary biliary cirrhosis in turn represents 2.2% of all deaths due to cirrhosis.

The number of deaths in successive years was 19, 29, 28, 26, and 63. This last figure (for 1971) is clearly higher than expected ($\chi^2_{(4)} = 31.1$, $P < 0.001$) and may represent deaths in cases of primary biliary cirrhosis diagnosed since the mitochondrial antibody test became generally available. Much of the rise was attributable to notifications outside London, supporting the idea of an artificial or 'diagnostic epidemic'.

Of the 165 deaths, 19 occurred in males. This corresponds to a male : female ratio of 1:9. Because of this, females only have been considered in subsequent calculations.

No deaths occurred before age 31 in females, but after this age mortality rose rapidly, reaching a peak in the 55-64 age group (fig 1). In this, there were 29 deaths, equivalent to a rate of 4.1 million⁻¹ year⁻¹. Thereafter deaths remained constant until age 75 and over, where mortality was only 1.2 million⁻¹ year⁻¹.

Standardized mortality ratios (as calculated from the composition of the 1969 population) varied between the standard regions (fig 2), from 52 in the North of England, ie, 52% of the national average, to 141 in the London Boroughs. No significant

Fig 2 Map of mortality from primary biliary cirrhosis 1967-71 (females) by standard regions.

Fig 3 Annual mortality from primary biliary cirrhosis by age group (females) for England and Wales 1967-71.

difference existed between the regional SMRs and the national figure of 100 ($\chi^2_{(8)} = 10.88$, $P > 0.20$).

There was a gradient of mortality due to primary biliary cirrhosis from city to country with rural districts SMR 65, urban areas 106, and conurbations 111 ($\chi^2_{(2)} = 3.61$, $P > 0.10$). No consistent Celtic predominance, ie, of deaths in Wales emerged, although the highest age-specific mortality of all was in Welsh women of 55 to 59 years (fig 3). However, since this rate is represented by just three deaths it is unjustifiable to draw any valid conclusion.

No relationship existed between regional mortality and altitude, rainfall, annual temperature variation, soil type (Warren, Delavault, and Cross, 1967), or the presence of heavy industry or mining.

There was a preponderance of deaths in social class I (professional, etc, occupations) with SMR 155 and a relative deficit in social class III (skilled manual

Fig 4 Standardized mortality ratio for primary biliary cirrhosis by social class (females) for England and Wales 1967-71.

Order (Wives of)	No. of Deaths Observed	No. of Deaths Expected ¹	χ^2
I Farmers, foresters, and fishermen	9	5	2.29
XVIII Labourers n.e.c.	3	7	2.09
XIX Transport or communication workers	11	10	0.06
XXI Clerical workers	16	16	0.00
XXIII Service, sport, and recreation workers	9	9	0.14
XXIV Administrators and managers	6	5	0.00
XXV Professional and technical artists	12	12	0.00
XXVII Inadequately described occupations	9	7	0.89

Table I Mortality for primary biliary cirrhosis by Registrar-General's occupational category

¹Figures are rounded to nearest whole number.

$\chi^2_{(7)} = 5.47$, $P > 0.50$

occupations) with SMR 66 (fig 4), ($\chi_{(4)}^2 = 8.98$, $P > 0.05$).

The highest mortality in the occupational groups belonged to the wives of farmers, fishermen, and foresters, and the lowest to the wives of labourers. In most groups the expectation of deaths is too low for statistical analysis and among the eight groups remaining (table I), the SMRs did not differ significantly from the national figure ($\chi_{(7)}^2 = 5.47$, $P > 0.50$).

The birthplace was recorded on less than half of all death certificates. However, it was noteworthy that only two of the deceased were born outside the United Kingdom—in India and Poland respectively.

Of all female deaths, 134 occurred in married women. The expected number was 110 ($\chi_{(1)}^2 = 2.46$, $P > 0.10$).

Discussion

No study exists of the occurrence of primary biliary cirrhosis in the general population and nothing is known of its aetiology. From the time of its earliest description, attention has been drawn to familial cases of the disease. Thus Boinet (1898) described a father and two children with Hanot's cirrhosis and three others of his children with enlarged spleens. Finlayson (1900) described three brothers and a sister, two of whom had Hanot's cirrhosis, one slight jaundice, and one hepatosplenomegaly. Weber (1903) established Hanot's disease at necropsy on a 14-year-old girl whose sister had died aged 19 with similar symptoms and signs, and Osler (1905) mentions two brothers with Hanot's cirrhosis. More recently Chohan (1973) has described well validated primary biliary cirrhosis in twin sisters presenting at ages 26 and 28. There is a definite familial trend in the occurrence of primary biliary cirrhosis, emphasized by the work of Feizi, Naccarato, Sherlock, and Doniach (1972) who found that of 27 patients investigated, two had relatives affected by chronic liver disease, and that of 126 relatives of the original 27 probands a significant

number had mitochondrial antibodies in the serum as well.

If a genetic basis exists for the disease it seems reasonable to look at racial incidence. In Ahren's series of 17 patients (1950), seven were Jewish, although the authors were careful to point out that their cases had been collected in a predominantly Jewish area of New York. Sherlock (1959), nine years later in London, found that of 27 cases, four were Welsh, two Scottish and one Irish, ie, over 25% were of Celtic origin. Most published series, eg, that of Foulk, Baggenstoss, and Butt (1959), mention a predilection of the disease for those of European descent, although cases in negroes are described (Ahrens, Payne, Kunkel, Eisenmenger, and Blondheim, 1950; Spellberg and Gattas, 1955) in the American literature.

Nevertheless at least one survey (Steiner, 1964) of the problem states that 'biliary cirrhosis . . . of the primary subtype probably occurs in all countries . . . at relatively low levels'. The issue is confounded by the poverty of medical services in some areas of the world and the reluctance of others to release official statistics on cirrhosis. Africa and most of South America are not represented in the literature on primary biliary cirrhosis, but Hong Kong (Lam, 1973), Japan, India (Samanta, Bhagwat, Mukherjee, Gupta, Sogal, and Datta, 1973) and the USSR (Teodori, Khazanov, Shultsev and Shtern, 1961) are. It is possible, though, from knowledge of the incidence of cirrhosis and what percentage primary biliary cirrhosis takes up in the various published series, to construct an approximate league table among the nations of the world (table II). From this it may be inferred that there is a rough correlation between deaths from all cirrhosis and deaths from primary biliary cirrhosis, and that in the two Asiatic countries represented in the table the latter is an excessively rare disease.

It was with this knowledge that the problem of England and Wales was approached. The popula-

Country	All Cirrhosis Deaths/Million	Primary Biliary Cirrhosis (%) in Published Series	'Best' Estimate for Primary Biliary Cirrhosis (deaths per million both sexes)
Austria	223	2.3 (Sneiderbaur, 1964)	5.1
Mexico	224	0.9 (Sepulveda <i>et al</i> , 1956)	2.2
West Germany	170	0.8 (Lent, 1969)	1.3
Australia	48	1.0 (Wood, 1959)	1.0
		2.9 (Powell <i>et al</i> , 1971)	
USA	109	1.0 (Reid <i>et al</i> , 1968)	1.0
Sweden	49	1.3 (Hällén and Krook, 1963)	0.6
England & Wales	27	1.4 (Parker, 1957)	0.6
		3.2 (Stone <i>et al</i> , 1968)	
		2.2 (this study)	
Thailand	47	0.7 (Viranuvatti, 1968)	0.3
Singapore	61	0.0 (Seah, 1968)	0.0

Table II Estimated death rates for primary biliary cirrhosis in certain countries

tions of the two countries are heterogeneous in respect of blood group (Kopéc, 1970) and disease susceptibility as well as some anthropomorphological characteristics (Ashley and Davies, 1966), and it was disappointing not to confirm earlier subjective impressions that the disease was commoner in Wales.

The reliability of the data material is difficult to estimate, but the necropsy rate was 46% and in 68% of cases the certificates recorded death due to well known complications of primary biliary cirrhosis such as haemorrhage from oesophageal varices or hepatic coma. There is no reason to believe that diagnostic habits vary widely in a small country where the majority of chronically sick are treated in specialist centres. In the General Register Office survey of cirrhosis deaths in 1959 Heasman and Lipworth (1959) found that only 60% of individual deaths assigned to this condition by the clinician were confirmed by the pathologist. Unfortunately no information is available as to error involving different types of cirrhosis, but there would be a tendency to misallocate primary biliary cirrhosis to the cryptogenic category. It is unfortunately impossible, owing to the confidential nature of these certificates, to compare the entries with hospital case notes and the possibility remains that diagnostic error exists. This criticism applies to all published series where modern criteria for diagnosis of the disease, such as positive mitochondrial antibody, are not adhered to. These factors must make our estimate of the incidence of primary biliary cirrhosis a very conservative one.

The high incidence of deaths among women and middle-aged women in particular confirms previous impressions from clinical series (Ahrens *et al*, 1950; Foulk *et al*, 1959; Sherlock, 1959). Such a sex ratio (9:1) is exceeded in few other medical conditions and the epidemiology of primary biliary cirrhosis is therefore the epidemiology of that disease among women.

It is not clear why mortality falls off over age 75. It may be because of deaths from other causes unconnected with primary biliary cirrhosis, or a tendency not to investigate patients of advanced years.

The frequency polygon (fig 1) for mortality by age may be sigmoid (up to age 74) or bimodal with peaks at ages 50-54 and 70-74. It is difficult to say which, as the numbers are small and figures in the higher age groups may not be as reliable. If we assume that all subjects are exposed from different ages to an agent which initiates intrahepatic bile duct destruction at a constant rate and that the induction period is normally distributed then there will be a simple power relationship between incidence and age (Doll,

1971). This is not found to be the case and we must reject this model of pathogenesis. Similarly, any modification of the model for exposure at constant age is invalid as we are dealing with a 'wild' population, and in any case this would show a single peak incidence. Other explanations are more likely: (1) The case of a sigmoid frequency distribution implies an infection, perhaps corresponding to the exhaustion of a susceptible population, followed at constant attack rate by an agent to which all women are exposed from just before the menopause, or (2) a bimodal distribution of deaths points to two classes of susceptibles, each being exhausted in turn by different agents, both appearing over the same years of life as in (1).

There is nothing in the data to suggest what sort of agent this might be, but the distribution of deaths is reminiscent of those found in carcinoma of the genital tract. Hormonal milieu, as suggested so many times before, may therefore be important in producing the disease. The slightly higher number of deaths among married women and the propensity for primary biliary cirrhosis to present in pregnancy supports this idea.

The unexpected finding of a relatively high urban mortality may reflect the tendency for patients with a chronically debilitating disease to gravitate to the towns where specialized centres and district hospitals are to be found. Hospital referrals from general practitioners are more frequent in the towns and cities and this would tend to earlier and more complete diagnosis.

In England and Wales the statistics for alcoholic and other forms of cirrhosis are no longer published separately. This could be the explanation for cirrhosis apparently affecting the heavily industrialized areas of South Wales and the Midlands rather more than the rest of the country. No consistent tendency for primary biliary cirrhosis to follow this pattern of distribution is found and it may be that the relationship between the incidence of primary biliary cirrhosis and all cirrhosis observed outside England and Wales does not hold here. The regional distribution of deaths follows that of facilities for good medical care only approximately.

Primary biliary cirrhosis joins infectious hepatitis as a disease affecting social classes I and II more than IV and V, as well as Hodgkin's disease, and other reticuloses among women (Office of Population Censuses and Surveys, 1970). The social gradient for cholelithiasis and cholecystitis runs counter to that for primary biliary cirrhosis among the classes, however. Although the differences observed were not statistically significant it does not follow that socio-economic factors are unimportant in causation of the disease. On the other hand occupational factors

were probably not significantly associated with mortality from primary biliary cirrhosis and figures here may be more reliable than with males, in whom there is a tendency to change from a strenuous job on the grounds of age or ill health. Again, the social class gradient suggests a correlation with better medical care.

The Commonwealth immigrants of Great Britain constitute less than 2% of the population (Office of Population Censuses and Surveys: 1973) so that it was not surprising to find them unrepresented in this small sample. Since the Immigration Acts of 1968-1971 halted the inflow and changed the age structure of the existing communities, it will be some time before a middle-aged female population at risk from the disease appears in significant numbers to contribute to total mortality.

Conclusions

Primary biliary cirrhosis is a very rare disease, both in Great Britain and in the rest of the world. There is a tendency for centre-based estimates of its frequency and distribution in the general population to be biased, so that the most practicable ways of assessing these is a mortality survey. This confirms its predilection for middle-aged married women, social class I, and city dwellers. No ethnic or occupational factors have been found. In particular subjective impressions of its prevalence amongst the Welsh remain unproved. If genetic mechanisms are important, as appears from familial reports, these must be as widely distributed in the general population as any postulated environmental influence, from the regional figures, would have to be. Future epidemiological research should be directed at elucidating international differences in the prevalence of the disease and explaining them.

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