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A Five-Year Prospective Study of the Health of Children in Different Ethnic Groups, with Particular Reference to the Effect of Inbreeding

Key Words
Consanguinity
Mortality
Morbidity
Ethnicity

Abstract

A 5-year prospective study of 4,934 children of different ethnic groups has demonstrated a 3-fold increase of postneonatal mortality and childhood morbidity in the offspring of consanguineous Pakistani parents. Most of these families contained more than one consanguineous union, resulting in a mean inbreeding coefficient for their children of 0.0686. It is estimated that 60% of the mortality and severe morbidity of this group of children could be eliminated if inbreeding ceased. However consanguinity is much favoured in this minority group, and health education will have to be carefully and sensitively handled.

Introduction

UK national statistics have consistently demonstrated higher death rates in infancy (i.e., the first year of life) for UK-born Pakistani children compared to other ethnic groups [1–3]. For example, OPCS data for England and Wales, 1982–1985, recorded a perinatal mortality rate for Pakistani babies of 18.8 per thousand, compared to rates of 10.2–13.4 per thousand for other ethnic groups [4]. Postneonatal mortality rates were 6.4 per thousand for UK-born Pakistani infants and 2.8–4.5 per thousand for other ethnic groups [3]. Thus, the overall infant mortality rate for UK-born Pakistanis is about 1.7-fold greater than that of other ethnic groups [2]. One major cause of this extra mortality in the 2.5-fold higher rate of lethal congenital malformations in Pakistanis compared to other groups, so that 41% of deaths of Pakistani infants are due to malformations [2, 5]. Some of these malformations are caused by autosomal recessive genes [6, 7] and have therefore been

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Table 1. Percentages of Asian children observed in special schools compared with expected percentages

Type of school or condition	Observed			Expected, %
	n	sample size	%	
ESN (S) schools in Walsall and Coventry[1] [10]	19	99	19.2	11.5
ESN (S) schools in Bradford [9]	54	93	58.1	27.0
Schools for the deaf in Bradford [11]	37	151	24.5	14.9
Schools for the partially sighted in Birmingham	13	46	28.3	9.5

ESN (S) = Severe educational sub-normality.

The control figures are from data kindly supplied by the Education Authorities for Walsall, Coventry, Birmingham, and Bradford, and by the Central Statistical Office, City of Birmingham and the 1981 census. The observed data come from the references indicated and unpublished observations from genetic eye clinics.

[1] Only boys with idiopathic mental retardation were studied.

attributed to the Pakistani custom of marrying relations. However, the presence or absence of parental consanguinity is not documented in national statistics and further study is required to assess its relevance to mortality and other aspects of children's health.

Birmingham, being a multiracial city, provides the opportunity to study the effect of inbreeding and other factors which may differ between ethnic groups. The largest ethnic minority group in Birmingham is the Pakistani community, which comprises 13% of Birmingham children. Between 60 and 70% of their marriages are between relatives and predominantly occur in families in which there have been earlier consanguineous marriages in the pedigrees [8].

Such family patterns allow an assessment to be made of the contribution of autosomal recessive diseases not only to childhood mortality but also to morbidity. The matter is important because observations from two of the areas where UK Pakistanis are particularly found (Bradford and Birmingham) show an excess of 'Asian' children at schools for those with mental and physical handicaps. Some observations are summarized in table 1. Unfortunately, their usefulness is diminished because patients sometimes, and controls usually, are classified as 'Asian' meaning originating from the Indian subcontinent. In Bradford, 80% of 'Asian' children are Pakistanis [9], and percentages are 54% for Birmingham and 25% for Coventry and Walsall [12].

In the light of the above observations we considered that the most appropriate way to obtain accurate data on the effect of inbreeding in different ethnic groups was by a prospective study, starting with an unselected cohort of births and following the children for 5 years, until they started school. Such a plan would enable a study of other aspects of health in Birmingham babies of different ethnic groups, and would provide controls of suitable socio-economic status. It would also allow a complete documentation of malformations, since one third are not recorded at birth [13]. A prospective study would also avoid the possible bias of preferential immigration of handicapped children into Birmingham or of reduced emigration of handicapped children out of the city. Other useful features of the proposed study were accurate

documentation of ethnic-group and inbreeding coefficients.

Such a prospective study would not just be of academic interest but would also be useful for paediatricians and clinical geneticists wishing to learn how much of childhood illnesses could be attributed to inbreeding and to what extent their assessment of an unusual illness in a Pakistani child should be influenced by the knowledge of parental consanguinity. The initial results of this study on perinatal and neonatal mortality have already been reported [14]. They indicated that only about half of the lethal malformations could be attributed to recessive diseases and that another important cause was an increased incidence of congenital heart malformations in recent immigrants. The present report describes postneonatal problems, namely mortality, congenital malformations and the development of serious conditions that adversely affect a child's health and/or schooling.

Methods

Details of the initial documentation are described in an earlier report on social features, race and consanguinity [8]. Briefly, mothers who had addresses within the City of Birmingham and who gave birth at one of three Birmingham hospitals on weekdays during 1986 and the first 4 months of 1987 were invited to participate in the study. All but 80 agreed; the consenting 4,886 mothers had 4,934 babies who were enrolled in the study. The mothers were interviewed on the postnatal wards (or at home if they were discharged promptly) using a 12-page questionnaire. Information was collected on the mother's health, the length of antenatal care, health and social class of the baby's father; the outcome of previous pregnancies and the health of sibs; the ethnic group and religion of both parents, whether they were consanguineous and if so, how. Enquiry was made about further consanguineous unions in the pedigree and the ways in which the parents and baby's grandparents were consanguineous. Thus, the pedigreee extended to the baby's grandparents if there was no consanguinity, but extended to two earlier generations in order to explain consanguineous relationships in the parents' or grandparents' generations. Information was also collected on the baby's clinical state at birth and its measurements. Five years later the families of 20 Pakistani children with developmental problems were visited to see if previously negative information about sibs was correct; no inaccuracies in the pedigrees or other family information collected at the time of birth were found.

Follow-up of the babies continued until they entered school. Many sources were used to ascertain their health problems. The death certificates sent to the District Medical Officers were scrutinized at the end of each year to discover if any babies had died. The Hospital Statistical Analyses (both Regional and District) were used to discover which babies had been inpatients in a Birmingham hospital during each year. In addition, the District Child Health Registers were searched each year for the hospital numbers of any of the babies who had been either an in- or an out-patient; they could be ascertained by first using the listing for a particular date of birth, and then seeing if any of the names (and addresses) corresponded to babies enrolled in the study. After thus obtaining hospital numbers, the help of medical-records officers was enlisted so that medical records could be scrutinized to determine which diseases were trivial, serious but treatable, or serious and needing prolonged treatment, perhaps resulting in chronic disability. In this way 2,700 records of 2,000 children were studied. Further sources were also used. The records of the Child Development and Assessment Units were searched; some children with developmental problems had only been seen in these units and were not registered at a hospital. The records of the City's Aural Clinic were searched for children in the study who might have severe hearing problems. The register for children with special educational needs which is held by the City of Birmingham Education Department was searched for the names of study children; further medical information was obtained about those few children who were on the Special Needs Register and who had not already been ascertained through the earlier sources. Finally, we wrote to all the general practitioners of children in the study and asked for information concerning current addresses and the presence or absence of serious chronic diseases. Whilst the most fruitful sources of information were the computerized registers of hospital in- and out-patients, all other sources revealed a few names not ascertained elsewhere.

Finally, the computerized records of the Family Health Services were used to find which of the original cohort of 4,934 babies were still living within the City of Birmingham.

Table 2. Chronic disabilities in survivors

	European (n = 2,214)	Afro-Caribbean (n = 441)	Indian (n = 613)	Pakistani consanguineous (n = 632)	Pakistani non-consanguineous (n = 289)	Bangladeshi (n = 212)	Mixed race (n = 348)
Cerebral palsy	11	2	3	1	0	0	4
Malformations[1]	11	2	1	5	2	0	2
Neurological sequelae of trauma, infection	4	0	0	0	0	0	0
Unexplained neurological problems with mental retardation	1	0	1	14 (11)	0	0	0
Severe mental retardation alone	1	1	0	3	0	1	2
Mild mental retardation	11	3	3	2	0	0	1
Idiopathic deafness	3	0	0	1	0	1	1
Metabolic and haematological disorders	5 (2)	3 (2)	1	9 (9)	0	0	0
Cancers	0	0	2	3	0	0	0
Epilepsy	2	3	1	2	0	1	0
Other chronic disorders[2]	8	1	2	4 (3)	0	0	1
Total	57	14	14	44	2	3	11
Rate, %	2.6	3.2	2.3	7.0[3]	0.7	1.4	3.2
Adjusted total[4]	50 (2.9)	13 (3.5)	14 (2.9)	42 (7.6)	2 (0.8)	3 (1.6)	10 (3.8)

Numbers of definite and probable autosomal recessive diseases are given in parentheses, and listed in Appendix 1.

1 Includes chromosomal abnormalities; see also table 4.

2 These were: juvenile arthritis (1); tuberculosis (1); coeliac disease (1); neurofibromatosis (1); type I diabetes mellitus (2); neuropathy (2); Duchenne muscular dystrophy (1); nephrotic syndrome (4); ichthyosis (1); spinal muscular atrophy (1); osteogenesis imperfecta (1). There was also congenital spherocytosis in an Iraqi child.

3 Significantly different from Europeans, Indians, non-consanguineous Pakistanis and Bangladeshis ($p < 0.001$) and from Afro-Caribbeans and children of mixed race ($p < 0.05$).

4 Removing those children who had left the City by 1992. The percent rate is given in parentheses.

Classification of Problems

We classified malformations into those causing death, those causing chronic problems (for example, Hirschprung's disease, optic-nerve coloboma); those which required treatment (operation or prolonged splinting) but which left the child healthy, and those which were trivial. The latter will not be described here. They include talipes equinovarus and congenital dislocation of a hip that did not require prolonged treatment, atrial or ventricular septal defect which closed spontaneously or that did not require operation, polydactyly, Poland's syndrome, patent ductus arteriosus due to prematurity, and umbilical hernia.

In recording chronic disabilities we included those listed in table 2, all of which needed constant care. We did not count children who made a total recovery from meningitis or encephalitis, those who had febrile convulsions only, or those who recovered from acute glomerulonephritis, or Henoch-Schönlein purpura. We did not include asthma because this was difficult to quantify from hospital records. Mental retardation was recognized when special education was required, and

was divided into 'mild' and 'severe', the latter children requiring constant care.

We classified certain, probable or possible autosomal recessive diseases as follows: 'certain autosomal recessive' conditions were those with distinctive clinical and/or laboratory features of established diseases; 'probable autosomal recessive' conditions were those often due to autosomal recessive genes, and with an additional feature such as parental consanguinity or an affected sib, and 'possible autosomal recessive' conditions were those with heterogenous aetiology but often due to autosomal recessive genes. The conditions are individually listed in Appendices 1 and 2.

Calculations

For assessing the proportion of mortality and morbidity which is attributable to inbreeding we used the formula designed by epidemiologists [15, 16]. In this, the attributable risk (AR) equals:

$$p(RR-1)/[1 + p(RR-1)]$$

where p is the frequency of the risk factor (in this case, consanguineous marriages) and RR is the relative increased risk attributable to the risk factor, using a control group not exposed to the risk factor, but otherwise matched for socio-economic and demographic features.

Results

Features of the Cohort of Children

The 4,934 babies enrolled in the study consisted of 2,241 babies of English/other European origin, 453 Afro-Caribbeans, 619 Indians, 952 Pakistanis, 216 Bangladeshis, 354 babies whose parents were of different races, and 99 babies of other races, namely Chinese, Vietnamese, Arabs and others. The babies of mixed race consisted of 211 Afro-Caribbean/European, 57 Asian/European and 57 other mixtures. Note that in earlier publications [8, 12, 14] the babies were classified by the mother's race. Of the European babies, 10 parental couples were consanguineous, and the corresponding numbers for other groups were 3 Afro-Caribbeans, 1 Indian Sikh, 3 Indian Hindus, 28 (out of 63) Indian Muslims, 656 Pakistanis, 28 Bangladeshis, 14 babies of other races and 8 babies of mixed race. The latter were all babies with one parent of mixed Asian/European origin who married a first cousin on the Asian side of the family. There was no difference in demographic features, social class or degree of antenatal care between those women who were related to their husbands and those who were not [8]. 624 of the 656 Pakistani mothers who were consanguineous with their husbands could describe their pedigrees fairly accurately: the mean inbreeding coefficient of their babies was 0.0686. This is a minimum estimate since 112 of these mothers knew of further consanguineous unions in their pedigrees but could not describe them accurately. Altogether 422 (68%) of the 624 Pakistani pedigrees and 16 of the other 71 consanguineous pedigrees which could be described contained more than one consanguineous marriage. In contrast, only 35% of the Pakistanis who had not married a relation had additional consanguineous unions in their pedigrees.

In subsequent analyses (tables 2–6) the babies have been classified by ethnic group, as described above. The Pakistani babies have also been grouped according to whether their parents were consanguineous, in order to assess the importance of this feature in contributing to mortality and morbidity. The low parental consanguinity rates in the other ethnic groups and the very few ill or dead babies amongst them meant that classification of other ethnic groups by parental consanguinity was not worthwhile.

Twenty-nine babies were stillborn and 56 children died during the first 5 years of life. About 80% of the original cohort were still living in Birmingham in 1992. The figures for those still in Birmingham for each ethnic group separately were: 78% of Europeans, 84% of Afro-Caribeans, 80% of Indians, 88%

Table 3. Postneonatal deaths in babies according to their ethnic group

	European	Afro-Caribbean	Indian	Pakistani		Bangladeshi	Mixed race
				consanguineous	non-consanguineous		
Numbers surviving 1st month	2,226	446	614	645	290	214	350
Cause of death							
Birth asphyxia or prematurity	1	0	0	1	0	0	0
Malformation[1]	6	2	0	3 (2)	0	1 (1)	1
Trauma, fire	1	1	0	0	1	0	1
Cot death	1	2	1	0	0	0	0
Infection	3	0	0	3	0	0	0
Metabolic disease	0	0	0	1 (1)	0	0	0
Other	0	0	0	4 (3)	0	1	0
Total	12	5	1	12	1	2	2
Rate, %	0.54	1.12	0.16	1.86[2]	0.34	0.93	0.57

Values in parentheses refer to recessive or probably recessive diseases and are listed in Appendix 1.

[1] See also table 4.

[2] Significantly higher than the European rate using the G-test of independence, $p < 0.002$ [17].

of Pakistanis (both consanguineous and non-consanguineous) and Bangladeshis, 75% of children of mixed race and 63% of children of other races. Some of the latter families were known to be temporary visitors to the UK as their fathers were students. Of the children known to have chronic illnesses or disabilities, 92% were living in the city.

Deaths

Deaths occurring in the first month of life have already been reported [14]; those occurring postneonatally are summarized in table 3. The Pakistani children had a significantly greater postneonatal mortality rate than European children ($p < 0.001$). This was largely due to an excess of autosomal recessive diseases amongst those Pakistani children who had consanguineous parents.

Malformations

The serious malformations including those which caused death in the neonatal period are listed in table 4 and treatable malformations are given in table 5. It is noteworthy that cardiac malformations (both serious and treatable) were commoner in the Pakistanis and Bangladeshis than in other groups: 14 out of 1,168 (1.20%) compared to 8 out of 2,241 Europeans (0.36%) and to 10 out of all other 3,766 children (0.27%). There was also an excess of malformations due to autosomal recessive conditions in the Pakistani babies who had consanguineous parents, so that this, together with the increase of cardiac malformations, meant that they had a greater than 3-fold risk of serious malformations compared to European babies. The malformation rates in the other groups have large 2 SE

Table 4. Serious malformations in 4,934 index babies

	European (n = 2,241)	Afro-Caribbean (n = 453)	Indian (n = 619)	Pakistani consan-guineous (n = 656)	Pakistani non-consan-guineous (n = 296)	Bangla-deshi (n = 216)	Mixed race (n = 354)
Lethal malformations							
Death in 1st month							
Multiple	0	0	(1)	2	0	0	0
Cardac	0	0	0	2	2	1	0
Other	0	0	0	1	0	0	0
Death after 1st month							
Multiple	0	0	0	2	0	1	0
Cardiac	5 (1)	1	0	1	0	0	0
Other	0	1	0	0	0	0	1
Chronic disability[1]							
Joint	1	0	0	1	0	0	0
Cardiac	1	0	0	2	0	0	0
Other	4 (5)	1 (1)	(1)	1 (1)	1 (1)	0	1 (1)
Non-chromosomal total	11	3	0	12	3	2	2
Non-chromosomal rate, %	0.49	0.66	0	1.83[3]	1.01	0.93	0.56
Numbers of definite and probable autosomal recessive conditions[2]	0	0	0	6	0	1	0

Serious malformations defined in the text; extra malformations due to chromosomal abnormalities are put in parentheses.

[1] These are also included in table 2.

[2] Listed in Appendix 1.

[3] Significantly different from the rate in Europeans using the G-test, $p < 0.001$.

ranges due to small numbers, but the difference in rates for European babies and for Pakistani babies was statistically significant ($p < 0.001$).

Eight children had Down's syndrome and 3 had other chromosomal abnormalities.

The other striking observation concerning the treatable malformations listed in table 5 is the near-restriction of pyloric stenosis and cleft lip and palate to children of European origin.

Chronic Illnesses and Disabilities

Firstly, we wished to assess whether we had ascertained all children with common diseases of known incidence. There were 8 babies with Down's syndrome (1.6 per thousand); 3 babies with cystic fibrosis (0.6 per thousand), and 5 children had X-linked disorders (2.0 per thousand males) which were fragile-X syndrome, Duchenne muscular dystrophy, adrenoleucodystrophy, Lesch-Nyhan syndrome and X-linked ichthyosis. In addition, 2 Afro-Caribbean children had sickle cell disease and 3 Pakistanis had thalassaemia.

Table 5. Treated malformations in 4,934 index babies

	European	Afro-Caribbean	Indian	Pakistani		Bangladeshi	Mixed race
				consanguineous	non-consanguineous		
	(n = 2,241)	(n = 453)	(n = 619)	(n = 656)	(n = 296)	(n = 216)	(n = 354)
Joint	8	0	3	4	0	1	0
Pyloric stenosis	10	0	0	0	2	0	1
Other gut	4	2	0	0	0	0	0
Genito-urinary	6	1	1	1	0	1	0
Cleft lip ± palate	5	0	0	0	0	0	1
Cardiac	2	0	1	5	1	0	1
Other	1	0	1	2	0	0	0
Total	36	3	6	12	3	2	3

The similarity of these observed incidences to those expected led us to conclude that ascertainment was complete.

Chronic illnesses and disabilities are listed in table 2. There are several differences between the different ethnic groups. Firstly, there is an excess of cerebral palsy in the European babies, due to two factors. There were more small babies amongst Europeans: 74 observed with birth weights under 2,000 g, whereas 51 would have been expected on the basis of population data from Oxford [18]. However, in addition to this, there were more cerebral-palsied children amongst survivors than expected (11 versus 7) although the numbers were too small to reach statistical significance.

A second observation to be made from table 2 is that the number of mildly retarded children amongst Europeans (11, or 0.50%) appears to be higher, but not significantly so, than the prevalence in other ethnic groups (a total of 9 children out of the remaining 2,634, or 0.34%).

The most striking observation however is the excess of chronic illnesses and disabilities in the offspring of consanguineous Pakistanis; their rate is significantly higher than the rate in all other ethnic groups and the excess is largely due to autosomal recessive diseases. These are listed in Appendix 1. They amount to 16/3,982 (0.40%) combining all ethnic groups except Pakistanis, and to 41/656 (6.3%) in consanguineous Pakistanis, i.e., about 16-fold greater. If we consider the UK earlier born sibs of index patients (whose information was collected in 1986–1987 without follow-up and which is therefore less complete) we find similar rates (see Appendices). For the non-Pakistani families there were 13 certain, probable or possible autosomal recessive diseases out of 4,193 earlier sibs (0.31%) whereas for sibs in the consanguineous Pakistani families the rate was 16-fold higher, namely 47/955 (4.9%). For the Pakistani index children born to non-consanguineous parents the rate was 0/296 and for their earlier sibs it was 1/553, giving a combined rate of 1/849 (0.12%).

The number of similarly affected sibs in the sibships of index patients with 'certain' or 'probable' autosomal recessive diseases was 14/82 (0.17; 2 SE range 0.09–0.25). This figure includes sibs born outside the UK. If only sibs born within the UK are counted, then the proportion of affected sibs becomes higher,

Table 6. Summary of abnormalities in different ethnic groups

	European	Afro-Caribbean	Indian	Pakistani		Bangla-deshi	Mixed race	Other race
				consan-guineous	non-consan-guineous			
	(n = 2,241)	(n = 453)	(n = 619)	(n = 656)	(n = 296)	(n = 216)	(n = 354)	(n = 99)
Deaths in 1st month[1]	15	7	5	11	6	2	4	0
Deaths after 1st month	12	5	1	12	1	2	2	0
Chronic disabilities	57	14	14	44	2	3	11	1
Total[2]	84 (78)	26 (25)	20	67 (64)	9	7	17 (16)	1
Rate, %	3.7	5.7	3.2	10.2	3.0	3.2	4.8	1.0
Range[3]	2.92–4.48	3.56–7.84	1.81–4.59	7.9–12.5	0.24–0.36	0.85–5.55	2.57–7.03	0–2.96

Treatable malformations are exluded from this table.

1 Described in ref. 14.

2 This refers to the number of abnormalities. The number of children, where different, is given in parentheses.

3 95% confidence limits, given by $^{1.96}\sqrt{pq/n}$.

namely 14/63 (0.22; 2 SE range 0.12–0.32). Both figures are compatible with the 0.25 expected value on the basis of autosomal recessive inheritance, but the higher second figure suggests that there may have been some under-ascertainment or underreporting of sibs born outside the UK. In contrast, amongst earlier born sibs of index patients with 'possible' recessive diseases, only 1 in 25 was affected (or 1 in 22 counting only sibs born in the UK).

A summary of total deaths and disabilities of index patients is presented in table 6. The rate of 10.2% (range 7.9–12.5) for the offspring of consanguineous Pakistanis is significantly greater than that for every other ethnic group. There is however on the present data no obvious increased rate of disability with higher levels of inbreeding, presumably due to small numbers. It is helpful to record that one third of the serious conditions in Pakistani children were either treatable, or the offer of prenatal diagnosis could be made for a subsequent pregnancy. A further observation from table 2 is the low rate of serious chronic problems in Pakistani children who are the offspring of non-consanguineous parents. The two problems were de novo chromosomal mosaicism and unilateral cataract.

Discussion

The multiple sources that were used in this study to ascertain serious health problems appears to have been complete, since the numbers of children with certain specific disorders agreed with the expected frequencies [19, 20]. For example the birth frequency of children with clinical chromosome disorders was 0.22 per thousand, with cystic fibrosis was 0.6 per thousand, and with X-linked disorders was 1 per thousand.

We considered whether we should exclude the children who had left the City of Bir-

mingham. However, such an exclusion leads to a higher prevalence of serious disabilities (table 2), presumably because some health problems were ascertained before children left the city. We therefore concluded that we should continue to ignore the 20% or so of children who had left; this might lead to an underestimate of health problems by missing diseases that developed later, but probably such numbers would be small. There was no serious discrepancy between the degree of emigration for the different ethnic groups.

The increased frequency of cardiac malformations in Pakistani children, also noted in other studies [5, 13] deserves further investigation. It might be due to exposure to a new teratogen by recent immigrants, or to poor diet. In any case, it appears not to be genetic as it is not associated with parental consanguinity (this study) or recurrence in sibs [13]. The exception however is malformation associated with situs inversus which may well be autosomal recessive [21].

The most striking feature of this prospective study is the 3-fold increase of postneonatal deaths and of serious chronic disease in the offspring of Pakistani couples who are consanguineous, usually multiply so. A 1.6-fold increase in deaths between 1 month and 9 years was recorded in consanguineous families from Lahore [22], and similar increases have been reported from other Pakistani cities [23]. A total of 16,171 pregnancies of 3,329 women were studied over a 4-year period and these large numbers enabled estimates to be made of B, the number of lethal recessive genes per gamete revealed by inbreeding, using the method of Morton et al. [24]. These estimates of B ranged from 0.74 to 2.26 in the seven cities, with some large standard errors [23]. In the present study, although the inbreeding coefficients had been accurately recorded, the numbers of children were too small to allow an accurate estimate of B. The present study has however clearly demonstrated a significant excess of serious chronic diseases in addition to deaths in the consanguineous families. The excess was accompanied by an increase of autosomal recessive diseases, such that 48% of serious problems in Pakistani children were due to certain, probable or possible recessive diseases, whereas the percentage for other ethnic groups combined was only 3.6.

From the practical point of view it is useful, although depressing, to learn that the empirical risk of death or serious disease in the offspring of consanguineous UK-born Pakistanis is about 1 in 10. Nearly half of these are mentally retarded but one third either had a treatable condition or one that could be recognized prenatally. It is interesting that the offspring of non-consanguineous Pakistanis are at low risk for serious disease, apart from the risk of congenital heart disease which applies to all Pakistani children. They had no recessive diseases but the number (296) of unrelated Pakistani couples was too small for this to be significant. However one would expect the Pakistanis with non-consanguineous parents to experience a lowered risk for autosomal recessive diseases, owing to a redistribution of recessive genes with their aggregation in those pedigrees in which consanguinity has been practised for many generations.

As we found no evidence that socio-economic factors distinguish the Pakistanis who practise consanguinity from those who do not, we considered that the excess of ill health amongst Pakistani children with consanguineous parents could be entirely explained by the practice of inbreeding. If we compare their rates to those of the offspring of non-consanguineous Pakistanis and all Bangladeshis and Indians (which serve as appropriate control groups) we find that the relative increased risk for mortality and morbidity in inbred Pakistanis is 3.2 (data in table 6) and that the risk attributable to inbreeding [15] is 0.6. Thus, if

the Pakistanis ceased to marry relations, their childhood mortality and morbidity would decrease by 60%.

The implications of these findings for the Pakistani community have to be gently and sensitively incorporated into health education. For there are many social, and economic advantages for members of a minority ethnic group to marry relations [25]. Our approach in Birmingham is three-pronged. Firstly, we need to improve the early detection and early management of health problems in Pakistani children. This involves not only improving access to detailed ultrasound scanning in pregnancy, and careful assessment of Pakistani children for developmental problems, but also in persuading Pakistani women to book at antenatal clinics early, to attend often, and to take their chidren regularly to infant development clinics. Secondly, genetic counselling to the Pakistani community should be made more available and should preferably involve Muslim genetic counsellors who are able to visit families in their own homes. Such counselling should be available preconception, in the antenatal clinic (where testing for the carrier state of thalassaemia takes place) and when a child develops a possible genetic problem. In the latter situation, counselling should be offered to relatives outside the nuclear family, since the presence of other consanguineous unions may mean that other relatives are at high risk of producing an affected child. Lastly, education regarding the risks of consanguinity should be directed to general practitioners, paramedics such as midwives, and to members of the Pakistani community themselves: their senior members as well as young people. Such education will have to be planned with great care; the low risks for non-consanguineous Pakistanis should be emphasized, and advice could be given that consanguineous marriages should only be planned for individuals no closer related than second cousins and also that both prospective partners should be tested for the carrier state of thalassaemia.

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QT = Prolonged Q–T interval on the electrocardiogram; COFS = cerebro-oculo-facio-skeletal syndrome.

1 Number who are dead given in parentheses.

2 Another sib had a different recessive disorder.

3 One or more similarly affected cousins.

4 Number in parentheses refers to sibs born in UK.

Appendix 1. Certain (CR), probable (PR) and possible (PO) autosomal recessive diseases in index patients

	Number of index patients[1]	Category of disease	Similarly affected sibs	Total number of sibs	Parental consanguinity
Europeans					
Cystic fibrosis	2	CR	0	0	0
Congenital deafness	3	PO	0	2	0
Peripheral neuropathy	1	PO	0	3	0
Severe mental retardation	2	PO	0	2	0
QT prolongation syndrome	1 (1)	PO	1	2	0
Afro-Caribbeans					
Sickle cell disease	2	CR	0	1	0
Severe mental retardation	1	PO	0	2	0
Pakistanis					
β-Thalassaemia major	3	CR	2	7	+
Mucopolysaccharidosis IV	2	CR	1	3	+
COFS syndrome	2 (2)	CR	1	2	+
Factor XII deficiency	1	CR	0	5	+
Tyrosinaemia I	1	CR	0	3	+
Non-ketotic hyperglycinaemia	1 (1)	CR	0	2[2]	+
Cystic fibrosis	1 (1)	CR	0	5	+
Epidermolysis bullosa	1 (1)	CR	1	1	+
Hydrocephalus	1 (1)	CR	0	0[3]	+
Severe mental retardation and spastic quadriplegia	6 (1)	PR	2	13[3]	+
Severe mental retardation and microcephaly	5	PR	3	18	+
Severe mental retardation and deafness	1	PR	0	0	+
Progressive neuropathy	1	PR	0	0	+
Microcephaly and heart block	1 (1)	PR	0	3[2]	+
Renal tubular acidosis	1	PR	2	2	+
Lactic acidosis	1	PR	0	1	+
Potter's syndrome	1 (1)	PR	0	3	+
Osteogenesis imperfecta	1	PR	1	2	+
Lethal multiple malformations	1 (1)	PR	0	3	+
Skeletal abnormalities and deafness	1	PR	1	1	+
Severe mental retardation and spastic diplegia	2	PO	0	5	+
Mild mental retardation and spasticity	1	PO	0	2	+
Severe mental retardation	3	PO	0	6	+
Congenital deafness	1	PO	0	2	+
Encephalopathy	1	PO	0	1	+
Bangladeshis					
COFS syndrome	1 (1)	CR	0	1	+
Congenital deafness	1	PO	0	3	0
Mixed races					
Acute spinal muscular atrophy	1 (1)	CR	0	6	+
Congenital deafness	1	PO	0	0	0
Totals	57 (13)	19 CR 20 PR 18 PO	15	112 (93)[4]	43/57

Appendix 2. Certain (CR), probable (PR) and possible (PO) autosomal recessive diseases in earlier UK-born sibs of index patients

	Number of affected sibs	Number of families	Category of disease	Parental consan-guinity	Listed in Appendix 1 (0 = no, + = yes)
Europeans					
Alpers' syndrome	2	1	CR	0	0, 0
Hurler-Scheie syndrome	1	1	CR	0	0
Severe mental retardation	2	2	PO	0	0, 0
QT prolongation syndrome	1	1	PO	0	+
Afro-Caribbeans					
Sickle cell disease	4	3	CR	0	0, 0, 0, 0
Congenital deafness	1	1	PO	0	0
Indians					
Infantile polycystic kidneys	1	1	CR	0	0
Myclonic epilepsy	1	1	PR	0	0
Pakistanis					
β-Thalassaemia major	2	2	CR	+	+, +
COFS syndrome	6	4	CR	+	+, 0, 0, 0, 0, 0
Non-ketotic hyperglycinaemia	1	1	CR	+	0
Oxalosis	2	1	CR	+	0,0
Epidermolysis bullusa	2	2	CR	+	0, 0
Factor V deficiency[1]	2	1	CR	+	0, 0
Hydrocephalus[1]	1	1	CR	+	0
Alpers' syndrome	1	1	CR	+	0
Roberts syndrome	1	1	CR	+	0
Lipid abnormality	1	1	CR	+	0
Mucopolysaccharidosis IV	1	1	CR	+	+
Cystinosis	1	1	CR	+	0
Infantile polycystic kidneys	1	1	CR	+	0
Skeletal abnormality with deafness	1	1	PR	+	+
Obstructive nephropathy with leucodystrophy	2	1	PR	+	0, 0
Microcephaly with multiple malformations	4	4	PR	+	+, 0, 0, 0
Microcephaly with spastic quadriplegia	3	3	PR	+	+, +, 0
Osteogenesis imperfecta	2	2	PR	+	+, 0
Renal tubular acidosis	2	1	PR	+	+, +
Chronic spinal muscular atrophy	1	1	PR	0	0
Buphthalmos	1	1	PO	+	0
Complex partial seizures	1	1	PO	+	0
Severe mental retardation	5	4	PO	+	0, 0, 0, 0, 0
Congenital deafness	4	3	PO	+	0, 0, 0, 0
Totals	61	51	30 CR 16 PR 15 PO	47/61	12/61

QT = Prolonged Q–T interval on the electrocardiogram; COFS = cerebro-oculo-facio-skeletal syndrome.

[1] One sib had both factor V deficiency and a distinctive type of hydrocephalus.

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