Annotations

Malformations in different ethnic groups

Depressingly little is known about the cause of malformations. Despite a history dating back to antiquity and an incidence approaching one in 30, over 50% of major congenital malformations, defined as those that seriously interfere with viability or physical well being, are unexplained. Thus any approach that may shed light on an area of such shameful medical ignorance is to be welcomed. The study of ethnic differences is one such approach.

Pitfalls and limitations

It is worth considering in some detail the problems confronting the epidemiologist wishing to explore this area, for they are formidable.

Definition. At the outset it will be necessary to define exactly what is meant by a malformation, which may be 'intrinsic', inferring that the organ was programmed to be abnormal, or 'extrinsic', resulting from damage by an external agent such as a drug or virus. Many surveys have also included 'deformations', such as talipes, and problems arise in trying to classify conditions such as congenital dislocation of the hip, which may be neurogenic in origin or arise from interaction between a genetic predisposition and an adverse environment. It will also be necessary to decide whether to include relatively trivial malformations, such as polydactyly, which is particularly common in babies of African origin.¹ A useful starting point in any such survey will be reference to the recently published recommendations of an international working party.²

Ascertainment. This should be unbiased, accurate, and full. Relying on forms completed by clerical officers or tired junior medical staff is of dubious value. Every diagnosis should be confirmed, an exercise that in many cases will involve recourse to expert opinion. Ideally, ascertainment should be as close as possible to complete in a well defined, and preferably stable, population rather than in a high risk maternity unit. Thus provision should be made for including the malformed stillbirths and babies born at home or in outlying small maternity units. Finally, consideration will have to be given to the ascertainment of infants with late presenting malformations.

Confounding variables. These are numerous. When comparing ethnic differences in incidence within a large community allowance will have to be made for differences in antenatal care, diet, maternal age and parity, social class, and occupation. These points are illustrated by a study from Leicestershire, which indicated that the relative risk for perinatal mortality due to congenital malformations was greater if the general practitioner was not on the obstetric list than for an Asian versus non-Asian mother.³

Implications. Care should be given to the possible consequences of identifying ethnic differences that may be attributable to cultural or religious practices. Attempts to introduce widespread sickle cell screening in the black population of North America were a disaster, and efforts to introduce screening for cystic fibrosis carrier detection in whites might be no more successful. If it should transpire that the administration of surma or the practice of consanguinity were disadvantageous this information would have to be handled with great sensitivity. In the author's experience many Muslims do not accept that consanguinity is deleterious, and if proven it would not be easy to convey these sentiments while at the same time retaining the confidence of that community.

Genetic or environmental?

Given this long list of preconditions, what can anyone realistically hope to achieve? Much energy has been invested for relatively little return, but fortunately some useful information has emerged. Establishing the cause of a malformation is a first vital step towards primary prevention.

Genetic. At one end of the aetiological spectrum careful family studies and pedigree analysis have revealed that some anomalies are entirely genetic in origin. Examples include the hydrolethrus syndrome characterised by hydrocephalus, polydactyly, and early lethality.⁴ This disorder shows autosomal recessive inheritance and is observed almost exclusively in Finland, presumably as a result of a founder effect in a relatively small and geographically isolated community. The study of such a rare disorder in a particular community enables its genetic aetiology

to be established so that recurrence risks and prenatal diagnosis can be offered.

Environmental. At the other end of the spectrum some conditions such as Minamata disease have been found to be entirely environmental. In this disorder, damage to the developing brain occurs as a result of maternal or postnatal ingestion of organic mercury, either in polluted fish and shellfish as in the original Japanese outbreak⁵ or as a result of grain having been treated with a fungicide containing methylmercury as occurred in Iraq.⁶ Having confidently identified such a potent teratogen it should not be too difficult to persuade even the most intransigent government to act.

Genetic and environmental. Many of the more common single organ malformations fall somewhere in the middle of the aetiological spectrum and show so called 'multifactorial' inheritance, implying a polygenic predisposition plus environmental insult. This is the case for neural tube defects and cleft lip (with or without palate), the geographical and racial distributions of which have been reviewed by Leck.⁷ For cleft lip it was noted that ethnic differences (high in Mongoloids, intermediate in whites, and low in Negroids) persist after migration, suggesting that the variation is largely genetic with a relatively small environmental contribution. In contrast incidence differences in neural tube defects, which are pronounced both between and within ethnic groups, are influenced considerably by migration, pointing to a major environmental component.

Consanguinity—good or bad?

In several ethnic groups, particularly those originating from the Indian subcontinent, first cousin and uncle-niece marriages are encouraged. Given that most humans probably carry at least one deleterious recessive gene, a strong case could be made for discouraging consanguineous marriages, in which rare recessive genes are more likely to 'meet up with themselves' than in an outbreeding society. At an anecdotal level the author has been impressed by the risks attached to consanguineous marriages.

Anecdote has a scientific value of less than zero, however, and it has been suggested that in a community that has been practising consanguinity for many generations all of the bad genes will have been bred out. Thus any study of the incidence of malformations in different ethnic groups, consanguineous and non-consanguineous, would be of value. Circumstantial evidence in the United King-

dom does point to consanguinity being deleterious, with increased perinatal mortality due to congenital malformations having been noted in the Asian, and in particular Pakistani, communities of Bradford⁸ and Birmingham.⁹ Consanguinity would be expected to increase the incidence of rare recessives and to a lesser extent of multifactorial disorders, so that it is interesting to note that a study from Manchester and Leeds found a high incidence of the possibly multifactorial polysplenia/asplenia syndrome in Muslim Asian children whose parents were consanguineous.¹⁰

Confirmation of a suspected deleterious effect of consanguinity would be of value for two reasons. Firstly, it would provide a basis for a programme of public education that could be integrated into the existing link worker schemes and school teaching programmes,¹¹ but only with the agreement and support of local ethnic leaders. Secondly, it would enable the genetic counsellor, when confronted by consanguineous parents with an abnormal child in whom no clear diagnosis can be made, to offer with confidence a recurrence risk of 25%, rather than a lower risk that might otherwise seem appropriate.

The future

There is clearly a need for well planned comprehensive and preferably prospective surveys of malformations in different ethnic groups sharing as far as possible the same environment. The study of individual malformations in different communities may help provide clues to aetiology, while the overall incidence of malformations may yield valuable information about the importance or otherwise of consanguinity, obstetric care, social circumstances, and other factors that may influence the embryonic milieu. The point has been made before, and is worthy of repetition, that the likelihood of discovering anything new in medicine is relatively small, but infinitesimal if no attempt is made.

References

- 1 Erickson JD. Racial variations in the incidence of congenital malformations. *Ann Hum Genet* 1976;**39**:315-20.
- 2 Spranger J, Benirschke K, Hall JG, et al. Errors of morphogenesis: concepts and terms. *J Pediatr* 1982;**100**:160-5.
- 3 Clarke M, Clayton DG. Quality of obstetric care provided for Asian immigrants in Leicestershire. *Br Med J* 1983;**286**:621-3.
- 4 Salonen R, Herva R, Norio R. The hydrolethrus syndrome: delineation of a 'new' lethal malformation syndrome based on 28 patients. *Clin Genet* 1981;**19**:321-30.
- 5 Harada M. Congenital Minamata disease: intrauterine methylmercury poisoning. *Teratology* 1978;**18**:285-8.
- 6 Amin-Zaki L, Majeed MA, Elhassani SB, Clarkson TW, Greenwood MR, Doherty RA. Prenatal methylmercury poison-

- ing: clinical observations over five years. *Am J Dis Child* 1979;**133**:172-7.
- ⁷ Leck I. The geographical distribution of neural tube defects and oral clefts. *Br Med Bull* 1984;**40**:390-5.
- ⁸ Gillies DRN, Lealman GT, Lumb KM, Congdon P. Analysis of ethnic influence on stillbirths and infant mortality in Bradford 1975-81. *J Epidemiol Community Health* 1984;**38**:214-7.
- ⁹ Terry PB, Condie RG, Setatree RS. Analysis of ethnic differences in perinatal statistics. *Br Med J* 1980;**281**:1307-8.
- ¹⁰ Gatrad AR, Read AP, Watson GH. Consanguinity and complex cardiac anomalies with situs ambiguus. *Arch Dis Child* 1984;**59**:242-5.
- ¹¹ Fitzsimmons JS. Classroom teaching in genetics and birth defects: the Nottingham experience. *J Med Genet* 1985;**22**:345-9.

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