PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Prevention and Avoidance of Congenital Malformations [and Discussion]

N. C. Nevin, Cyril Clarke, N. Nevin and A. E. H. Emery

Phil. Trans. R. Soc. Lond. B 1988 **319**, 309-314
doi: 10.1098/rstb.1988.0052

Phil. Trans. R. Soc. Lond. B **319**, 309–314 (1988)
Printed in Great Britain

Prevention and avoidance of congenital malformations

By N. C. Nevin

Department of Medical Genetics, The Queen's University of Belfast, Tower Block, Belfast City Hospital, Belfast BT9 7AB, U.K.

Many congenital abnormalities do not have either a Mendelian pattern of inheritance or an identifiable chromosome abnormality and are described as 'multifactorial' as it is assumed they are determined by several genes, each with added effects and modified to a greater or lesser extent by environmental factors. They include spina bifida and anencephaly, cleft lip or cleft palate or both, congenital heart defect and congenital dislocation of the hip, and they constitute a major community health problem. Developments in genetics, biochemistry and cytogenetics have presented new approaches to the prevention and avoidance of congenital abnormalities. The approaches available for the avoidance of congenital malformations include the avoidance of harmful environmental factors, the screening of the newborn and early treatment, genetic counselling and antenatal monitoring with selective termination. The prevention of neural-tube defects in 'high risk' mothers can be achieved by periconceptional vitamin supplementation. In Northern Ireland, of 438 fully supplemented women, only 4 (0.98%) infants or fetuses among 407 infants and fetuses examined had a neural-tube defect, whereas of 356 unsupplemented women, 16 (4.7%) infants or fetuses among 337 infants or fetuses examined had a neural-tube defect.

If of all words of tongue and pen
The saddest are, 'It might have been'
More sad are these we daily see
'It is but hadn't ought to be'

Frances Brett, *Mrs Judge Jenkins*

Introduction

How often the thought 'It is but hadn't ought to be' has crossed the mind of the doctor as he examines an infant with a serious congenital malformation. However, it should not take the birth of an abnormal baby to alert the parents to the likelihood of such an event. With advances in medical genetics and techniques of preventing and avoiding congenital malformations, couples can be advised before embarking on a pregnancy, rather than having to experience the birth of an abnormal baby to realize that this tragic event could perhaps have been avoided. The need for counselling on the prevention and avoidance of congenital malformations has been heightened by the growing burden of congenital abnormalities in Western communities. The Medical Research Council (1978), in a review of clinical genetics, emphasized that 'handicaps due to a genetic disorder or congenital malformation, are the major child-health problem today'. During the present century, infant and neonatal mortality has steadily declined owing to effective control of infectious diseases, the improvement in obstetric care and

the amelioration of social and environmental conditions. Congenital malformations, however, have not shared this improvement and thus congenital malformations and genetic diseases have become a major community problem.

Types of congenital malformation

Most congenital malformations can be classified into four main groups: those associated with abnormalities of the chromosomes (chromosomal abnormalities); those due to a single abnormal gene or abnormal gene pair (genic disorders); those caused by the interaction of several abnormal genes, each with small detrimental effects and environmental influences (multifactorial conditions); and those due solely to environmental factors (environmental abnormalities). This classification is to some extent arbitrary: the genic disorders are influenced by other genes as well as by environmental factors and all are, to some degree, multifactorial. Even in the multifactorial conditions, the influence of a single locus may often be identified.

The prevalence of chromosomal abnormalities has been established by studies of unselected consecutively live-born infants to be about 6.1 per 1000 live-births (Jacobs *et al.* 1974; Hamerton *et al.* 1975). Genetic disorders due to single abnormal genes have typical patterns of inheritance (McKusick 1986). Although individually rare, cumulatively these account for a substantial burden of ill health in our society. Stevenson (1959) estimated that in Northern Ireland perhaps 5% of the population suffer from a genic or partly genic disorder. Many disorders exist in which there does not appear to be any Mendelian pattern of inheritance and in which there is no identifiable abnormality of chromosome morphology. These disorders are described as 'multifactorial' and include such congenital malformations as anencephaly, spina bifida, cleft lip or cleft palate or both, congenital dislocation of the hip, congenital heart defect and congenital talipes equinovarus. The prevalence of some of the common congenital malformations is shown in table 1.

In Northern Ireland, approximately 1 in 50 infants born has a major congenital abnormality. In particular, there is a high prevalence of congenital malformations of the central nervous system. In the period 1974–1976, the prevalence rate was 85.9 per 10000 total births (Nevin 1979), and for the period 1980–1984 the figure had fallen to 42.1 per 10000 total births (table 2).

Table 1. Prevalence rate (per 10000 total births) of congenital abnormalities in Northern Ireland, 1980–1984

central nervous system	42.1
congenital heart defects	34.3
eye abnormalities	9.0
ear abnormalities	13.2
total clefts	17.2
tracheo-oesophageal atresia	3.3
anal atresia	4.5
renal abnormalities	6.2
hypospadias	8.5
limb reduction defects	8.9
other skeletal defects	16.0
abdominal wall defects	6.3
diaphragmatic hernia	3.1
total	172.6

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Table 2. Prevalence rate (per 10000 total births) of central nervous system congenital abnormalities in Northern Ireland, 1980–1984

anencephaly	11.2
spina bifida	18.1
encephalocoele	2.5
hydrocephaly	5.0
microcephaly	5.3
total	42.1

Environmentally determined disorders are important as they enter into differential diagnosis of malformation syndromes. Congenital malformations may be due to maternal infection such as rubella and cytomegalovirus. They may be associated with the ingestion of drugs such as thalidomide, phenytoin sodium, sodium valproate, warfarin, lithium or alcohol. The effects of accidental, diagnostic and therapeutic radiation may also have a detrimental effect on the embryo. Table 3 shows the available approaches to the avoidance and prevention of congenital abnormalities.

Table 3. Approaches to the avoidance and prevention of congenital abnormalities

avoidance of harmful environmental factors
neonatal screening and early treatment
detection of carriers of genes and translocations
early diagnosis of index patient and genetic counselling
antenatal monitoring and termination

Genetic counselling

Genetic counselling has a role to play in the avoidance and prevention of common congenital abnormalities. The majority of couples seeking genetic advice are healthy couples who have had a child with a serious congenital abnormality and who are anxious to know whether or not this tragic event is likely to recur in any future pregnancy. Among the others are parents who, though themselves healthy, have relatives with some congenital abnormality and are anxious to know if their offspring could be affected.

Genetic counselling of families with multifactorial conditions is not straightforward and reliance is placed on 'empirical risk figures'. Although the recurrence risk is known for many congenital abnormalities, this may not be applicable in every community. For example, the recurrence risk after an infant with a neural-tube defect is higher in an area of high prevalence (Nevin & Johnston 1980; Seller 1981). Several important practical points must be considered when counselling parents who have had an infant with a congenital abnormality. First, the risk is higher among close relatives and rapidly decreases with those more distant. Secondly, when a congenital abnormality has an unequal sex distribution, the risk is higher for the relative of the patient of the rarer affected sex. Thirdly, the recurrence may be greater the more severe the abnormality. Fourthly, the risk increases with the number of affected children.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Antenatal monitoring and termination

One major advance in genetic counselling has been the development of methods for the detection of congenital abnormalities in the fetus in the second, and more recently in the first, trimester. With widespread use of these techniques there has been a tendency to use antenatal diagnosis as a substitute for genetic counselling rather than as a powerful tool supporting it (Harper 1981, p. 78). Antenatal diagnosis must be an integral part of the overall counselling strategy and should be discussed and planned before a pregnancy occurs rather than consideration left until during a pregnancy. This is desirable because, during the pregnancy, the couple are not necessarily in a state of mind to assess the factors for and against antenatal fetal diagnosis objectively.

The methods available for antenatal diagnosis include ultrasonography, amniocentesis, fetal blood sampling, fetoscopy, radiography and chorion villus biopsy. The recognition that levels of amniotic fluid α-fetoprotein are raised in the cases of anencephaly and spina bifida has provided a major advance in the avoidance of these serious abnormalities (Brock & Scrimgeour 1972; Nevin *et al.* 1973). Some malformations of the central nervous system, such as closed spina bifida or encephalocele covered with skin, cannot be detected. The antenatal diagnosis of open neural-tube defects has been enhanced by the finding of an abnormal acetylcholinesterase electrophoretic pattern (Smith *et al.* 1979) in the amniotic fluid. The application of antenatal diagnosis of neural tube defects in at risk groups, e.g. parents with a previous affected infant and among relatives of such couples, has resulted in the reduction of neural-tube defects. The level of these malformations has been further reduced by serum α-fetoprotein screening.

Periconceptional vitamin supplementation

Spina bifida and anencephaly are major problems in the U.K. The causes of these abnormalities are unknown. Evidence of a possible genetic factor is suggested by the increase in frequency among relatives and to some extent also from studies of twins. The seasonal and long-term cyclical variations and the relation with social class, being more frequent in the lower socio-economic groups, however, indicate that environmental factors also play a part.

Maternal nutrition may be a possible environmental factor. Women exposed to the Dutch famine of 1945 had an increase of anencephaly and spina bifida among their offspring (Stein *et al.* 1975). Folate deficiency has been associated with congenital abnormalities (Hibbard & Smithells 1965). More recently, a prospective study of approximately 1000 pregnancies has been reported in which red-cell folate and leucocyte ascorbic acid were determined in the first trimester (Smithells *et al.* 1976). The mean red-cell folate value of the mothers of infants with neural-tube defects was significantly less than the mean of the controls ($p < 0.001$), as was the mean leucocyte vitamin C concentration ($p < 0.05$). These observations suggested that vitamin deficiencies may be one of the environmental factors in the aetiology of neural-tube defect and, if so, may prove to be one correctable factor.

In a prospective study of this possible association Smithells *et al.* (1980) prescribed a multivitamin and iron preparation for at least 28 d before conception and until the second missed menstrual period to a group of mothers who had one or more infants with a neural-tube defect. The control mothers who also had one or more infants with a neural-tube defect and

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

who had been recruited into the study before 12 weeks gestation, were left to their normal routines. Only one infant with a neural-tube defect was born to 178 mothers in the treated group (0.6%), whereas 13 affected infants or fetuses were born to the 260 control mothers (5%). The recurrence rate in the control group was that normally expected in mothers with an affected child.

A similar reduction in the recurrence of neural-tube defects in the offspring of mothers with a previous affected infant has been reported by Laurence *et al.* (1981) who treated mothers with 4 mg of folic acid per day before and during early pregnancy. Since the initial report of Smithells *et al.* (1980), these authors have continued periconceptional vitamin supplementation in women at risk. Three infants with a neural-tube defect have now been born to 397 mothers in the treated group (0.8%) whereas 23 affected infants and fetuses occurred in 493 control pregnancies (5.2%) (Smithells *et al.* 1981).

Although the study of Smithells *et al.* (1980) was not designed as a double-blind randomized trial and that of Laurence *et al.* (1981) had problems with methods, the most straightforward interpretation of the results is that vitamin supplementation has prevented some cases of neural-tube defects. There is a strong argument for periconceptional vitamin supplementation of all mothers who are at risk of having a child with a neural-tube defect. This has been the policy in Northern Ireland since 1977. The data up to the end of 1986 show an apparent beneficial effect of periconceptional vitamin supplementation within Northern Ireland (Table 4). Of 356 unsupplemented women, there were 16 (4.7%) infants and fetuses with a neural-tube defect among 337 infants or fetuses examined. Of 438 fully supplemented women, there were 4 (0.98%) infants or fetuses with a neural-tube defect among 407 infants or fetuses examined. Although the Northern Ireland study was not designed as a double-blind randomized trial, the results show an apparent beneficial effect of periconceptional vitamin supplementation with Pregnavite Forte F.

TABLE 4. OVERALL RECURRENCE OF NEURAL-TUBE DEFECTS (NTD) IN UNSUPPLEMENTED WOMEN (US) AND IN WOMEN AFTER FULL PERICONCEPTIONAL SUPPLEMENTATION (FS) IN NORTHERN IRELAND

	US	FS
total pregnancies	356	438
no. of twins	3	4
spontaneous abortion: not examined	22	35
babies and fetuses examined: no NTD	321	403
NTD	16	4
NTD: total	16:337	4:407
recurrence	1 in 21 (4.7%)	1 in 101 (0.98%)

REFERENCES

Brock, J. D. H. & Scrimgeour, J. B. 1972 Early prenatal diagnosis of anencephaly. *Lancet* ii, 1252.

Hamerton, J. L., Canning, N., Ray M. & Smith, S. 1975 A cytogenetic survey of 14,069 newborn infants. Incidence of chromosome abnormalities. *Clin. Genet.* **8**, 223–243.

Harper, P. S. 1981 *Practical genetic counselling*. Bristol: John Wright.

Hibbard, E. D. & Smithells, R. W. 1965 Folic acid metabolism and human embryopathy. *Lancet* i, 1254–1256.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Jacobs, P. A., Melville, M., Ratcliffe, S., Keay, A. J. & Syme, J. 1974 A cytogenetic survey of 11,680 newborn infants. *Ann. hum. Genet.* **37**, 359–376.

Laurence, K. M., James, N., Miller, M. H., Tennant, G. B. & Campbell, H. 1981 Double-blind randomized control trial of folate treatment before conception to prevent recurrence of neural tube defects. *British med. J.* **282**, 1509–1511.

McKusick, V. A. 1986 *Mendelian inheritance in Man. Catalogs of autosomal dominant, autosomal recessive and X-linked phenotypes*. Baltimore and London: Johns Hopkins University Press.

Medical Research Council 1978 *Review of clinical genetics: a report to the Council's Cell Biology and Disorders Board by the M.R.C. sub-committee to review clinical genetics*. London: Medical Research Council.

Nevin, N. C. (1979) The importance of screening for genetic disease. *R. Soc. Hlth J.* **99**, 37–40.

Nevin, N. C. & Johnston, W. P. 1980 A family study of spina bifida and anencephalus in Belfast, Northern Ireland (1964–1968). *J. med. Genet.* **17**, 203–211.

Nevin, N. C., Nesbitt, S. & Thompson, W. 1973 Myelocele and α-fetoprotein in amniotic fluid. *Lancet* i, 1383.

Seller, M. 1981 Recurrence risks for neural tube defects in a genetic counselling clinic population. *J. med. Genet.* **18**, 245–248.

Smith, A. D., Wald, N. J., Cuckle, H. S., Stirrat, J. M., Bobrow, M. & Lagercrantz, H. 1979 Amniotic fluid acetylcholinesterase as a possible diagnostic test for neural tube defects in early pregnancy. *Lancet* i, 685–688.

Smithells, R. W., Sheppard, S., Schorah, C. J. 1976 Vitamin deficiencies and neural tube defects. *Archs Dis. Childh.* **51**, 944–950.

Smithells, R., Sheppard, S., Schorah, C. J., Seller, M. J., Nevin, N. C., Harris, R., Read, A. P. & Fielding, D. W. 1980 Possible prevention of neural tube defects by periconceptional vitamin supplementation. *Lancet* i, 339–340.

Smithells, R. W., Sheppard, S., Schorah, C. J., Seller, M. J., Nevin, N. C., Harris, R., Read, A. P. & Fielding, D. W. 1981 Apparent prevention of neural tube defects by periconceptional vitamin supplementation. *Archs Dis. Childh.* **59**, 911–918.

Stein, Z., Susser, M., Saenger, G. & Marolla, F. 1975 *Famine and Human Development: the Dutch hunger winter of 1944–1945*. New York: Oxford University Press.

Stevenson, A. C. 1959 The load of hereditary defects in human populations. *Radiat. Res.* **1**, (suppl.) 306–325.

Discussion

Sir Cyril Clarke, F.R.S. (*Royal College of Physicians Research Unit, London, U.K.*). In Professor Nevin's opinion, does a 'rhesus' baby have a 'congenital malformation'? It seems to me that this is certainly the case, and the genetic and environmental factors are clear cut. However, clinical geneticists always seem to ignore the disorder in their talks on congenital malformations.

N. Nevin. Sir Cyril is absolutely correct: a 'rhesus baby' has a 'congenital abnormality'. The reason clinical geneticists ignore the disorder is that the prevention of rhesus isoimmunization by anti-D has been so successful that it is now seldom seen in the newborn.

A. E. H. Emery (*The Medical School, University of Edinburgh, U.K.*). With supplementation there is still a recurrence in 4 out of 407 pregnancies of neural-tube defects, an incidence still higher than among Irish immigrants in Boston, U.S.A. Why is this?

N. Nevin. Why the recurrence rate in fully supplemented mothers is higher than among the Irish immigrants is unclear. It may be that the recurrences indicate these mothers may have some intestinal defect in vitamin absorption. Dietary loading studies in these mothers may provide some answers.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES