Regular Review

Severe mental handicap: pathogenesis, treatment, and prevention

M D'A CRAWFURD

Severe mental handicap is mostly characterised by microcephaly or other gross brain abnormalities and is, therefore, generally considered to be due to specific environmental or genetic factors. This view is reinforced by two observations: severely handicapped children usually have parents of normal intelligence, and their siblings show a clear segregation between normal and affected. Estimates of prevalence vary between about 0.3% and 0.4% of the childhood population.

Despite the many individual environmental and genetic causes that have been identified in individual patients, a substantial proportion of cases remain of unknown aetiology. The respective contributions of environmental, chromosomal, single gene, and unknown causes were discussed in a leading article in the *BMJ* in January of last year.¹ Among the difficulties of estimating the size of these different aetiological groups are the differing age groups studied, differing ascertainment biases in institutional as opposed to community-based surveys, and differing criteria for assignment of patients to particular categories.

Institutional studies may be based on hospitals, such as Penrose's pioneering Colchester survey² and the more recent study of Angeli and Kirman at Queen Mary's Hospital, Carshalton,³ or on assessment centres, such as that of Opitz and his colleagues in Wisconsin,⁴ the latter having the advantage of greater diagnostic precision; but inevitably they suffer from bias in the selection of patients referred to them. The results of Angeli and Kirman³ and of Opitz and colleagues⁴ agree on the distribution of the main groups, despite the fact that the former study was limited to children aged under 16 while the latter covered referrals of all ages. The average of the two studies showed that around 20% of patients had environmental causes; 14% had chromosomal abnormalities, mostly Down's syndrome; 8% had single gene disorders; and in 60% the handicap was of unknown aetiology. The unknown group included pure mental handicap, specific syndromes, and handicap associated with neurological disorders of unknown cause such as cerebral palsy and epilepsy.

Community-based studies are generally more representative of the total population of severely handicapped people, but they do not usually achieve diagnostic precision and lack family data. An attempt to ascertain cases in the community and then to complete their investigation and family history was made by Laxova and her colleagues in Hertfordshire.⁵ They classified 146 children born between the beginning of 1965 and the end of 1967 into 4% with environmental causes, 33% chromosomal (all but one with Down's syndrome), 14% with defects due to single genes, and 49% "multifactorial" or

of unknown aetiology. Other community studies^{6,7} have produced similar low proportions with clearly environmental and single gene defects and between about a quarter and a third with chromosomal defects. Apart from Gustavson and co-workers,⁷ all have been forced to assign half or more of the total to the category "no specific cause."

All studies have found an excess of boys. This led Lehrke⁸⁻¹⁰ to postulate a specific X-linked gene for mental handicap and verbal disability accounting for this excess and for 20% or more of all male mental handicap. Clare Davison reached similar conclusions from the findings of her Oxfordshire survey,¹¹ as did Turner from her Australian studies.^{12,13} Other groups have reported individual families in which mental handicap in males appeared to be inherited in an X-linked recessive manner, either with a non-specific clinical picture¹⁴⁻¹⁶ or with features subsequently recognised as constituting specific syndromes.¹⁷⁻²⁰ During the 1970s several reports appeared of X-linked mental retardation associated with macro-orchidism and other more variable phenotypic features.^{4,21-24} Earlier Lubs had observed a marker X chromosome in patients from a family with X-linked mental handicap.²⁵ This marker has subsequently been shown to carry a heritable fragile site near the tip of the long arm.²⁶ Turner and her colleagues found in a study of 16 families with mental handicap that the fragile X chromosome was present in six of these families and was consistently associated with macro-orchidism in the males.²⁷

The frequency of the gene for the fragile X chromosome and mental retardation probably varies among populations, and no reliable population studies have been published. A male birth incidence of nearly one per 1000 has been estimated, with the suggestion that about half of all X-linked mental retardation is due to this gene.²⁸ Since the much better known Down's syndrome has a birth incidence of one in 600, clearly the fragile-X syndrome makes a substantial contribution to the numbers of patients with severe and moderate mental handicap. If looked for in future population studies it will substantially reduce the proportion of cases of unknown aetiology.

Management

Considerable advances have been made in the treatment and management of the mentally handicapped in recent years, both in non-specific management in mental hospitals and the community and in specific treatment of particular disorders. Advances in treatment aimed at maintaining normality in people who would otherwise become handicapped have

largely been confined to endocrine disorders and inborn errors of metabolism. Neonatal screening for congenital hypothyroidism, which has a birth incidence of about one in 4000,²⁹⁻³² has led to a successful programme of hormone-replacement treatment and has proved one of the most effective screening procedures yet introduced.³³⁻³⁵ Infants treated before the onset of clinical signs have a normal distribution of intelligence³⁵; and since virtually all affected infants are now being detected early enough the screening programme is now preventing handicap in approaching one in 4000 infants. The exceptions are infants in whom thyroid tissue is totally absent, who have signs of hypothyroidism at birth. Even these children are helped by early treatment.

Advances in inborn errors of metabolism were the subject of a symposium held last September at the Medical Research Council's Clinical Research Centre.³⁶ The most effective treatments have been achieved in those diseases amenable to dietary manipulation. The prototype is classic phenylketonuria, for which neonatal screening has been established for longer than for congenital hypothyroidism. The effectiveness of a low phenylalanine diet has been proved in long-term studies with treatment starting within eight weeks of birth.³⁷⁻³⁸ How long the diet needs to be maintained is still disputed but so long as it is maintained intellectual development is within the normal range. Phenylketonuric mothers not having dietary treatment during early pregnancy are liable to have severely damaged infants with intrauterine growth retardation, microcephaly, and various congenital malformations, especially of the heart.³⁹ Over 90% of infants born to such mothers show mental handicap.⁴⁰ Even dietary treatment of the mother from the fifth week after conception fails to protect the fetus from damage,⁴¹ though treatment established before conception does appear to afford such protection.⁴² As increasing numbers of phenylketonuric girls successfully treated throughout childhood reach reproductive age it is going to be vital to impress on them the importance of temporarily resuming dietary treatment before conception and during early pregnancy. Some two dozen other inborn errors are responsive to treatment by diet or with oral vitamins.⁴³ These include galactosaemia and several amino-acidurias.

A variation of dietary treatment is continuous replacement of products by frequent drinks during the day and an intranasal gastric drip by night. This approach has been used successfully for giving glucose to patients with type I glycogen storage disease (von Gierke's disease) and for fructose-1,6-diphosphatase deficiency and with phosphate administration in X-linked hypophosphataemia.⁴⁴ Enzyme replacement is an attractive but still largely experimental approach to the treatment of inborn errors of metabolism. Some methods of delivering enzymes to tissues are still at the stage of animal studies, such as using red-cell ghosts as enzyme carriers, using artificial cells, or linking enzymes to albumin to form a polymer that can be targeted to a specific tissue. Other methods that have been subjected to preliminary clinical trials include simple infusion of purified enzyme, which may produce transient reversal of metabolic abnormalities but with effects that are too short lived to be of clinical value; and fibroblast transplantation, which also failed to produce any clear clinical improvement in children with Hurler's disease, a mucopolysaccharidosis with progressive mental handicap.⁴⁵ This apparent lack of clinical benefit is probably due to insufficient enzyme reaching the sites where it is needed. Some improvement in adult Gaucher's disease has been reported using enzyme entrapped in liposomes.⁴⁶

Bone marrow transplantation (usually preceded by chemotherapy with or without irradiation to destroy host stem cells) has been used for the past quarter of a century for the treatment of leukaemia and other severe blood diseases. In these disorders successes are frequent enough for the risks to be acceptable, though the prolonged period in hospital with isolation in a sterile tent is still an ordeal, especially for a young child. Since the donor cells repopulate the patient's marrow substantial numbers of proliferating donor cells can be established and might supply a missing gene product. This approach has been championed by J R Hobbs, who has reviewed its potential in some detail.⁴⁷ A trial in a boy with Hurler's disease has given sufficiently encouraging initial results⁴⁸ for further trials of individual children to be started. This patient and others will need to be followed up for several years before a proper assessment can be made of the value of bone marrow transplantation in inborn errors.

A more speculative recent suggestion is that of Jerome Lejeune that folic acid treatment may be beneficial in X-linked mental retardation with a fragile X chromosome.⁴⁹ He and his colleagues have observed reduced expression of the fragile X in cultured cells from patients and an improvement in the symptoms of seven out of eight patients with behaviour disorders.⁵⁰⁻⁵¹ More time is needed to assess any effect of folic acid treatment on their intellectual state.

Far more speculative is the prospect of treatment based on genetic engineering—gene rather than enzyme replacement. Genetic transformation of mammalian cells by donor DNA incorporated in a suitable vector can be performed *in vitro*, albeit with rather low efficiency.⁵² To obtain similar results *in vivo* with the required gene introduced into the right cells in sufficient quantities is still a distant aim and has not even been achieved in studies on living animals beyond the fertilised ovum stage, let alone man.

Prevention

Prevention of mental handicap can be envisaged at several different levels: prevention of the conception of affected embryos or of development of disease in the fetus; prevention of manifestation of the disease in an infant with an established defect; and prevention of the birth of an affected baby—that is, termination of pregnancy after prenatal diagnosis.

Prevention of the conception of an embryo destined to become a mentally handicapped child can be a byproduct of genetic counselling. When parents are advised that they run a high risk of having a severely handicapped child most will decide not to take that risk. This is especially so for disorders for which prenatal diagnosis is not available. Such advice, however valuable to the individual family, seems unfortunately unlikely to have much effect on the incidence of specific genetic diseases in the community as a whole.

The value of dietary treatment of women with phenylketonuria before conception and during pregnancy has already been discussed. Analogous problems may arise in other metabolic diseases and these require study. For example, women with untreated Wilson's disease abort spontaneously,⁵³ but we do not know the outcome of pregnancy in women at an early stage of treatment. Early trials of vitamin prophylaxis before conception for the primary prevention of neural-tube defect have given encouraging results⁵⁴ and, if these are confirmed, may help to reduce the prevalence of mental handicap secondary to hydrocephalus in spina bifida. The precise vitamin or other substance that confers protection remains to be identified.

Another very successful programme of prevention has been the reduction in the numbers of infants affected by maternofetal incompatibility for the rhesus blood groups.^{55 56} In addition to preventing perinatal death and immediate morbidity some long-term mental handicap from kernicterus must also have been avoided, though how much is difficult to judge. Estimates of the prevalence of handicap due to rhesus incompatibility among patients in mental handicap hospitals vary from one in 326⁵⁷ to one in 106.⁵⁸

The prevention of manifestation of an established defect in the fetus has already been discussed in relation to early detection and treatment of congenital hypothyroidism, phenylketonuria, and other inborn errors of metabolism. Another way in which this can be done is through antenatal diagnosis in the last trimester with a view to immediate treatment at birth. Unfortunately only a few disorders lend themselves to this approach. The best known example is adrenal hyperplasia with 21-hydroxylase deficiency detected by assay of 17-hydroxyprogesterone in amniotic fluid.⁵⁹ Other examples include diagnosis of life-threatening but surgically correctable birth defects by ultrasound scan. These include exomphalos⁶⁰ and possibly even certain types of congenital heart defect.⁶¹

Early prenatal diagnosis with termination when the fetus is shown to be affected is unacceptable to those who object to termination on religious or conscientious grounds, but for most people in Britain termination is preferable to running the risk of having a handicapped child or to refrain from having a family at all. The subject is too large to review in detail here so attention will be focused on recent developments of particular relevance to the avoidance of mental handicap.

The principal established methods for prenatal diagnosis are amniocentesis, fetoscopy with or without sampling of fetal blood or tissue, and fetal ultrasound scanning. By using one or more of these methods it is now possible to make a prenatal diagnosis in mid-trimester of neural-tube defect; several other congenital malformations, either as single malformations or as components of a dysmorphic syndrome; various inborn errors of metabolism, haemoglobin disorders, and coagulation defects; and any chromosome abnormality detectable by standard karyotyping methods.

Mental handicap may develop in spina bifida cystica secondary to hydrocephalus but is not a dominant feature of this birth defect. Nor is neural-tube defect an important contributor to the total prevalence of mental handicap. Prenatal diagnosis based on assay of alpha-fetoprotein in amniotic fluid is now well established, with false-positive and false-negative rates of about 0.5% and 2.0% respectively.⁶² Currently the assay of alpha-fetoprotein is usually complemented by an independent test, such as acetylcholinesterase electrophoresis, which substantially reduces the number of false-positive diagnoses.⁶³ High-risk mothers can be selected for amniocentesis in a maternal serum alpha-fetoprotein screening programme. Two studies in Britain indicate that about 80% of cases of open spina bifida will be detected in such a programme, after retesting serum and ultrasonography, with a false-positive rate of about 2%.^{64 65} Up to 90% of the population of pregnant women could be screened at a cost of £5.54 per woman at November 1978 prices (Black Report).⁶⁶ Since the publication of the Black Report several papers have thrown doubt on the value of maternal serum screening in populations with a low incidence of neural-tube defect.^{67 68} At the same time preliminary assessment of fetal ultrasonography with diagnosis of spina bifida has given encouraging results,⁶⁹ and when a fuller assessment becomes available a

reappraisal of methods of screening may become necessary with consideration of ultrasonography as the primary screening procedure rather than just as an adjunct to other methods. Another possibility is that vitamin prophylaxis before conception may prove an effective method of primary prevention and thereby render prenatal diagnosis either unnecessary or no longer cost effective. Whichever direction these developments take, a small reduction in mental handicap is inevitable owing to fewer babies with neural-tube defect being born. Whether for the reasons discussed above or other unknown reasons, a fall in incidence has already been observed in England and Wales.⁷⁰

Other types of congenital malformation may be diagnosable by fetoscopy,⁷¹ fetal ultrasonography,⁷² or a combination of the two methods. Single malformations are not usually associated with mental handicap, but it is a feature of many dysmorphic syndromes with multiple birth defects. Many of these syndromes are sporadic in occurrence. Others, such for example as Smith-Lemli-Opitz syndrome, are potentially detectable prenatally, are simply inherited, and carry a risk of recurrence within families. Their prenatal detection would make a small contribution to the prevention of the births of mentally handicapped children. An examination of the inherited syndromes listed by Opitz and colleagues in their review of patients with mental retardation and multiple congenital anomaly seen in Wisconsin⁴ suggests that perhaps about 1% of mental handicap might be avoidable in this way, but this is a very crude estimate and may well be overoptimistic.

Recent years have seen a rapid expansion of facilities for the early prenatal diagnosis of inborn errors of metabolism. There are now laboratories in six cities in Britain undertaking assays on a supraregional or national basis for about 50 different inborn errors, DNA repair defects, immune-deficiency disorders, and coagulation defects.⁷³ Many of the inborn errors are associated with progressive mental handicap. As many metabolic defects show genetic heterogeneity the essential first step in their prenatal diagnosis is precise definition of the biochemical abnormality in the individual family. Commonly, this will require enzyme assay on the first affected child, or, if he is not available, on the parents to establish heterozygous levels of the enzyme to be assayed prenatally. When the index patient represents a sporadic case of an X-linked disorder a biochemical assay will be needed to determine whether or not the mother is a heterozygote. It is this necessity for preliminary biochemical studies (and often for further heterozygote detection within such families for genetic counselling purposes) that dictates that laboratories undertaking biochemical prenatal diagnosis should be the ones that also undertake postnatal diagnosis. For the same reason biochemical prenatal diagnosis requires careful planning and precise timing, and this in turn depends on close liaison between the clinicians looking after the patient, clinical geneticists, and the laboratories. This liaison is fostered when the laboratories concerned are part of, or closely associated with, a regional genetics centre.

The haemoglobin disorders provide a model for the direction of future development in biochemical diagnosis. Established methods of prenatal diagnosis of these disorders are based on the analysis of the types and rates of synthesis of haemoglobin chains in fetal blood obtained at fetoscopy. Recently molecular genetic techniques using cultured amniotic fluid cells have been reported. These techniques depend on recognising DNA polymorphisms closely linked to the mutant gene⁷⁴ and on the direct detection of deletions⁷⁵ or of base substitutions within the gene itself that affect a restriction

endonuclease cleavage site.⁷⁶ Similar techniques are currently under development in several different laboratories for the prenatal diagnosis of inborn errors of metabolism. These will be especially valuable in those disorders due to deficiencies of enzymes not expressed in amniotic fluid cells, such as phenylketonuria,⁷⁷ or those in which the interpretation of enzyme assays is not always clear cut, as in heterozygote detection for X-linked disorders.

A further recent advance which will be of value in this subject, and possibly other areas of prenatal diagnosis including cytogenetic diagnosis, is the development of biopsy techniques for the chorionic villi. This has the dual advantages of employing the less invasive transcervical route for sampling and being applicable at an earlier stage of pregnancy, six to 12 weeks, than amniocentesis.^{78 79}

Down's syndrome is the most common single known cause of mental handicap. Most cases are due to primary non-disjunction during gametogenesis in one or other parent. Since we do not know the cause of non-disjunction, or the reasons for the increasing incidence of trisomy 21 and other trisomies with maternal age, primary prevention is not at present possible. Secondary prevention through prenatal diagnosis is the only feasible approach. This can be offered in the relatively small proportion of high-risk pregnancies such as those where one parent has a balanced translocation affecting chromosome 21 or is mosaic for normal and 21 trisomic cells. In most patients referred for prenatal diagnoses for chromosome abnormality the risk is moderate, as when there has been a previous child with Down's syndrome born to a mother then aged under 30 or where the mother is aged 37 or over. Many centres in Britain and the United States run a screening programme for Down's syndrome based on the offer of amniocentesis to older pregnant women. The cut-off age varies from 35 to 40. The overall population incidence of major chromosomal abnormality at birth is about 0.5% but at ages 35-39 is about one in 64 and at ages 40-44 is about one in 40.⁸⁰ Nevertheless, since the peak age for having children is in the 20s fewer than half of all infants with Down's syndrome are born to mothers over the age of 35. Alberman and colleagues estimated that by 1979 nearly half of all mothers aged 40 or more were being seen for prenatal diagnosis in their region, with about 70% (and so 35% of all mothers of 40 or more years) accepting the offer.⁸¹ In another

British region, however, only about 16% of such mothers were obtaining amniocentesis.⁸²

Children with Down's syndrome are brachycephalic, and this is so at birth. Measurement of the biparietal diameter of the fetal head in mid-trimester is a routine ultrasound procedure. Measurement of the anteroposterior diameter is technically more difficult, but in skilled hands it is perfectly feasible. Thus it is possible to measure the fetal cephalic index and if this is increased in early mid-trimester, as it is at birth, then ultrasound may provide a means of screening all pregnancies for Down's syndrome and, of course, other fetal abnormalities. A single case of prenatal diagnosis of Down's syndrome by this means has already been reported,⁸³ and an assessment of this method is in progress. If it should prove sensitive and specific enough then an important new way of preventing the birth of mentally handicapped children would become practicable.

The other common chromosomal cause of mental handicap, X-linked mental retardation with a fragile X chromosome, was not at first thought to be amenable to prenatal diagnosis because, while the fragile X was readily detectable in peripheral blood lymphocytes, it could not be induced in cultured fibroblasts. Late last year this problem was reported as having been circumvented by a positive prenatal diagnosis on fetal blood obtained at fetoscopy.⁸⁴ Shortly afterwards technical advances that permit detection of the fragile X in fibroblast cultures were reported as having been successfully applied to prospective prenatal diagnosis on cultured amniotic fluid cells.⁸⁵ Present techniques would probably not permit its detection on routine amniotic fluid cell culture, though this may eventually become possible.

No reliable estimate can be made of the proportion of mental handicap that is preventable by existing methods of primary and secondary prevention. At a very crude guess it is unlikely to be less than 10-15% of the total handicap that would occur but for these measures. Our hope must be that this meagre figure can be built upon in the future.

M D'A CRAWFURD

Consultant Clinical Geneticist,
Clinical Research Centre,
Harrow,
Middlesex HA1 3UJ

¹ Anonymous. The aetiology of mental handicap. *Br Med J* 1981;282:92.

² Penrose LS. *A clinical and genetic study of 1280 cases of mental defect*. London: HMSO, 1938. (Medical Research Council Special Report, No 229.)

³ Angeli E, Kirman B. Genetic prognosis in severe mental handicap. *J Ment Defic Res* 1975;19:173-93.

⁴ Opitz JM, Kaveggia EG, Durkin-Stamm MV, Pendleton E. Diagnostic/genetic studies in severe mental retardation. *Birth Defects* 1978;14(6B):1-38.

⁵ Laxova R, Ridler MAC, Bowen-Bravery M. An etiological survey of the severely retarded Hertfordshire children who were born between January 1, 1965 and December 31, 1967. *Am J Med Genet* 1977;1:75-86.

⁶ Elliott D, Jackson JM, Graves JP. The Oxfordshire mental handicap register. *Br Med J* 1981;282:789-92.

⁷ Gustavson KH, Holmgren G, Jonsell R, Blomquist HKS. Severe mental retardation in children in a northern Swedish county. *J Ment Defic Res* 1977;21:161-80.

⁸ Lehrke R. Theory of X-linkage of major intellectual traits. *Am J Ment Defic* 1972;76:611-9.

⁹ Lehrke RG. Theory of X-linkage of major intellectual traits. *Am J Ment Defic* 1972;76:626-31.

¹⁰ Lehrke RG. X-linked mental retardation and verbal disability. *Birth Defects* 1974;10(1):1-100.

¹¹ Davison BCC. *Genetic studies in mental subnormality*. London: British Journal of Psychiatry, 1973. (Special publication, No 8.)

¹² Turner G, Turner B, Collins E. X-linked mental retardation without physical abnormality: Renpenning's syndrome. *Dev Med Child Neurol* 1971;13:71-8.

¹³ Turner G, Turner B. X-linked mental retardation. *J Med Genet* 1974;11:109-13.

¹⁴ Martin JP, Bell J. A pedigree of mental defect showing sex-linkage. *J Neurol Neurosurg Psychiatry* 1943;6:154-7.

¹⁵ Losowsky MS. Hereditary mental defect showing the pattern of sex influence. *J Ment Defic Res* 1961;5:60-2.

¹⁶ Opitz JM, Segal AT, Kløve H, Mathews C, Lehrke RG. X-linked mental retardation: study of a large kindred with 20 affected members. *J Pediatr* 1965;67:713-4.

¹⁷ Allan W, Herndon CN. Retinitis pigmentosa and apparently sex-linked idiocy; in single sibship. *J Hered* 1944;35:41-3.

¹⁸ Allan W, Herndon CN, Dudley FC. Some examples of the inheritance of mental deficiency: apparently sex-linked idiocy and microcephaly. *Am J Ment Defic* 1944;48:325-34.

¹⁹ Renpenning H, Gerrard JW, Zaleski WA, Tabata T. Familial sex-linked mental retardation. *Can Med Assoc J* 1962;87:954-6.

²⁰ Dunn HG, Renpenning H, Gerrard JW, Miller JR, Tabata T, Federoff S.

- Mental retardation as a sex-linked defect. *Am J Ment Defic* 1963;**67**: 827-48.
- ²¹ Escalante JA, Grunspun H, Frota-Passoa O. Severe sex-linked mental retardation. *J Genet Hum* 1971;**19**:137-40.
 - ²² Turner G, Eastman C, Casey J, McLeay A, Procopio P, Turner B. X-linked mental retardation associated with macro-orchidism. *J Med Genet* 1975;**12**:367-71.
 - ²³ Howard-Peebles PN, Stoddard GR. X-linked mental retardation with macro-orchidism and marker X chromosomes. *Hum Genet* 1979;**50**: 247-51.
 - ²⁴ Turner G, Daniel A, Frost M. X-linked mental retardation, macro-orchidism, and the Xq27 fragile site. *J Pediatr* 1980;**96**:837-41.
 - ²⁵ Lubs HA. A marker X chromosome. *Am J Hum Genet* 1969;**21**:231-44.
 - ²⁶ Sutherland GR. Marker-X chromosomes and mental retardation. *N Engl J Med* 1977;**296**:1415.
 - ²⁷ Turner G, Till R, Daniel A. Marker X chromosomes, mental retardation and macro-orchidism. *N Engl J Med* 1978;**299**:1472.
 - ²⁸ Herbst DS, Miller JR. Nonspecific X-linked mental retardation. II. The frequency in British Columbia. *Am J Med Genet* 1980;**7**:461-9.
 - ²⁹ Hulse JA, Grant DB, Clayton BE, et al. Population screening for congenital hypothyroidism. *Br Med J* 1980;**280**:675-8.
 - ³⁰ Fisher DA, Dussault JH, Foley TP Jr, et al. Screening for congenital hypothyroidism: results of screening one million North American infants. *J Pediatr* 1979;**94**:700-5.
 - ³¹ Delange F, Beckers C, Höfer R, König MP, Monaco F, Varrone S. Progress report on neonatal screening for congenital hypothyroidism in Europe. In: Burrow CN, Dussault JH, eds. *Neonatal thyroid screening*. New York: Raven Press, 1980:107-31.
 - ³² Dockeray S, Cahalane SF, Brody M, Mullins C, Cullen MJ. Screening for congenital hypothyroidism in the Republic of Ireland. *Br Med J* 1980;**281**:1519-22.
 - ³³ Walter R, Noël P, deCock P, et al. Neuropsychological study in treated thyroid dysgenesis. *Acta Paediatr Scand* 1979;suppl 277:41-6.
 - ³⁴ Dussault JH, Letarte J, Glorieux J, Morisotto J, Guyda H. Psychological development of hypothyroid infants at age 12 and 18 months. Experience after neonatal screening. In: Burrow GN, Dussault JH, eds. *Neonatal thyroid screening*. New York: Raven Press, 1980:271-95.
 - ³⁵ New England Congenital Hypothyroidism Collaborative. Effects of neonatal screening for hypothyroidism: prevention of mental retardation by treatment before clinical manifestations. *Lancet* 1981;ii:1095-8.
 - ³⁶ Crawford M d'A, Gibbs DA, Watts REW, eds. *Advances in the treatment of inborn errors of metabolism*. Chichester: John Wiley, 1982.
 - ³⁷ Smith I, Wolff OH. Natural history of phenylketonuria and influence of early treatment. *Lancet* 1974;iii:540-4.
 - ³⁸ Schmid-Rüter E, Grubel-Kaiser S. Phenylketonurie: Früherfassung und geistige Entwicklung. *Monatsschr Kinderheilkd* 1977;**125**:479-81.
 - ³⁹ Mabry CC, Denniston JC, Coldwell JG. Mental retardation in children of phenylketonuric mothers. *N Engl J Med* 1966;**275**:1331-6.
 - ⁴⁰ Howell RR, Stevenson RE. The offspring of phenylketonuric women. *Soc Biol* 1971;**18**, suppl:29-29.
 - ⁴¹ Smith I, Erdohazi M, Macartney FJ, et al. Fetal damage despite low-phenylalanine diet after conception in a phenylketonuric woman. *Lancet* 1979;ii:17-9.
 - ⁴² Brenton DP. Modifying the maternal environment of the foetus. In: Crawford M d'A, Gibbs DA, Watts RWE, eds. *Advances in the treatment of inborn errors of metabolism*. Chichester: John Wiley, 1982:7-17.
 - ⁴³ Bickel H, Schmidt H. Dietary and coenzyme therapy. In: Crawford M d'A, Gibbs DA, Watts RWE, eds. *Advances in the treatment of inborn errors of metabolism*. Chichester: John Wiley, 1982:33-52.
 - ⁴⁴ Stacey TE. Postnatal product replacement. In: Crawford M d'A, Gibbs DA, Watts RWE, eds. *Advances in the treatment of inborn errors of metabolism*. Chichester: John Wiley, 1982:21-32.
 - ⁴⁵ Gibbs DA. Fibroblast implantation in lysosomal storage diseases. In: Crawford M d'A, Gibbs DA, Watts RWE, eds. *Advances in the treatment of inborn errors of metabolism*. Chichester: John Wiley, 1982:95-108.
 - ⁴⁶ Belchetz PE, Braidman IP, Cripps JCW, Gregoriadis G. Treatment of Gaucher's disease with liposome-entrapped glucocerebrosidase: β -glucosidase. *Lancet* 1977;iii:116-7.
 - ⁴⁷ Hobbs JR. Bone marrow transplantation for some inborn errors. In: Crawford M d'A, Gibbs DA, Watts RWE, eds. *Advances in the treatment of inborn errors of metabolism*. Chichester: John Wiley, 1982:109-21.
 - ⁴⁸ Hobbs JR, Hugh-Jones K, Barrett AJ, et al. Reversal of clinical features of Hurler's disease and biochemical improvement after treatment by bone-marrow transplantation. *Lancet* 1981;ii:709-12.
 - ⁴⁹ Lejeune J, Maunoury C, Rethore MO, Prieur M, Raoul O. Site fragile Xq27 et métabolisme des monocarboxés: diminution significative de la fréquence de la lacune chromosomique par traitement in vitro et in vivo. *Comptes Rendus Académie des Sciences, Paris* 1981;**292** (ser III):491-3.
 - ⁵⁰ Lejeune J. Le métabolisme des monocarboxés et le syndrome de l'X fragile. *Bull Acad Natl Med (Paris)* 1981;**165** (session Dec 1, 1981): 1197-206.
 - ⁵¹ Lejeune J. Is the fragile X syndrome amenable to treatment? *Lancet* 1982;ii:273-4.
 - ⁵² Wigner M, Sweet R, Sim GK, et al. Transformation of mammalian cells with genes from procaryotes and eucaryotes. *Cell* 1979;**16**:777-85.
 - ⁵³ Klee JG. Undiagnosed Wilson's disease as cause of unexplained miscarriage. *Lancet* 1979;iii:423.
 - ⁵⁴ Smithells RW, Sheppard S, Schorah CJ, et al. Vitamin supplementation and neural tube defects. *Lancet* 1981;iii:1425.
 - ⁵⁵ Combined study from centres in England and Baltimore. Prevention of Rh-haemolytic disease: results of the clinical trial. *Br Med J* 1966;iii: 907-14.
 - ⁵⁶ Combined study from centres in England and Baltimore. Prevention of Rh-haemolytic disease: final results of the "high-risk" clinical trial. *Br Med J* 1971;ii:607-9.
 - ⁵⁷ Böök JA, Grubb R, Engleson G, Larson CA. Rh-incompatibility and mental deficiency. *Am J Hum Genet* 1949;**1**:66-78.
 - ⁵⁸ Berg JM. Discussion on the aetiology of mental defect: some pathological factors. *Proceedings of the Royal Society of Medicine* 1959;**52**:789-91.
 - ⁵⁹ Nagamani M, McDonough PG, Ellegood JO, Mahesh VB. Maternal and amniotic fluid 17 alpha-hydroxyprogesterone levels during pregnancy: diagnosis of congenital adrenal hyperplasia in utero. *Am J Obstet Gynecol* 1978;**130**:971-4.
 - ⁶⁰ Cameron GM, McQuown DS, Modanlou HD, Zemlyn S, Pillsbury SG Jr. Intrauterine diagnosis of an omphalocele by diagnostic ultrasonography. *Am J Obstet Gynecol* 1978;**131**:821-2.
 - ⁶¹ Hackelöer BJ. The value of combined real-time and compound scanning in the detection of fetal heart disease. *Contrib Gynecol Obstet* 1979;**6**: 115-8.
 - ⁶² UK Collaborative Study on Alpha-fetoprotein in Relation to Neural-tube Defects. Second Report. Amniotic-fluid alpha-fetoprotein measurement in antenatal diagnosis of anencephaly and open spina bifida in early pregnancy. *Lancet* 1979;ii:651-61, 2.
 - ⁶³ Collaborative Acetylcholinesterase Study. Report. Amniotic fluid acetylcholinesterase electrophoresis as a secondary test in the diagnosis of anencephaly and open spina bifida in early pregnancy. *Lancet* 1981;iii:321-4.
 - ⁶⁴ UK Collaborative Study of Alpha-fetoprotein in Relation to Neural-tube Defects. Report. Maternal serum-alpha-fetoprotein measurement in antenatal screening for anencephaly and spina bifida in early pregnancy. *Lancet* 1977;ii:1324-32.
 - ⁶⁵ Ferguson-Smith MA, Rawlinson HA, May HM, et al. Avoidance of anencephalic and spina bifida births by maternal serum-alpha-fetoprotein screening. *Lancet* 1978;ii:1330-3.
 - ⁶⁶ Working Group on the Screening for Neural Tube Defects. Report. London: Department of Health and Social Security, 1979.
 - ⁶⁷ Fisher NL, Lathy DA, Peterson A, Karp LE, Williamson R, Chang E. Prenatal diagnosis of neural tube defects: a predictive value of AF-AFP in a low risk population. *Am J Med Genet* 1981;**9**:201-9.
 - ⁶⁸ Standing SJ, Brindle MJ, Macdonald AP, Lacey RW. Maternal alpha-fetoprotein screening: two years' experience in a low-risk district. *Br Med J* 1981;**283**:705-7.
 - ⁶⁹ Campbell S. In: Milunsky A, ed. *The prevention of genetic diseases and mental retardation*. 2nd ed. London: WB Saunders (in press).
 - ⁷⁰ Office of Population Censuses and Surveys. *Congenital malformations*. London: HMSO, 1980.
 - ⁷¹ Prenatal Diagnosis Group Laboratories/Services. *Information supplement*. 4th ed. January, 1982. (Obtainable from Dr Alan McDermott, SW Regional Cytogenetics Centre, Southmead Hospital, Bristol BS10 5NB.)
 - ⁷² Robinson H. Detection of birth defects by ultrasonography. *Birth Defects* 1981;**17**(1):17-30.
 - ⁷³ Dozy AM, Forman EN, Abuelo DN, et al. Prenatal diagnosis of homozygous alpha-thalassemia. *JAMA* 1979;**241**:1610-2.
 - ⁷⁴ Kan YW, Dozy AM. Antenatal diagnosis of sickle-cell anaemia by DNA analysis of amniotic-fluid cells. *Lancet* 1978;ii:910-1, 2.
 - ⁷⁵ Ottolenghi S, Lanyon WG, Paul J, et al. The severe form of alpha thalassaemia is caused by a haemoglobin gene deletion. *Nature* 1974;**251**:389-92.
 - ⁷⁶ Chang JC, Kan YW. Antenatal diagnosis of sickle cell anaemia by direct analysis of the sickle mutation. *Lancet* 1981;ii:1127-9.
 - ⁷⁷ Crawford M d'A, Gibbs DA, Sheppard DM. Studies on human phenylalanine mono-oxygenase. I. Restricted expression. *J Inherited Metab Dis* 1981;**4**:191-5.
 - ⁷⁸ Niazi M, Coleman DV, Loeffler FE. Trophoblast sampling in early pregnancy. Culture of rapidly dividing cells from immature placental villi. *Br J Obstet Gynaecol* 1981;**88**:1081-5.
 - ⁷⁹ Williamson R, Eskdale J, Coleman DV, Niazi M, Loeffler FE, Modell BM. Direct gene analysis of chorionic villi: a possible technique for first-trimester antenatal diagnosis of haemoglobinopathies. *Lancet* 1981;ii: 1125-7.
 - ⁸⁰ Milunsky A. *The prenatal diagnosis of hereditary disorders*. Springfield, Illinois: Charles C Thomas, 1973:36-7.
 - ⁸¹ Alberman E, Berry AC, Polani PE. Planning an amniocentesis service for Down syndrome. *Lancet* 1979;ii:50.
 - ⁸² Edwards JH, Webb T. Amniocentesis rates in older women. *Lancet* 1979;iii:1301.
 - ⁸³ Buttery B. Occipitofrontal-biparietal diameter ratio. An ultrasonic parameter for the antenatal evaluation of Down's syndrome. *Med J Aust* 1979;ii:662-4.
 - ⁸⁴ Webb T, Butler D, Insley J, Weaver JB, Green S, Rodeck C. Prenatal diagnosis of Martin-Bell syndrome associated with fragile site at Xq27-28. *Lancet* 1981;ii:1423.
 - ⁸⁵ Shapiro LR, Wilmut PL, Brenholz P, et al. Prenatal diagnosis of fragile X chromosome. *Lancet* 1982;ii:99-100.