CURRENT SURVEY

Congenital malformations

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The search for causes

Whilst stillbirth and infant mortality rates in Great Britain have been falling to gratifying low levels, the number of perinatal deaths attributable to congenital malformations has shown remarkably little change over the years. The mortality from some defects (e.g. congenital heart disease, intestinal obstructions, myelomeningocele) has been reduced, but the prevention of malformations must await wider knowledge of their causes.

The concept of congenital anomalies being caused *either* by genetic *or* by environmental factors has given way to the belief that most are of multifactorial origin. There are apparent exceptions, such as mutant genes and thalidomide, but mutations may be triggered by environmental factors and the action of teratogenic agents may be modified by genetic constitution. In the last analysis, the division between 'nature' and 'nurture' is untenable.

This probably explains the disappointing results of single-factor studies. In the quarter-century since Gregg demonstrated the significance of maternal rubella, extensive animal and human virus studies have failed to incriminate any other virus. Suspicions have been cast on the viruses of poliomyelitis, Asian influenza, infective hepatitis and smallpox but the doubts have not been confirmed. The latest to come under scrutiny is mumps virus, and the results of further work in this field will be awaited with interest (St. Geme, Noren & Adams, 1966).

It is more difficult to investigate the teratogenic properties of drugs in the human, particularly once it has been alleged that the drug in question is harmful to the embryo. Since the identification of thalidomide as a teratogen in 1961, many other drugs have been accused of embryopathic activity. Only one of these, meclozine, has been extensively studied by acceptable techniques, and no teratogenic action has been demonstrated.

Chromosome studies have been of limited help. Since the discovery in 1959 of an extra autosome in mongols, two other autosomal trisomy syn-

dromes have been identified and a number of rare syndromes have been associated with structural chromosome abnormalities. Apart from mongolism, these conditions account for only a very small proportion of congenital defects. In the investigation of particular malformed infants, chromosome studies are unlikely to be fruitful unless there are multiple physical defects associated with mental defect.

The environment of the embryo is, broadly speaking, the mother. There may therefore be something to learn from a comparison of the mothers of malformed infants with the mothers of normal infants. In studies of this kind it is now almost traditional to compare maternal age, parity, blood groups and socio-economic status. The effect of maternal age is only really striking in mongolism. Socio-economic factors appear relevant to neural tube defects. Blood group studies have so far been unfruitful.

More recently a search has been made for biochemical differences between these two groups of mothers. The somewhat increased incidence of congenital defects amongst the offspring of diabetic and pre-diabetic women has been recognized for a long time. A recent study showed the presence of insulin antagonists in the serum of non-diabetic mothers of malformed infants much more frequently than in controls (Wilson & Vallance-Owen, 1966). The suggestion that the mothers of mongols excrete increased amounts of urinary dehydroepiandrosterone has not been confirmed. Outside the endocrine field, a preliminary study has shown a correlation between maternal folic acid deficiency and congenital anomalies in the offspring, particularly neural tube defects (Hibbard & Smithells, 1965). This finding awaits confirmation but has well-known parallels in experimental animal teratology.

An entirely different approach from the search for causes is through studies of groups rather than of individuals. Family studies, twin studies and pedigree analyses help to elucidate the genetic contribution to specific defects. Population studies

help to demonstrate regional, national and racial differences in the incidence of malformations. In Great Britain, population studies have been in progress in a few centres for many years, and on a national basis more recently. A much more ambitious scheme on an international level, covering almost half a million births at twenty-six centres in fourteen countries has recently been published by the World Health Organization (Stevenson *et al.*, 1966). An investigation of this kind provides a wealth of information. The most striking of the early findings include a high incidence of mongolism in Yugoslavia (corrected for maternal age), a high incidence of neural tube defects in Alexandria, and a positive correlation between the incidences of neural tube defects and dizygotic twinning.

Natural history of congenital malformation

It has been known for over 30 years that a very high proportion of early abortuses ('blighted ova') are malformed. In recent years cytogenetic techniques have been applied to the tissues of aborted embryos with extremely interesting results. The incidence of abnormalities of chromosome number in abortuses is very much higher than in full-term infants (e.g. Carr, 1963). It can be calculated that virtually 100% of triploid embryos are aborted, 80% of mongols and 98% of embryos with XO sex chromosomes. The child born with serious defects is therefore a biological failure not so much because it is defective as because the aborting mechanism has not been triggered.

Early diagnosis

The prenatal diagnosis of congenital defects has until recently been confined to the recognition of gross deformities of which the obstetrician needs foreknowledge (e.g. anencephaly, hydrocephalus, conjoined twins). Conditions such as these can be recognized by clinical and radiological techniques. Recently more sophisticated methods have been applied earlier in pregnancy, using liquor amnii as a source of information about the foetus.

The cellular content of liquor consists predominantly of foetal squames. These can be stained and examined for nuclear chromatin and the foetal sex may be reliably determined. The cells can also be grown in tissue culture and the chromosomes studied by the usual techniques. It is thus possible to diagnose, for example, mongolism as early in pregnancy as a specimen of amniotic fluid can be obtained. It has so far proved difficult to obtain fluid before the 4th or 5th month of pregnancy. If this technique becomes applicable a little earlier in pregnancy, and if new legislation permits therapeutic abortion on the grounds of foetal defect, it may become possible to terminate

a pregnancy because the foetus is a mongol rather than because of a calculated risk.

Amniotic fluid receives a substantial contribution from foetal urine and this provides a further opportunity to learn something of foetal biochemistry from liquor studies. The adrenogenital syndrome (virilizing adrenal hyperplasia), for example, has been diagnosed before birth by the demonstration of raised levels of 17-ketosteroids and pregnanetriol in the liquor (Jeffcoate *et al.*, 1965). In this condition, early and accurate diagnosis may be life saving.

Early post-natal diagnosis of congenital defects hangs upon three pegs—the routine clinical examination of the newborn; the early recognition and correct interpretation of symptoms; and in certain circumstances the application of screening tests. One of the Rights of Man not included in the United Nations Charter is the right to be competently examined within 24 hr of his birth. This examination will include measurement of the head circumference (it is often useful to be able to refer back to this); testing the hips for instability; palpating the femoral pulses; inspecting the perineum (which often means cleaning it up first); and looking closely at the midline of the back for a dermal sinus.

Routine screening tests are designed primarily to detect biochemical disorders—malformations of molecules—and are beyond the scope of this review. They are expensive and time-consuming but offer the best hope for the first phenyl-ketonuric child in a family. An unreliable test is possibly more dangerous than no test at all because a false normal result may engender a false sense of security. It seems probable that the Guthrie test will ultimately supplant the 'Phenistix' test for the detection of phenylketonuria. The writer is not aware of any attempt to screen infants for congenital hypothyroidism.

Management of congenital defects

The development of better pre- and post-operative care, improved anaesthetic techniques and the introduction of phased operations, have helped to lower the mortality rate amongst very small babies undergoing surgery. For myelomeningocele early closure is now widely accepted as the treatment of choice. Ventriculo-cardiac shunts are firmly established in the treatment of hydrocephalus. These two operations, together with the medical and surgical control of urinary tract infection, have resulted in a much higher survival rate for spina bifida children. Amongst survivors, physical handicap is common, but mental handicap is rare. An increase in the educational facilities for these children is an urgent necessity. In the

field of congenital heart disease, transposition of the great vessels is now being successfully tackled in several centres.

The enzyme defects of phenylketonuria, galactosaemia, maple syrup urine disease and some other rare metabolic disorders have been managed by elimination diets. A surgical approach to biochemical disorders has been brought closer by the recent report of a child with glycogen storage disease treated by portacaval transposition (Riddell, Davies & Clark, 1966). The long-term result of this technique is not yet known, but it illustrates the imaginative approach that is needed if further advances are to be made in the prevention and treatment of congenital malformations.

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