MEDICAL PRACTICE

Contemporary Themes

Obstetric Prevention of Mental Retardation*

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A complex society has need of as much intellectual capital as it can obtain. Mental subnormality of any degree is obviously to be minimized for the benefit of individuals and the society in which they live. Some progress has been made in the management of mental retardation, but the education of those impaired already is not likely to make much impact on the total problem. Prevention of brain and psychological damage is the better objective. There is now good evidence that a vulnerable time for the brain is during embryonic and fetal life. One aim of obstetric practice must therefore be to prevent such damage.

The long history of obstetrics has shown shifting emphases. Maternal deaths were its first concern. When mothers were safe, attention changed to the prevention of stillbirths and neonatal deaths; then came another change to the prevention of perinatal mortality. Now the combination of obstetrics with paediatrics has, with social changes, brought about an almost constant yearly reduction in the death rates of fetuses, newborn, and infants. But there is a continuous spectrum running from death, through impairment—both physical and mental—to normality. It may be that with increasing success in reducing mortality there is a corresponding increase in impairment. It is this worrying possibility that has again changed the emphasis in obstetrics and paediatrics.

It is now certain that obstetric practice can make a contribution to the reduction of the total amount of mental retardation.

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Very Early Development

It is during the phases of fertilization, morula and blastocyst formation, embedding and placentation that probably the genetic anomalies arise. Fortunately the evidence suggests that many of the embryos affected by gross abnormalities are aborted spontaneously, but still some of them are carried to term and may grow to childhood and beyond. Such may be ovarian agenesis, Klinefelter's syndrome, superfemales with mental retardation, Down's syndrome, Tay-Sachs disease, Huntingdon's chorea and some muscular dystrophies, and there are many others. The obstetrician's part in such disorders is to help in the recognition of disease in utero and then to consider sterilization or abortion. Each case requires much individual attention, and each is an area for co-operation between obstetricians, paediatricians, neurologists, geneticists, and pathologists. Frequently abortion or sterilization or both must be considered with the patient and her husband on the grounds of relative statistical risk, but there are cases where selective abortion may be performed on the basis of the results obtained from amniocentesis. This is best done at about 14 to 16 weeks' gestation, for by then amniocentesis is fairly easy and chromosome or enzyme investigations in the laboratory are also relatively easy. Until recently, chromosome investigations could take up to three weeks since culture was required, but with present techniques it is often possible to give an answer within one or two days.[1] Often the late time of diagnosis of an at-risk fetus will mean that abdominal hysterotomy may have to be performed, though prostaglandins to induce abortion in the mid-trimester may soon obviate the need for operation.

One might hope for a less emotionally upsetting method than amniocentesis possibly to be followed by abortion, but for many disorders this is all that there is, unless the couple intend never to have children. Though operation may be traumatic it is almost certainly, in the present climate of opinion, better than the bearing of an abnormal child or one which may become so. Such is present opinion that a case can be made for amnio-

centesis to be done in all women over the age of 40 years to see if the fetus has Down's syndrome.

Phase of Differentiation

Classically the embryo has differentiated most if not all its organs by about 14 weeks. This concept is based on older embryological methods. Now it is apparent that much continuing physiological and biochemical development is going on after this period, even into the time of postnatal life.[2] This seems to be true of the liver, myelination of nervous tissue and adipose tissue, and is almost certainly true of other organs and tissues as well.

It is during differentiation that the embryo and fetus is especially vulnerable to external agents such as drugs, irradiation, viruses, other infections such as syphilis and toxoplasmosis, and to maternal diabetes.[2] The thalidomide story is well known. Other drugs such as aminopterin and cyclophosphamide are known to cause abnormalities, and antithyroid drugs can cause cretinism, but there is the disturbing thought that other commoner drugs may also cause abnormalities in susceptible individuals. That is, it may be easy to see gross defects when all fetuses are affected by a given drug, but if a common drug should affect only those susceptible because of some minor error of metabolism, then the condition will be far from obvious. A glance at the pharmacopoeia shows the vast range of drugs which primarily affect the central nervous system—analgesics, hypnotics, sedatives, tranquillizers, antidepressants, anticonvulsants, and anaesthetics. Little enough is known of their effects in the adult brain and nothing of their effects on the developing brain. Obviously this should not lead to therapeutic nihilism but a constant awareness that the use of drugs in pregnant women might damage the fetal brain. Such harm may be slight and may well not show itself structurally, but only in the intimate biochemistry of cells and perhaps in mild intellectual impairment. The potential genius might be converted into an average child, and the potentially average into a retarded one.

So many noxious agents have their major effects on the nervous system. Irradiation during the two to six weeks after fertilization has been associated with microcephaly, hydrocephaly, Down's syndrome, mental deficiency, spina bifida, blindness, and eye defects. Rubella causes eye and ear defects. Cytomegalovirus has been given as the cause of microcephaly, spasticity, seizures, blindness, and kernicterus. Even herpes simplex may cause encephalitis. The effects of syphilis are well known. The babies of diabetic mothers have brains which are small for the body size.[2] Erythroblastosis is a disease where proper management can prevent mental subnormality.

If an embryo is inadvertently exposed to drugs, irradiation, or viruses known to be associated with abnormality a decision for or against termination of the pregnancy will have to be made. Better still, drugs dangerous to the embryo, and irradiation, should be avoided in the second half of the menstrual cycle, and certainly if any periods have been missed, unless the risks of pregnancy are really negligible. Diabetic mothers and those showing rhesus isoimmunization need the most intensive care if their babies are not to suffer.

Geography and Social Class

The perinatal mortality survey of 1958[3] and *Perinatal Problems*[4] show many regional differences in the incidence of central nervous system anomalies. In general these are commoner in western areas of England and Wales. Cerebral birth trauma was also commoner in these western regions. Apart from causing death, lesser degrees of brain trauma could be the cause of mental backwardness. The survey also showed the inequitable distribution of maternity hospital beds and probably, therefore, of consultant cover also. It seems probable that some regions may be producing more than their proper share of mental retardation because of lack of resources.

There is a gradient of increasing incidence of nervous system anomalies running from the least number in social class I to the most in social class V.[4] There is a difference in the distribution of the social classes in various parts of the country, there being relatively more of the upper social classes in the south-east.

Obstetric accidents in rural surroundings carry a higher mortality for the fetus than if they occur in urban places.[4] Again it seems probable that some babies saved from death may ultimately be shown to be mentally impaired, so rural arrangements for obstetric practice need a close scrutiny.

Phase of Growth

For present purposes this phase is taken to be from about 14 weeks' gestation to delivery, though obviously it extends well into postnatal life. Growth can be by an increase in the numbers of cells or by an increase in size of cells already present. It is most likely that the early phase of growth is largely concerned with increasing cell numbers and later growth, especially postnatally, mainly by increasing cell size, though both processes go on at the same time. If the growing organism fails to lay down its optimal number of cells at certain critical phases it may then be that it has lost the opportunity for ever. If on the other hand it has its optimal number of cells then it at least has a chance of further growth by increasing the size of each cell. Since fetal life is especially a time of growth by cell replication, retardation of growth in utero is potentially of serious significance.

Allometric growth is the term used to describe the growth of organs and tissues in relation to one another.[5] It is obvious from the shape of the newborn that growth is especially advanced in the head region, abdomen, and chest, while there is relatively little growth of the limbs. Post natally there is especial growth in the limbs until they attain adult proportions, but skeletal growth, nervous system, lymphatic, and genital growth all proceed at their own rates though maintaining harmony with one another. In the fetus nervous system growth by increasing numbers of cells may be critical from about 15 to 30 weeks, though it almost certainly continues at a diminished rate throughout the rest of fetal life and into the postnatal period.

In normal growth of the fetus the incremental curve shows that there is a peak increase in weight per week at about 34 to 36 weeks and thereafter there is a diminution.[5] After birth the incremental gain in weight picks up again and almost attains the levels of the peak in utero. This shows that the placenta is failing fully to support growth potential during the last few weeks of intrauterine life.[4] In twins this relative failure begins at about 28 weeks, and in some singleton pregnancies there is also earlier failure. It is probably this which is responsible for the light-for-dates infant.

The growth of the fetus depends on its own genetic growth potential and its intrauterine food supply as delivered by the placenta. Some poor growth is observed when there are congenital abnormalities, and possibly rubella may directly affect the growing cells of the fetus, but most cases of poor growth are due to placental insufficiency. This is mainly because of relative failure in the maternal blood flow, though it could be due to failure of the placental parenchyma or the fetal blood flow, but little is known of these last two. From the clinical point of view it is of great importance to be able to detect poor growth of the fetus. If this can be done then there are two choices; either the fetus can be removed from its deteriorating environment or the placental insufficiency can be corrected. At the moment there is no sure method of improving the function of the placenta except by bed rest, so at St. Thomas's we have concentrated on delivery of the fetus either by induction of labour or by caesarean section, as appropriate, when growth is thought to be retarded.

Light-for-dates Infant

Growth curves for normal pregnancy have been constructed by many workers for different populations.[4 6-8] The St. Thomas's curve is virtually identical with that of Thomson *et al.*[7] so their figures have been used as the standard. The light-for-dates baby has been defined as one which is more than two standard deviations below the mean for the length of gestation, making allowances for the sex of the baby and the maternal weight at 20 weeks' pregnancy.

A retrospective survey of 120 light-for-dates babies, so defined, was then carried out by Miss P. A. Gilford, a research midwife. Follow-up was for up to five years and each child was subjected to appropriate psychometric tests as described by Egan *et al.*[9] Altogether, 11 children were found to be definitely mentally retarded and 10 (about 18%) almost certainly so, which accords with the findings of other workers and confirms that there is a high risk of mental backwardness in light-for-dates neonates.

Small-for-dates Pregnancy

To carry out a prospective survey to see if mental retardation could be prevented by selective delivery it was necessary to define an "at-risk" group of mothers and then monitor them intensively throughout pregnancy. The following categories were used.[10]

(1) General factors: age 16 or under; age 40 or over; involuntary infertility for five years or more; chronic renal disease. (2) Past reproductive factors: previous light-for-dates baby; perinatal death—cause unknown; mentally retarded or spastic child; severe fetal distress or neonatal anoxia; recurrent abortion; hypertension for which admitted to hospital; abruptio placentae; anaemia of 8 g/100 ml or less. (3) Present pregnancy: vaginal bleeding; hypertension; infection; twins; haemoglobin 8 g/100 ml or less; failure to gain weight; failure of uterus to increase in size.

Little explanation of these factors is required. Hypertension is defined as two readings of 140/90 mm hg recorded on two or more occasions before the twentieth week of pregnancy; failure to gain weight is defined as less than 0·5 kg a week over three successive weeks. The growth of the uterus was estimated by the usual clinical methods together with the height of the fundus above the symphysis pubis and the girth at the umbilicus using a tape measure. A factor making for special difficulty in interpretation was that in over 20,000 patients almost 20% were not sure of the date of their last menstrual periods. This ought to be a special area for health education of the public as this vital information is necessary for the interpretation of much obstetric data.

In a year in which about 4,000 patients were delivered in the St. Thomas's group of hospitals about 500 patients (12·5%) came within the "at-risk" category. This indicates the special load. All "at-risk" patients had pregnanediol estimations performed on 24-hour saves of urine at 28 and 34 weeks' pregnancy, the value of which has been established in this unit.[8]

If there was any doubt about growth then further intensive monitoring by oestriol estimations in urine, by measuring biparietal diameter growth, and by measuring human placental lactogen (human chorionic somatomammotrophin) in serum was done. On the basis of the clinical and laboratory investigations a decision was then made about induction of labour.

Results

The policy so far seems to have been highly successful. Of 52 light-for-dates babies born in this series 50 had been identified and the pregnancies had been intensively monitored. The two that were missed were in women who did not attend the antenatal clinic more than three times. The children have now been followed up for at least a year by Miss P. A. Gilford, and psychometric tests, as before, have been applied by Dr. C. J. E. Wynne-Williams. So far there are no mentally retarded children, when perhaps 10 might have been expected. It is intended that the follow-up shall be continued over the next few years.

Implications

With about 800,000 births annually and about 7% of all babies weighing less than 5½ lb (2·5 kg), then there are about 56,000 small babies born each year. If only 20% of these are light-for-dates infants, then there are 11,000 children potentially at risk of being mentally retarded, about 25% of which may ultimately be retarded, giving a figure of the order of 2,000 to 3,000. Probably much of this could be prevented by intensive care, but it will need adequately staffed units and the facilities for intensive monitoring on a nationwide scale. However, this would probably cost far less than the money now expended on caring for the mentally backward, and if the disorder can be prevented at the rate of about 2,000 new patients a year there must be a strong case for action.

Social Factors

Mental development depends not only on growth in utero, but also on housing, nutrition, mothering, and education. As a result of Dr. Eva Frommer's work at St. Thomas's [11 12] it is now possible quite simply to identify a group of mothers whose care for their infants will probably fall below average standards, and they will therefore need help with their mothering problems. The identification rests on the question "Were you ever separated from one or both parents before you were aged 11?" For the purpose of this study it was possible to identify 45 women so "deprived." They were British born and married and matched for age and social class with women who had answered the discriminating question in the negative. Follow-up interviews took place when the babies were about 3 months, 7 months, 9-10 months, and 13 months old. All the interviews were conducted "blind" by a social worker. A questionnaire devised by Dr. Frommer asked what they thought about the clinics, how often the baby cried, how often the baby wakened at night, if the baby was ever propped up in the pram to feed from a bottle on its pillow, what was the attitude to breast feeding, whether contraceptive advice has been sought, and questions were also asked about the marital relations and the mother's health.

The details will be published elsewhere,[12] but in general the results were very clear-cut. The "deprived" women complained more about the care they received in the clinics, yet they attended less. More of them wanted to breast feed their babies, yet they failed to do so more often. Their babies cried more, woke at night more, and were more often left to feed themselves from a bottle. The women sought contraceptive advice less frequently, and in six cases the husband and wife had parted temporarily or permanently before the infant was a year old. In the "non-deprived" group no husband had left his wife. When the results were finally analysed it was seen that some of those in the "non-deprived" group appeared from their own and their babies' behaviour as though they ought to have belonged to the "deprived" group. To our astonishment, when they were further interviewed it was found that they had indeed been separated from one or other parent but had temporarily forgotten the fact. It is obvious that much can be done to secure the future mental development of many children by better social support of this group of mothers.

The Future

It seems preferable in the growth-retarded fetuses to stimulate placental function rather than deliver prematurely. Investigations by Young[13] are being directed to the physiology of placen-

tal function, and especially the transfer of amino-acids to the fetus. The utilization of amino-acids seems to be maximal before about 16 week's pregnancy whereas at term it is very much diminished as compared with the early phase. So far we seem able to pick up growth retardation from about 28 weeks onwards, but Young's observations suggest that this may already be too late. Also, it appears from animal experiments that there is a maximum rate at which amino-acids will cross the placenta, and saturating the maternal plasma with them will not increase the rate of transfer and utilization. This is something of a disappointment but is being investigated further. Another disappointment is that increasing the maternal placental blood flow also cannot increase the rate of transfer above a certain maximum. This probably explains our disillusionment over the use of low molecular weight dextran infusions in trying to increase placental blood flow and so fetal growth. Bed rest, however, does seem to be of value in allowing the best possible conditions for fetal growth. It is difficult to prove, except clinically, but in some patients who are at risk of having a growth-retarded baby, growth in utero may seem to hang fire for about three to four weeks and then, almost suddenly, the fetus may attain a normal growth rate.

Conclusion

There can be little doubt that the obstetrician has a very real part to play in the prevention of mental retardation, which is such an important problem today. He can do this at many phases of pregnancy and by his care in labour. He can also help to identify those mothers whose babies may be at special psychological and social risk in their early postnatal life. Above all he requires a very high index of suspicion of matters going wrong and then an intensification of his monitoring in pregnancy and in labour. These methods of monitoring ought now to be provided on a nationwide scale.

This paper could not have been written without the willing co-operation of all the members of the obstetric, midwifery, and paediatric staff of St. Thomas's, but special thanks are due to Mr. R. W. Taylor, senior lecturer, who was the moving spirit in the whole investigation; to Miss P. A. Gilford, who did much of the slogging co-ordinating work; to Dr. Michael Brush and Mrs. Gillian Tye, who did the steroid work; to Dr. Maureen Young and her team, who did the physiological work; to Dr. Vivian Peckar and his wife, who measured biparietal diameters with sonar; to Dr. Eva Frommer and Mrs. G. O'Shea, who worked on the psychosocial study; and to Dr. C. J. E. Wynne-Williams, Dr. R. Hallett, and Dr. S. Williamson, who did the psychometric testing. In a wide ranging survey such as this it is obvious that there are hosts of others, especially midwives and nurses, who have been involved and thanks are due to them, sometimes for their forbearance. Some of the money to support the work has come from the St. Thomas's Hospital Endowment Fund, some from the St. Thomas's Charitable Trust, and some from the Lambeth Endowed Charities, and we are especially grateful to all these bodies.

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Hospital Topics

Lead Intoxication in Children in Birmingham

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Summary

Of 38 children investigated between 1966 and 1971 who had a blood lead concentration greater than 37 μg/100 ml eight had encephalopathy and one died; all these eight had a blood lead concentration of 99 μg/100 ml or above. Blood lead levels are related to haemoglobin concentrations and anaemia is common in children with blood lead concentrations of 37-60 μg/100 ml, levels previously accepted as harmless.

Children with blood lead concentrations greater than 60 μg/100 ml show radiological evidence of lead intoxication, and treatment for this should be considered when blood lead concentration exceeds 37 μg/100 ml. Children presenting with unexplained encephalopathy should be radiographed for evidence of lead intoxication.

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Introduction

The relation between pollution and lead intoxication has recently attracted increasing public attention, and the effect of chronic exposure to lead on childhood development is of particular