Antenatal Paediatrics by Amniocentesis

The finding that amniotic fluid contains living cells which may be cultured (Fuchs, 1966; Steele and Breg, 1966; Nadler, 1968) offers important and interesting prospects for antenatal paediatrics. There is, however, much yet to be learnt both about the safety of the operative procedure and about the techniques of culturing the cells. The only extensive experience of amniocentesis hitherto has been in relation to Rh isoimmunization, and here the procedure is carried out later in pregnancy. The operation is best carried out suprapublically at the 12th to 14th post-conceptional week, with the withdrawal of 5 to 10 ml amniotic fluid (Nadler, 1968). The risk of infection is small, the risk to the mother is small, the risk to the fetus is not yet reliably established. An approach through the anterior fornix may be made two or three weeks earlier, but probably carries a higher risk of infection and of inducing abortion. The alternative procedure of chorion biopsy (Hahnemann and Mohr, 1969) also makes cells available two or three weeks earlier in pregnancy, but appears less reliable and less safe.

The first application has been in genetic counselling: for the diagnosis of chromosome anomalies in pregnancies where the mother is already known to have a high risk of producing an abnormal child. An example is where a mother has a D/G translocation with perhaps a 1 in 5 chance of producing a liveborn child with Down's syndrome, and both parents are asking for a termination (Jacobson and Barter, 1967; Nadler, 1968). In this case the procedure is being used essentially to avoid the unnecessary termination of a normal pregnancy. In these circumstances the small risk of producing an abnormal child by the procedure is acceptable, as is the small risk of damaging the fetus. The procedure has also been used when parents with similar risks have wished deliberately to plan a pregnancy on the understanding that if the fetus is found to be abnormal they will be offered a termination. Amniocentesis at the 14th week followed by 3 weeks of cell culture makes possible termination before the 18th week.

A similar and more widespread potential use of amniocentesis in genetic counselling is where there is a high risk of an inborn error of metabolism. The list of metabolic errors detectable in amniotic cells is growing fast, and includes, for example, the autosomal recessive conditions, galactosaemia, cystathioninuria and homocystinuria, and the X-linked conditions, the Lesch-Nyhan hyperuricaemia syndrome and G6PD deficiency. In these instances culture of the cells is unnecessary, and the enzyme deficiency, it is claimed, may be demonstrated directly on the cells in the amniotic fluid (Nadler and Gerbie, 1969). Amniocentesis has already been used where the mother was a known carrier of the gene for the Lesch-Nyhan syndrome (Fujimoto et al., 1968). In other instances, for example in Hurler's syndrome, some weeks of culture are at present necessary before the accumulation of mucopolysacharides is demonstrable, and here the homozygote cannot be distinguished reliably from the heterozygote (Danes and Bearn, 1966). There is, however, a good chance that the metabolic errors that are demonstrable in fibroblast culture—and this includes most of them, with phenylketonuria a notable exception—will also be demonstrable in amniotic cell culture. A biochemical test for the fetus with cystic fibrosis would be especially valuable and the demonstration of metachromasia in both fibroblast and lymphocyte culture (Danes and Bearn, 1969) from such patients suggests that such a test may not be too far away, though the metachromasia itself is too non-specific to be useful. The prevention of conditions such as cystic fibrosis is likely to come from the detection before they marry of the 5% of the population in Britain who are heterozygotes, combined with the offer of pregnancy testing for homozygous fetuses when two heterozygotes do marry each other. Looking to future advances, a test for women heterozygous for the gene for X-linked muscular dystrophy combined with a test for the male fetuses who are hemizygous for the gene would be of great value, and permit a reduction of the frequency of affected boys to those affected by a fresh mutation—perhaps to about a third of the present frequency. There is even a prospect that amniocentesis may play a
part in genetic counselling in dominant conditions of late onset, such as Huntington's chorea, if either a biochemical test can be found to detect the fetuses which carry the gene, or a close linkage can be found between a gene and a marker gene locus demonstrable in amniotic cells.

These genetic counselling uses of amniocentesis, though of great value to the families concerned, are applicable to only a small proportion of all families. The second stage in the development of amniocentesis, of greater public health import, will be its use as a screening procedure in a considerable proportion of all pregnancies. Obviously for such screening procedures a much more stringent standard of safety with respect to inducing an abortion and fetal damage will be needed. A risk to the fetus of, say, 1% is acceptable where the mother is asking for a termination unless the fetus can be shown to be normal, but such a risk would be unacceptable in a screening test. In addition a great extension of cytogenetic facilities, accompanied perhaps by computerized screening of chromosome spreads, will be needed. It is probable that a start of this second stage in the use of amniocentesis will be made for mothers over 40 years, and the screening will be primarily for chromosome anomalies, especially the G trisomy of Down's syndrome. In recent years some 2½% of pregnancies in England and Wales have been to mothers over the age of 40 years, but it may be estimated that these pregnancies produce nearly 20% of all patients with Down's syndrome. Further, some 11% of pregnancies are to mothers over the age of 35 years, and these produce some 45% of all patients with Down's syndrome. The same is perhaps true with respect to the E trisomy (Edwards' syndrome) and D trisomy (Patau's syndrome). A few parents on religious or other grounds will not wish to avail themselves of such screening procedures, since they will not in any case be willing to accept an offer of termination. The potential value, however, of such screening values in reducing the heavy load of Down's syndrome, now the major single cause of severe mental subnormality, is apparent.

In summary, amniocentesis will offer a valuable aid to genetic counselling. It is also likely to provide the opportunity to push preventative paediatrics well back into the antenatal period. For this purpose, however, the safety of the operative procedure needs to be accurately evaluated, and there is an urgent need for the improvement of techniques to permit earlier diagnosis, by the discovery of ways both of getting cells earlier in pregnancy and of shortening the required period of cell culture.

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