The Effect of Antihypertensive Drugs on the Fetus

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FETAL PHARMACOLOGY

Until the thalidomide disaster there had been relatively little interest in the effect of drugs on the embryo or fetus. Before this most drug studies had been carried out on adult animals. Thalidomide changed all this, and it is now mandatory for new drugs to be screened for their effects in pregnancy. However, the effects sought are morphological changes in the embryo; there has been little interest in the more subtle effect of drugs later in pregnancy, when morphogenesis is largely complete and the fetus is growing rapidly. Indeed, in clinical obstetrics there is much the same casual attitude towards the use of new drugs in the last trimester of pregnancy as once there was towards the use of new drugs in the first trimester. Systematic animal fetal pharmacology is not carried out on new drugs; the sum of knowledge on the effect of drugs on the fetus is small. There are some signs that interest in this field is beginning. Symposia are being held (e.g. Boreus, 1973) and incidental observations on fetal pharmacology made during the course of physiological experiments are now beginning to be collated.

ANTIHYPERTENSIVE DRUGS AND THE FETUS

The present unsatisfactory situation in fetal pharmacology is well illustrated by our knowledge of the effect of antihypertensive agents on the fetus. The use of antihypertensive drugs in the general population is increasing. There are several reasons for this. There is greater awareness amongst physicians of the long-term hazards of raised arterial pressure, so that patients with
mild and asymptomatic hypertension are now being actively treated with drugs. This trend is facilitated by the availability of acceptable antihypertensive drugs with few side effects. Inevitably among the women taking these drugs some will become pregnant. Furthermore obstetricians now consider treating women with raised arterial pressure first discovered during pregnancy. Yet the fetal effects of these drugs have been little investigated in animals. A particular example is that of the beta-blockers.

**FETAL EFFECTS OF BETA-ADRENOCEPTOR ANTAGONISTS**

Beta-blockers are now widely used for the treatment of hypertension. Their use has increased since the first discovery that propranolol was an effective antihypertensive agent with few side-effects. Incidentally the way in which these drugs lower blood-pressure is still unknown. Almost 10 years ago I was consulted about the likely consequences which would result if the human fetus was exposed to propranolol being taken by its mother. It was known that propranolol crossed the mammalian placenta (Masuoka and Hanssen, 1967). On theoretical grounds I was concerned that such exposure might have a serious consequence for the fetus for the following reasons.

**Thermogenesis**

First, as Hull (1964) has shown, non-shivering thermogenesis in the newborn mammal is dependent on beta-adrenergic stimulation of brown adipose tissue and this process is inhibited by beta-blockade. Since human babies also depend on this mechanism for thermal control in the immediate postnatal period it was likely that babies born to mothers who had been given propranolol up until delivery might be less able to control their body temperatures and would thus be at greater risk from hypothermia.

**Cardiac effects**

More importantly, it was likely that the blockade by propranolol of the positive chronotropic effects of catecholamines on the fetal heart which had, not surprisingly, already been observed in the lamb by 1968 (unpublished observations) would at least obtund the heart-rate changes on which obstetricians depended to assess fetal health. This in itself might be hazardous, leading to unnecessary interventions in the pregnancy or conversely lack of awareness that a fetus was at risk. Quite apart from these diagnostic considerations the effects of beta-blockers in abolishing the inotropic effects of catecholamines (i.e. the increase in the contractility of the fetal heart) should limit the ability of the fetus to maintain its internal environment, especially in hypoxia.