Foetal Hazards from Maternal Therapy in Late Pregnancy

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It has long been known that drugs given to a pregnant woman for therapeutic purposes may cross from the maternal to the foetal circulation. Very few do not. Page (1957) has studied the possible ways in which drugs and other substances can cross the so-called "placental barrier"; and the passage of drugs across the placenta is extensively reviewed by Moya and Thorndike (1962) and by Hagerman and Villee (1960). In fact the tissues of the placenta are very active metabolically and it is difficult to understand how this concept of a "barrier" between the maternal and foetal circulations was sustained — on this score the efficiency of the placenta is minimal (Villee, 1960).

A considerable amount of work in experimental animals has repeatedly demonstrated that various drugs given during pregnancy can result in foetal malformations and disease. Experimental teratogenesis in mammals probably dates from the discovery by the American veterinarian Hale (1933), that deficiecy of Vitamin A in the diet of pregnant sows resulted in the birth of piglets without eye-balls. Thirty years lapsed by, yet the subject never seemed to arouse much interest in clinicians. It required the Thalidomide Disaster of international extent to stir up concern and activity.

To-day many clinicians are on the alert for the detection of possible associations between drugs administered to pregnant mothers and the appearance of congenital deformities in their offspring. Many pharmaceutical firms are known to be carrying out a systematic check on all their drugs for teratogenic properties. Meanwhile, the extra caution to be exercised before prescribing *any* drug to a pregnant woman has been emphasized several times recently (Dent *et al.*, 1962), especially since the problem of assessing the dangers of a particular drug to the human embryo is beset with difficulties (Lancet, 1963 a). The action of drgus on the embryo was discussed recently in the Section of Experimental Medicine of the Royal Society of Medicine ,Woollam *et al.*, 1963).

Teratogenicity, however, is not the entire story. Nor is it true that the drug-induced hazards for the foetus are confined to the first two or three months of its intra-uterine life.

As a result of certain drugs given to the mother late in pregnancy or during labour, the human foetus faces the risk, not of congenital malformations, but of death or disease.

These are real hazards. Yet it is not unlikely that their existence and importance are not adequately realized. This is all the more unfortunate in view of the fact that the resultant neonatal complication can, in most cases, be foreseen and even prevented.

The purpose of this paper is to review the drugs which may seriously harm the foetus if administered to the mother late in pregnancy or during labour.

Synthetic Vitamin K. It has been shown that Synkavit and other water-soluble analogues of vitamin K can produce neonatal jaundice (Nyhan, 1961). This is primarily due to increased hae-

molysis of the red blood cells. The infant will suffer from haemolytic anaemia, and the resultant hyperbilirubinaemia exposes him to the dreaded risk of kernicterus. This hazard is greater if the baby is premature.

Vitamin K can cross the placenta, and large doses given to the mother before delivery will raise the risk of severe jaundice in the newborn (Lucey and Dolan, 1959). The danger of kernicterus is so real that many of these infants require treatment by exchange transfusion soon after birth.

If the obstetrician or midwife feels that the administration of vitamin K is indicated in a particular labour, then the practice to-day is to avoid giving big doses: 1mg if given to the baby, and 5mg to 10 mg if given to the mother in labour.

Sulphonamides and Related Drugs. Here again there is the danger of kernicterus, particularly in the premature baby. This toxic effect was first observed clinically by Silverman and co-workers (1956) in relation to sulphafurazole (Gantrisin); other sulphonamides have been shown to be equally harmful. These compounds displace bilirubin from its albumin bond in the plasma. There is a consequent rise in the amount of free bilirubin, which diffuses readily into the tissues, including the brain — and kernicterus sets in.

Most of the sulphonamides have been shown to cross the placenta: within three hours the concentration of these drugs in the foetal blood equals that in the maternal blood, and may then exceed it. Indeed, two of the long-acting sulphonamides (which are marketed as Lederkyn, Madribon and Midicel), when administered to women in labour, may persist in their infants' blood for four to six days after birth (Lucey and Driscoll, 1959).

In such circumstances these long-acting sulphonamides may carry a greater hazard for the baby about to be born, on account of their persistence in the infant and their tendency to bind more securely to plasma proteins than the shorter-acting sulphonamides (Newbould and Kilpatrick, 1960).

It would seem prudent to avoid the use of sulphonamides during labour, especially the long-acting compounds. This is particularly true in cases of premature labour.

Ward (1963) points out that a number of other drugs carry the same risk of crossing the placenta and producing hyperbilirubinaemia in the newborn if used close to term. Phenothiazine drugs and phenylbutazone are two examples.

Chloramphenicol. There have been no reports of foetal damage from the use of chloramphenicol in the parturient mother, but there are certainly some grounds for sounding a word of warning. It is probably very fortunate that this drug has had little therapeutic indication in the treatment of infections associated with late pregnancy or labour.

Chloramphenicol is normally detoxified in the liver, mostly by glucuronide conjugation. In the newborn, however, all the functions of the liver are relatively inefficient: this includes the ability to form glucuronides. Consequently chloramphenicol is only slowly metabolized by the liver of the normal newborn infant. The premature infant and the foetus must be even less capable of handling this drug by conjugation and detoxification in the liver. The excretion of the drug by the kidney is also slower than in the adult.

Ordinary dosage may thus result in unduly high blood levels, and toxic effects will be produced. The administration of chloramphenicol to newborn infants has caused severe collapse (the "gray syndrome"), and even death (Weiss *et al.*, 1960).

While it is true that the effect that

chloramphenicol may have on the foetus is still unknown, yet present knowledge would suggest a distinct possibility of severe toxicity.

Tetracyclines. The major toxic effects of tetracyclines group of drugs are only recently coming to be recognized (Lancet, 1963b). Most writers on this subject find no difference in toxicity between the various tetracyclines.

All this group of antibiotics crosses the placenta readily, and they are rapidly taken up by growing bones and teeth. An impressive case is described by Bennet (1963), illustrating the rapidity with which tetracyclines become fixed in foetal bone after passing from the maternal circulation: the mother had not had more than 1.5g of tetracycline, all within 18 hours of parturition.

One effect of maternal therapy with these antibiotics is that they tend to produce yellow staining of the infant's deciduous teeth. This deposit in the dentine may interfere with the development of the tooth and with enamel formation.

A more alarming possibility is that, given late in pregnancy, tetracycline may become rapidly deposited throughout the skeleton of the foetus. This would interfere considerably with the growth and development of the foetal bones.

There is no doubt that tetracyclines are not without serious hazards when given to pregnant women.

Streptomycin. It is probably true to say that the chances of encountering a toxic effect in the foetus of a mother who has been given streptomycin are smaller than the general incidence of toxicity from this drug.

Streptomycin and dihydrostreptomycin both cross the placenta. If the maternal dose is adequate they may reach bacteriostatic levels in the foetal blood.

Friend (1963) says that isolated cases of damage to the eighth cranial nerve have been reported; one child was found to be deaf at 2½ months of age. Kern (1962) has collected four such cases, and he believes that these two drugs should not be used in pregnancy.

Ganglion-blocking Drugs. These agents are widely used in the treatment of hypertension and toxaemia of pregnancy. They readily cross the placenta: when injected into the mother, they may appear within two minutes in the foetal blood. Autonomic activity in the foetus may then be disturbed.

Morris (1953) recorded two fatal cases of paralytic ileus and one of delayed passage of meconium in the newborn babies of mothers who had been given a hexamethonium compound during pregnancy.

The danger of inducing ileus in the newborn is almost certainly present with all ganglion-blocking drugs. On the other hand the risk is practically abolished if the drugs are discontinued five to seven days before the expected date of confinement.

Wilson (1962) has drawn attention to a recently recognized drug-induced complication in newborn babies whose mothers were treated with reserpine (Serpasil) for toxaemia up to two days before delivery. The infant's nasal mucous membrane, unusually responsive to reserpine, becomes oedematous. This may give rise to a non-infective discharge or even nasal obstruction. The condition usually clears up in less than a week, but it may cause embarassment to the infant and require prompt treatment with decongestant nose-drops.

Sympathomimetic Amines. These drugs can jeopardize the foetus if they are given to the mother in labour. They should be avoided if there is the least suspicion of placental insufficiency or foetal distress.

The injection of these amines into

the maternal circulation during labour may produce anoxic effects on the foetus. This has been shown to be the direct result of their vasoconstrictive action on the uterine vessels (Beard, 1962). Probably they do not appreciably reach the foetal circulation, because they are inactivated by the placental enzymes. Outside labour it appears that the foetus is less sensitive than the mother to the pressor action of these amines.

Anticoagulants. Anticoagulants therapy is to-day considered to be indicated during pregnancy in cases of phlebothrombosis and of pulmonary embolism. Francis (1963) points out that the choice of anticoagulant drugs in pregnancy is restricted by the small molecular size of the coumarin derivatives.

Pregnant cows fed on contaminated sweet clover may have calves with the typical haemorrhagic lesions of coumarin poisoning. In the human, Dicoumarol and related derivatives cross the placenta with ease, and very often the foetus dies *in utero* or sometimes in the neonatal period. The case of the twin pregnancy described by Gordon and Dean (1955) is typical: The anticoagulant was stopped one week before delivery, yet the first twin was stillborn and the second died on the thirtheenth day with extensive haemorrhages.

Dicoumarol is too dangerous to be used in pregnancy. Heparin is safer for two reasons. Its molecule is too large to cross the placenta. Used intravenously, its duration of action is less than the length of all but precipitate labours. There has been no report of an effect on the foetus from heparin given to the mother.

Analgesics, Sedatives, Anaesthetics. This composite group of drugs is used extensively in labour. It has undoubtedly achieved a great deal in relieving the pain of parturition and in facilitating obstetric manoeuvres.

The majority of these drugs cross the placenta readily, and harmful effects on the foetus are not uncommon. The only notable exception is the muscle-relaxant succinylcholine, which crosses only in small amounts and does not appear to affect the foetus (Stead, 1955).

There is no need to enlist the agents used in obstetric analgesia and anaesthesia; it is well known that they often cause respiratory depression in the newborn. Thus, morphine and its derivatives readily cross the placenta, and so does pethidine; fortunately either drug has a highly specific antidote, which rapidly improves the infant's condition if its respiratory depression is due to the analgesic drug.

In connection with morphine and pethidine there is a further associated danger that is very important. Several observers have found the mono-amine oxidase inhibitors (Marsalid, Nardil, Niamid, Marplan) to exert a highly potentiating effect on the action of pethidine and morphine. The manufacturers of these new drugs warn that morphine and pethidine are contra-indicated not only while their drugs are being taken but also for a fortnight after stopping them. These agents, therefore, should not be prescribed after the 38th week of pregnancy in view of the the fact that morphine and pethidine are so commonly used during labour.

An interesting study by Brazelton (1961) showed that heavy barbiturate premedication of the mother in labour could render the neonate rather drowsy for some days and might impair his ability to establish adequate breast-feeding. A similar picture may be expected in the case of an epileptic mother receiving high doses of phenobarbitone and phenytoin right up to the day of confinement.

Conclusion. It is evident that many forms of maternal therapy in late pregnancy or labour may constitute a very real danger to the foetus soon to be born. Indeed, it may well be that several serious risks are awaiting to be discovered and recorded. It is the duty of the doctor or midwife, not merely to avoid prescribing drugs that are known to create an early neonatal hazard, but constantly to observe and study the possibility of disease in the infants of mothers who have received any drugs during pregnancy or labour.

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