THE EFFECTS OF DRUGS ON THE FOETUS

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I. INTRODUCTION

Any general review concerned with pharmacological actions on the foetus is at once beset with two difficulties, namely a working definition for foetus and a reasonable limitation of the infinity of chemicals which are called drugs at the whim of the pharmacologist.

The dictionary definition of a foetus although it may be precise is usually useless and inadequate for those concerned with developmental anatomy and physiology. To the reviewer the term foetus means a mammal at stages of intrauterine development in which it is generically recognisable and possesses a well-established placental circulation; organogenesis is over and normal progress depends on unimpeded growth. This state is not arrived at suddenly, and so it is never possible to state an exact time for the beginning of foetal as opposed to embryonic life; moreover, the period in gestation during which the change occurs varies with the species. At the completion of foetal existence, although the transition to the newborn is abrupt and definite enough in the placental mammals, yet anatomically and physiologically the degree to which some of the organs and tissues possibly retain an immaturity akin to that of the late foetal state again depends upon the species. The action of drugs upon tissues or upon whole animals within such a developmental period does not appear to have been the subject of an attempt at a general review before, though one extensive aspect, namely the effects of analgesics and anaesthetics, has received an excellent contribution from Snyder (289). On the other hand there are comprehensive critical accounts of

chemical embryology (221), the physiology and pathology of the foetus (15, 210, 248, 340), and of the newborn (282). Attention has also been drawn to the importance of enzymes in the developing nervous system (137, 322).

In the present review the object has been to assess what is known of the actions on the foetus of drugs commonly used for human therapy, or used in the laboratory, including agents of specific toxicity for the foetus. Textbooks of pharmacology give meagre information on the subject beyond mentioning whether transplacental passage of certain drugs is known to occur. It is surprising that so little emphasis has been placed on an aspect of pharmacology which is of such practical importance, but where there is lack of positive information it is suggestive that the drugs concerned, if used frequently, are at least of no lasting harm to the foetus when given to the mother in the usual therapeutic doses.

Where evidence for the placental transmission of drugs has been found, it has been quoted, but no detailed consideration has been given to the special problem of placental permeability in general. This important topic could not be reduced for review within a review and it has been covered in an extensive survey recently (288).

In general it is true that the placenta is less of a barrier to drugs than might be thought. As a broad approximation it has been said that on the whole drugs with molecular weights of less than 1,000 can cross (79), but notable exceptions to this occur such as tubocurarine and decamethonium salts. The whole problem becomes even more involved when toxaemia is present (100).

Since the number of histologically demonstrable layers in the placental barrier varies according to species it might be supposed that permeability would differ likewise, but, with the exception of substances for which transmission is poor even across a haemochorial placenta, it seems likely that differences in transmission would be quantitative only. The barrier breaks down completely on occasions as is shown by reports of foetal red cells in the maternal circulation (36, 59), or of foetal anaemia due to haemorrhage into the mother (53, 109, 123, 277). Such episodes probably have no general significance with regard to the transmission of drugs, although it is conceivable that they initiate a production of maternal antibodies that might otherwise not occur.

Hormones, other than agents of neurohumoral transmission, have also been omitted; their effects are inextricably woven into the physiology of normal development, sexual development in particular, and the combined subject is vast and specialised. Cortisone and closely related corticosteroids have been dealt with since their use has become widespread so comparatively recently and they may be dangerous to the foetus. Anti-thyroid drugs have been included for similar reasons.

The choice of drugs may appear haphazard, but it is the reviewer's hope that this is really due to the lack of routine drug tests upon foetuses and not to inadvertent omissions on his part. Much of what is known has been learnt on man, for therapeutic necessity has produced many impromptu human experiments in this field.

II. CENTRAL NERVOUS SYSTEM

A. Powerful analgesics

It might have been expected that the painful nature of human childbirth would have provided an irresistible stimulus for research concerning the effects of powerful analgesics upon the foetus. But the variety of drugs used, recourse to general anaesthesia, and the elaboration of techniques of regional anaesthesia point to the continuing hazards of analgesics for use in childbirth. Most clinical publications are concerned with the effects of mixtures of drugs, and the resulting state of the newborn is seldom correlated with the duration and the nature of labour. From such data it is usually impossible to judge the degree of transmission of analgesics to the foetus. In short, qualitative data are abundant and suggestive, but quantitative facts are scarce.

Morphine. Even for the opium alkaloids information is so meagre as to have prompted Kreuger, Eddy and Sumwalt, in their encyclopaedic account (177), to remark "A good deal has been written but very little done, on the transport of morphine between mother and child." It is generally acknowledged that morphine given to the mother within a few hours before the delivery of her child may result in its being slow to breathe spontaneously and that this danger is greatest for premature infants. Some authors (278, 279) have denied that morphine is especially dangerous in this respect and even Snyder (289), working with unanaesthetised rabbits in which the spinal cord had been cut, thought that the main effects of morphine upon the foetus were due to the prolongation of labour. This was his opinion for the rabbit even though he clearly demonstrated that morphine, given to the pregnant doe, depressed the intra-uterine respiratory movements of her foetuses. Presumably such foetal respiratory movements might have been due to anoxia caused by the experimental conditions, and morphine might have acted indirectly by improving the placental blood flow.

On the other hand there is a convincing amount of evidence to show that morphine really does cross the placenta and has pronounced effects on the foetus. Chemical tests for morphine in the newborn have been few but positive (278), and specific biological observations have also given a definite answer. Thus, typical pin-point pupils have been seen in the newborn when resuscitated (278), an abstinence syndrome has been seen in the newborn of addicts (110, 237, 270a), and nalorphine is highly effective in initiating respiratory movements when injected into the newborn of morphine treated mothers (20, 48, 80, 290). Nalorphine is also effective when given to the mother shortly before delivery, so presumably it, too, crosses the placenta (20, 80).

Goodfriend, Shey and Klein (110) have reviewed the recorded cases of morphine addiction developed *in utero*, they have added observations upon their own cases, and emphasized that morphine addiction *in utero* is a phenomenon which is probably much more frequent than is realised, and that it is no doubt missed because of lack of recognition of withdrawal signs from one to three days after birth. So definite is the withdrawal picture that it can be the clue to addiction in the mother. Presumably newborn babies diagnosed as addicted have also

acquired tolerance, as otherwise they might have perished of asphyxia at birth. Withdrawal signs can occur *in utero*, as markedly increased foetal activity has been observed in the pregnant addict when beginning to crave for a dose, but such effects might be secondary to the maternal disturbance. It has also been noted that the newborn of addicted mothers who had their last dose ten days or more before delivery developed no withdrawal signs, suggesting that the addicted foetus may also be easily cured *in utero*. Such observations raise the interesting question of whether an individual who was an intra-uterine morphine addict, but who was cured also *in utero*, or within the first week of separate existence, would be especially likely to become an addict later in life. Has the intra-uterine addict been only physically dependent on the drug or has there been a prenatal psychic dependence also?

It is at first surprising that there are apparently no studies correlating the effect of morphine on the foetus or on the newborn infant with the concentration of morphine present in the cord blood on delivery, but this does not seem so strange when it is remembered that information concerning the distribution and fate of morphine in the body in general is not abundant.

Diamorphine (heroin). Precise information is even less concerning this morphine derivative, and no references were found to observations upon the foetus of species other than the human. In one brief report (259) based on 200 obstetric cases it was held to be so safe as to be suitable for administration by midwives. Others also agree about the relative lack of depression of the foetus (76, 191, 319) and Lund and Harris (191) make a good point when they say that it has never had a fair trial as an analgesic in childbirth because it was banned from the United States of America in 1915, and from 1902 onwards obstetric practice had been dominated by the "twilight-sleep" of morphine and scopolamine. On reflection it must be admitted that pharmacologists are in difficulties when called upon to give a detailed comparison of the properties of morphine with those of its diacetyl derivative, and this comparison seems worth further investigation, as regards foetal effects. However, as only to be expected, heroin like morphine can produce addiction or at least physical dependence *in utero* (175, 178, 257, 300).

Synthetic substitutes for morphine. Pethidine (meperidine, isonipecaine, ethyl-1-methyl-4-phenylpiperidine-4-carboxylate) soon established itself as the safest of the powerful analgesics as regards the foetus at birth (19, 95, 255) administered either in individual doses to mothers or by continuous intravenous infusion (97, 132); investigation as to its passage to the foetus was apparently not made, however, until after its clinical acceptance. Such investigation showed that in the human subject pethidine certainly reached the foetus, as judged by chemical tests on the urine of the newborn (327), but attempts to correlate blood concentrations of the drug in the newborn with the clinically estimated degree of depression, and oxygen saturation of cord blood, have not been successful (8, 122). This is not altogether surprising, since the anoxia suffered during birth varies greatly in duration and severity.

From the standpoint of clinical obstetrics the realistic view must surely be

that any drug which results in respiratory depression of the newborn is undesirable. Nevertheless, Gordon and Plinker (113) in drawing attention to the degree of depression of the newborn when the mother has received large doses of pethidine emphasized the safety of these large doses provided that nalorphine was subsequently given intravenously to the mother five minutes before the estimated time of delivery.

Presumably, as with morphine and diamorphine, intra-uterine addiction can occur when administration has been repeated over a suitable period, but this has not featured in recent reports of narcotic addiction in the newborn.

Alphaprodine (Nisentil, α-1:3-dimethyl-4-phenyl-4-propionyloxypiperidine) from its chemical similarity to pethidine might be expected to behave similarly in the foetus, and clinical assessment of its effects in obstetrics agree with this, the general impression being that it has no real advantages over pethidine (83, 154). Methadone (amidone, Physeptone, (±)-6-dimethylamino-4:4-diphenylheptan-3-one) was condemned by some as being too depressant to the foetus for recommendation in childbirth soon after its introduction, but this judgement has been challenged by others (63) on the grounds that the published series of cases were too small to justify such definite conclusions and that in their own series of a thousand cases methadone had not caused more severe depression of the newborn than various other drugs.

Nalorphine (*Lethidrone, N-allylnormorphine*). Although this is not a powerful analgesic it is similar in structure to morphine, and can modify the effects of this and other powerful analgesics, so that it is best considered together with them. Nalorphine strongly opposes the depressant effects of morphine and pethidine upon the newborn (20, 48, 80, 113, 116, 233, 290) and since it does this either when injected into the mother before delivery, or when given into the umbilical vein, its transplacental passage must occur readily. When its stimulant effect is subsequent to umbilical vein injection in a newborn baby who has received no analgesic directly, then this action may be taken as indicating transplacental passage of the analgesic concerned, since the effect of nalorphine alone upon the newborn would presumably be depressant. So reliable is it as an antagonist that the opinion has been expressed that nalorphine has altered the whole position of opiates in obstetric practice (232). For infants likely to be physically dependent themselves, because of addiction of their mothers during pregnancy, its use would presumably be as dangerous as in the addicted adult.

It is a powerful reflection upon the progress made in eliminating the dangerous depressant effects of those analgesics which are used in childbirth if it has to be admitted that the greatest advance has been the development of a competitive antagonist.

B. MILD ANALGESICS

Salicylates. The literature is lacking in reports of foetal damage attributable to the salicylates. From their widespread and uncontrolled use this might indicate their safety, at least when used in therapeutic doses by the mother. Jackson (156), recording a miscarriage in a patient who had attempted suicide by aspirin, has

concluded that the textbook warnings on the dangers of salicylates to the foetus have for fifty years been based only on the experimental work of Binz (29a). Binz found that pregnant rabbits aborted when given repeated injections of salicylates, but he did not prove that this was due to a direct effect on the foetuses, for the pregnant rabbits themselves became severely ill with abscesses caused by the injections. Mosher (215) has since found that sodium salicylate can cause small haemorrhages in the scala tympani of the foetal guinea-pig, but his results need verifying.

Jackson found salicylate in the umbilical cord blood, showing that it reached the human foetus (156) and in experimental work he confirmed its passage in rabbits (156); it is also known to cross the placenta in the guinea-pig (156). His experiments, on pregnant rats and rabbits each given a single large subcutaneous injection of sodium salicylate in the last week of pregnancy, showed no obvious toxicity for the foetus, until a dose was reached which killed one out of the four rabbits receiving it. In one of the surviving rabbits four of its thirteen foetuses were dead. In rats, whenever the mother survived so did the foetuses.

These experiments of Jackson's are not extensive enough to warrant his conclusion that salicylates are not more toxic for the foetus than for the mother. Larger numbers of animals and more species should be investigated and administration should be for longer periods. His statement that chorea of pregnancy can be treated with large doses of salicylates without foetal damage is no proof that all near-suicidal doses would be so harmless, though in his recorded case foetal death was attributable to a tentorial tear.

C. SEDATIVES, HYPNOTICS, INTRAVENOUS AND LOCAL ANAESTHETICS; TRANQUILLISERS

Hyoscine. It is surprisingly difficult to find good accounts of the action of hyoscine on healthy adults, apart from reports of its action in motion sickness. With regard to foetal effects these are even more often obscured by the presence of other powerful drugs, but Snyder has provided a good summary (289).

In cats even large doses given to the pregnant animal failed to suppress generalised foetal activity and respiratory movements, although transplacental passage was proved by mydriasis in the eye of the adult cat when the foetal urine was applied locally. Direct injection of the foetuses through the umbilical veins did not cause marked foetal depression with the doses used, and the newborn kittens after such procedures were apparently normally active, though in one experiment they died after a few hours when the mother had received an unspecified but enormous dose of hyoscine. The relative safety of hyoscine, from the point of view of the foetus, is probably also true for the dog, although Snyder (289) only quotes one experiment with this species.

The clinical reports, quoted by Snyder (289), almost all prove the safety of hyoscine for the foetus, and again transplacental passage of the drug was proved by the mydriatic effect (on frogs) of the urine of the newborn. These tests detected hyoscine in this urine within fifteen minutes of injection of the mothers, but were negative again within a few hours. Whether hyoscine ever has a strange

stimulant effect upon the foetus, as it does occasionally in the adult, does not appear to have been observed, and its actions by virtue of its anti-muscarinic properties do not appear to have been described for the foetus either.

Paraldehyde. Snyder (289) gives a full account of the literature on the use of this drug in obstetrics. It was introduced for childbirth by Rosenfield and Davidoff (258) who noted that it was easily detectable by its odour in the breath of the newborn sometimes for two or three days after maternal administration. This proof of its passage to the foetus was recorded by several others (209, 289) and must be common knowledge to all who have used it. Snyder had observed that in experiments on spinal rabbits it could diminish foetal intra-uterine respiration when the mother was given doses too small to have observable effects on her, but in obstetrics its effects on the newborn are difficult to analyse since it has nearly always been used in combination with other depressants. Apparently it does not prolong labour although it may reduce uterine contractions for a short while; the babies at birth are not usually slow to breathe but maternal overdose can result in a child that is drowsy for a day or two. Gardner, Levine and Bodansky (98) were the first to record its levels in maternal blood and in umbilical cord blood, and the figures were almost identical. Cord blood levels apparently may not parallel the degree of depression of the newborn, for in their series of thirteen cases the three most depressed babies had blood levels only one-half or less of those of three with no apnoea at birth. Observations on many more are needed to determine this point.

Chloral hydrate. Clinical obstetrics must be able to furnish innumerable proofs of the relatively innocuous effects of chloral hydrate upon the foetus when it has been administered to the mother, but there appears to have been no assay of its placental passage before the work of Bernstine, Meyer and Hayman (28) who reported on the foetal and maternal blood levels attained in 52 cases in which local anaesthetics were the only other drugs used. By chemical methods they detected the breakdown products trichloroethyl alcohol and trichloracetate, as well as the chloral hydrate itself, in the foetal blood within fifteen minutes of chloral hydrate's being given per rectum to the mother in labour. Trichloroethyl alcohol was the compound most frequently detected in the amniotic fluid, in the few instances in which uncontaminated samples were available. No evidence was given concerning the breakdown of the parent compound in the newborn infant, and so the breakdown products recorded could have come entirely from the mother. No correlation was found between the time the infants took to utter their first cries and their blood levels of the drugs, and none of the infants was obviously depressed.

Daily administration to pregnant bitches for several weeks has caused liver damage in their foetuses (47), but this does not appear to have been reported for other species and contrasts strangely with the resistance reported for the foetal dog to chloroform damage of the liver (334).

Ethyl alcohol. Positive evidence that the maternal ingestion of alcohol can directly damage the foetus has proved elusive. Taylor briefly mentions that such damage is said to occur but does not substantiate his statement (307). Possibly

suggestions have often been the result of emotional bias, or of the reputed abortifacient properties of various alcoholic drinks, of which it is often forgotten that alcohol is only one constituent. It is reasonable also to speculate that foetal damage in alcoholics might result from inadequate vitamin intake or acquired maternal disease. The work of Stockard and Papanicolaou (302) suggested that alcohol damaged not the foetus but the germ plasm, with resultant physical degeneracy of the offspring for several generations. No mention of foetal damage is made in the publications of the World Health Organization (347), and the report of the Medical Research Council (203) refutes the findings of Stockard as being due to genetic faults in some of his animals. Nicloux (224) demonstrated by chemical estimations that the passage of alcohol from mother to foetus, or in the reverse direction, was rapid in several species, including the human, but he mentioned no deleterious effects upon the foetus other than the possible development of congenital alcoholism, which does not appear to have materialised.

With regard to the consumption of alcohol during labour the position is clear, midwives having administered alcohol for many years, as Chapman and Williams have commented (50). Recently intravenous alcohol sufficient for analgesia, not anaesthesia, has received a trial in over 200 obstetrical cases (23, 35, 50, 87). A mixture of alcohol and pethidine was found particularly satisfactory, and unusual depression of the newborn was the exception. Chemical estimation of blood levels of the alcohol (23, 87) confirmed the early work of Nicloux.

It does not appear to be known whether disulfiram, which opposes the metabolism of alcohol, crosses the placenta and whether foetal metabolism of alcohol might be more sensitive to its action than is that of the adult.

Tribromoethyl alcohol. The solution of this alcohol in amylene hydrate (bromethol) has had a disastrous history in obstetric anaesthesia. It appears to be profoundly depressant to the foetus, and newborn infants have remained relatively inactive for up to four days after its use for basal anaesthesia for the mother during labour (289). No special reasons appear to have been produced for its pronounced effect on the foetus and it seems fair to speculate that at the time of birth the liver is not able to combine it with glucuronic acid as it can in the adult.

Barbiturates. a. Intermediate and long-acting. Boucek and Renton (31) appear to be the first to have studied the effects of barbiturates upon the foetuses of laboratory animals. They were interested by conflicting reports about the degree of depression these drugs caused in the newborn when given in human labour.

Anaesthetic doses of amylobarbitone (amobarbital, Amytal, 5-ethyl-5-isopentylbarbituric acid) were injected into pregnant white rats near term, and the liveliness of foetuses observed when exposed *in utero* and mechanically stimulated at varying times afterwards. They concluded that the drug did not reach the foetuses, a) because foetal response remained brisk, and b) because, as they stated, doses of amylobarbitone calculated on the basis of the gross weight of the pregnant animals killed them, whereas doses calculated on the basis of gross weight minus estimated weight of uterine contents did not. However, foetal liveliness does not mean absence of placental transmission, and the deaths of their anaesthetised mother rats could be attributed to their use of doses recom-

mended by other workers rather than of doses determined on their own non-pregnant stock. They were startled to find that amylobarbitone injected into the foetal abdomen *in utero* could anaesthetise the mother, and concluded that this drug could pass from foetus to mother but not in the reverse direction. Their conclusions have certainly not been confirmed in the human. Ploman and Persson (245), using the spectrophotometric quantitative assay method of Goldbaum (106), have recently shown in a series of 35 human foetuses, from therapeutic abortions at the fourth to seventh month of gestation, not only that amylobarbitone sodium does reach the foetus but that it can accumulate in brain, liver and placenta. This was also true for barbitone (5:5-diethylbarbituric acid) and phenobarbitone sodium (sodium 5-ethyl-5-phenylbarbiturate), but none was found in the foetal urine. These authors, probably the first to have examined quantitatively the distribution and fate of barbiturates in the foetus, also claimed that all three drugs were present in higher concentration in the fourth ventricle than in the cerebral cortex, and suggested this as the basis for selective medullary depression in the newborn.

Flowers (89), using a modification of the quantitative method of Butler (45), also showed the transplacental passage of sodium barbitone in 23 human deliveries and this occurred from two minutes to five hours after intravenous administration. In 13 of his samples of cord blood the level of this barbiturate was higher than that of the maternal blood, and this might appear to be an indication of the error of the assay method. His conclusions were that sodium barbitone reaches the foetus in the first minute after intravenous administration and that foetal and maternal blood levels equalise very rapidly and remain so for many hours. Such work supports the conclusions of Dille (71, 72), who had shown much earlier that barbitone crossed easily from mother to foetus in the rabbit, cat and guinea-pig, and who also showed in the rabbit that amylobarbitone reached the foetus. He also found that in these species repeated administration of sodium barbitone could cause abortion or foetal death, but he did not quote any results with control pregnant animals subjected to the same disturbance of repeated administration, a surprising omission since he did use controls to show that laparotomy, to confirm the pregnancy, did not itself cause abortion.

Pentobarbitone sodium [sodium 5-ethyl-5-(1-methylbutyl) barbiturate] was investigated by Dreisbach and Snyder (289) because various clinical reports, mainly without controls, suggested that babies are often depressed for a day or two after birth when the mother has had this drug during labour. In rabbits they found that pentobarbitone sodium injected intravenously to the doe caused the almost immediate depression of foetal respiratory movements with a definite relationship between dose and duration. Even the smallest doses of pentobarbitone used had a demonstrable cumulative effect for the duration (two to three hours) of the experiments, and the largest doses, producing partial anaesthesia, also caused the foetal depression to last for the whole of this time. Such evidence, without chemical assay of barbiturate, is presumptive that the foetal effect is by direct drug action, but further experiments were made to determine the effects of barbiturate upon the survival of newborn rabbits by comparing the length of

time for which respiratory efforts persisted when pentobarbitone sodium was given to them directly and then asphyxia induced by tracheal occlusion. Controls, without pentobarbitone, made respiratory efforts for a rather shorter time, which was interpreted as meaning that the barbiturate at least did not jeopardise neonatal survival. However, it might be that the asphyxial struggles of the treated newborns were less vigorous and less frequent and therefore enabled life to persist longer. It would be better to use a test which imposed partial rather than total asphyxia so that it could then be observed whether any overlay of barbiturate depression might turn serious conditions into lethal ones within a given time.

Amongst the mass of clinical literature dealing with pentobarbitone sodium in human labour the work of Fealy (86) stands out as an attempt to correlate the state of the newborn with the blood level of pentobarbitone and to ascertain how quickly and to what extent equilibrium is established between maternal and foetal blood concentrations of the drug. In a series of 69 labours in which the mothers received only pentobarbitone intravenously, compared with 100 who had other anaesthetics or analgesics, or spinal anaesthesia, he found that the state of foetuses was better in the group having pentobarbitone alone, that the foetal blood level of this drug reached over 70 % of the maternal level within one minute of maternal injection, and that these relative levels were maintained for roughly three hours.

Barbiturates. b. Short-acting. It is with regard to the short-acting thiobarbiturates and to thiopentone sodium (sodium 5-ethyl-5-(methylbutyl)-2-thiobarbiturate) in particular that the greatest interest appears to have been aroused. Following experimental observations upon rabbits in which brief depression of foetal respiratory movements was shown (289), most clinical obstetricians appear to have been swayed by the work of Hellman, Shettles, Manahan and Eastman (143) who showed that in the human there seemed to be a delay of about five minutes between the intravenous injection of the drug into the mother and its appearance in any quantity in the foetal blood, and that even after ten minutes there was less in the foetus than at fifteen or twenty minutes. As Crawford (58) has recently pointed out, this opinion was dominant for about ten years, although several authors (52, 124, 160, 200, 337) observed that no serious extra depression of the newborn resulted if the time from injection to delivery exceeded ten minutes. McKechnie and Converse (200) also showed in 15 cases that sodium thiopentone was detectable in foetal blood within forty-five seconds of maternal injection, but no correlation was observed between total dose injected, maternal and foetal blood levels, and degree of depression of the newborn. Their opinion that transplacental transmission of the drug is very rapid has been independently confirmed by the results of Crawford (58) on 41 cases in which he found maternal and foetal blood levels approximately equal for 3 to 30 minutes. He also briefly and critically reviewed the literature on the effects of thiopentone in labour.

It should be emphasized that the evidence of a slower rate of transfer found earlier by Hellman and associates (143) was from only 7 of their cases, as they stated clearly, and it is possible that undue weight has been mistakenly attached to their results since their whole series in which thiopentone was used comprised

1,415 cases. It must also be said in defence of these workers that they did also recommend that their data on rate of transplacental passage should not become an indication that delivery by Caesarean section under thiopentone should be hurried.

With regard to barbiturates in general it therefore seems that transplacental passage is easy and rapid, and much more careful observations are needed with accurate methods of chemical assay to try to establish the relation between maternal dosage and danger to the foetus. It might also prove important to learn the effects of barbiturates upon the foetal heart and blood pressure, and even whether there is any possibility of intra-uterine addiction occurring, as has been established for morphine and diamorphine (*q.v.*). At least it does not seem likely that thiopentone causes foetal laryngospasm in the doses used for obstetrical anaesthesia, nor that chronic medication with barbiturates, *e.g.*, phenobarbitone, is likely to cause abortion or congenital deformity in the human.

Local anaesthetics. Various techniques employing local anaesthetics, usually procaine (ethocaine, Novocain, 2-diethylaminoethyl-*p*-aminobenzoate hydrochloride) or cinchocaine hydrochloride [dibucaine hydrochloride, Nupercaine hydrochloride, 2-butoxy-N-(2-diethylaminoethyl) quinalone-4-carboxyamide hydrochloride] in obstetrics have become established and from the excellent reports concerning the state of the newborn infants it seems that the foetus at least cannot be specially sensitive to the deleterious effects of such drugs upon the central nervous system (289). However, estimates of local anaesthetics crossing the placenta are not in evidence although presumably excellent opportunities are afforded when they are deliberately injected intravenously for their central analgesic action, occasionally even in doses which have caused maternal convulsions (5, 289).

Tranquillisers. The confused impression of the action of tranquillisers, only now beginning to be cleared by adequate, strictly controlled trials, is not a good basis on which to attempt to assess their effects upon the foetus, but at least it seems that clinical experience does not throw them under any special suspicion of being selectively toxic for the foetus. Chlorpromazine, whilst being accepted as safe to administer in pregnancy, has been shown, by virtue of its potentiating action upon depressants, to reduce the dose of analgesics needed in labour, but probably the usual effects of depression of the foetus are equally enhanced (130, 148). Trilafon has been shown to have a similar result (131) and reserpine has been associated with the incidence of a non-infective type of nasal discharge in the newborn of mothers treated within two days of delivery (40). This discharge cleared up spontaneously in from one to five days. Methylpentynol, declared not to be harmful to the foetus, was not detected in human umbilical cord blood (34), but it might have been detected had larger doses been used, and it has been proved to cross the placenta in the cat (197).

D. Gaseous and volatile anaesthetics

It would be strange if gaseous and volatile anaesthetics, favoured in anaesthetic practice because of their rapid rates of diffusion, did not cross the placenta

with the greatest of ease. In fact, purely clinical impressions about the degree of narcosis of the newborn being in proportion to the depth and duration of maternal anaesthesia are just what might be expected and are particularly well proven for ether (29b, 88, 189, 283). It is in this field that Snyder (289) has made his most useful review and has contributed by means of his special techniques for the observation of foetal respiratory movements in rabbits, but it is still true that the majority of observations concerning the effect of anaesthetics upon the foetus are clinical assessments, many very carefully controlled, but nearly always without any estimations of drug levels reached in foetal and maternal blood. The exceptions usually deal only with blood levels of ether and of cyclopropane (7, 88, 281), but there are more references dealing with the oxygen saturation of the blood of the newborn (78, 305, 326).

Ether and cyclopropane. It has been clearly shown that neither ether nor cyclopropane reduces further the low oxygen saturation of the infant's blood at birth, so that any apnoea must be due to a direct narcotic effect (7, 305). In the case of ether, correlation was shown between its concentration in cord blood and the degree of narcosis of the infant, but the reliability of estimations of ether in blood is always in doubt. For cyclopropane such a correlation was not demonstrated (7). These results are in agreement with experimental observations on rabbits, where it was found that foetal respiratory movements did not persist when surgical anaesthesia of the mother was maintained by ether, whereas deep surgical anaesthesia with cyclopropane was possible with uninterrupted foetal respiratory movements (289).

Nitrous oxide. Depressant effects upon the foetal rabbit due to nitrous oxide anaesthesia of the doe were attributable to anoxia, and this has been found also in clinical experience, where ethylene, which possesses greater anaesthetic potency, is quoted as causing asphyxia neonatorum only half as often as does nitrous oxide, when conditions are similar (289).

Chloroform. The major concerns with chloroform, when it was used widely, were with the safety of the mother either when administration was brief and there was excessive excitement, or when administration was prolonged and there came the expected deterioration of blood pressure and fear of delayed chloroform poisoning. The foetal liver is apparently much more resistant to the action of chloroform, at least in the dog, since in this species when foetal and maternal blood levels of chloroform had continued at the same concentration during anaesthesia only the foetal livers escaped damage (334).

Trichloroethylene. The safety of trichloroethylene for analgesia in midwifery practice is now accepted, but full anaesthesia with it can result in sluggishness in the newborn (275). Experiments upon pregnant sheep and goats (142) showed that it crossed readily to the foetus and reached a higher concentration in the blood of the foetal sheep than in that of the ewe after only sixteen minutes. This was also observed in one experiment out of the three made upon goats. *In vitro* experiments showed that foetal blood could take up more trichloroethylene than could maternal blood, and the likely explanation was offered that this related to the greater total mass of red cell envelope per unit volume of foetal

blood, since the anaesthetic concentrates in the lipid of the cell wall. No undue alterations of the electrocardiographic pattern of the foetal goat were noted when trichloroethylene was used.

E. Carbon monoxide

Within the last five years the effect upon the foetus of maternal poisoning with carbon monoxide has been the subject of a thorough review (60) covering the experimental work from 1877 and observations upon human cases since 1859; further experiments upon rabbits were also reported and discussed. The relative affinity of foetal haemoglobin for oxygen and for carbon monoxide has been recently determined for the sheep (169) and found to be the same in the ewe and her foetus.

The picture that has emerged is clear and is much the same as would be expected with a gas which forms a very slowly dissociating combination with haemoglobin, and in so doing reduces its oxygen-carrying capacity. The earlier controversy as to whether carbon monoxide could leave the maternal blood and reach the foetal haemoglobin has been resolved, since it became clear that *in utero* the percentage saturation of foetal haemoglobin with carbon monoxide depends not only on the degree of saturation of the maternal haemoglobin with the gas, but also very much on the duration of exposure. Damage to the foetus occurs then in proportion to the severity and duration of the anoxia which it has to suffer, and this anoxia may be mainly due to the reduced oxygen-carrying power of the maternal blood, or it may have as a contributory factor varying degrees of foetal carboxyhaemoglobinaemia. Variations of carbon monoxide in the inspired air, combined with varied durations of exposure, can therefore result in three types of situation, 1) both mother and foetus are killed by the maternal anoxaemia, 2) the foetus dies from the combined effects of maternal anoxaemia and some degree of saturation of the foetal haemoglobin with the carbon monoxide, 3) mother and foetus both survive after some degree of anoxaemia for both.

The implications of these findings for obstetrics are illustrated by the reports of brain damage to the foetus by the anoxaemia, and are reinforced by the established ability of foetuses to remain alive under anoxic conditions lethal to the adult. It would seem a dramatic piece of life-saving to remove the living infant from the moribund or freshly dead mother who has been the victim of carbon monoxide, but this could result in an individual severely crippled by brain damage; presumably difficult decisions sometimes have to be made in the light of the evidence of the duration of the foetal anoxia. Similarly, in cases of severe carbon monoxide poisoning with survival, earlier in gestation, the question of the therapeutic termination of pregnancy might be raised.

III. RELAXANTS OF SKELETAL MUSCLE

Curare. Preyer (249) is credited with the first publication concerning the action of curare upon the foetus as long ago as 1885. He found that the crude preparation injected directly could paralyse the newborn guinea-pig or postmature foetuses of this species, but that full term or immature foetuses were re-

sistant to indirectly received doses big enough to paralyse adults. Whether transplacental passage of the drug occurred from mother to foetus remained unanswered, but he made the startling discovery that transmission could occur in the reverse direction, as evidenced by maternal paralysis following foetal injections. It is not surprising that little advance was made in this field for over sixty years, for it was fifty years before the acceptance of acetylcholine as the humoral transmitter of the nervous impulse to striated muscle. However, Rückert (261) within this period showed that in the foetal guinea-pig certain muscles exhibited contractures when acetylcholine was applied, and that this pattern of response persisted into neonatal life for times which depended upon the particular muscle. Angulo y Gonzalez (108), a few years later, briefly reported on the paralysis of rat foetuses following direct injections of curare.

It was therefore against a rather uncertain background that curare was boldly introduced by Whitacre and Fisher (335) as an adjunct to obstetric anaesthesia. After 100 Caesarean sections in which *d*-tubocurarine (Intocostrin) was used, they thought that further trial was warranted since they had been able to reduce the amount of inhalation anaesthetic, and consequently the depression of the newborn was only slightly more than that resulting after deliveries with the mothers under spinal or local anaesthesia. Their results were confirmed by Gray (115), and repeated on more patients by themselves (336) even with very large doses, and tubocurarine soon became universally accepted into obstetrical anaesthetic practice. Such results coupled with evidence from dogs and their foetuses (134, 135) which could be paralysed by direct but not by maternal injections of curare, made it likely that curare preparations did not normally harm the foetus because they did not cross the placenta. In short, it was assumed that the neuromuscular junction of the mature foetus would function very similarly to that of the adult and that any curare reaching it would act in the normal manner. In one brief letter (32) mention was made of the spastic response of a nineteen week human foetus following the injection of tubocurarine into its umbilical vein, but this does not appear to have been confirmed.

The work of Buller and Young (42) stands out as the first serious attempt to study foetal neuromuscular block by tubocurarine. They investigated the effects of tubocurarine upon foetal rabbits and guinea-pigs, and one human foetus, still in placental connection with their mothers, and upon isolated phrenic nerve diaphragm preparations from foetuses of these species. The four human foetuses were of twenty to twenty-two weeks gestational age. A special feature of the experiments upon the intact foetal rabbits and guinea-pigs was the care taken to ensure adequate placental blood flow, both so as to give the tubocurarine every chance of crossing the barrier and so as to avoid the complication of foetal anoxia. Their foetal rabbit and guinea-pig phrenic nerve diaphragm preparations were about as sensitive to tubocurarine as preparations from the adult rat, but their human foetal preparations were less sensitive, and they commented that the human preparations were about four times as thick as those of the foetal rabbit and guinea-pig. In all three species potassium ions or neostigmine antagonised tubocurarine neuromuscular block. Against this background of established

efficacy of tubocurarine on the foetus it seemed clear at least that the drug injected into the mother did not reach the foetuses in concentrations sufficient to cause any demonstrable block. It was established from injections into rabbit foetuses that transplacental passage could occur to the mother (*cf.* Preyer, with guinea-pigs) but that uterine contraction could play an important part in delaying this, presumably by impairment of circulation.

More recently various determined attempts have been made to show that tubocurarine must cross the placental barrier at least in traces (52, 244), but chemical assays for the drug in umbilical cord blood of human infants after intravenous administration to the mothers have been uniformly negative, even after high dosage. However, Crawford (58), using a frog-rectus bio-assay technique, has now demonstrated traces of a muscle relaxant in cord bloods of curarised mothers, but these traces could be correlated neither with the size of the initial dose nor with the time between its administration and the time of delivery in the small number of cases studied. In dogs (242) by using doses about ten times those necessary on a weight basis to produce apnoea, and by injecting such doses into the uterine arteries, it has proved possible to reduce the activity of exposed foetuses and to determine chemically their blood level of tubocurarine. Thus it seems that this recent work in no way alters the clinical impression that it is perfectly safe for the newborn that tubocurarine be used as an adjunct to maternal anaesthesia. The observations of Stead (299) upon relaxants and the newborn infant support the belief that curare crosses the human placenta in infinitesimally small amounts, if at all, for he found that in the neonatal period infants are very sensitive to tubocurarine. After direct administration of the drug their respiratory efforts were recorded from a tambour and lever system connected through an endotracheal tube. He likened their response to that of the myasthenic.

Gallamine triethiodide (*bencurine iodide*, *Flaxedil*, *1:2:3-tri(2-diethylaminoethoxy) benzene triethiodide*). The situation with regard to another relaxant of the non-depolarising type, gallamine, may be different. Whilst some have found equal safety to the foetus with the clinical use of most of the commonly available relaxants (313) the technique of injection of high doses into the uterine artery in the dog has revealed that gallamine probably reaches the foetus more easily than does tubocurarine (243). This as an observation by itself might not imply clinical danger, but Crawford (58) has found that in the human subject the foetus can rapidly receive from the mother amounts which are easily detectable on biological assay. The levels in cord serum could reach the same order as maternal levels, and he suggests that tests of the muscular power of the newborn more sensitive than mere clinical assessment might reveal impairment of function. As with tubocurarine there was no discernible correlation between foetal levels, maternal dose, and time after administration.

Myasthenia gravis. It might be expected that interesting revelations about the nature of myasthenia gravis and of foetal neuromuscular development might be forthcoming from a study of infants of myasthenic patients. However, Viets (320) in a comprehensive review of the literature of this disease in pregnancy points out its rarity and states that pregnancy can cause either remissions or

exacerbations, but he mentions no specific effects as regards the foetus. Others (268) have pointed out that a truly congenital myasthenia gravis and a brief neonatal form exist, but that only about twelve cases of the latter have been reported. Speculation is made that the neonatal form may be due to the persistence of a maternally transmitted toxin, but that at least the long continued administration of neostigmine to the mothers does not seem to affect foetal neuromuscular development.

Decamethonium iodide (*C10, decamethylenebis-(trimethylammonium iodide)*). This was the first of the depolarising type of relaxant to find a use with obstetric anaesthesia. Following its cautious introduction into this field (231), in which it appeared to be safe, Young (350, 351) analysed its effects upon human foetuses as well as those of the guinea-pig and rabbit. The experiments were similar to those already done with tubocurarine (42). Again it was shown that foetal neuromuscular transmission could be blocked by the drug when it was administered to the foetus or to foetal phrenic-nerve diaphragm preparations, and again no foetal effects could be shown when administration was to the mother. Pentamethonium, tested upon the isolated preparations, failed to antagonise its action. In contrast to tubocurarine there was no evidence of transmission of decamethonium to the mother when it was injected into the foetus. It seems that the only contradictory evidence against the alleged safety of decamethonium to the foetus in obstetrics is the clinical impression of Ellerker (81) who thought that thirteen infants born by Caesarean section after the mothers had decamethonium were more depressed than usual after the anaesthetic technique used. This evidence is poor and it is difficult to assess the significance of the accompanying comment that decamethonium appears to cross the placenta, but less easily than does tubocurarine. Injections into the uterine artery of the pregnant dog caused no paralysis of the foetus (243).

Suxamethonium chloride (*succinylcholine chloride, 2-dimethylaminoethyl succinate dimethochloride dihydrate*). Thesleff (309) using the technique of Buller and Young (42) first reported on this short-acting depolarising type of relaxant with regard to the foetus. He could demonstrate no diminution in foetal activity for rabbits five to ten minutes after intravenous injection of the pregnant does. Human foetuses of from three to five months gestational age retained brisk reflex activity even after the drug had been injected into the maternal uterine artery from one to eight minutes previously. Mention was also made of the successful clinical use of suxamethonium in Caesarean section. Contrasting with this report there is evidence that dog foetuses can be paralysed when the drug is injected into the maternal uterine artery (243), and there is a clinical suspicion that the human foetus can be affected when doses to the mother are rapidly repeated (188).

It is interesting that the paralysis of the dog foetuses persisted as spastic for three to five minutes, also that the paralysis in this species was observed very rapidly after injection. It might be that in the experiments quoted by Thesleff (309) too long a time interval elapsed between maternal injection and the observation of the foetuses. On the other hand Stead (299) has found a distinct resist-

ance to suxamethonium in the newborn infant, in spite of cholinesterase levels being low, and so it is possible that the lack of paralysis of the newborn reported by the others may be due not to an absence of transplacental passage but to the fact that the amount which passes the placenta is too small to affect the foetus which is very resistant to the drug. It is presumably this work of Stead (299), with suxamethonium, which has given rise to the impression that foetuses are resistant to depolarising relaxants in general.

Throughout the literature concerned with the effects of relaxants on the foetus there is a marked lack of reference to any special features of foetal neuromuscular transmission. Until recently the only research on the foetal neuromuscular junction has been anatomical. Paterson (232) has reviewed and extended the work in a comparative study of the properties of foetal, neonatal and both normal and denervated adult muscle. He worked chiefly with the isolated phrenic-nerve diaphragm of the rat, though some observations were also made upon foetal material from the cat, sheep, rabbit, guinea-pig and man. He confirmed previous work showing that the application of depolarising substances caused varying degrees of contracture in neonatal striated muscle, and he extended this observation to the foetus, finding that as in the adult such contracture is accompanied by electrical 'silence.' It became apparent that the time in foetal or neonatal life at which this type of response was lost depended upon the particular muscle and upon the species of the animal used. Where the newborn was very immature (rat) the contractural responses persisted well into neonatal life, but where the newborn was relatively mature (guinea-pig), or where gestation was long (sheep, man), this response disappeared early in neonatal life or even by the middle of gestation. Such contractural responses to applied depolarising drugs occurred when functional innervation was already established, and neuromuscular block to nerve stimulation was caused at the same time. Both the block and the contracture were opposed by hexamethonium in the experiments of Paterson, whereas Young (351) found that pentamethonium did not oppose block of the foetal nerve muscle preparation by decamethonium. It would be interesting to know whether the difference in the ages of the foetuses used by these two workers has any bearing on their contrasting results, for Paterson noted that the contractural response had nearly vanished in human foetuses by the twentieth week. He correlated the onset of this contractural response with the transition of the developing muscle from the myotubular stage to the more adult form, and he also warned against deductions made solely from anatomical study, since he had found innervation to be functional at stages when histology suggested this to be highly unlikely. Paterson also quoted the interesting observation that in the foetal rat at seventeen days, stimulation of the nerves to the hind limbs caused muscle twitches, although motor end plates were not distinguishable, and the nerve endings formed only a plexus round the muscle fibres (353). He further quoted (232) that in the extraocular muscles of certain mammals even in the adult state, the situation is very similar anatomically (312) and further resemblance to the foetal state exists in their contractural response to acetylcholine with eserine accompanied by electrical 'silence' (38). It may be added

that the newborn infant has been found to be specially sensitive to tubocurarine (299) and it is well known that the extraocular muscles are among the first to be affected by this drug in the adult. The conclusion seems therefore irresistible, though paradoxical, that adult mammalian extraocular muscles may prove useful for studying reactions of the foetal type.

In contrast to a stage of abnormal muscular response to depolarizing drugs, not unexpected in a developing tissue, there appears to be no sound evidence yet for any stage of abnormal response to competitive inhibitors such as tubocurarine which in fact is also reasonable if neuromuscular block by such agents turns out to be purely competitive. Perhaps the main difference between the reaction of adult and foetal muscle to competitive inhibitors may be only quantitative. However, if there really is any depolarising element in the block by the tubocurarine class of drugs it might be clearly revealed by muscles in the early stage of foetal development. This raises the point concerning the suitability of foetal muscle studied so far, for the younger the foetus the greater the difficulties of technique, and in order to study muscle as immature as possible the tendency has been to use that from near-term foetuses of species in which the newborn is relatively immature. The muscle chosen is now mainly the diaphragm, both because it is usually thin enough to survive well by simple immersion in well-oxygenated solutions without any need of highly difficult cannulation, and because as a respiratory muscle its behaviour is of particular interest to medicine. It might be more revealing to use other muscles from species sufficiently large to permit adequate vascular cannulation. Convenient muscles might be found in which development was much slower than that of the diaphragm, and this would make possible the easier study of even earlier stages of developing neuromuscular function.

IV. CARDIOVASCULAR SYSTEM

Experiments with drugs of pronounced cardiovascular activity have been made upon a) the foetus with intact circulation (30, 43, 65, 66, 67, 75, 227), b) isolated perfused hearts (2, 12, 99, 190) and c) perfused umbilical vessels (10, 14, 84, 256). The drugs which have attracted most attention are adrenaline and noradrenaline (12, 65, 66, 75). Cardiac glycosides (2, 12, 227, 228) and hexamethonium (30, 65, 213, 352) have received rather less attention in this field and others, including acetylcholine (2, 12, 65, 99), have been almost ignored as yet except in experimental work upon the placental vessels (14, 256).

A. The foetus with intact circulation

Adrenaline (epinephrine) and noradrenaline (levarterenol). In recent years the effects of these sympathomimetic amines upon the foetus have been examined, and earlier work has been discussed, by Dawes and Mott and their colleagues (65, 66) and by Dornhorst and Young (75).

Dawes, Mott and Rennick (66), using sheep anaesthetised with sodium pentobarbitone, compared the cardioacceleration produced by injections of adrenaline and noradrenaline into the jugular and femoral veins of foetuses. It was found

that the foetal heart rate was increased more by the femoral injections, as would be expected if previous observations (67) were correct concerning the course of the foetal circulation, and this was equally true in foetuses at mid-gestation and at term. Injections of acetylcholine produced a greater bradycardia by femoral injection.

With adrenaline and noradrenaline the umbilical blood flow increased in proportion to the rise of foetal blood pressure registered from a femoral artery. This suggests that in the doses used adrenaline and noradrenaline could have had no powerful constrictor effect upon the umbilical or foetal placental vessels. It was also found that foetuses at mid-gestation experienced a greater degree of cardio-acceleration in proportion to pressor effect from adrenaline than did the mature foetuses, the most likely reason being the development of autonomic depressor reflexes during the second half of pregnancy. This is supported by evidence from other experiments (30) in which hexamethonium iodide was injected intravenously into five foetal sheep. A marked fall of blood pressure occurred in the three mature ones but not in the two others, which were of less than 100 days gestational age. Similarly, intravenous nicotine hydrogen tartrate caused a rise of blood pressure and heart rate in five foetuses of 73 to 133 days.

Increased pressor responses were obtained to adrenaline and noradrenaline when the umbilical cords were tied and artificial respiration commenced. This could have been due merely to the removal of the damping effects of the umbilical circulation, but again, as was pointed out, important contributory factors could have been dilution of the drugs by a smaller volume of blood, or the effects of improved oxygenation or closure of the ductus arteriosus.

From the results of injecting adrenaline and noradrenaline into a small series of foetal guinea-pigs and rabbits, under urethane anaesthesia, Dornhorst and Young (75) concluded that pressor responses to these drugs could be obtained in the foetus only with doses twenty times as big as those which were required in the adult. They also found no evidence of their placental transmission either from mother to foetus or in the reverse direction. They commented that all these results agreed with the findings of previous workers, and that the established presence of high concentrations of mono-amino oxidase in the placenta possibly accounted for the role of this organ as a barrier in this case. The injection of these pressor amines into the maternal circulation produced asphyxial effects upon the foetuses, and this was shown to be solely due to their vasoconstrictor effect upon the uterine vessels and not to the uterine contractions they caused, since oxytocin stimulated the uterus strongly but caused only slight placental cyanosis. When cardiac slowing was produced in the rabbit foetuses by asphyxia it was not abolished by atropine (75) and so it was probably not of vagal origin.

In a large series of rabbits anaesthetised with pentobarbitone, Dawes, Handler and Mott (65) compared the relative sensitivity of mother and foetus to the pressor action of adrenaline and noradrenaline by direct intravenous injection into each. Since the foetal blood pressure is very low they considered that a fair comparison of relative effects on mother and foetus could be achieved only if the rise of pressure in each case was expressed as a percentage of the resting level, and

on this basis they showed mother and foetus to be equally sensitive. On the other hand Dornhorst and Young (75), with rabbits anaesthetised with urethane, found the foetus to be far less sensitive than the mother to the pressor action of these amines. They expressed the changes in blood pressure only as mm of mercury, but converting their figures to percentage changes still does not abolish the discrepancy between the two sets of results; Dawes and his colleagues always obtained measurable responses in foetal rabbits with doses twenty-five times less than those which Dornhorst and Young found not consistently effective. Although the situation has been fully discussed (65, 75) and no real explanation seems to have emerged it does seem likely that the difference in the anaesthetics may have played a bigger part than was realised.

Hexamethonium. The placental transfer of this drug has been investigated very thoroughly in the rabbit by Young (352) using as an assay method the activity of plasma or amniotic fluid samples upon the superior cervical ganglion of the cat. She found that after intravenous injection into the unanaesthetised doe hexamethonium activity was demonstrable within ten minutes in plasma from foetuses of twenty-three days or older; younger foetuses yielded insufficient blood for reliable assay. In spite of injections repeated every half-hour for up to twelve hours, the foetal blood concentrations reached only one-third of the maternal. In contrast, the hexamethonium activity of the amniotic fluid exceeded that of the doe's blood after four hours of injections and continued to rise throughout the duration of the experiments. Its source was deduced to be the foetal urine since tying the vitelline veins did not prevent its appearance but umbilical occlusion did. Foetal rabbits did not yield enough urine for assay but hexamethonium was found in the urine of foetal guinea-pigs. It was possible to collect enough amniotic fluid for assay from foetuses as early as the nineteenth day, or even from those of the fourteenth day, and in these younger foetuses hexamethonium reached the amniotic fluid much more slowly.

Experiments to determine the rate of disappearance of the drug from the amniotic fluid showed that 24 to 36 hours were needed for it to be completely cleared, and when large single doses were injected directly into the amniotic fluid, with the does under urethane, detectable blood levels occurred in the foetal plasma. The lack of a detectable maternal level of drug in this instance is probably due to the slow rate of re-absorption and placental transfer from the foetus (offset by re-excretion by the foetus), compared with the rate of maternal renal excretion, for direct injection of the foetuses with high doses through a branch of an umbilical artery resulted in detectable maternal blood levels. Young (352) comments that the slow removal of hexamethonium from amniotic fluid does not accord with concepts of a rapid turnover of this fluid, but the validity of that argument surely depends upon the amnion's being freely permeable to the drug in question.

Special note should be taken that the blood pressure fell and cardiac slowing was pronounced in foetuses of sheep and rabbits when hexamethonium was injected directly (30, 65). The resulting fall in umbilical circulation must have produced some foetal anoxia. It is essential that ganglion blocking drugs used on pregnant women should all be carefully examined in the light of this if the

autonomic cardiovascular control of the human foetus is well-developed before birth. Morris has shown that hexamethonium crosses to the human foetus (213).

Cardiac glycosides. The study of the transplacental passage of digitoxin affords one of the few examples of the use of radioactive tracers for following drug distribution between mother and foetus.

Preliminary work upon pregnant rats and guinea-pigs showed that the drug crossed the placenta and reached a higher concentration in the foetal than in the maternal heart (227). This has been confirmed in the human (228) by results upon three foetuses obtained from therapeutic terminations of pregnancy at the eleventh to twelfth week, and one case of stillbirth at the thirty-fourth week. The drug was injected intravenously to the mothers several hours before the foetuses were removed or the foetal heart stopped. The three younger foetuses contained less than 0.1 % of the total dose injected into the mothers as unchanged digitoxin, and less than 0.33 % as metabolites. The older foetus contained appreciably larger amounts but not out of proportion to its greater size. The younger ones also showed the highest concentrations in heart and kidney tissue, but the other showed nearly as much in its liver, gall-bladder and intestine, and this presumably shows that this path of excretion has developed by that stage. The high ratio of digitoxin metabolites to unchanged digitoxin found in the livers suggests that the foetuses were able to metabolise the drug, but of course it is possible that the metabolites had all come from the mothers.

One comparison was made between the concentration of radioactive digitoxin in the foetal hearts and that in an auricular appendage from an adult which had received the same dose as was used on the mothers. This revealed that the foetal heart had up to ten times the concentration per unit weight of tissue as held by the maternal hearts, but it was pointed out that the explanation of this may be simply that in later stages of development, both intra- and extra-uterine, only the size of the myocardial cells increases whilst the number of cells remains constant, so that the same concentration of digitoxin could be present for adult and foetus when calculated on the basis of molecules per cell.

The radioactive digitoxin was also detected in the foetal brains, so that the glycoside would be in a position to exert its known central nervous activity.

No attempt was made to get electrocardiographic evidence of actions upon the foetal heart, and the general conclusion was drawn that cardiac glycosides in the usual therapeutic doses in humans are harmless to the foetus although they reach it.

Renin and angiotonin. These substances have been the subject of one paper with regard to the foetus (43), but it is difficult to reconcile the summary and conclusions with the experimental procedures and the results as recorded in the body of the paper. All that can be said to emerge is that renin caused a drop in foetal but a rise in maternal blood pressure when it was injected to the pregnant animals, whereas by direct injection to the foetus it caused a rise in foetal blood pressure. The picture for angiotonin is less clear, but apparently it had much the same effect as renin upon the maternal blood pressure. Its foetal pressor action when injected to the foetus directly was discussed but reference to the text does

not make it clear whether it was observed. Evidence offered that the foetus is less responsive than the adult rat is poor and the criticism of Dawes, Handler and Mott (65) is again valid that such comparisons of pressor effect should be on the basis of percentage rather than absolute rise, and that the site of injection into the foetal circulation is of crucial importance.

B. Isolated perfused foetal hearts

At later stages of intra-uterine life than those dealt with by Patten in his review on the early heart beat (236) few observations have been made, but since they were mostly on human hearts a detailed account is given.

Lloyd (190) perfused two human foetal hearts of six months with Ringer-Locke's solution by Langendorff's method. The injection of high doses of calcium chloride improved the strength of the beat of auricles and ventricles and reduced the irregularity in one experiment where this was present. The beat was also restarted by calcium chloride on several occasions when it had ceased. Such results confirm the known action of calcium upon the strength of the beat of adult mammalian hearts. Garrey and Townsend (99) used isolated auricles and ventricles of a human foetus of about fifteen weeks. These myocardial strips were bathed in an oxygenated modified Ringer's solution. Under these conditions the auricles were the more sensitive to acetylcholine and to adrenaline, and the action of acetylcholine was potentiated by eserine and inhibited by atropine as in the adult. These authors state that the preparations were very insensitive to these drugs compared with the hearts of adult mammals of different species. It is not clear whether they believe the drugs to act directly or by stimulating nerve endings, but they conclude that at this stage of foetal life the human vagus can exert little effect. Such results are not in accord with some preliminary observations (13) where it was found that human auricles isolated from the heart of a thirteen week foetus were as sensitive to adrenaline and acetylcholine as were those of young rabbits, and much more sensitive than those reported by Garrey and Townsend. These thirteen week foetal auricles also responded to nicotine by a reduction followed by an increase of rate and strength of beat; such effects of nicotine are possibly due to stimulation of nerve endings and not necessarily of the cell bodies in ganglia.

The hearts of nine human foetuses ranging from sixteen to twenty-four weeks have also been perfused with Locke's solution by Langendorff's method (12). In four of these a comparison was made between adrenaline and noradrenaline by observing the amplitude of beat; noradrenaline proved to be from three to sixteen times less powerful than adrenaline. The effects upon coronary flow were measured and it is at first sight surprising that both adrenaline and noradrenaline reduced the coronary flow in seven out of eight hearts. However, it is by no means certain that in the adult human subject these drugs are dilator upon this system (12), and further, it is well known that in such perfusions of various organs it is always easier to obtain vasoconstriction than vasodilation. Acetylcholine was also constrictor to the coronary vessels in the four hearts into which it was injected.

To study whether there were any changes in sensitivity to adrenaline during development from late foetus to young offspring, and similarly whether a constrictor coronary response altered to dilator, preliminary experiments were made upon a few cats and guinea-pigs (12). In two pregnant cats the cardiac response of the mothers and six foetuses to equal concentrations of adrenaline was similar, rate and amplitude of heart beat being increased to the same extent and the coronary vessels dilated. In the case of a pregnant guinea-pig adrenaline caused less foetal cardiac acceleration but was equally effective upon amplitude of beat, and was constrictor to the coronaries of both mother and foetuses.

Ouabain exerted the expected effect in strengthening the force of beat in human foetal hearts and it also enhanced the action of acetylcholine in slowing the heart (2, 12). Acetylcholine by itself failed to start three isolated human foetal auricles when they were allowed to beat until they stopped spontaneously, but adrenaline started two of them (12). It is not felt that these few results are necessarily incompatible with those of the larger series of Bülbring and Burn, who started fourteen out of twenty-two exhausted adult rabbit auricles with acetylcholine alone (41).

C. Perfused umbilical vessels

The foetal vessels of the placenta and the umbilical vessels have been investigated frequently because of the physiological problem of how their efficient closure is naturally effected at birth. They are also readily obtained from human material. The results of purely qualitative experiments on their reactions to drugs have been reviewed by Barclay, Franklin and Prichard (14) and by Rogers (256). Drugs have been given by direct application to the placenta or by perfusion through the umbilical arteries, as well as by addition to a bath containing isolated segments of vessel. With such techniques barium chloride, adrenaline, posterior pituitary extract, ergotoxine and ergotamine can produce the expected response of vasoconstriction. Histamine is also vasoconstrictor. After ergotoxine, adrenaline is vasodilator or without action, and after cocaine it is potentiated, although the tissue is free from nerves. The effects of acetylcholine are variable or negligible, and are inhibited by atropine, but they are only sometimes potentiated by eserine.

Rogers (256) made most searching experiments upon perfused full-term human umbilical arteries with apparatus by which he recorded for the first time not only the flow through the artery but also the volume of the cord. He confirmed the results of earlier workers in regard to oxygen tension and in regard to drugs, and made the interesting new discovery that changes in cord volume were not always accompanied by changes in flow. Thus he found that adrenaline always decreased volume and flow and that acetylcholine acted similarly. The immediate effect of ergotoxine was the same as that of adrenaline or of acetylcholine but the flow recovered more quickly than the volume. Adrenaline after ergotoxine increased flow and volume. The cords were ten times more sensitive to histamine than to adrenaline and acetylcholine; in the lowest effective concentration histamine gave large reductions in volume either with no reduction in

flow or occasionally with an increase. Amyl nitrite was the only drug used which consistently caused an increase in flow, even up to five times, yet with little rise in cord volume. However, there was also an increase in the usual slow leakage of fluid from the cord into the plethysmograph, yet no increase in the slow rate of oedema formation in the cord. Leakage round the cannulae was eliminated as the cause, and it was concluded that the nitrite increased an unusual and unexplained arterial permeability.

Rogers concluded that the main resistance to flow through the arteries was probably due to very short areas of constriction with relatively long and dilated segments in between. Dilation of such constricted areas would give large increases in flow with little change in volume, while further constriction of such areas would similarly decrease flow. Changes in tone of the segments between could cause large volume changes without necessarily causing changes in flow. He supported these conclusions with anatomical evidence, suggesting that the sites of the main resistance to flow may be the folds of Hoboken (256, 297) of which a possible functional significance has not been previously demonstrated. It has been suggested that these folds, thoroughly examined by Spivack (297), may be the result of a special physiological reactivity which produces anatomical artifacts at birth (14).

In all such perfusions of umbilical vessels *in vitro* the rates of flow achieved have been very low compared with those which must obtain *in vivo*, and concentration upon the reactions of preparations of cord vessels only has obscured the far greater importance of the small foetal placental vessels as the main site of vascular resistance in the foetal placental circulation. A recent report (10) on the flow through human placentae perfused via arterial cannulae, and with the venous effluent kept at placental level, showed a sensitivity to the vasoconstrictor effect of 5-hydroxytryptamine (serotonin) about ten times as great as to that of adrenaline. The results with 5-hydroxytryptamine and various antagonists were held to be comparable with those obtained on perfused lung vessels by Ginzel and Kottegoda (103) and to emphasize the comparison made earlier by von Euler (84) concerning the similarity in reaction of lung and umbilical vessels.

Barclay, Franklin and Prichard (14), from a study of the literature on the pharmacological reactions of the extra-abdominal portions of the umbilical vessels, concluded that their relative insensitivity to adrenaline and acetylcholine *in vitro* supported the anatomical evidence, notably that of Spivack (298), for complete lack of innervation. This raises the old question of whether the sensitivity of organs to the agents of humoral transmission is in fact increased by innervation. It might seem that comparing the sensitivity of such permanently nerve-free vessels with typically innervated ones, for instance those of the human fingers (230), would be a clear way of settling the question, and such a comparison showed the innervated finger vessels to be much more sensitive. However, marked changes in receptivity can occur during development without innervation being responsible, for Ueda (317) found that the vessels of the human placenta reacted to barium chloride by constriction at the fourth month

of gestation but would not react to adrenaline until the sixth month. Further, the umbilical vessels are very specialised structures and therefore any such comparison of sensitivities should be between that of their nerve-free extra-abdominal portions and that of their intra-abdominal roots. These roots are not only innervated but in their distal portion, from bladder to umbilicus, seem equally specialised since they also contract completely at birth. Such a comparison does not appear to have been made.

V. ANTICOAGULANTS

Thrombosis in the pregnant woman has raised the question of the safety of therapy with anticoagulants as regards the foetus.

Heparin. It is doubtful whether observations have been made concerning the transplacental passage of heparin. Walton (323, 324) has criticised a report that large injections of heparin into pregnant rats, rabbits, and guinea-pigs caused abortions and produced deposits of metachromatic material in reticulo-endothelial tissues (9), as he was unable to reproduce these effects, which may have been due to impure heparin. It would not seem likely that heparin can cross the placenta freely, being of comparatively large molecular size, having a high electronegative charge and crossing membranes with difficulty (159, 240). Information concerning the human placenta and passage of heparin seems to be lacking although heparin has been used in conjunction with dicoumarol in thrombosis complicating pregnancy.

Dicoumarol and its substitutes. Far more seems to be known about the transplacental passage of dicoumarol and its substitutes, and Gordon and Dean (114) have given a good critical summary of the situation. In the original investigations thirty years ago into the association between the consumption of spoiled sweet clover hay and haemorrhagic disease in cattle, Schofield (270b) reported that the active agent, then not known to be dicoumarol, could produce transplacental effects. From pregnant cows fed on the sweet clover hay he mentions one calf which developed typical signs and died in a few hours, and an aborted foetus with well marked haemorrhagic lesions. It is notable that the mothers of these remained unaffected. More recently it has been shown that pregnant bitches fed with dicoumarol are more resistant to its effect than are their foetuses (250), and that seriously affected newborn pups from mothers receiving dicoumarol can be protected by vitamin K. The susceptibility of the foetus has also been shown in rabbits (174). In both these species it was possible to prolong the maternal prothrombin time to a degree which allowed the mothers to survive but which killed the foetuses or resulted in offspring with prothrombin times so prolonged that they died from haemorrhages within a few days of birth. The investigators therefore suggested that dicoumarol therapy was contraindicated in human pregnancy, and its dangers have probably not been overestimated. Although there are now several reported series of cases where dicoumarol (4, 195, 349) or ethyl biscoumacetate (348) has been used in pregnancy without foetal damage, there are also reports of foetal or neonatal deaths with multiple haemorrhages (114, 264, 304). It is not easy to compare the degree to which

prothrombin time was affected in the mothers of unharmed and of morbid offspring owing to the different ways of expressing prothrombin time which were used, but apparently careful control of the maternal prothrombin time is no guarantee of safety for the foetus (114, 264).

If the foetus manufactures all its own prothrombin and other factors affected by dicoumarol, then so far the evidence shows that dicoumarol and ethyl biscoumacetate must cross the placenta, but if the foetus receives much of the relevant clotting factors from the mother, then the anticoagulants may not be producing effects directly on the foetus. In one series of cases (4) dicoumarol was given only during labour, and since it takes thirty hours for its effect to become manifest, prothrombin times of the newborn infants followed for some days could have yielded good evidence concerning transplacental passage of the drug. Unfortunately no such estimates were made.

Now that there are available safer anticoagulants, such as ethyl biscoumacetate with its shorter duration of action, the danger to the newborn of treated mothers may be lessened, but it would seem wise to give doses of vitamin K even larger than those often given routinely for normal newborn babies. More information of a quantitative nature must be sought concerning anticoagulant dosage, prothrombin times of mother and foetus, and the incidence of foetal damage, both from further animal experiments and from clinical observation. The evidence so far from all species examined is that foetal harm can result, and although this is not invariable it does seem to be unpredictable. In short, it appears best to avoid the dicoumarol class of anticoagulants in pregnancy except where maternal life would be endangered by their denial.

VI. ALIMENTARY CANAL

As opposed to observations concerned with the more strictly physiological aspects of the development of activity in the foetal gut (282, 340) very little seems to have been recorded in the nature of pharmacological experiments by the direct application of drugs.

Preparations of the full length of the oesophagus from human foetuses of 20 to 26 weeks of gestation responded in Krebs' solution at 37°C to acetylcholine, pilocarpine, or eserine with immediate and well-sustained contractions, and atropine exerted an inhibitory effect when tried against the acetylcholine (153). Histamine and barium chloride were also stimulant and oxytocin was without effect. Adrenaline inhibited the large spontaneous contractions that were present in preparations either of the whole thickness of the oesophagus or of its muscularis mucosae, but it gave a general relaxation only of the whole preparation. In one instance it caused a contraction and this was relieved by ergotoxine.

Very little can be deduced from these results apart from the fact that the appropriate receptor and effector mechanisms were developed at the stages of gestation studied.

With segments of intestine isolated from mature guinea-pig foetuses (216), and perfused in Krebs' solution at an unspecified temperature, it was found that both adrenaline and noradrenaline caused contraction of the terminal ileum

whereas the duodenum usually responded with a brief relaxation followed by contraction, although either pure contraction or relaxation occurred in some duodenal specimens. Intermediate sections relaxed or gave no response. Atropine potentiated the stimulant action of adrenaline and abolished its depressant effect. Noradrenaline produced responses like those for adrenaline only weaker, and each of these two amines could reduce the effect of the other.

Since under the same conditions adult guinea-pig duodenum responds to adrenaline by relaxation, and the terminal ileum with contraction, it can be concluded only that in the foetal guinea-pig at term the receptor mechanism of the gut is still developing. It seems a likely suggestion (216) that differentiation between sphincter muscle and duodenum is incomplete in the guinea-pig foetus.

Brief mention has been made (216) that the gut of the foetal rat and rabbit showed only inhibitory responses to adrenaline, as in the adults of those species, and this is surprising in view of the contrast between the apparent immaturity of the newborn rats and rabbits and the maturity of the newborn guinea-pig.

Results from the perfusion of intestinal segments from four human foetuses from eleven to sixteen weeks old with Locke's solution at 37°C contribute a little to knowledge of developing sensitivities since adrenaline was without effect on the youngest foetus, whereas acetylcholine was effective even at one-tenth of the maximum adrenaline concentration tested, and atropine antagonised acetylcholine (201).

Incidental to the main investigations concerning the general toxicity of quinine for the foetus, experiments were mentioned upon the action of this drug upon human foetal gut in order to find out whether this could have any bearing on the reported high incidence of the production of meconium during labour induced by quinine (265). In a single experiment upon isolated gut, revived in Tyrode's solution at 38°C after removal from a stillbirth at least fourteen hours before, quinine was reported to be relaxant only. This suggested that relaxation of the sphincter ani might account for the meconium, but it is unlikely that this experiment has much significance.

VII. CHEMOTHERAPY AND ANTIBIOTICS

Quinine. The earliest observations on the transplacental passage of quinine were summarised and extended by Dilling and his colleagues (13, 265) as well as by more recent workers (44, 251, 339). It is thus established that quinine crosses the placenta in the human, cat, dog and rabbit, and can be concentrated in the urine of the newborn.

A very few recorded cases of foetal death attributable to no obvious cause, but associated with the maternal ingestion of quinine, seem to have sufficed to give this drug a sinister obstetrical reputation. Thus Torland (316) records idiosyncrasy of a mother to quinine, with death of her foetus, once in a series of about seventy cases who were given the drug. Gellhorn (101) attributes one foetal death to quinine but in reviewing the literature prior to 1927 states that nearly all previous observers regarded quinine as harmless for the foetus. King (170) usefully discusses the recorded work on the alleged oxytocic property of

quinine and suggests that three more foetal deaths be added to those suspected as being due to quinine. He criticises Torland for giving no record as to when the foetal heart was last heard prior to quinine being given, but omits the same information in two of his own cases. From these accounts no assessment of the frequency of suspected damage by quinine is possible, for only Torland mentions an approximate total of treated patients.

In contrast are the experiences of Marchetti, Kuder and Fitch (196) who gave quinine daily for the last three weeks of pregnancy to 500 cases and found no deleterious effects upon the foetuses compared with those from 500 cases where no quinine was given. Mitchell (207), Buddee (39), and Ganner (96), on 400, 100, and 50 cases respectively, but without recorded controls, reported similarly.

The dosage schedules used might explain the differences, for in those series in which foetal death was reported nearly 2 g of quinine were usually given over 3 hours on a single day, but in those which were uneventful only 300 to 400 mg were given daily although this was continued for three or four weeks. However, the most careful and extensive experiments of Dilling and his colleagues (73, 265) did not entirely confirm the danger of the higher dosage. They found some evidence for foetal cumulation of the alkaloid and reported that in a series of 765 births eight stillbirths might have been due to quinine, but they could find no correlation of foetal death with size of dose or time of its administration. They concluded that although quinine might cause intra-uterine death the risk of stillbirth from its use was no greater than that from unknown causes (265). A possible sign that more foetuses were adversely affected by quinine was that meconium was present in the amniotic fluid about six times more often when the drug was used than when it was withheld (265). It is not clear whether this was due to a direct action on the foetal intestine rather than being the result of foetal distress, for the reaction of the isolated intestine to quinine was tried only in one instance, and that in a stillborn infant fourteen hours after death. In this case quinine only diminished the tone and the authors suggested that it might be able to relax the anal sphincter of the foetus, but the direct action of quinine upon foetal intestine does not appear to have received further attention. In the case of surviving infants observed for their first ten days of life there was no difference in the rate of gain of weight of those from 200 quinine-treated and 201 untreated mothers, thus suggesting that prenatal exposure to quinine has no deleterious result in the neonatal period.

Apart from the lethal effects of quinine it has also been held to be a cause of congenital defect, especially by Taylor, who maintained in a series of articles (306, 307, 308) that it was a frequent cause of congenital deafness. However, his original evidence was poor and he mainly repeated it, instead of strengthening it by numerical additions, in his continued publications. Winckel (339) has criticised Taylor's evidence severely and could collect from the literature only seventeen cases of congenital defects of ear or eye following maternal ingestion of quinine. The defects were not more frequent or extensive when quinine dosage had been excessive than when it had been moderate, nor was the incidence of deaf-mutes higher in malarious areas with high quinine consumption than in

areas with very low consumption, and all these observations were made before the congenital effects of maternal rubella were known. Thus quinine was hardly the proven cause of damage.

Little experimental work on animals appears to have been done on the problem of quinine and the foetus. Covell (56), using three pregnant guinea-pigs, found mitochondrial changes in the stria vascularis of the cochlea and the changes were more marked in the foetuses than in the adults. West (333), whose results are not easy to follow, concluded from work with three pregnant rabbits that quinine could cause degenerative changes in the nervous elements of the cochlea. Mosher (215) is equally obscure but found haemorrhages in the scala tympani of foetal guinea-pigs after the mothers were given quinine. Burton and Kelsey (44) have found some correlation in rabbits between the stages of pregnancy at which most maternal quinine reaches the foetus and the varying power of the maternal liver for destroying quinine. They could find no cumulation of quinine in the foetal rabbit, but Oldham and Kelsey (229) have found that the foetal rabbit liver has very little quinine oxidase activity.

Thus, the danger of foetal damage by quinine seems to be much less than has sometimes been stated in the textbooks. The work of Dilling and his colleagues (73, 265) is particularly revealing and the evidence of damage to experimental animals is tenuous. It is reasonable to suppose that quinidine could behave like quinine upon the foetus and it would be particularly interesting to know the toxicity of quinine and quinidine upon the foetal as compared with the adult heart. It is now accepted that even large doses of quinine, as may be needed in malaria therapy, are at least of far less danger to the foetus than is the disease itself (119). No reports have been found of foetal damage by the modern antimalarial drugs.

Sulphonamides. The use of these compounds in pregnancy has been reviewed by von Friesen (93). It is possibly not generally realised that there are now nearly twenty-five years of experience with the use of sulphonamides in pregnancy, for Lacomme (179) was using prophylactic sulphonamido-crysoïdin as early as 1935, and in 10,000 cases (180) with an equal number of controls she did not find any deleterious effects on the foetus from small doses of this drug. Kayser (165) has since shown that sulphonamido-crysoïdin itself does not cross to the human foetus but that its sulphanilamide (*p*-aminobenzenesulphonamide) constituent does. Most observations have been made on the transplacental passage of sulphanilamide itself, apparently first by Lee, Anderson and Chen in rabbits (186) where it was noted that the foetus appeared to acetylate less of the drug than did the adult. Barker (16), Speert (293) and Adair, Hasseltine and Hac (3) estimated its transmission to the human foetus, Barker noting that even where the drug had caused severe maternal cyanosis from methaemoglobinaemia, this did not occur in the foetus. Since then free transplacental passage has been shown for sulphapyridine [2-(*p*-aminobenzenesulphonamido)-pyridine] (6, 165), sulphacetamide [N-*p*-aminobenzenesulphonylacetamide] (165), sulphathiazole [2 - (*p* - aminobenzenesulphonamido) - thiazole] (295), sulphadiazine [2 - (*p* - aminobenzenesulphonamido) - pyrimidine] (295), sulpha-

somidine [4 - (*p* - aminobenzenesulphonamido) - 2:6 dimethylpyrimidine] (141), sulphamethizole [2 - (*p* - aminobenzenesulphonamido) - 5 - methyl 1:3:4-thiadiazole] (93), sulphamerazine [2-(*p*-aminobenzenesulphonamido)-4-methylpyrimidine] (93), and sulphamethoxypyridazine (3-sulphanilamido-6-methoxypyridazine) (292, 354). In general all these reach the foetus very rapidly and attain blood concentrations 10 to 20% below the maternal, sometimes within fifteen minutes. Equilibrium between the two concentrations is usually established in about three hours, the foetus ridding itself of the drug the more slowly. The level of drug in the foetal blood may thus for a while equal or exceed the maternal value, but at this stage the absolute values are not necessarily very high. Sulphadiazine gives the highest concentrations in foetal blood. In the amniotic fluid, usually in about six hours from the time of maternal drug injection, the sulphonamides, especially sulphacetamide, may be so concentrated as to exceed their level in the maternal bloodstream. However, at this stage the absolute concentration of sulphacetamide may not be great; sulphathiazole and sulphadiazine seem to attain the highest levels for amniotic fluid. It is reasonable to suppose that high levels in the *liquor amnii* are mainly dependent on concentration in the foetal urine, but von Friesen (93) has shown that this is not necessarily true, for he found high values for the fluid of three out of five foetuses whose mothers had received sulphonamide only after foetal death.

In animal experiments the sulphonamides have been shown to damage the foetus when administered to the mothers in very large dosage and for a long period compared with the total length of gestation. Speert (294) found that sulphanilamide added to the diet of rats throughout pregnancy caused a high death rate both in the intra-uterine and in the neonatal period, with a high proportion of offspring with stunted growth. Adair, Hasseltine and Hac (3) produced less convincing evidence of foetal and neonatal death in rabbits, for their control death rates were high. Inhibition of calcification in foetal rats, and to less extent in foetal mice, has been reported when the pregnant animals were given sulphanilamide or sulphapyridine in huge doses for the last week of gestation (26). Föllmer and Bockenheimer (90) found retardation of the growth of foetal rats and an increased number of foetal deaths with high dosage of Protocid (sulphamerazine with sulphanilamido-ethyl-thiodiazole) or Supronal [sulphamerazine with sulphatolamide (Marbadal, the *p*-aminobenzenesulphonylthiourea salt of *p*-sulphamoylbenzylamine)]. Administration of B vitamins antagonised the effect of the first mixture only, while *p*-aminobenzoic acid increased the toxicity of both. These last results to some extent agree with others (22) who have shown that sulphadiazine kills the mouse embryo and early foetus without being antagonised by folic acid. In this work, however, most results were obtained on embryos of a few days, rather than foetuses, and the effect of the sulphadiazine was possibly by a different mechanism, for it was antagonised by a progesterone-oestrone mixture or by gonadotrophic hormones. Von Friesen (93) lists the recorded cases of human foetal damage after sulphonamide therapy, but they are few in number and difficult to assess since controls are not quoted, they have no obvious common features, and are all also associated with the

maternal infections for which the sulphonamides were being used. Perhaps the most suggestive are one of the two cases quoted by Ginzler and Chesner (104) and the case of Heckel (138). In the first case a newborn child became jaundiced on its fourth day of life and died on the eighth day, post-mortem revealing liver necrosis and focal necroses in the adrenals and spleen. The other case recovered after severe jaundice and anaemia commencing on the fourth day of life. In both instances the mothers had received sulphanilamide, and reactions of this type are known to have occurred rarely in adults.

One obvious deficiency in the available information is the degree of transmission of the sulphonamides to the foetus at different stages of pregnancy, as nearly all observations have been made at full-term. Speert (295) was able to make one observation on a foetus aborted at the fifth month, and he found maternal sulphapyridine had reached the foetus freely. The potential toxicity of the sulphonamides for the human foetus is also not really known, for gross overdose for long periods, which would be the equivalent of the conditions in the animal experiments, is not likely to occur, but probably the foetus is no more likely to show toxic effects from their therapeutic use than is the adult. It seems important to investigate the possibility of foetal damage by sulphonamides which are excreted very slowly, such as sulphamethoxypyridazine, for it has been found that excretion of this drug by the foetus and the newborn is much slower even than by the adult (292), and it is possible that such long-acting sulphonamides might be hazardous to the foetus in mothers nutritionally deficient in folic acid.

Antibiotics. Antibiotics in general appear to reach the foetus in therapeutic concentrations when administered to the mother, as shown by the levels of penicillin (21, 51, 117, 147, 181, 345, 346), chloramphenicol (51, 272, 301), the tetracyclines (51, 145, 146, 246, 276), erythromycin (140, 168), vancomycin (184), and cycloserine (214, 220) found in the foetal blood or amniotic fluid. No foetal damage appears to have been reported from these drugs. The majority of workers have dealt with only one antibiotic under their particular experimental conditions, but in a study primarily concerned to discover whether therapeutic concentrations were likely to be achieved for the prevention of intra-uterine pneumonia, Charles (51) measured the transplacental passage of penicillin, chloramphenicol, streptomycin, chlortetracycline, and oxytetracycline all in similar series of patients. He confirmed that adequate concentrations of all these reached the foetus even after single doses to the mother, but in his experiments only penicillin was detected in quantity in the amniotic fluid, and this he suggested might either be due to the extremely rapid excretion of penicillin by the foetal kidney or due to some selective absorption of penicillin by amniotic lipid with subsequent release into the fluid. He concluded that antibiotic treatment of the mother should give good protection against intra-uterine pneumonia and quoted some clinical prophylactic successes, with cases where the membranes had ruptured prematurely, to support his evidence from foetal blood levels of antibiotics.

Penicillin is now established as the most powerful protection for the foetus

against syphilis acquired from the mother. Its transplacental passage was first recorded by Greene and Hobby (117) and since then it has been amply confirmed (21, 51, 147, 181, 345, 346). The concentrations attained in the foetal bloodstream differ widely from one report to another, and the same is true of the times elapsing before peak values are reached, so that it is likely that individual variation is considerable, although the varying initial doses and subsequent times of assay make it difficult to form a clear picture. In most instances peak levels were reached in foetal blood from thirty to sixty minutes after maternal injection, and these peak levels were well below maternal blood levels but Woltz and Zintel (346) found that by continuous infusion of the mother foetal and maternal blood levels could become equal. In the case of long-acting penicillins, such as procaine penicillin and penethamate hydriodide, single injections to the mothers resulted in therapeutic levels in foetal blood for twenty-four hours, with the foetal levels exceeding maternal after the first six hours, presumably due to the maternal excretion being the more rapid. But in the same series of 186 cases no penicillin was detected in the foetuses of six of them, a fact upon which the authors did not comment (21) but which possibly is a further example of the great individual variation already mentioned.

Since streptomycin and dihydrostreptomycin are known to damage the eighth cranial nerve in the adult they have been carefully examined in the foetus with this danger in view. Sakula (266) has summarised the work and pointed out that the foetal blood usually attains bacteriostatic levels when the mother's dosage is adequate, and that it is not definitely established that damage to the eighth cranial nerve may occur in the foetus. Such damage to the foetal eighth nerve seems to have been reported only once (187), when the baby of a woman treated with streptomycin in pregnancy was found to be deaf at two and a half months of age but had normal vestibular function and balance. In view of the numerous cases reported where there was no damage detected, even this case might have been due to other causes. Watson and Stow (325) who were the first to report on the use of streptomycin in human pregnancy, described two cases where the vestibular function of the mother was damaged but the babies were normal. In other animals the picture may be different, for in guinea-pigs (253) it was shown that streptomycin and dihydrostreptomycin crossed to the foetus and could cause death, though surviving foetuses appeared normal. Placental damage was also recorded in these experiments. A further possible danger was seen (208) when it was found that the growth of young rats was retarded by streptomycin but this does not appear to apply to the foetus, at least in the human, although information seems to be lacking for other species.

The synthetic chemotherapeutic agent isoniazid has been shown to reach the foetus easily and foetal blood levels can exceed maternal (37). No foetal damage has been reported and in general the antituberculous drugs at present in use are thought to be devoid of danger to the foetus.

Organic arsenicals and bismuth. The observations of Eastman (77) upon the arsenic content of the human placenta, after treatment of the mother with arsphenamine, revealed that there was a concentration mainly on the foetal side

of the placenta, and that this concentration was detectable for up to fifteen days after the last dose had been given. His interest had been aroused by the birth of non-syphilitic babies from syphilitic mothers who had received doses of arsphenamine too small to affect the disease in the adult, and by reports that another arsenical, neoarsphenamine, accumulated in the placentae of rabbits and cats. His findings are in agreement with his idea that organic arsenicals probably protect the foetus by being slowly liberated from their area of concentration in the placenta.

Further support for Eastman's conclusions was obtained by Snyder and Speert (291) who also give a good summary of previous experimental work. Experiments with rabbits showed that in this species neoarsphenamine also concentrated in the placenta and that the rate of transmission of arsenic to the foetus increased as pregnancy progressed. They suggested that the failure of earlier workers to find arsenic in the foetus, when arsenicals had been given to the mother, was probably due to less sensitive methods of analysis and to observations being too early in pregnancy. They confirmed that there was no interference with pregnancy and no harm to the foetus even though their dosage of neoarsphenamine was greater on a body weight basis than that for human therapy.

Thompson, Steadman and Pommerenke (314) have surveyed the literature concerning bismuth preparations and the foetus. Apparently the relatively insoluble compounds concentrate to some extent in the placenta, and less drug is detectable in the foetus, whereas the soluble compounds rapidly cross the placenta to become easily detectable in the foetal blood. In their own series of human cases bismuth reached its peak concentration in foetal and maternal blood from one to two hours after the mothers had taken a soluble sodium bismuthate (Sobisminol) by mouth. As with the arsenicals no specific foetal damage seems to be caused.

The advent of penicillin as the antisyphilitic drug of choice has temporarily decreased the interest and importance of the placental transmission of preparations of arsenic and bismuth.

VIII. ANTITHYROID DRUGS

Radioactive iodine. In its capacity of a tracer element radioactive iodine in small doses, usually as sodium iodide, has been used to determine the earliest time at which iodine uptake and thyroid function commence in the foetuses of various species (18, 49, 111, 112, 126). Such studies have in general confirmed previous work in showing that the earliest iodine uptake just precedes colloid formation. From this time onwards the quantitative aspects of uptake by the foetal thyroid, especially in relation to uptake by the maternal thyroid, are important in assessing radioactive iodine in its other capacity of therapeutic agent or radiation hazard. Thus with pregnant mice it was found (296) that doses of radioactive iodide large enough to damage the maternal thyroid inflicted severe damage upon the foetal thyroids if administered after the sixteenth day of pregnancy. Offspring of mothers so treated showed complete thyroid regeneration by

the fifth month of life, but this could be followed at the ninth to twelfth month by involution and colloid goitre. Chromophobe adenoma was also seen in the pituitary, presumably the result of excessive demands on this gland through the thyroid-pituitary axis. The authors commented that the doses used were, on a weight basis, about ten times those needed for the therapy of human thyrotoxicosis but within the range of those necessary for the treatment of thyroid carcinoma. Such results endorse the plea for caution in the use of radioiodine expressed by Corner (49), several years earlier, from observations upon uptake by the human foetus. More recently there has been a report of marked uptake of radioiodine by a foetus obtained by abdominal hysterectomy from a woman treated for thyroid carcinoma (107). One possible way round the difficulty of foetal concentration of radioiodine has been suggested by Rugh and Booth (263) who demonstrated in mice that the administration of thyrotropic hormone to the mother diverted radioiodine from the foetuses by increasing the avidity of the maternal gland. However, any precaution which aims only at protecting the foetal thyroid from an acutely damaging dose of radiation is not enough in view of the possibility of smaller doses being able to bring about changes which in later years might result in thyroid carcinoma. This concept, of the transplacental initiation of neoplasia, may hold true for other agents and is mentioned again in the section on carcinogens.

Thiouracils and other inhibitors. There are very numerous reports of human foetal thyroid enlargement resulting from the use of these drugs in pregnancy. The bulk of such reports has been well summarised and commented upon (82, 128, 144, 176, 267). Similar observations have been made in various other species (92, 164, 176, 238, 271, 328). As regards the mechanism of the foetal thyroid effect it seems generally assumed that the antithyroid drugs cross the placental barrier and directly affect the thyroid-pituitary axis in the same way that they do in the adult. Experimental work confirms this, as the evidence seems to be clear that thyrotropic hormone does not reach the foetus from the mother (139, 225, 315, 338), and that normally thyroxine and triiodothyronine can only do so in amounts too small to be of any significance (27, 120, 152, 192, 219, 267), although Peterson and Young (238) found that in pregnant guinea-pigs the simultaneous administration of propylthiouracil and thyroxine produced smaller foetal goitres than did the administration of propylthiouracil alone. They found also that thyroxine when given by itself to pregnant guinea-pigs caused the foetuses to have smaller thyroids than usual. More recently it has been shown that large doses of thyroxine administered synchronously with propylthiouracil to pregnant rats prevented the development of both maternal and foetal goitre. Astwood also suggested that the simultaneous administration of thyroxine and an antithyroid to the thyrotoxic pregnant patient could prevent the development of foetal goitre, but this does not appear to have been confirmed (11).

Myant (219), from results with labelled thyroxine and triiodothyronine on human foetuses of eleven to twenty-five weeks, has raised the question of the time in foetal life at which thyroxine-binding protein (TBP) is developed in the blood, and pointed out that this substance could have a dominant role in govern-

ing the transplacental flow of thyroxine. Triiodothyronine, for which maternal TBP has much less affinity, was found to reach the human foetus more rapidly than was thyroxine, but for both transplacental passage was very slight.

Direct evidence for the transplacental passage of a thyroid inhibitory substance was obtained by Freisleben and Kjerulf-Jensen (92) who treated pregnant rats with propylthiouracil and then fed their newborn offspring to other adult rats which in their turn developed goitres. Indirect evidence of transmission was also found in guinea-pigs in which thyrotropic hormone did not cross the placenta yet propylthiouracil did cause foetal goitres (238), and mice in which thiouracil and methimazole could divert iodine from foetuses to mother (263). However, the quantitative aspects of transplacental passage of the antithyroid drugs seems largely unexplored, and a review of as many human cases as possible in the literature does not reveal any obvious reason why some foetuses developed goitres and others did not when there was maternal treatment with antithyroid drugs. Hepner (144) attributed such foetal goitre development to lack of maternal medication with iodine, but the cases quoted in his own review do not support this idea and he appears to have slightly misinterpreted McGinty and Sharp (199) on this point. Others (198) also disagree with the idea that iodine therapy can influence thiouracil goitre.

To obtain some quantitative estimate of the frequency of congenital thiouracil goitre in clinical obstetrics is difficult since presumably there is a tendency to publish when it does occur and the multitude of more fortunate but less spectacular normal cases goes unpublished. The cases quoted in the reports and reviews already mentioned (1, 24, 82, 94, 144, 167, 176, 241, 252, 274) reveal that of about a hundred instances of the use of thiouracils or methimazole in pregnancy the details were inadequate or medical therapy was the prelude to surgery in about thirty, and there were abnormalities attributable to the therapy in the offspring of about twelve of the remainder. The abnormalities ranged from transient congenital goitre to goitre lasting several months and associated with delayed development. In one case the baby became thyrotoxic from the second until the fifth months of its life. Thiouracil and its propyl derivative appear to be about equally likely to cause foetal abnormalities but methylthiouracil *seems* to cause trouble in a much higher percentage of cases, but of course such estimates are deceptive in the absence of any evidence about the frequency of use and misuse by overdosage of the drugs concerned.

The problem of what factors influence the production of foetal thiouracil goitre in the human does not appear to be solved, but suspicion falls most heavily upon the size and duration of maternal dosage after the onset of foetal thyroid function, for in other species it appears to be easy to induce foetal goitre by deliberate maternal overdose with the antithyroid drug. It is disappointing and surprising that more effort was not directed at quantitative determinations of placental transfer of antithyroid drugs, and it seems probable that their lapse into therapeutic disfavour has removed the stimulus for such work. Assuming from the available evidence that the foetal thyroid-pituitary axis does normally function independently of the maternal it seems logical that any drug which de-

presses the synthesis of thyroid hormone and which crosses the placenta could produce foetal goitre. Thus it is not surprising that foetal goitre has been reported in guinea-pigs when potassium perchlorate was given in pregnancy (247), and this recalls the briefly recorded observation of Macdonald (193) as long ago as 1903, well before the modern era of antithyroid drugs, of an association between human foetal goitre and the administration of potassium chlorate to the mothers.

Quite apart from locally dramatic effects of antithyroid drugs on the thyroid itself there arises the question of retardation of general foetal development by lack of thyroid hormone. Myant (219) briefly discussed this and suggested that belief in the necessity of thyroid hormone for normal foetal growth probably stems from knowledge of amphibian development and may have no existence in fact, and he quoted some clinical evidence to show that gross lack of thyroid hormone does not affect the early stages at least. If such is the correct view then the delayed ossification that has been reported in the human (94, 211) may be a direct effect of the antithyroid drug concerned rather than a result of thyroid deficiency, and this is made more likely by the observation of delayed appearance of ossification centres in foetal rats during maternal treatment with thiouracil before the onset of foetal thyroid function (329). A more sinister site for toxic effects of antithyroid drugs is the leucopoietic tissue, but apparently infants of treated mothers have not yet been found with agranulocytosis, although it is not evident from the literature how often or how thoroughly the blood picture was examined.

IX. CARCINOGENIC DRUGS

Benzanthracene, dibenzanthracene, benzpyrene, methylcholanthrene. The direct application of established carcinogens has caused tumours in transplanted embryonic tissue. Greene (118) reported briefly that methylcholanthrene applied to transplants of embryo skin, lung, stomach, intestine and cartilage of several species could produce cancers in thirty to thirty-five days, whereas adult tissues so treated required ninety to a hundred days. His results agree in the main with those of Rous and Smith (260, 284, 286) and of Klein (173) who worked with embryo mouse tissue, although they did not always find that embryo tissue reacted more quickly than did adult tissue to the methylcholanthrene. These authors also noted that induced tumours were always of adult tissue type, and that from embryo stomach they could never induce adenocarcinomata but only squamous carcinomata as a result of metaplasia. Metaplasia of bronchial and of alveolar epithelia was also pronounced (285).

Such experiments can give no information about the earliest age at which foetal tissue can undergo neoplastic change, for the transplants may mature in their host and the applied carcinogen may then be acting on virtually non-foetal tissue. The problem has not been solved by injecting these drugs into the pregnant animal so as to achieve a presumably brief exposure of the foetus. When they have been given to the pregnant rat or mouse only failures to produce tumours in the offspring have been reported, except when injection has been directly into the amniotic fluid (183). However, experimental work on this aspect

of carcinogenesis does not seem to have been extensive with the commonly used drugs, and the transplacental passage of the drugs themselves has not been reported in any of the experiments.

Hain (125), in a few rats out of a large series primarily for the investigation of transplacental hormone passage, found that benzpyrene, alone or with oestrone on the twentieth or twenty-first days of pregnancy, when given to the pregnant rats had no obvious effect on the foetuses, but the exposure, if any occurred, was very short. Wolf and Bryan (342) gave benzpyrene, benzanthracene, and dibenzanthracene to pregnant rats both from the beginning of gestation and in a few cases in the last week of pregnancy. The early injections caused uterine bleeding with foetal death and resorption, and the later ones had no effect upon the foetuses, which were born and reared successfully. These authors pointed out that the haemorrhagic effects are probably not related to the carcinogenic property of the substances. One strange effect was that treated animals resorbed litters in subsequent pregnancies, and this was attributed to the possible persistence of drug at the injection site. Strong and Hollander (303) using methylcholanthrene on mice, obtained similar results as regards haemorrhages and lack of carcinogenesis, and they suggested that the haemorrhages might be due to lack of vitamin A, since methylcholanthrene depleted rat and mouse livers of this vitamin, and similar haemorrhages were seen in pregnancies in vitamin A deficient animals.

Law (183) succeeded in producing tumours in foetal mice by injecting dibenzanthracene into the amniotic fluid. Again abortion, resorption or stillbirth were common, but of the offspring which survived and were killed after five months most had lung carcinoma and a few primary carcinoma of the liver as well. Figures for controls were not given.

Urethane. The knowledge that urethane is a carcinogen was the result of an incidental observation of Nettleship and Henshaw (223) who were working on mice which had developed lung tumours. Smith and Rous (287) subsequently chose urethane as probably possessing the qualities they required for a soluble and short-acting carcinogen which would be likely to cross the placental barrier. Their experiments showed that its administration to pregnant mice greatly increased the incidence of lung tumour in the offspring, and that such tumours appeared even as early as the third day of postnatal life. Since many control foetuses were found to have in their lungs clusters of a few cells with staining properties which differed from those of the general mass of lung tissue, these authors suggested that the urethane might act merely by increasing the rate of development of cells which are potentially neoplastic. It is possible that the urethane may have been directly responsible for the effects, but no formal proof of its transplacental passage was given by these or by subsequent authors. Independently of Rous and Smith, Larsen (182) also found that urethane would cause tumours in mouse offspring after its administration to the mother, and he presented evidence for the effect's being greater the nearer to delivery time the urethane was administered. Rous and Smith did not confirm this, but Klein (171, 172) confirmed Larser's results and pointed out that their mice were made

temporarily ill by the urethane and that foetuses were underweight and slow in developing. He therefore suggested that tumour growth was not as regular in their series as it should have been.

In addition to these observations upon growing foetal tissue Cowen (57), in a few experiments only, found that tumours could not be induced in transplanted mouse embryo tissue when urethane was given to the host, but his evidence is inconclusive as the implants failed to continue to grow. Sinclair (280) found urethane effects upon the mouse foetus other than carcinogenesis by injections of the drug into mice at various stages of pregnancy. On the seventh day it prevented closure of the foetal brain but not of the cord, and on the eighth day it could cause the degeneration of early motor cells throughout the central nervous system. Höglund (151) using very small doses in mice, found no interference with foetal form but noted a reduced size of litters.

In none of the quoted studies is there any mention of the possible biochemical mode of action, but Sinclair (280) does point out the various biochemical actions of urethane. Rogers (256a) has now shown it to be likely that urethane exerts its carcinogenic effect by interfering with nucleic acid synthesis possibly at the level of ureidosuccinic acid. The physiological mechanism by which urethane selects the lungs for its carcinogenic action is discussed. If maternal respiratory depression by the drug is severe enough to cause foetal anoxia this might initiate foetal intra-uterine respiratory movements, so that urethane might reach the foetal lung via the amniotic fluid as well as via the foetal blood. However, it is also pointed out that in the adult mouse urethane causes lung tumours by whatever route it is given (171), and there is also evidence that it can cause liver tumours as well in rats (158). The literature already contains at least one case of hepatoma in a human adult after prolonged medication with urethane for a chronic leukaemia (85). As regards time of tumour production in the experimental animals, namely a few days at least after birth and never before birth, this may be largely a matter of the minimum time in which neoplastic change can occur and then manifest itself, although the operation of postnatal factors is possibly necessary too. Wells (332) in his very careful review of primary congenital malignant neoplasms in the human, even suggests that since usually a large part of the life cycle is normally needed for the development of neoplasms, then those manifest at or soon after birth may depend on a different mechanism.

Whatever the precise mechanism involved, the fact of transplacental carcinogenesis, possibly with a long latent period in the offspring, is now before us, and an investigation of many drugs used in therapy or for pleasure might be rewarding in this light.

X. DRUGS SELECTIVELY TOXIC TO THE FOETUS

In this section the intention is to bring together such drugs as have been found to be more toxic to the foetus than to the pregnant animal, but viral or bacterial poisons are not included.

As might be expected from the nature of foetal tissue, immensely active in metabolism and cell division, drugs with the greatest power to kill or damage

the foetus prove to be nucleotoxic. Robson and his co-workers (69) have grouped them into spindle poisons, chromosomal poisons, and antimetabolites, but there are others with even less well-understood modes of action. Some drugs which readily come to mind as having fallen under suspicion from time to time as regards the foetus include quinine, salicylates and the antithyroid drugs, but review has not proved the suspicion well founded for the first two, and the antithyroid drugs seem to harm the foetus only when given to the pregnant animal in doses large enough to affect the adult thyroid grossly also. Similarly, carcinogenic agents apparently affect the foetus no more than the adult. Accordingly all these substances are dealt with elsewhere in this review. On the other hand it is surprising that a dye such as trypan blue, or substances such as nicotine or cortisone should be selectively harmful to the foetus.

1. Spindle poisons, chromosomal poisons, and antimetabolites. In a recent review Jackson (157a) has covered the subject as far as various cytotoxic agents in these categories are concerned, including folic acid and purine antagonists, cytotoxic alkylating agents, antimitotics, and certain antibiotics. Only a few points are therefore selected here for further comment.

Although many of these drugs have some proven anti-neoplastic activity it has been pointed out by Robson and his colleagues (69) that only for the spindle poisons, such as podophyllotoxin (69, 70), colchicine (69, 166, 318) and trimethyl colchicinic acid methyl ether (69) could there be demonstrated a relation between therapeutic ratio as anti-neoplastic drugs and therapeutic ratio (so-called) as foeticidal drugs. This tempts speculation concerning especial similarities in the processes of spindle formation in foetal and in neoplastic tissue.

The nitrogen mustards such as mustine [mechlorethamine, Mustargen, di(2-chloroethyl) methylamine] first reported upon by Haskin (136) and confirmed by others (149, 217, 218), as damaging the rat foetus, illustrate how difficult it may be to prove that a foetal effect is due to a direct action upon the foetus. Thus it was found in pregnant rats that a subcutaneous injection on a certain day could produce anterior limb lesions in the foetus whereas injection a day later produced posterior limb lesions. Since the active life of mustine in the animal is very short, and in the rat development of the anterior limb is one day ahead of that of the posterior limb, this may mean that mustine acts directly on the foetus. A further point in favour of this evidence suggesting a direct action seems to be that the pregnant animals themselves were debilitated and without appetite for about six days after injection; thus, had the limb abnormalities been due to maternal illness it would be reasonable to expect deformities of both anterior and posterior limbs as a result of the earlier injection.

Ethionine, known to cause a diffuse pancreatitis in rats has been tried on pregnant rats in an ingenious attempt to obtain animals for the study of congenital cystic fibrosis of the pancreas (185). This attempt failed, with the production of stillbirths, resorptions, various foetal deformities, or newborn which were undersized, but pancreatic lesions were not produced, except in the mothers, and possibly the foetal effects were secondary. Presumably the foetal pancreas was not using the amino acid methionine, normally needed by it in adult life, at the

foetal stage studied, so neither would the homologue ethionine be likely to become metabolically involved.

Aminopterin (N-4-aminopteroyl-L(+)-glutamic acid), an antagonist of folic acid, stands out amongst the antimetabolites as an agent of specially selective toxicity to the foetus since it was courageously introduced for trial in clinical obstetrics, after preliminary animal experiments, by Thiersch (310). He sought to achieve the termination of pregnancy in human cases, for essential therapeutic reasons, without resorting to surgery, and reported on twelve cases in which aminopterin was used. In nine cases, where pregnancy had lasted less than three months the embryos or foetuses were killed and expelled from five to thirty days after treatment, but in three of these the placentae remained and had to be removed surgically. The three foetuses of three months gestational age or more were all deformed, the two older ones having to be removed surgically because the aminopterin had failed to cause death. One had a cleft palate and hare lip and the other was hydrocephalic. The remaining one did die *in utero* and was spontaneously expelled, but it had a large meningoencephalocoele. In all cases where it was possible to discern the cellular pathology, it was clear that there was very little blood formation in liver, spleen, or bone marrow. Medically the results were thus disappointing but the information fell into irresponsible hands, apparently aided by a magazine article, and cases of aminopterin poisoning, with congenital deformity, have resulted from attempts at criminal abortion (33, 204).

2. Miscellaneous. i. Ionising radiations. These agents have not been generally regarded as pharmacological, but newer knowledge concerning their chemical mode of action, together with the growth of the study of mutagenic and nucleotoxic drugs, is revealing their similarities. A recent review clarifies their relation to pharmacology and illustrates how the study of antiradiation drugs forges a further link (239). Rat foetuses were protected from the effects of irradiation of their mothers when these were given cysteamine prior to irradiation (194) and the same was true of mouse foetuses with cysteamine and cysteine (262). The protective effect measured was the gross one of prevention of death either *in utero* or within thirty days of birth, and no information was obtained concerning protection against radiation effects. In another series reported in the review (239) rats from irradiated mothers which had received cysteamine did not have a normal life span and the males were sterile. More recent work (344) with mice has shown that the incidence of many deformities produced *in utero* by x-rays may be markedly reduced by cysteamine, but one apparently very little influenced by this drug in these experiments was cleft-palate. This, the authors point out, might be explained on the grounds that the mice were irradiated on the twelfth day of gestation, at which time the palate is at its most sensitive to irradiation.

If protection afforded to the irradiated foetus by antiradiation drugs parallels that for the adult, then protection against all the long-term effects is not to be expected (239).

ii. Cortisone and hydrocortisone. There is abundant evidence that cortisone and hydrocortisone can interrupt the normal course of pregnancy or result in neonatal death when they are administered during gestation to various species,

including the rat, mouse, rabbit and Rhesus monkey (55, 64, 68, 105, 254, 269, 273). Abortion, resorption or stillbirth may occur according to the species and the time in pregnancy at which these drugs are given, but the doses have to be large per kg of body weight compared with those generally in use for human therapy. The primary site of action for these effects has not been proved. Changes in the ground substance of the placenta have been suggested (273) although apparently not verified, but other interesting observations suggest that a derangement of the carbohydrate metabolism of the foetus may be the cause, since in rabbits abortion associated with a marked drop in foetal placental glycogen once a certain dosage of cortisone was exceeded has been reported (150).

Most reports concerned with foetal death due to cortisone or hydrocortisone do not contain detailed information concerning the occurrence of congenital defects in the foetuses, but such observations as have been made have led to much work on the type of deformity which can be produced and its possible relationship to congenital defects reported in human pregnancy where cortisone has been used (74, 133, 155, 161, 163, 206, 343). It appears that in the early days after the introduction of cortisone, when it was tried for practically any type of disease, its use in major or minor illnesses during pregnancy was widespread and there was a tendency to throw suspicion upon it as a cause of various foetal defects (17, 121, 331). The particular congenital defect which has received most attention experimentally is that of cleft palate, starting with work showing that in a strain of mice in which there was already a low spontaneous incidence of the defect, the incidence could be greatly increased by maternal dosage with cortisone or hydrocortisone (91, 161). It was also shown, using cortisone on rats, that the incidence of congenital defects in the head due to hypervitaminosis-A could be greatly increased (206, 343).

The careful observations of Ingalls and Curley (155) on mice with hydrocortisone have not only emphasised the specific nature of the type of congenital cleft palate induced but have made the occurrence of this lesion in the human foetus seem more likely to be occasionally causally related to large dosage with corticoids during pregnancy. They pointed out that the clefts induced by hydrocortisone are always of the posterior palate only and never include hare lip. This has also been commented upon for the rat (343). They showed also that in another strain of mouse, where there was a higher spontaneous incidence of cleft palate, this was associated with hare lip, whereas cleft palate induced in this strain by corticoids remained confined to the midline. The necessary timing of dosage to produce the defect was determined, and it was found essential to give the hydrocortisone at least a day before fusion of the palate began, or three days before with smaller doses. On the other hand anoxia produced the deformity only when induced on the day on which fusion began. They compared this type of cleft with that reported in two human cases in which cortisone had been given during pregnancy (74, 133), and in one of these the authors themselves pointed out that the cortisone treatment was begun a week before fusion of the palate was probably due to begin and the dose was high enough to be within the dangerous range calculated on a body weight basis.

As in the case for the mode of action of cortisone in producing abortion, still-

birth, or resorption, there appears to be little known about the manner in which it can produce congenital defects; Ingalls and Curley (155) speculated that the effect may be due to some vascular failure and therefore mediated through anoxia. At least it does seem reasonably likely that the effect is a direct one upon the foetus, for cortisone and corticotrophin given to the pregnant animal can both cause a low foetal adrenal weight (64, 55, 269) and hydrocortisone given to the pregnant woman has been detected and estimated in umbilical cord blood (205).

iii. Trypan blue. Gillman, Gilbert and Gillman (102) first demonstrated that the subcutaneous injection of this dye into the rat could cause foetal death, or deformities in the survivors. Where injections were made during pregnancy it was found that only those on the eighth and ninth days produced deformities such as hydrocephalus and eye, ear or tail defects in the offspring. This early stage is only the threshold of foetal life, since the embryo is at the critical stage of changing from a yolk sac placenta to an ectoplacenta, and the authors suggested that the known absorption of the dye by plasma albumin might have been interfering with foetal nutrition. In their experiments the dosage was high enough for the pregnant rats themselves to suffer changes such as anaemia, fatty liver cells, and grossly enlarged adrenals, and it was also suggested that the foetal effects might be due to these in some way. The dye apparently does not cross to the foetus, or not in its coloured form, except to the early yolk sac placenta, where Waddington and Carter (321), using mice, commented upon its concentration and also suggested it might in some unknown manner be affecting the main channel of nutrition. They confirmed the effects seen by the earlier workers, but found in their survivors that the only defects were mild tail kinks or haematomata. They suggested that their strain of mice might be less sensitive as they failed to observe the pseudencephaly and spina bifida seen by Gillman, Gilbert and Gillman (102) and by Hamburgh (127). Waddington and Carter attributed the deformities mainly to a possible action of trypan blue in upsetting body fluid composition, which could account for the observed early sub-epidermal blebs, neural tube dilatation, and the haematomata which occur later.

It is interesting to note their observation that trypan blue at an embryonic stage caused a higher intra-uterine death rate amongst female embryos than amongst male embryos. In fact they pointed out that this is probably one of the earliest sex differences demonstrable, and that it is present before macroscopic sex differentiation takes place. Presumably such leads concerning the ability of drugs to kill embryos of one sex might well be followed up for the possible benefit to various forms of livestock breeding. Other dyes possessing a diazotised orthotolidine grouping, and able to cause foetal deformities have been mentioned by Wilson (341).

iv. Lead. Before 1925, the predominant view seems to have been that lead abortion, stillbirth, or weakly offspring after lead poisoning were due to a combination of a germ plasm effect in the mother or father (25, 330), to placental haemorrhages, and to an increased uterine irritability.

In 1925, Bell, Hendry and Annet (25) emphasized that although writers on

lead poisoning from the earliest times had mentioned sterility and abortion yet there had been more speculation than experiment in support of the idea that placental haemorrhages or a stimulant effect on the uterus were responsible. Their own carefully controlled histological experiments, with pregnant rabbits receiving intravenous colloidal lead, revealed a coagulation necrosis of the chorionic epithelium with doses only about half as large as those which poisoned the mother. Copper, thallium and thorium were much less specific. Datnow (62), using a variety of lead compounds, confirmed these results and found also placental haemorrhages after large doses. Haemorrhages and abortion also occurred after colloidal cadmium and selenium in doses which were liable to kill the mother. The demonstration of the mechanism by which lead can kill the foetus may have diverted attention from the claims that offspring born alive of lead-poisoned mothers are often underweight and develop more slowly than normal. In fact although no specific damage within the foetus has been shown, it is likely that the observed poor development is not merely secondary to maternal effects, because the transmission of lead to the foetus has been demonstrated for various species (46, 61, 129, 212). Hansman and Perry (129) in a review of the distribution of lead in man, mentioned that distribution in the foetus is much the same as in the adult. They called attention also to the occurrence of foetal anaemia in lead poisoning and they suggested that when the foetal skeleton begins to be laid down the deposition of lead could protect the foetus in the same way that it may in the adult.

From the evidence reviewed it seems probable that whereas too high a concentration of maternal lead early in pregnancy may cause foetal death by trophoblastic necrosis or by haemorrhages in the early placenta, surviving foetuses, or those not poisoned until later, may then show a less specific picture of underdevelopment, the precise mechanism of which is unknown.

v. Cigarette smoking; nicotine. Evidence must be extremely sound for it to point the finger of suspicion firmly at ingrained national habits and finance, and therefore the report of Simpson and Linda (279) on over seven thousand human births is only preliminary. They found that the prematurity rate was twice as high when the mothers were smokers, and from a review of the literature they concluded that cigarette smoke, probably by virtue of its nicotine content, was damaging to the foetus, although it was also likely that smoking might have deleterious foetal actions by its effect upon maternal diet. On the other hand the work of Nishimura and Nakai (226), having its origin in the known effects of nicotine as a mitotic poison, has demonstrated that in mice nicotine certainly has a teratogenic action, affecting mainly the skeleton and especially the joints. As with the other substances reviewed, the placentae were nearly always unharmed.

vi. Apiol, rue, savin, artemisia. Published experimental work on the human with these substances, rumoured as abortifacients, is likely to be rare. Investigation upon non-pregnant and pregnant rabbits and guinea-pigs (234, 235) has revealed them to be powerful poisons with virtually no selective action upon the foetus, except possibly in the case of apiol. Hepatitis and congestive nephritis were the main types of damage, with apiol and artemisia affecting both kidney

and liver equally but the others mainly the kidney. In pregnant animals all were unreliable abortifacients and when abortion did occur it often only just preceded death of the mother. Maternal death could also occur without abortion. With apiol there was some evidence for a selective haemorrhagic effect upon the placental site, in addition to its hepato-nephritic action, but the rest did not cause placental haemorrhages any more often than they caused haemorrhage at other sites.

Discussion. The study of drugs selectively toxic to the foetus seems to stem mainly from practical reasons concerned with man's own survival. The most obvious reason is to learn which drugs are to be avoided in pregnancy, or how they, or ionising radiations, may be safely employed at such a time if they are of vital therapeutic necessity in connection with maternal illness. The results with nucleotoxic drugs have confirmed the logical suspicion that they could selectively poison the foetus, and the observation that the therapeutic ratio for the spindle poisons against neoplasms parallels their anti-foetal activity (69) is a further lead. The position of cortisone in human obstetrics is not so clear, but the results of animal experiment have at least sounded a reasonable warning that congenital defects are likely to result if its use is too vigorous early in pregnancy. Its therapeutic successors are even less known quantities to be reckoned with in this sphere. However, results with the trimethyl ether of colchicinic acid (69) upon mice and rabbits illustrate species difference as a complicating factor in assessing foeticidal drugs.

Therapeutic termination of pregnancy, when absolutely necessary, would at first seem to be best achieved by drugs which select primarily the foetus, but the various reports on animals in which placentae have often survived after foetal death, reinforced by the results of Thiersch (310) with aminopterin on the human, now show this not to be necessarily true. In fact it might be better for this purpose to try to find drugs which attack primarily the placenta, when such measures have to be used at such an advanced stage of pregnancy.

The work of Waddington and Carter (321) with trypan blue raises the interesting point of selectively killing foetuses of one sex, and this lead, if confirmed, surely might be profitably followed up in the world of animal breeding.

XI. CONCLUSIONS AND SUMMARY

If this review is in fact based on a fair cross section of the literature it is clear that the main stimulus for research into the action of drugs upon the foetus has come from clinical obstetrics. This is right and proper from the point of view of sheer medical expediency, but it is time that the conclusions so revealed were backed by an appropriate depth of academic investigation into fundamentals. The small volume of recorded work upon adrenaline and acetylcholine in relation to the foetus is but one example which testifies to the past lack of academic concern in this sphere.

In spite of improvement in techniques, an important reason for the comparative lack of precise information on the acute effects of drugs on the intact foetus of the smaller and more commonly used laboratory animals is still, of course, the

difficulty of access with the maintenance of satisfactory physiological conditions. Even when drugs have been given to the pregnant animal without apparent disturbance, and the foetuses subsequently observed, analytical proof of passage to the foetus has usually been lacking; quantitative information is even more rare, and so far disappointingly little use has been made of radioactive drugs.

Although there is a large volume of work concerning drug effects upon the foetus it has been relatively piecemeal. Thus the whole field is open for systematic, fundamental, and quantitative investigation. Two points need special note: 1) in all future work special care must be directed to assessing the degree of foetal oxygenation and to controlling it as necessary in experimental procedures; and 2) much more attention should be given to drugs of potential hazard to the foetus, especially the analgesics, anticoagulants, antithyroid drugs, nucleotoxic drugs, antimetabolites, and the adrenal cortical hormones. Kalter and Warkany have given a timely emphasis to this latter aspect of the action of drugs on the foetus, in a recent review (162), by pointing out that at the present time many more children die from congenital malformations than from certain contagious diseases which were dangerous before the modern era of chemotherapy.

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