Response of the Fetus and Newborn to Drugs

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THE INFLUENCE of human developmental maturity on the course of disease is nowhere more dramatically evident than in the abnormal responses of the fetus and young infant to agents used in the treatment of disease. Infants in the first month of life may have alarming toxic reactions to doses of drugs which are quite safe in older infants and adults even when appropriate corrections for body size are made [1]: and, in the fetus, grotesque congenital anomalies may result from agents whose effect on the mother are mild indeed. Many of the syndromes resulting from drugs in these populations are newly described; others may currently go unrecognized and further applications of drug therapy in this age group will probably result in new types of drug toxicity. The existence of these forms of drug toxicity and the need for their prevention indicate the importance of a systematic developmental pharmacology.

Most drugs with a molecular weight less than 1,000 pass easily through the so-called placental barrier. The response to a drug given early in fetal life may be death; during organogenesis, particularly in the first trimester of pregnancy, there may be malformation. Late in pregnancy or during labor, drugs may cause perinatal toxic reactions and morbidity. These responses and those of the infant in the approximately 30 day neonatal period constitute the subject of this review. A number of reviews have previously been published on the subject.[1-6]

Fetal Pharmacology—Teratogenesis

The pregnant woman is an unusually commonly chosen candidate for drug administration. Peckham and King [7] recently found that 92 per cent of women had at least one drug prescribed by their physicians during pregnancy and 3.9 per cent were given ten or more. It can be assumed that all of these drugs reach the fetus and it is now clear that some of these produce congenital malformations. The etiology of approximately 90 per cent of the human congenital malformations remains unknown,[8] but further research on chemical agents, viral infections,[9] and ionizing radiation [10] may be expected to yield additional information on this problem. On the other hand, data from the Columbia Fetal Life Study,[13] on 3,200 pregnancies during 1953–1957, indicate that "drugs in general" are not an important factor in congenital malformations. This may provide a perspective, but human teratology is still in the descriptive phase. It is therefore important to examine current knowledge of drug-induced human teratogenesis.

Thalidomide. Quantitatively, the most important experiment in human teratology was the outbreak of thalidomide embryopathy which has had far-reaching influence on research in the field as well as on the practical aspects of food and drug legislation. This experience lasted from 1959–1962 with highest frequency in West Germany, but significant numbers in Great Britain, Australia and Canada. According to estimations of the German Ministry of Health, there were approximately 6,000 infants involved in the German Federal Republic of whom about 3,000 are living. The first cases of phocomelia in Germany were demonstrated in September of 1960 by Kosenow and Pfeiffer.[12] As the number of cases increased, these began to assume the pattern of an epidemic of malformations. The clinical syndrome was characterized by Wiedemann,[13] who described the findings in 27 children. Malformations of the extremities were the outstanding feature with phocomelia or seal-like

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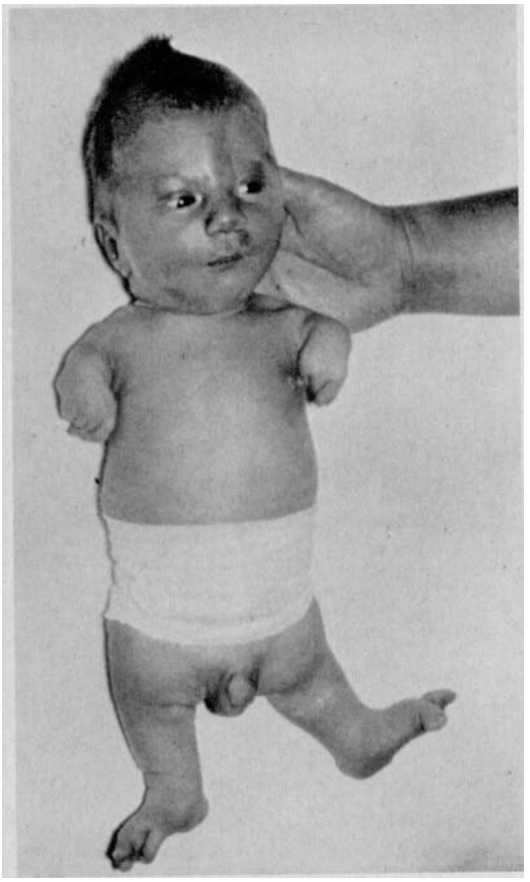


FIG. 1. Thalidomide-induced phocomelia. (Courtesy of Dr. Helen Taussig.)

extremities the hallmark (fig. 1). A few malformations of the intestinal tract, the ears, and the heart were seen. Also characteristic was a midline hemangioma of the face. The infants were entirely normal mentally. The association between the ingestion of the drug during pregnancy and phocomelia was established by Lenz.[14] Similar observations were made by McBride[15] in Australia. The relationship between thalidomide and malformations that ensued was confirmed through study of the histories of early pregnancy in the mothers of affected infants. This was an impressive example of medical detective work and a striking example of the value of retrospective studies. Lenz[14] established consumption of thalidomide in more than 80 per cent of the women in his first group of 129 cases of phocomelia.

The chemical structure of thalidomide is indicated in figure 2. It is a relatively simple compound of phthalic and glutamic acid, which cyclize to form the ring structure, α(N-phthalimido)-glutarimide. The compound was first synthesized in 1954, but abandoned because the expected pharmacological effects could not be discerned in animals. Nevertheless, in 1957, the drug was tried as an antiepileptic in man. Although worthless in epilepsy, in the course of these studies it became obvious that thalidomide was extraordinarily safe and effective in inducing sleep.[16] Because of the seeming lack of toxicity and pleasant effect without hangover, almost overnight it became West Germany's most popular sleeping medication. The only adverse effect noted in adults was the occurrence of a few cases of peripheral neuritis. This was the property that delayed its official approval in the United States.

The studies of Lenz[14] indicated that the period in which the embryo is sensitive to thalidomide is quite brief. Malformations were seen in the offspring of women who took the drug between the thirty-seventh and the fiftieth day following the first day of the last menstrual period, or, when data could be obtained, between the twenty-seventh and fortieth day after conception. Statistical analysis of the data indicated that it was extremely unlikely that such an association could have occurred by chance ($\chi^2 = 207$). Further evidence for the validity of the association has been the decline in incidence of phocomelia almost to negligible figures within 8 months after the attendant publicity and withdrawal of the drug from the market. The story of the thalidomide-induced outbreak of embryopathy has been extensively described.[17, 18]

The effect of thalidomide on organogenesis is among the most highly specific biological effects of a chemical agent. Doses of the drug which produce only pleasant sleep in the mother result in distinct and severe malformation in the embryo. Many experiments have since been carried out on pregnant animals. Large numbers of rats, mice, chick embryos, and other species have been studied with negative results. Somers[19] has been able to produce lesions similar to those observed in man by the administration of much larger doses to

an inbred strain of New Zealand white rabbits. It is becoming apparent that there are marked genetically determined differences in the responses of animals or man to the effects of drugs; the teratogenic effect of thalidomide is an example of this newly recognized field of pharmacogenetics. The problem of reproducing the human disease in a suitable experimental model dramatically highlights the difficulty of developing adequate methods for the screening of drugs prior to release for use in man. The requirement that all drugs be screened in pregnant animals represents an important legislative advance. It is, however, quite clear that mandatory screening programs would not have predicted or prevented the thalidomide tragedy.

These observations indicate the need for research in the field of developmental pharmacology. Methods of screening need elucidation and refinement. For instance, it might be of interest to explore the use of isotopically labeled compounds in screening programs in order to assess transmission of drug to the fetus: if there is no transmission of the drug to the fetus the likelihood of teratogenesis would appear to be small.[20]

Another apparent example of the discrepancy between teratogenesis in the animal and in man is that of meclizine. This compound (1-[*p*-chloro-α-phenyl benzyl]-4-[*m*-methylbenzyl]piperazine) has been shown by King [21] to produce malformations in the rat fetus when administered to the mother. The doses employed have been large but not unreasonably so; the lesions have constituted a distinct syndrome with particular effect on the face and skeleton; and the defects could be produced in essentially 100 per cent of the animals exposed. This constitutes strong evidence for chemical teratogenesis. On the other hand, this drug is widely employed as an antiemetic. It is considered by many obstetricians to be the drug of choice in emesis gravidarum and has been given to thousands of pregnant women. The weight of this clinical experience indicates it to be without effect on the human fetus.[8] Therefore, comparative data on this compound in man and animals make a point just opposite to that of the thalidomide story. Close analysis of human experience is in order and is now proceeding; It would be

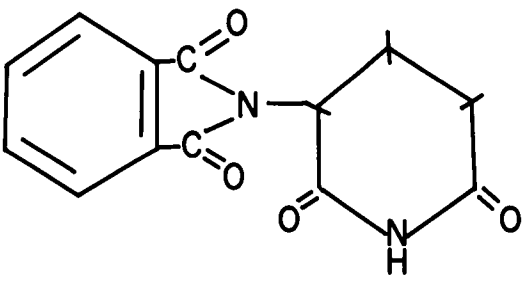


FIG. 2. Structure of thalidomide, α-(N-phthalimido) -glutarimide.

surprising if such a clearcut teratogenic agent in one species were to be without effect on at least some human subjects. Thalidomide does have an effect on some experimental animals, but this is not easily demonstrable. Meanwhile, the avoidance of all drugs in women in the latter portion of the menstral cycle and certainly in the first trimester of pregnancy would appear to a be a good general rule.

Chemotherapeutic Agents in the Treatment of Cancer. Experimental teratology [22] and cancer chemotherapy are closely related fields. Many of the agents developed in the search for effective drugs against cancer have teratogenic effects in laboratory animals. In fact, chick and other embryos are used in screening programs for new drugs in cancer research.

Experiments on pregnant rats and mice have demonstrated that aminopterin produces abortion or death and resorption of fetus.[23] As a result, this drug was considered as a therapeutic abortant and Thiersch [24] reported that, after giving aminopterin to 12 pregnant women, successful abortion occurred in 10. In 2 cases, however, abortion was not achieved and malformations such as cleft palate and harelip, hydrocephalus, and meningoencephalocele were found in the offspring. Two other instances of attempted abortion were reported [25, 26] in which multiple malformations were observed. It is of interest that the reported malformations produced by this folic acid antagonist have differed from one another in contrast to the uniform syndrome produced by thalidomide. Malformations of the eyes, cleft palate and early neonatal death [27] were seen in the baby of a leukemic mother treated with the alkylating agent busulphan (Myleran). This woman

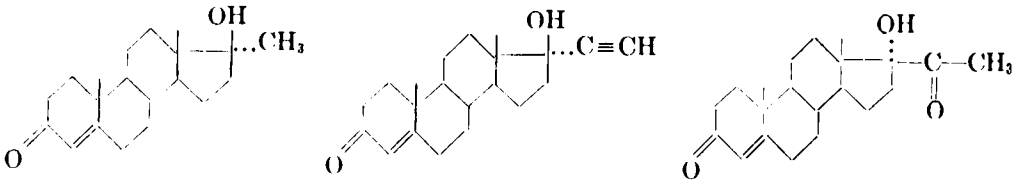
also received 6-mercaptopurine during the pregnancy, but had also received this drug during a previous gestation in which the infant was normal. With these exceptions, there is little documentation of human embryopathy following chemotherapeutic agents in the treatment of cancer. In a thorough review, Sokal and Lessmann [28] assessed the effects of cancer chemotherapy in 50 patients. Only the folic acid antagonists (aminopterin, amethopterin) could be shown to be definitive teratogenic agents when administered during the first trimester of pregnancy. These compounds are effective inhibitors of the de novo synthesis of nucleic acid purines via the inhibition of the enzyme dihydrofolic acid reductase. Thus, it appears that it may be easier to produce malformations in experimental animals with these agents than in man. Experimentally, of course, larger doses are generally employed.

Antidiabetic Compounds. Larrson and Sterky [29] reported a possible teratogenic influence of sulfonylurea therapy in the occurrence of multiple congenital anomalies in the infant of a mother treated with tolbutamide. Diabetics in general have a larger number of offspring with congenital anomalies, and it is difficult to distinguish the effects of disease from the treatment. Jackson and his colleagues [30] compared a group of diabetic mothers receiving sulfonylureas with a group who received insulin and dietary therapy only. The group treated with sulfonylurea had a higher fetal death rate, even with good diabetic control. In comparing the individual drugs, chlorpropamide was associated with the highest fetal mortality (63 per cent), whereas tolbutamide was associated with the same figure as insulin. Congenital malformations in rats have been produced by treatment of the pregnant female with the hypoglycemia-producing sulfonamides.[31] In man, a teratogenic effect for the sulfonylureas has not yet been established.

Adrenal Steroids. Cortisone administration in pregnant mice results in cleft palate without concomitant cleft lip, a distinct abnormality in the mouse as it is in man.[32] Susceptibility to this effect is genetically closely regulated and in some strains 100 per cent of offspring of treated mothers develop the lesion. Cleft palate has also been reported in the rabbit following cortisone administration [33] and in this species cortisone enhances the teratogenic effect of an excess of vitamin A.[34] Several case reports have appeared [35, 36] associating cortisone treatment in early human pregnancy with this palatal lesion in the infant. However, many women have been treated with adrenal steroids during pregnancy. Review of some 344 instances recorded in the literature [37, 38] revealed 4 infants with cleft palate. This seems to be a significant but low level of association.

Drug-Induced Masculinization of the Female Fetus. The production of female pseudohermaphroditism would be a result one would expect intuitively from the administration of testosterone during pregnancy. A large body of experimental data indicates that before sexual structures differentiate they are susceptible to the influence of exogenous endocrine substances. Nevertheless, methyltestosterone has been employed in the management of hyperemesis gravidarum. Cases have been reported [39] in which the degree of masculinization was so striking that it was not recognized for as long as 6 months that the infant was actually a female.

A more frequent problem has resulted from the use of synthetic agents administered for progestational activity. Wilkins [40] collected 100 cases of iatrogenic masculinization of the human fetus, most of which followed the use of oral progestins for habitual or threatened abortion. Clinically, the infants presented with a picture identical to that observed in the adrenogenital syndrome, in that they resembled cryptorchid males with normal female internal structures and female sex chromatin bodies in the buccal smear. The 17-ketosteroid excretion was, however, not increased. Treatment of the mothers with progestins was usually begun before the tenth week of gestation. The agents employed were 17-α-ethinyltestosterone and 17-α-ethinyl-19-nortestosterone, which are marketed under suggestively feminine names such as Pranone, Lutocylol, Progesterol and Norlutin. Examination of the chemical structures (fig. 3) indicates that in the natural product, progesterone, the hydroxyl at 17 is in the alpha position, while in the synthetic progestins the hydroxyl at 17 is in the beta position and the alkyl group is



17-α-methyltestosterone 17-α-ethinyltestosterone (anhydro-β-hydroxyprogesterone) 17-α-hydroxyprogesterone

FIG. 3. Comparison of the structure of a synthetic progestin with those of progesterone and testosterone.

alpha. These configurations indicate that these compounds are structural analogues of testosterone, the 17-α methyl-β hydroxy structure of which is shown. Androgenic activity would not be a surprising result. This has now been tested in experimental animals, these compounds do produce masculinization of the rabbit or rat fetus. It has been suggested that masculinization in the fetus may represent an abnormality in hormone metabolism in the women thus treated. These data suggest, however, that the compounds are simply androgenic. The possibility of a genetic error in steroid metabolism seems more likely in the instance of a small number of mothers in whom fetal masculinization followed the use of progesterone.[40] Instances have also been reported[41] in which this syndrome followed estrogenic therapy with diethylstilbesterol.

The efficacy of progestational and estrogenic steroids in the management of pregnancy and prevention of abortion is still uncertain. If their use is indicated, the natural product, progesterone, would appear to be the agent of choice. The synthetic progestins represent practices in the development of new drugs that existed in the past. Such drugs were synthesized and found to be active in animals. Testing for toxicity in adult animals and man indicated their safety. It is now evident that if there had been the requirement before release for clinical use that these drugs were to be tested in pregnant animals and the fetuses examined, this syndrome would have been recognized in the animal and the human fetus would have beeen spared the clinical experiment.

Thyroid Medications. The occurrence of goiter in the infant of a hyperthyroid mother who has been treated during pregnancy with propylthiouracil is a relatively common clinical experience. These babies are generally quite well and do not show clinical or chemical signs of thyroid malfunction. Spontaneous regression of the thyroid enlargement takes place over a period of months. This syndrome has also been observed with thiouracil and other antithyroid drugs.[42] Treatment is usually not indicated for these infants, but they should all be studied because an occasional case of hypothyroidism has been observed.[42] Congenital hypothyroidism has also been reported following treatment of the pregnant woman with ^{131}I.[43] In this instance, a dose of 14.5 mc. was given at the end of the first trimester to a thyrotoxic woman not known to be pregnant.

Neonatal goiter has been seen in infants whose mothers received iodides for the treatment of asthma during gestation.[44] These goiters have been among the largest reported and have resulted regularly in death by suffocation shortly after birth. In infants so affected, emergency tracheotomy is recommended in order to relieve the obstruction produced by the huge thyroid gland. On the other hand, prevention is preferable. Uncontested data supporting the fact that potassium iodide is of benefit in respiratory disease, particularly asthma, are not available. Its use during pregnancy can only be condemned.

Anticoagulants. Dicumarol and its derivatives have been reported to cause intrauterine hemorrhage and fetal death.[45, 46] The fetus may be particularly sensitive to these agents, for even small dosage with good maternal control of prothrombin time has been associated with severe hemorrhage in the fetus. In the

rare instance when an anticoagulant is really needed in pregnancy, it is probably safer to use heparin, a larger molecule thought not to cross the placenta readily.

Anesthetic Agents. The possibility that anesthetic agents might possess teratogenic activity is of considerable concern, not because of their use in labor but because women may be anesthetized and operated on earlier in pregnancy for unrelated conditions, particularly in the vulnerable period before pregnancy has been diagnosed. Studies in this field are being actively pursued, but it is premature to calculate the effects.

Nitrous oxide has been found to exert cytopathogenic effects on mouse heart myoblasts in tissue culture.[47] Growth disturbances, decreased hatch rate of chicks as well as occasional spastic paralysis in surviving chicks have been observed following exposure of developing eggs to atmospheres of 80 per cent N_2O in 20 per cent O_2.[48] A survey of the effects of anesthetic agents on the developing chick embryo has been undertaken by Smith and Moya[49] who observed an increased incidence of fetal anomalies and higher fetal death rates with exposure to clinical concentrations of the fluorinated volatile anesthetics, methoxyfluorane, fluroxene and tetrafluorobromomethane. In similar studies by Gaub, Smith and Moya[49] diethyl ether and trichlorethylene did not result in significant differences from the controls, in the production of fetal anomalies. These investigators have cautioned against application of these results to man because of marked differences in the biological systems, and experimental conditions from those of clinical practice. However, the data do suggest caution in employment of elective surgery in early pregnancy and indicate the need for further research in mammalian systems.

Paranatal Pharmacology

Agents administered to the mother during labor usually can be expected to be transmitted across the placenta and the infant may be born still under the influence of these drugs. Some of these agents such as tetracycline (which will be discussed later) produce effects that are not too different whether administered early in fetal life, close to term or to the infant. Similarly, the hemolysis induced by the water soluble vitamin K preparations is similar whether administered to the infant or to the mother at term. On the other hand, agents administered to the mother to ease the course of labor would almost never be administered directly to the neonate. Anesthetics, analgesics and tranquilizers largely constitute the area of paranatal pharmacology. Knowledge in this field is of a most general nature and experience and, therefore, will be considered only briefly.

Reserpine. Reserpine is a relatively mild tranquilizer; for this reason, it is not surprising that it has been employed to ease the course of labor. The adverse effects in the adult are not disturbing, stuffiness in the nose being a frequent complaint. A stuffy nose in the newborn may, on the other hand, produce severe respiratory embarrassment because of the relative inability of the infant to breathe through the mouth. Budnick and colleagues[50] reported a series of 12 infants with nasal stuffiness and discharge whose mothers had been given reserpine during labor. In all of the infants evidence of respiratory obstruction was seen in marked thoracic retraction. Three became cyanotic and 2 died. Among a group of 77 mothers who received the drug, symptoms were found in 16 per cent of the infants. There appears to be little reason not to interdict this agent in the management of labor.

Antihypertensive Agents. Hexamethonium has been shown to pass readily through the human placenta. Paralytic ileus has been reported in infants whose mothers received hexamethonium bromide for the treatment of toxemia.[51] The syndrome in the infant may be fatal. In surviving infants, symptoms may last as long as three weeks.

Hypnotics and Narcotics. It is common experience and well known to anesthesiologists that hypnotics and narcotics administered to the mother may adversely affect the fetus. Resultant depression of the respiratory center is often seen in the immature, as evidenced by apnea or signs of hypoxemia. It has been shown that barbiturates are transported in large amounts to the human fetus and accumulate preferentially in the fetal liver and in the brain near the fourth ventricle.[52] Concentrations in cord blood were found to be higher than those of maternal blood. There are data

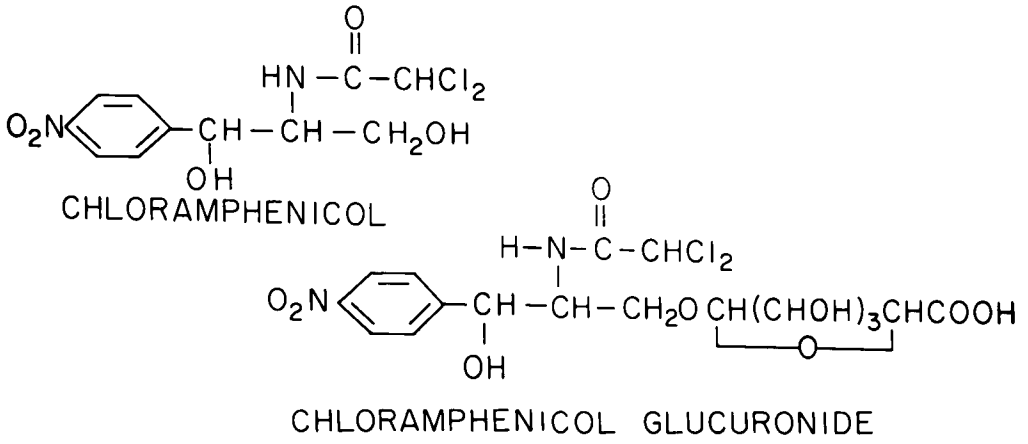


FIG. 4. Structure of chloramphenicol and the glucuronide.

to indicate an unusual respiratory depressant susceptibility of the newborn infant to morphine (*v.i.*). It has recently been demonstrated[53] that infants undergoing cyclopropane anesthesia are more likely to develop bradycardia and arrhythmias with scopolamine than with atropine. Nalorphine and levallorphan are effective in combating neonatal respiratory depression induced by maternal administration of morphine or related narcotics such as codeine, heroin, methadone, dihydromorphine, meperidine, racemorphan, metopon and alphaprodine. The narcotic antagonists are, at the same time, themselves respiratory depressants and should therefore not be used in babies depressed for other reasons. Clinical data also indicate that prolonged respiratory depression may follow the use of chlorpromazine for obstetrical analgesia.[54] It is, in general, surprising that respiration functions so well in the newborn after the usually administered maternal analgesia and anesthesia.

Narcotic addiction in the pregnant mother may lead to withdrawal symptoms in the infant after birth. Fatal reactions have been described. In a survey of the literature, Schneck[55] collected more than 50 cases of newborn infants born to addicted mothers. Most of these women were heroin addicts. Withdrawal symptoms in the infants consisted of tremors, vomiting, diarrhea, cyanosis, anorexia, inanition and increased secretions in the respiratory tract. The severity of symptoms depended to a large extent upon the time that the mother had received the last dose of narcotic. Despite judicious treatment with opiates and tranquilizers, a high mortality ensued.

Thiazide Diuretics. A relation between thrombocytopenia in the newborn and the antepartum administration of thiazide or chlorthiazide to the mother has recently been reported by Rodriguez and associates.[56] Seven cases of neonatal thrombocytopenia were observed with one fatality. The bone marrows examined appeared to be deficient in the production of platelets. It is not yet clear whether this was a direct chemical depressant effect in the marrow or the result of an antigen-antibody reaction.

Neonatal Pharmacology

At one time the special aspects of pediatric pharmacology were restricted to a consideration of the size of the patient as reflected in the calculation of drug dosage in terms of units of body weight or surface area. This problem will not be discussed in this review because it is not considered safe to extrapolate to the newborn dosage of drugs determined in older age groups. In order to predict neonatal responses, the reaction of newborn animals and humans *per se* must be studied.

Developmental Enzymology and Drug Toxicity

Neonatal Toxicity of Chloramphenicol. Toxic responses may result from incomplete metabo-

lism of drugs, as a consequence of the fact that the infant may lack certain enzymes which are synthesized later. In the absence of an enzyme involved in the metabolism of a drug, high blood levels may result from conventional therapeutic doses. One example is the demonstrated toxicity of chloramphenicol in the young infant.[57]

Chloramphenicol is detoxified by conjugation (fig. 4). The resulting glucuronide is more soluble than the free compound, and is secreted by the renal tubules, while free chloramphenicol is excreted by glomerular filtration. Anatomical or physiological renal immaturity could contribute to neonatal toxicity.[57] However, adults with anuria have been given large doses of chloramphenicol without development of toxic symptoms. In these individuals, there were high levels of chloramphenicol metabolites, but the levels of free chloramphenicol were low. It is therefore unlikely that renal mechanisms account for the untoward neonatal response to chloramphenicol and attention must be directed to the mechanisms by which the nontoxic glucuronide is formed.

The carbon source for glucuronidation is glucose. The following reactions are significant:

(1) G-1-P + UTP $\leftrightharpoons$ UDPG + PP

(2) UDPG + 2 $DPN^+ \leftrightharpoons$ UDP Glucuronic acid + 2 DPNH + $2H^+$

(3) UDP Glucuronic acid + ROH $\leftrightharpoons$ R-glucuronide + UDP

The R in the third reaction signifies compounds conjugated at a hydroxyl group, (chloramphenicol) or at an amino or carboxyl group. Compounds of biological importance which are conjugated with glucuronic acid include bilirubin, thyroxine and hydrocortisone. The development of these enzymes was studied by Brown and Zuelzer [58] in an investigation of the mechanisms underlying neonatal hyperbilirubinemia. It was found that glucuronyl transferase which catalyzes reaction 3 was virtually absent in fetal guinea pig or rat liver, and markedly reduced in that of the newborn. Increase in activity to adult levels took place within the first month of life. The activity of UDPG dehydrogenase (reaction 2) was also low in fetal and neonatal liver and increased gradually to adult levels over the first two weeks. Inefficient glucuronidation has also been documented for the human infant, but the data available do not indicate when the enzyme deficiency is overcome.

The observed deficiency is consistent with the production of higher levels of free chloramphenicol in the blood of the newborn than in the older child or adult, following the same dose. Very high blood levels have been documented in infants dying of chloramphenicol intoxication.[59] Infants in the first week of life develop considerably higher blood levels than do older children following the same dose of chloramphenicol,[57] and these levels are maintained for longer periods of time.

The clinical findings in infants with chloramphenicol intoxication have consisted of a characteristic syndrome of ashen gray cyanosis, hypothermia and flaccidity. These symptoms have been indicative of cardiovascular collapse, followed shortly by respiratory failure and cardiac arrest. Symptomatology of this sort might be expected to occur in any age group, if miscalculation or other events led to overdosage. However, in newborn or premature infants this picture has been observed with regularity with doses of 100 mg./kg. or more. It has been recommended that daily doses for full term and premature infants not exceed 50 and 25 mg./kg., respectively. A better way to insure safety would be to determine dosage by the estimation of the levels of the drug in blood.

Toxicity of Other Compounds Metabolized by Glucuronidation. The inefficiency of the newborn in carrying out conjugations with glucuronic acid is potentially a general mechanism by which toxic reactions could occur in this age group. Few examples have as yet been documented. Acetanilid, which is seldom employed in the newborn, thyroxine or hydrocortisone are likely possibilities, and progesterone has been found to be considerably more toxic in infant mice than in the adult. Morphine, which is excreted as a glucuronide conjugate, exhibits a greater toxicity in the infant than in the adult rat.

Acetylations. Acetylation is another mechanism for the inactivation of drugs. Sulfonamides are acetylated inefficiently by the newborn and premature infant; but this does not increase toxicity because acetylated sulfona-

mides are less soluble and therefore more likely to cause renal complications. However, the failure of newborns to acetylate sulfonamides efficiently suggests that other acetylations may not take place efficiently, leading to greater toxicity in the newborn. Isonicotinic acid hydrazide (isoniazid, INH) is excreted almost quantitatively as the acetyl derivative, and acetylation does appear to decrease the toxicity of this compound. The relative ability of the newborn to acetylate this compound is not known.

Microsomal Oxidative Systems. Drugs which are metabolized by enzymes in the hepatic microsomes are not metabolized by the livers of newborn rabbits.[60] These compounds include hexobarbital, aminopyrine, amphetamine, acetanilid, nitrobenzoic acid, phenacetin and chlorpromazine. Similarly, doses of hexobarbital that have little effect on the adult mouse cause prolonged sleeping time in the newborn. Caution is in order in the application to man, in that Vest [61] found that the human newborn readily metabolizes acetanilid to N-acetyl-*p*-aminophenol; subsequent, however, glucuronidation of this compound is inefficiently carried out.

Interrelations of Enzymes, Substrates and Cofactors

Toxicity of Vitamin K Analogues. Water soluble derivatives of menadione, Hykinone, and Synkayvite (fig. 5) have been widely employed for their activity as vitamin K analogues. A syndrome has recently been recognized in neonates receiving large doses of these compounds. Nearly all have been premature infants given at least 30 mg. of drug. Following the administration of the drug, Heinz bodies have been seen in the erythrocytes, over the next few days. As the Heinz bodies disappeared, progressive anemia was observed over the ensuing two weeks. Icterus was maximal at 1 to 2 weeks. The incidence of kernicterus in premature infants increased twofold when 30 mg. or more were administered, as opposed to 1 to 2 mg.[62] The concentrations of bilirubin in the serum have consistently been higher in infants receiving 30 mg., than in untreated controls. Hyperbilirubinemia and kernicterus can also be produced in the infant if large doses of water soluble vitamin K preparations are administered to the mother at term. Levels of bilirubin in those receiving 1 mg. did not differ from controls, nor did those of infants receiving vitamin K_1 (Mephyton). In fact, it appears that vitamin K_1 increases the ability of the neonatal liver to handle bilirubin.

The mechanism by which menadione produces hemolysis is not known, but it is probable that multiple factors are involved. There is evidence that such compounds are directly toxic to circulating erythrocytes, for Synkayvite induces Heinz body formation *in vitro*. Hemolysis and hemoglobinuria have been produced by these compounds in the rat, but only in the presence of vitamin E deficiency. In this respect, there is a considerable body of evidence indicating that levels of vitamin E are markedly lower in the newborn than in older children. There are similarities between the toxic effects of vitamin K analogues in the newborn and syndrome of the drug-sensitive erythrocyte. A variety of compounds, including acetylphenylhydrazine, primaquine and naphthalene, as well as menadione and its derivatives, are capable of producing hemolysis in both conditions. The drug sensitive erythrocyte represents a genetically determined defect in red cell metabolism in which erythrocytes possess a decreased concentration of reduced glutathione (GSH): there is also an altered GSH stability test, in that the GSH decreases sharply after incubation with acetylphenylhydrazine. The direct expression of the abnormal gene is seen in the decreased activity of the enzyme, glucose-6-phosphate dehydrogenase. The alteration in GSH metabolism appears to be a secondary defect, for the oxidation of glucose through pathways involving glucose-6-phosphate dehydrogenase results in the generation of reduced triphosphopyridine nucleotide (TPNH); TPNH is a cofactor for the enzyme glutathione reductase which catalyzes the generation of GSH from its oxidized form GSSG. The studies of Zinkham [63] have indicated that glucose-6-phosphate dehydrogenase activity is normal in the erythrocytes of the newborn and that the concentrations of GSH are normal. However, there is marked GSH instability. The addition of glucose *in vitro* prevented the abnormal GSH stability test of the newborn, but was, of course, without effect on the genetically deter-

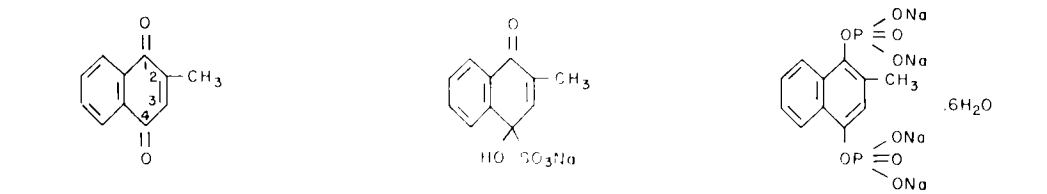


FIG. 5. Menadione and the water soluble derivatives with vitamin K activity.

mined reactor. The mechanism of hemolysis appears to be related both to the concentration of glucose and to that of tocopherol, but the relative contributions remain to be determined. Nevertheless, it is clear that adverse reactions to vitamin K analogues can be prevented simply by the routine use of vitamin K_1 or the use of doses in the range of 1 mg., which are more than adequate to prevent the hypoprothrombinemia of the newborn.

Methemoglobinemia. Methemoglobinemia is not rare in young infants and may be life-threatening. Among the reported series of children with methemoglobinemia, the patients are nearly always under 3 months of age. The fact that the neonate and young infant still carry large amounts of fetal hemoglobin may account for the tendency to develop methemoglobinemia, for hemoglobin F is more sensitive to oxidation. The young may also evidence an insufficient amount of the enzyme diaphorase which is active in the reduction of hemoglobin. The characteristic finding is the chocolate color of the blood, the skin and mucous membranes showing a brown-gray cyanosis.

More than few substances have been found to cause methemoglobinemia. As early as 1886 and as recently as 1963, the danger to the infant of aniline dyes has been demonstrated, as in the case of diapers marked with aniline containing ink.[64, 65] Well water containing nitrate which is reduced to nitrite by intestinal bacteria, remains a common cause of methemoglobinemia in the infant.[66] Acetophenetidin (Phenacetin) and acetanilide are common antipyretics and analgesics which may produce methemoglobinemia; reactions have been seen with 10 to 15 mg./kg.[67] of phenacetin.

Naphthalene may produce methemoglobinemia as well as hemolytic anemia in the infant. Naphthalene toxicity is usually caused by accidental ingestion of moth balls or cough syrups containing naphthalene. Similarly, menthol is found in cough preparations and nasal inhalers: methemoglobinemia has been reported following the inunction of a menthol containing ointment to the chest of an infant with respiratory infection.

Distribution of Drugs and Neonatal Toxicity

The toxicity of chemical compounds in the infant may be affected by a variety of factors that influence the absorption or uptake of drugs as well as their distribution. Little detail is available on these points and this would appear to be a fruitful area for research. Studies will be reviewed here that have been carried out on protein-binding in relation to distribution of drugs and metabolites.

Sulfonamides and Kernicterus. The sulfonamides have been incriminated in the production of kernicterus in newborn and premature infants. This association was first discovered by Silverman and his colleagues [68] who found a considerably greater mortality and kernicterus in a group of premature infants receiving penicillin and sulfisoxazole prophylactically, than in a control group receiving oxytetracycline. These infants did not have hyperbilirubinemia. In fact, levels of bilirubin in the serum were much lower in the group treated with sulfisoxazole. Johnson *et al.*[69] held sulfisoxazole to be the agent most likely responsible for the increased incidence of kernicterus in treated rats of the Gunn strain, in which there is a genetic deficiency of glucuronyl transferase. A reciprocal fall in serum bilirubin with rise in the serum level of Gantrisin was documented.

These findings have been elucidated by the experiments of Odell [70] who found that sulfisoxazole competes effectively with bilirubin for binding sites on serum albumin. In this way, protein-bound bilirubin was displaced by sulfisoxazole, and free bilirubin could then be dialyzed or pass by ultrafiltration through membranes which retain protein-bound bilirubin. Thus, the lowered bilirubin levels of infants or rats treated with sulfisoxazole have been interpreted to reflect displacement of bilirubin from the serum proteins, and diffusion into tissues. This effect of sulfisoxazole is not at all specific, but is a property of a variety of organic anions, including other sulfonamides, caffeine sodium benzoate and salicylate.

Central Nervous System Permeability and Metabolism. Kernicterus, in general, occurs only in the neonatal period. This sensitivity to bilirubin reflects a general increase in the permeability of the neonatal central nervous system to substances circulating in the blood. Experiments on the development of the blood-brain barrier of the infant mouse have indicated that dyes such as trypan blue readily enter the brain from the blood, while in the adult animal impermeability is the rule. Similar evidence of a differential permeability in the infant and adult has been obtained using glutamic acid and the radioactive isotopes of phosphorus, chloride or potassium. C^{14}-labeled phenobarbital has been observed to penetrate the brain of the kitten much more rapidly than that of the cat, and there appeared to be an inverse relation between the degree of myelinization and the cerebral drug concentration attained. It is consistent with these observations that infant animals have shown increased sensitivity to both hexobarbital and pentobarbital.

Differences have also been observed when metabolism in the infant brain is compared with that of the adult. Increasing resistance of the animal to barbiturate intoxication over the first 2 to 3 weeks of life has been correlated with decreasing ability to withstand anoxia. The brain progresses from a relative dependence on glycolysis as an energy source to a predominantly oxidative metabolism. During the neonatal period iodoacetate, primarily an inhibitor of glycolysis, is relatively more effective in inhibiting brain metabolism, while malonate, which inhibits oxidative metabolism through the inhibition of succinic dehydrogenase, becomes more effective with maturity. In contrast to the effects of most drugs, ethanol has been found to be less toxic in the newborn than in the adult.[71]

Hepatic Function—Novobiocin. Sutherland and Keller [72] reported an epidemic of jaundice in a newborn nursery, which they were able to relate to the administration of novobiocin: there was no evidence of hemolysis. Icterus was also produced by the antibiotic in experimental animals and the toxicity of novobiocin was considerably greater in newborn animals than in adults.[73] Experiments in rabbits indicated that novobiocin interferes with the excretion of bilirubin via the bile. It has more recently been found [74] that novobiocin is an inhibitor of the enzyme glucuronyl transferase. These data indicate that drug-induced hyperbilirubinemia may result from enzymatic inhibition as well as effects on the erythrocyte.

Tetracycline and Dentition. Tetracycline is deposited in growing bones and in teeth undergoing calcification. It has recently been recognized that treatment of infants and children during the period of odontogenesis results in hypoplasia and staining of enamel. This effect is seen in the permanent as well as deciduous teeth and the areas involved are dependent on the stage of odontogenesis at the time of treatment with tetracycline. The degree of discoloration or hypoplasia is a function of the dose of the drug.[75] The amounts of drugs transported across the placenta during treatment of the mother with ordinary doses are sufficient to produce the abnormality in the infant.[76]

The involved teeth are usually of a yellow color. They can be distinguished from other types of teeth with staining or hypoplasia of the enamel by the brilliant fluorescence seen in ultraviolet light. Exposure of the teeth to sunlight results in a gradual change to a brown color with concomitant loss in fluorescence.

Inhibition of bone growth has also been observed with administration of tetracycline to premature infants and young rats. This effect is transient, while the effects on the teeth appear to be permanent.

General Conclusions

Responses to drugs in the very young infant are sufficiently novel to warrant establishment of a systematic developmental pharmacology. Even when quantitative adjustments for the size of the patient have been made, surprising qualitatively different responses are observed. It is clear that it is never safe to extrapolate to the neonate pharmacologic results obtained at other times of life, and, the effect on the fetus can never be predicted. Optimal therapeutics requires that the response to drugs of the newborn and fetus be determined experimentally before the compound is used clinically.

The following abbreviations have been used: G-1-P—glucose-1-phosphate; UTP—uridine triphosphate; UDPG—uridine diphosphoglucose; PP—inorganic pyrophosphate; DPN^+ and DPNH—the oxidized and reduced forms of diphosphopyridine nucleotide; UDP—uridine diphosphate; ATP—adenosine triphosphate; UDPGlucuronic acid—uridine diphosphoglucuronic acid; GSH and GSSG—the reduced and oxidized forms of glutathione; TPNH—reduced triphosphopyridine nucleotide.

References

1. Nyhan, W. L.: Toxicity of drugs in the neonatal period, J. Pediat. **59**: 1, 1961.
2. Baker, J. B. E.: The effects of drugs on the foetus, Pharmacol. Rev. **12**: 37, 1960.
3. Sandberg, D. H.: Drugs in pregnancy, their effects on the fetus and newborn, Calif. Med. **94**: 287, 1961.
4. Lucey, J. F.: Hazards to the newborn infant from drugs administered to the mother, Ped. Clin. N. Amer. **8**: 413, 1961.
5. Lampert, F.: Iatrogene Schaeden, Med. Klin. **59**: 961, 1001, 1964.
6. Apgar, V.: Drugs in pregnancy, J.A.M.A. **190**: 840, 1964.
7. Peckham, C. H., and King, R. W.: Study of intercurrent conditions observed during pregnancy, Amer. J. Obstet. Gynec. **87**: 609, 1963.
8. Mellin, G. W., and Katzenstein, M.: Meclozine and foetal abnormalities, Lancet **1**: 222, 1963.
9. Medearis, D. N., Jr.: Viral infections during pregnancy and abnormal human development, Amer. J. Obstet. Gynec. **90**: 1140, 1964.
10. Brill, A. B., and Forgotson, E. H.: Radiation and congenital malformations, Amer. J. Obstet. Gynecol., **90**: 1149, 1964.
11. Mellin, G. W.: Drugs in the first trimester of pregnancy and the fetal life of homo sapiens, Amer. J. Obstet. Gynec. **90**: 1169, 1964.
12. Kosenow, W., and Pfeiffer, R. A.: Micromelie, Haemangiom und Duodenalstenose. Wissenschaftliche Ausstellung Nr. 39, 59. Tagung der Deutschen Gesellschaft fuer Kinderheilkunde. Kassel, 1960.
13. Wiedemann, H. R.: Hinweis auf eine derzeitige Haeufung hypo- und aplastischer Fehlbildungen der Gliedmassen, Med. Welt **37**: 1863, 1961.
14. Lenz, W., und Knapp, K.: Die Thalidomid-Embryopathie, Deutsch. Med. Wschr. **87**: 1232, 1962.
15. McBride, W. G.: Thalidomide and congenital anomalies, Lancet **2**: 1358, 1961.
16. Lasagna, L.: Thalidomide—A new nonbarbiturate sleep-inducing drug, J. Chron. Dis. **11**: 627, 1960.
17. Taussig, H. B.: A study of the German outbreak of phocomelia. The thalidomide syndrome, J.A.M.A. **180**: 1106, 1962.
18. Mellin, G. W., and Katzenstein, M.: The saga of thalidomide. Neuropathy to embryopathy, with case reports of congenital anomalies, New Engl. J. Med. **267**: 1184, 1238, 1962.
19. Somers, G. F.: Thalidomide and congenital anomalies, Lancet **1**: 912, 1962.
20. Zbinden, E.: Experimental and clinical aspects of drug toxicity, Adv. Pharmacol. **2**: 1, 1963.
21. King, C. T. G.: Teratogenic effects of meclizine hydrochloride on the rat, Science **141**: 353, 1963.
22. Wilson, J. G.: Experimental teratology, Amer. J. Obstet. Gynec. **90**: 1181, 1964.
23. Thiersch, J. B., and Philips, F. S.: Effect of 4-aminopteroyl glutamic acid (Aminopterin) on early pregnancy, Proc. Soc. Exp. Biol. Med. **74**: 204, 1950.
24. Thiersch, J. B.: Therapeutic abortions with a folic acid antagonist, 4-aminopteroylglutamic acid (4-amino PGA) administered by the oral route, Amer. J. Obstet. Gynec. **63**: 1298, 1952.
25. Meltzer, H. J.: Congenital anomalies due to attempted abortion with 4-aminopteroylglutamic-acid, J.A.M.A. **161**: 1253, 1956.
26. Warkany, J., Beaudry, P. H., and Hornstein, S.: Attempted abortion with aminopterin, A.M.A.J. Dis. Child. **97**: 274, 1959.
27. Diamond, I., Anderson, M. M., and McCreadie, S. R.: Transplacental transmission of busulfan (Myleran®) in a mother with leukemia. Production of fetal malformation and cytomegaly, Pediatrics **25**: 85, 1960.
28. Sokal, J. E., and Lessmann, E. M.: Effects of cancer chemotherapeutic agents on the human fetus, J.A.M.A. **172**: 1765, 1960.
29. Larrson, Y., and Sterky, G.: Possible teratogenic effect of tolbutamide in a pregnant prediabetic, Lancet **2**: 1424, 1960.
30. Jackson, W. P. U., Campbell, G. D., Notelovitz, M., and Blumsohn, D.: Tolbutamide and chlorpropamide during pregnancy in hu-

man diabetes, Diabetes **11** (Suppl.): 98, 1962.
31. Tuchmann-Duplessis, H., and Mercier-Parot, L.: Sur l'action teratogène d'un sulfamide hypoglycémiant: étude experimentale chez la ratte, J. Physiol. Path. Gen. **51**: 65, 1959.
32. Fraser, F. C., Kalter, H., Walker, B. E., and Fainstat, T. C.: Experimental production of cleft palate with cortisone and other hormones, J. Cell. Comp. Physiol. **43** (Suppl. 1): 237, 1954.
33. Fainstat, T. C.: Cortisone-induced congenital cleft palate in rabbits, Endocrinology **55**: 502, 1954.
34. Woollam, D. H. M.: The experimental approach to the problem of the congenital malformations, Ann. Royal Coll. Surg. **22**: 401, 1958.
35. Doig, R. K., and Coltman, O. M.: Cleft palate following cortisone therapy in early pregnancy, Lancet **2**: 730, 1956.
36. Harris, J. W. S., and Ross, I. P.: Cortisone therapy in early pregnancy: relation to cleft palate, Lancet **1**: 1045, 1956.
37. Bongiovanni, A. M., and McPadden, A. J.: Steroids during pregnancy and possible fetal consequences, Fertil. Steril. **11**: 181, 1960.
38. Popert, A. J.: Pregnancy and adrenal cortical hormones, Brit. Med. J. **1**: 967, 1962.
39. Grunwaldt, E., and Bates, T.: Nonadrenal female pseudohermaphrodism after administration of testosterone to mother during pregnancy; report of a case, Pediatrics **20**: 503, 1957.
40. Wilkins, L.: Masculinization of the female fetus due to use of orally given progestins, J.A.M.A. **172**: 1028, 1960.
41. Bongiovanni, A. M., DiGeorge, A. M., and Grumbach, M. M.: Masculinization of the female infant associated with estrogenic therapy alone during gestation: Four cases, J. Clin. Endocr. **19**: 1004, 1959.
42. Elphinstone, N.: Thiouracil in pregnancy. Its effect upon the foetus, Lancet **1**: 1281, 1953.
43. Fisher, W. D., Voorhees, M. L., and Gardner, L. I., Congenital hypothyroidism in infant following maternal I^{131} therapy; with a review of hazards of environmental radioisotope contamination, J. Pediat. **62**: 132, 1963.
44. Petty, C. S., and DiBenedetta, R. L.: Goiter of the newborn; Report of an unusual case, New Engl. J. Med. **256**: 1103, 1957.
45. Gordon, R. R., and Dean, T.: Foetal deaths from antenatal anticoagulant therapy, Brit. Med. J. **2**: 719, 1955.
46. Epstein, W. A.: Antepartum fetal death during anticoagulant therapy for thromboembolism, J. Mt. Sinai Hosp. **26**: 562, 1959.
47. Kieler, J.: The cytogenic effect of nitrous oxide at different oxygen tensions, Acta Pharmacol. Toxicol. **13**: 301, 1957.
48. Rector, G. H. M., and Eastwood, D. W.: The effects of an atmosphere of nitrous oxide and oxygen on the incubating chick. (Work in Progress Abstract), ANESTHESIOLOGY **25**: 109, 1964.
49. Smith, B., Moya, F., and Gaub, M.: Personal communication.
50. Budnick, I. S., Leikin, S., and Hoeck, L. E.: Effect in the newborn infant of reserpine administered antepartum, Amer. J. Dis. Child. **90**: 286, 1955.
51. Hallum, J. L., and Hatchuel, W. L. F.: Congenital paralytic ileus in a premature baby as a complication of hexamethonium bromide therapy for toxaemia of pregnancy, Arch. Dis. Child. **29**: 354, 1954.
52. Ploman, L., and Persson, B. H.: On the transfer of barbiturates to the human foetus and their accumulation in some of its vital organs. J. Obstet. Gynecol. Brit. Emp. **64**: 706, 1957.
53. Bachman, L., and Freeman, A.: The cardiac rate and rhythm in infants during induction of anesthesia with cyclopropane, J. Pediat. **59**: 922, 1961.
54. Hodges, R. J. H., and Bennett, J. R., Some contra-indications to the use of chlorpromazine (with particular reference to obstetrical analgesia and anesthesia), J. Obstet. Gynecol. Brit. Emp. **66**: 91, 1959.
55. Schneck, H.: Narcotic withdrawal symptoms in the newborn infant resulting from maternal addiction, J. Pediat. **52**: 584, 1958.
56. Rodriguez, S. U., Leikin, S. L., and Hiller, M. D.: Neonatal thrombocytopenia associated with ante-partum administration of thiazide drugs, New Engl. J. Med. **270**: 881, 1964.
57. Weiss, C. F., Glazko, A. J., and Weston, J. K.: Chloramphenicol in the newborn infant. A physiologic explanation of its toxicity when given in excessive doses, New Engl. J. Med. **262**: 787, 1960.
58. Brown, A. K., and Zuelzer, W. W.: Studies on the neonatal development of the glucuronide conjugating system, J. Clin. Invest. **37**: 332, 1958.
59. Burns, L. E., Hodgman, J. E., and Cass, A. B.: Fatal circulatory collapse in premature infants receiving chloramphenicol, New Engl. J. Med. **261**: 1318, 1959.
60. Fouts, J. R., and Adamson, R. H.: Drug metabolism in the newborn rabbit, Science **129**: 102, 1959.
61. Vest, M.: Studien zur Entwicklung des Glukuronidbildungsvermoegens der Leber beim Neugeborenen, Schweiz. Med. Wschr. **89**: 102, 1959.
62. Crosse, V. M., Meyer, T. C., and Gerard, J. W.: Kernicterus and prematurity, Arch. Dis. Child. **30**: 501, 1959.
63. Zinkham, W. H.: An *in vitro* abnormality of glutathione metabolism in erythrocytes from normal newborns. Mechanism and clinical significance, Pediatrics **23**: 18, 1959.
64. Rayner, W.: Cyanosis in newly born children caused by aniline marking ink, Brit. Med. J. **1**: 294, 1886.

65. Holczabek, W.: Methaemoglobinvergiftungen durch frisch mit Anilinfarben gestempelte Windeln, Wien. Med. Wschr. **113**: 230, 1963.
66. Sattelmacher, P. G.: Methaemoglobinaemie durch Nitrate im Trinkwasser. Stuttgart, Fischer, 1962.
67. Schumacher, P.: Nilnocere! Akute Phenacetinvergiftung beim jungen Saeugling, Muench. Med. Wschr. **101**: 1083, 1959.
68. Silverman, W. A.: Andersen, D. H., Blanc, W. A., and Crozier, D. N.: A difference in mortality rate and incidence of kernicterus among premature infants alloted to two prophylactic antibacterial regimens, Pediatrics **18**: 614, 1956.
69. Johnson, L., Sarmiento, F., Blanc, W. A., and Day, R.: Kernicterus in rats with an inherited deficiency of glucuronyl transferase, A.M.A. J. Dis. Child. **97**: 591, 1959.
70. Odell, G. B.: Studies in kernicterus. I. The protein binding of bilirubin, J. Clin. Invest. **38**: 823, 1959.
71. Chesler, A., LaBelle, G. C., and Himwich, H. E.: The relative effects of toxic doses of alcohol on fetal, newborn and adult rats, Quart. J. Stud. Alcohol. **3**: 1, 1942.
72. Sutherland, J. M., and Keller, W. H.: Investigation of the relationship between novobiocin administration and an epidemic of neonatal hyperbilirubinemia, A.M.A. J. Dis. Child. **101**: 447, 1961.
73. Michael, A. F., and Sutherland, J. M.: Comparative toxicity of antibiotics in newborn and adult rats, A.M.A. J. Dis. Child. **101**: 442, 1961.
74. Lokietz, H., Dowben, R. M., and Hsia, D. Y.: Studies on the effect of novobiocin on glucuronyl transferase, Pediatrics **32**: 47, 1963.
75. Witkop, C. J., Jr., and Wolf, R. O.: Hypoplasia and intrinsic staining of enamel following tetracycline therapy, J.A.M.A. **185**: 1008, 1963.
76. Kline, A. H., Blattner, R. J., and Lunin, M.: Transplacental effect of tetracyclines on teeth, J.A.M.A. **188**: 178, 1964.

PLACENTAL CIRCULATION Perfusion of the *in situ* placenta with dextran solution containing constant concentrations of carbon monoxide (CO) and nitrous oxide (N_2O) was carried out in pregnant ewes breathing oxygen to determine relationships between placental and maternal circulation. The concentration of CO in the perfusion fluid after placental passage was found to be 19 per cent of its original concentration, that of N_2O 14 per cent. The finding of CO in the effluent perfusate after passage through the placenta substantiated a physiologic shunt mechanism whereby part of the fetal blood did not contact maternal blood. Further, because an efficient countercurrent pattern between placental and maternal blood flows would be expected to reduce the concentration of N_2O to zero in the effluent placental perfusate, the finding of an appreciable concentration of this gas in the perfusate (after suitable allowance was made for the shunting mentioned) was interpreted as evidence against an exclusively countercurrent concept. (*Metcalfe, J., and others: Transfer of Carbon Monoxide and Nitrous Oxide in the Artificially Perfused Sheep Placenta, Circ. Res. 16: 95 (Feb.) 1965.*)

MATERNAL DEATHS Between 1955 and 1962, 145 maternal deaths were reported in the Province of British Columbia. One hundred of them were due to obstetrical causes, and of these, five cases (5 per cent) were classed as anesthetic deaths. These included two cases of cardiac arrest encountered under general anesthesia, one sensitivity reaction to lidocaine infiltration, one anoxia and pulmonary edema associated with thiopental induction, and one case of pulmonary edema associated with the administration of intravenous ether. Avoidable factors were noted in four of these five deaths. (*Carpenter, C., and Bryans, F.: Maternal Mortality in British Columbia: A Study of 145 Deaths from 1955 to 1962, Canad. Med. Ass. J. 92: 160 (Jan. 23) 1965.*)