PERINATAL PHARMACOLOGY[1,2]

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The recent occurrence of several pharmacologic mishaps involving infants has focused attention upon the therapeutic implications of immaturity. The problem of teratogenic effects of drugs was reviewed last year by Karnofsky (1), but the *Annual Review* has not previously considered the problem of the interactions of immaturity, development, and pharmacologic response at later stages of incomplete development. Thus, the reviewer's task is made somewhat more formidable in that it seems necessary to provide considerable background to any consideration of recent events. To accomplish this within the space allotted, it will be possible to attempt only a general review of the overall problem. Hopefully, this will allow subsequent reviewers to focus more attention upon current developments. A limitation on the size of the bibliography will be accomplished by making extensive reference to a recent review (2); references cited therein will usually not be repeated here, but will be supplemented by later ones and by references to the prenatal administration of drugs (which was not considered in the earlier review). Additional attempts to limit the size of the bibliography will be made by similarly utilizing reviews of others (3–10).

For purposes of this report, I have taken considerable liberty with the term "perinatal," stretching the usual definition to include the entire period from viability (beyond about 27 weeks' gestation in the human) through early infancy. Semantics notwithstanding, this is justified on the practical grounds that influences upon the fetus would be expected to be relatively independent of time of occurrence once organogenesis is complete, and generally to parallel the neonatal effects except for rare circumstances wherein the placenta or maternal physiology intervene. However, it is important to recognize that the latter are rare. From the pharmacological standpoint, the "placental barrier" is largely a myth, the rather voluminous literature on the placental passage of this or that substance, reviewed elsewhere (11–14), indicating that almost any drug given to the pregnant female can be expected to be found in the fetus during these later stages of gestation. There may, however, be occasional instances in which maternal processes may intervene to protect the fetus against materials with which the fetus itself would be unable to cope.

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TABLE I

ADVERSE PERINATAL EFFECTS OF DRUGS

Drug	Effect on baby	References[a]
Analgesic-antipyretics		
Acetophenetidin	Methemoglobinemia	(2, 16), C3
	Hemolysis[c]	(17), C2
Salicylates	(??Fetal loss)[b]	(15)
	(Kernicterus)[c]	(2), D
	Hemorrhage	(5, 6), C4
Anesthetics, general	Neonatal depression[b]	(3, 8, 18)
Local (-caine's)	Methemoglobinemia	(2), C3
Anticoagulants, coumarin	Hemorrhage[b]	(8, 9, 19), C4
Antidiabetic sulfonylureas	Perinatal death[b]	(20, 21)
Antihypertensives and/or diuretics		
Ganglionic blocking agents	Paralytic ileus[b]	(22–24)
Nitrites	Methemoglobinemia	(2, 11), C3
Reserpine	Nasal stuffiness, respiratory obstruction[b]	(8, 25, 26)
Thiazides	Thrombocytopenia[b]	(27)
	?Maternal pancreatitis and fetal death[b]	(28)
Antimicrobials		(29)
Broad spectrum, various	??Cataracts[b]	(31)
Chloramphenicol	Fatal cardiovascular collapse	(2), B
Colistin	?Renal tubular damage	(30)
Nitrofurantoin	Hemolysis[c]	(17), C2
Novobiocin	Hyperbilirubinemia[c]	(32), C1
Penicillin	(Growth retardation)[b]	(33), E1
Streptomycin	Deafness and vestibular disturbance	(34–37)
Sulfonamides (esp. long-acting)	Kernicterus[c]	(38, 39), D
	Hemolysis[c]; jaundice[b]	(17), C1, C2
	Methemoglobinemia	(40), C3
Tetracyclines	Retarded bone growth	(41, 42), E1
	Tooth staining and enamel hypoplasia	(9a, 43–45), E1
	?Maternal liver and/or pancreas injury and fetal death[b]	(46–49)
	(?Kidney damage)[b]	(50)
	(?Splenomegaly)	(51)
	?Pseudotumor cerebri	(52)
Endocrines		(53)
Androgens, Estrogens, Progestins	Virilization, advanced bone age[b]	(54–57), E1
	?Estrogen feminization of male	(53, 58), E1
	(??Disturbed sexual behavior and functions)	(59–65), E2
Adrenal corticoids	?Adrenal insufficiency[b]	(9, 66)
	Growth retardation	(67, 68), E1
Epinephrine, norepinephrine	(?Fetal hypoxia, ECG changes, learning difficulties)[b]	(8, 69, 70)
Narcotic analgesics	Neonatal depression	(3, 8, 18, 71)
	(Aspiration amniotic fluid)[b]	(10)
	(Mental and neurologic deficits)[b]	(65), E2

TABLE I (*Continued*)

Drug	Effect on baby	References[a]
Sedatives and tranquilizers		(3, 65)
Barbiturates	Neonatal depression	(3, 8, 18)
Meprobamate	?Decreased adaptive and learning capacity	(7●, 72–74), E2
Ataractics	(Behavioral disturbances)	(65, 75), E2
Antidepressants	(Mental and neurologic deficits)	(65), E2
Thyroid suppressants		
Iodides, thioureas, methimazole	Goiter, hypothyroidism,[b] ?mental retardation	(6, 7, 9, 53, 76–78)
Vitamin K (synthetic, in excess)	Hyperbilirubinemia[c]	(2, 17), C2
Miscellaneous: Ammonium chloride	Acidosis[b]	(5, 6)
Nitrates, nitrites	Methemoglobinemia	(2, 11), C3
Quinones	Hemolysis[c]	(17), C2

(Evidence from animal studies only.)

[a] Letters refer to sections which follow in the text.

[b] From antepartum administration to mother.

[c] Hemolysis and/or hyperbilirubinemia imply a potential etiologic relation to kernicterus. The notation "kernicterus" above denotes another mechanism such as changes in bilirubin distribution (see D. below).

ADVERSE PERINATAL EFFECTS

The newborn or fetus may, of course, be subject to many of the same adverse effects as occur in mature individuals, but this discussion will be limited to deleterious effects which are (or may be) peculiar to, or accentuated during, the "perinatal period." Table I lists various adverse perinatal effects which have been identified in humans or in experimental animals. Those which have been observed so far only in animals are included in parentheses. Even though relevance of the latter to humans may be highly questionable, the reactions represent at least potential human effects and may also have relevance to drug testing studies in pregnant or newborn animals.

To facilitate discussion, effects which share common mechanisms or characteristics are considered together in the sections which follow; Table I makes reference to the appropriate sections. Some effects which are not so discussed are deserving of comment. The situation with regard to salicylates is far from settled, a fact which is particularly unfortunate in view of the fact that aspirin, although rarely given to newborns, is probably the drug most commonly ingested by pregnant women. The administration of aspirin from the sixth day of pregnancy onward in rather large doses produced a very high incidence of fetal loss among mice and rats (15). Lower doses produced similar effects in one study (79), but not in another (80); however, no studies could be found in which aspirin was administered only during the last trimester of pregnancy. The antidiabetic sulfonylureas, most notably chlorpropamide, have also been linked to fetal losses (20, 21), and this plus the factor of relatively poor response to these agents by the gravid

female have led many to abandon the use of oral hypoglycemic agents during pregnancy. The administration of reserpine late in pregnancy may cause nasal congestion and obstruction in the newborn infant (25, 26); since the newborn is essentially an obligatory nose-breather, the result may be severe, potentially fatal, respiratory distress. Colistin methane sulfonate has been reported to cause the appearance of abnormal "renal tubular" cells in the urines of newborn infants (30), but the significance of this finding remains to be determined. Streptomycin has toxic effects upon the eighth nerve, which are well-known, but there are some evidences that the fetus and newborn infant are particularly sensitive to this effect (35, 36, 37). Tetracyclines have been suspected of causing fatal liver and pancreas injury preceded by fetal loss in pregnant women (46–49), but a similar form of liver disease has been noted during pregnancy in the absence of tetracycline. The additional finding (50) of fatty infiltration of the convoluted tubules of the kidney in newborn rats whose mothers received tetracyclines during the last days of pregnancy is of unclear significance as yet; however, the fact that similar changes were not found in the mothers suggests an increased sensitivity of fetal kidney tissue to this effect. Also of unknown practical significance is the finding of splenomegaly in immature rats given tetracycline (51). Tetracycline has been implicated as a cause of benign intracranial hypertension (pseudotumor cerebri) in infants (52), a reaction which may or may not be accentuated in the perinatal period but perhaps is merely more obvious there because of patency of the fontanel. Epinephrine or norepinephrine administration to the pregnant animal has produced ECG abnormalities and learning disabilities in the offspring, and the similarity of the changes to those produced by uterine anoxia suggests another possible mechanism for the production of adverse perinatal effects (8, 69, 70). Finally, the results of maternal treatment with antithyroid medications such as iodides, thiourea derivatives, or methimazole deserve comment (6, 7, 9, 53, 76, 77, 78). Such treatment has not infrequently resulted in the development in the offspring of goiter and sometimes hypothyroidism resulting in mental retardation. How early treatment with these preparations must be started before such an effect on the baby will occur is not precisely known; in some instances the medication was not started until the second trimester of pregnancy (78), but it is conceivable that effects may result from even later treatment.

A. IMMATURITY AND SENSITIVITY

Aside from the aforementioned adverse perinatal effects, information about the comparative sensitivity of immature and mature organisms to drug effects are almost entirely restricted to acute toxicity studies. Thus, it may be worthwhile to consider the latter together with the former as a possible basis for making predictions about additional perinatal deviations of therapeutic response. Table II (see p. 194) presents the data which could be found concerning the comparative acute toxicities of drugs in infant and adult animals. These data suggest that infant animals have a greater

sensitivity to the acute toxic effects of CNS depressants (with the possible exception of ethanol) than adult animals. The reasons are not entirely clear, but there are suggestive evidences that the degree of maturity may affect the distribution of the drugs, at least in the case of the barbiturates (87) and the narcotics (88, 89, 89a). Whether this is related simply to incomplete development of the "blood-brain barrier" (2, 90) is uncertain since the toxicities of all drugs affecting the CNS are not increased in newborn animals. In contrast to the lethal effects, it is possible that sensitivity to therapeutic effects of these agents is reduced in immature animals: effective anesthesia could not be achieved in infant rats and rabbits with phenobarbital in less than toxic doses (91), and the analgesic response to morphine was found to be less in immature, than in mature, guinea pigs (92). Recent studies of Way and co-workers (93) are of considerable practical importance, as they show that when doses representing constant fractions of the analgesic or respiratory depressant doses for human adults were given to newborn infants, the latter were depressed far more with morphine than with meperidine, there being little or no difference with age in the response to meperidine. These findings suggest that meperidine may be preferable to morphine for perinatal use.

The immature animal is resistant to maximal seizure provocation by electroshock applied to the brain (94, 95), but not to the spinal cord (96). Thus, it is perhaps to be expected that the infant animal would be protected somewhat against the lethal effects of cortical excitants. It is not clear, however, why infant animals should be similarly protected against the action of strychnine (85) while having greatly increased sensitivity to the lethal effects of picrotoxin (97).

Among adrenergic drugs, there was no consistent pattern. The somewhat lesser toxicity of ephedrine in newborn animals may have a parallel in the recent finding of a diminished uptake of norepinephrine by the heart during the newborn period in the rat (97a). The anticholinergic drugs, atropine, mepenzolate, and pipenzolate had markedly increased toxicity in newborn as opposed to adult, experimental animals. The organophosphate anticholinesterases have all been found to be more toxic in newborn than in adult animals, with the exception of octamethylpyrophosphoramide (OMPA). These agents are relatively inactive themselves, but are converted to potent anticholinesterases by a metabolic process which may be deficient in the newborn animal (98); possibly the system particularly involved with OMPA is not similarly deficient.

The toxic effects of cardiac glycosides are the same or somewhat less in newborn animals as compared with the adult. This would seem to be in keeping with the longstanding, empirical observation that infants require larger doses (on the basis of body weight) than do older individuals. A clinical exception to this generalization is the premature infant which may be intolerant of digoxin doses which are appropriate (on a body weight basis) for term infants (99).

TABLE II

ACUTE DRUG TOXICITY IN INFANT VERSUS ADULT ANIMALS

Drug	Species[a]	Toxicity ratio[b]	References
Depressants			
Barbiturates	Rat, Mou	1.3–4.6	[c](81, 82)
Meprobamate	Rat	4.3	(82)
Narcotics (except codeine)	Rat, Rab, Mou	1.2–10.0	[c](81)
Mephenoxalone	Rat	5.8	(83)
Ethanol	Rat, Mou	0.6–1.7	[c](81)
Excitants			
d-Amphetamine	Rat	0.5	(82)
Pentylenetetrazol	Rat, Mou	0.2–0.4	[c](82, 84)
Picrotoxin	Rat	6.0	—[c]
Strychnine	Rat	0.4	(85)
Thebaine	Rab	0.9	—[c]
Codeine	Rab	0.7	—[c]
Tranquilizers and antidepressants			
Chlorpromazine	Mou	4.2	(81)
Desipramine	Rat	2.5	(82)
EX 4883 (MAO inhibitor)	Rat	1.3	(82)
Autonomic drugs			
Adrenergic:			
Ephedrine	Rat	0.6	—[c]
Protokylol	Rat	0.8	(82)
Fencamfamin	Rat	1.6	(82)
Anticholinergic:			
Atropine	Rat, Rab, Mou	1.8–2.6	[c](81)
Mepenzolate	Rat	4.0	(82)
Pipenzolate	Rat	5.8	(82)
Anticholinesterases:			
Organophosphates (except OMPA)	Rat	1.2–14.0	—[c]
OMPA	Rat	0.2	—[c]
Cardiac glycosides	Cat, Rab, GP	0.6–1.0	—[c]
Antibacterials			
Chloramphenicol	Rat, Mou	2.6–>16	[c](81, 86)
Erythromycin ("Estolate")	Rat	>3.5	(86)
Nalidixic acid	Mou	2.6	(81)
Neomycin	Rat	1.1–1.9	(82)
Novobiocin	Rat	2.8	—[c]
Penicillin G	Rat	7.2–>12	—[c]
Streptomycin	Rat	1.1	—[c]
Tetracycline	Rat	2.5	—[c]

TABLE II (*Continued*)

Drug	Species[a]	Toxicity ratio[b]	References
Miscellaneous			
Acetaminophen	Rat	5.7	(82)
Chlormerodrin	Rat	0.9	(82)
Dicumarol	Rat	10.4	(82)
Ferrous sulfate	Rat	1.3	(82)
Iron dextran	Rat	1.2	(82)
Menadiol Na diphosphate	Rat	0.7	(82)
Menadione	Rat	1.1	(82)
Meralluride	Rat	0.7	(82)
Procaine	Mou	2.1	(81)
Salicylates	Rat, Mou	1.5–2.7	[c](81, 82)
Tetracaine	Mou	0.9	(81)
Thiourea	Rat	<0.02	—[c]

[a] Abbreviations: Mou = mouse, Rab = rabbit, GP = guinea pig.

[b] Toxic dose, adult/infant (usually LD_{50}, but sometimes LD or MLD). A ratio of greater than one indicates greater toxicity for infant than for adult animals. "Adult" values used for this calculation were from the youngest age group studied beyond the average age of sexual maturity for a given species; "infant" values were from the youngest animals studied and included only those which were at or below the usual age of weaning.

[c] See Table I of earlier review (2) for references.

The majority of antibacterial agents have been found to have enhanced toxicity in infant animals. However, with the exception of chloramphenicol, which is discussed below in detail, there would appear to be no obvious connection between the findings of these studies of acute toxicity and any known adverse perinatal effects. Noteworthy, however, is potassium cillin G, a drug which people have thought could be used with relative impunity, but which has markedly enhanced toxicity in infant animals. Two groups of workers (100, 101) found that the newborn rat had a definite ceiling of tolerance to penicillin. The possibility that a similar ceiling may exist in the human newborn must be kept in mind; certainly, there are no data presently available to rule out this possibility. (The potassium content of the preparation appeared not to be responsible for the observed differences, since the LD_{50} in newborn animals was similar for the sodium and potassium salts.)

The enhanced toxicity of acetominophen for the newborn rat (82) is deserving of note and further investigation. This material is promoted as an aspirin substitute especially for use in infants because it can be made available in liquid form and supposedly is less toxic. The greatly enhanced

toxicity of dicoumarol is somewhat difficult to explain; the early death following a single dose would not likely be attributable to any effect upon prothrombin; consequently, an additional toxic mechanism seems likely.

B. DETOXIFICATION AND EXCRETION

Many of the aberrant responses of the immature organism to drugs can undoubtedly be accounted for on the basis of qualitative or quantitative differences in metabolism and excretion. A review of the status of detoxification and excretion processes in the infant is therefore worthwhile not only from the standpoint of explaining some of the aforementioned aberrations of therapeutic response, but also from the standpoint hopefully of prognosticating about other possible aberrations.

Among the available studies, those which involve Phase I detoxification processes have been found uniformly to be relatively deficient in activity in newborn or fetal animals (2). Among these, the oxidative pathways appear to be the most deficient, so that such processes as the side-chain oxidation of hexobarbital, the aromatic hydroxylation of acetanilid or naphythylamine, the deamination of amphetamine, the dealkylation of aminopyrine, codeine or acetophenetidin, or the sulfur oxidation of chlorpromazine were carried out only to a very minor degree by newborn animals or their tissues. Reduction reactions including the nitro-reduction of *p*-nitrobenzoic acid, the azo-reduction of Neoprontosil, and the keto-reduction of cortisol were also deficient, but somewhat less so.

There is less uniformity among studies of Phase II (synthetic, conjugation) processes, the findings varying somewhat depending upon species, substrate, or the type of tissue preparation (2). The majority of studies of formation of both the ester- and ether-type glucuronide linkages demonstrate deficient activities in infant animals and humans *in vivo* and by liver and kidney *in vitro* (2, 102). However, there are discrepant results, including the conjugation of *p*-nitrophenol by the liver of the infant rat but not the human being (103) or monkey (104), the completely adequate glucuronidation of salicylate by tissues of the newborn rat and rabbit (105), and the finding that the glucuronidation of *o*-aminophenol during the newborn period was deficient in whole liver homogenates from the guinea pig or rat, but adequate in liver slices from the rat (106). These discrepancies may relate to the probability that the responsible transferase enzyme(s) is (are) different in characteristics among various animals, at various stages of development, and for different substrates. Data suggesting that even within one species there may be more than one, perhaps several, "glucuronyl transferases" include such findings as the effective glucuronidation of *p*-nitrophenol (103) and aniline (107) by the Gunn rat which cannot conjugate bilirubin, enhancement of the formation of ester and ethereal glucuronides but not N-link glucuronides by solubilization of glucuronyl transferase (108), a differing effect of experimental liver injury on the conjugation of various substrates (109), and barbital induction of glucuronidation of bilirubin but not phenolphthalein or *o*-aminophenol in the rat (110).

nal distention after several days' treatment, and was followed by the development of respiratory difficulty, hypothermia, flaccidity, and a peculiar ashen-gray cyanosis (which gave rise to the designation "the gray syndrome"). The reaction was usually fatal within 24 to 48 hours after onset of severe symptoms. Autopsy findings were insufficient to account for the deaths. The underlying mechanism is not precisely known, but inefficient elimination of the drug leading to its accumulation is a contributing factor. This appears to be related both to inadequate glucuronide conjugation and retarded renal excretion.

C. DRUG-ENZYME INTERACTIONS

Some altered perinatal responses to drugs are the result of deficiencies of activities of enzymes which bear no direct relationship to the drug itself. Thus, because of certain metabolic concomitants of immaturity, drugs may produce effects which would occur less readily or not at all in the biochemically mature organism.

1. Drugs and Bilirubin Metabolism

Transient hyperbilirubinemia of the unconjugated variety occurs universally among newborn infants and is more severe the more immature the infant. In its overt form, this is referred to as "physiologic jaundice." The factors involved in this phenomenon are reviewed elsewhere (2); briefly, an increased load of hemoglobin breakdown products is presented to a liver which is relatively inefficient in converting bilirubin to the glucuronide conjugate (*vide supra*). Free bilirubin appears to be involved in the development of a form of brain damage known as kernicterus or bilirubin encephalopathy. Any factor which increases the availability of bilirubin to the CNS is capable of increasing the incidence and severity of kernicterus.

In vitro inhibition of bilirubin conjugation has been produced by a number of drugs including novobiocin (117, 118), chloramphenicol (119), streptomycin (119), and adrenal corticoids (120). However, the only clinical correlate which has been established with certainty is with regard to novobiocin, which has been found to produce hyperbilirubinemia in newborn humans and rats (32). The related experimental work is summarized elsewhere (2, 116); the bulk of evidence suggests noncompetitive inhibition of glucuronyl transferase activity by the drug.

Several drugs have been studied for possible hyperbilirubinemic effects, but with negative results. The report of an increased incidence of jaundice in premature infants whose mothers received phenothiazine tranquilizers during labor (120) has not been substantiated by other studies (2, 121–123). Negative results have also been found with erythromycin (2), oxytetracycline (2), meperidine (2, 121, 122), and scopolamine (121). A possible relationship between the maternal administration of sulfamethoxypyridazine and neonatal hyperbilirubinemia has been reported and deserves further investigation (124).

In all such studies, it must be borne in mind that the tendency of a drug to aggravate neonatal hyperbilirubinemia may well be masked by a simultaneous alteration of bilirubin distribution (see D. below), under which circumstances the drug is likely to be more of a threat than were it to produce hyperbilirubinemia alone. Hopefully, studies of protein-bound versus free bilirubin, such as those presently underway in this laboratory, will shed some light on this problem.

2. Drug-Induced Hemolysis

Certain biochemical peculiarities of the erythrocytes of newborn infants render them susceptible to the hemolytic effects of certain drugs and chemicals (2, 125–127). The factor(s) responsible for the vulnerability of neonatal erythrocytes to hemolysis have not been elucidated completely. There are known to exist two inherited enzymatic defects, involving deficiencies of glucose-6-phosphate dehydrogenase or glutathione reductase, which resemble the neonatal defect in the sense that the affected individual does well until exposed to certain drugs or chemical agents, but the basic defects are different in that erythrocytes of newborn infants are not deficient with respect to the activities of these particular enzymes. However, the drugs and chemicals capable of causing hemolysis in each of these situations are probably similar and are well reviewed (17, 127). They include antimalarials, sulfonamides, nitrofurans, certain antipyretics and analgesics, naphthalene, water-soluble vitamin K analogues (in large doses), and perhaps certain antibiotics.

Vitamin K.—The most widespread difficulties have been with the administration of the water-soluble, synthetic analogues of vitamin K: menadiol sodium diphosphate (Synkayvite) or menadiol sodium bisulfite (Hykinone) (2). Neonatal jaundice, sometimes responsible for kernicterus, has developed when these drugs were used in large doses, usually in excess of 30 mg. Fortunately, the doses which are required as prophylaxis against hemorrhagic disease of the newborn are far lower (in the microgram range) so that safe and effective use of these drugs is possible. Vitamin K_1 preparations, menadione, and menaphthone have not been implicated. Thus, the use of the latter agents, or the former ones in doses of about 1 mg administered directly to the infant, can be recommended.

3. Methemoglobinemia

Newborn infants are inordinately susceptible to the introduction of methemoglobinemia by drugs, most likely as a result of deficient activities of methemoglobin reductase and diaphorase in the erythrocytes (128–130).

As is indicated in Table I and elsewhere (2), a wide variety of oxidizing agents is capable of producing methemoglobinemia in infants, including nitrates in well water, bismuth subnitrate, benzocaine and related local anesthetics, aniline-containing inks or dyes absorbed percutaneously from freshly stamped diapers or dyed shoes, the absorption through the skin of

chloraniline compounds used to rinse babies' bedding, and from long-acting sulfonamides, especially sulfamethoxypyridazine. The seemingly unique ability of the infant to convert nitrates to nitrites which are capable of producing methemoglobinemia has been attributed to low gastric acidity which promotes the growth in the upper gastrointestinal tract of microorganisms that are capable of reducing nitrates (131).

4. Hypoprothrombinemia

The coumarin derivatives, bishydroxycoumarin (dicumarol), ethyl biscoumacetate (Tromexan), and warfarin (Coumadin) (8, 9, 19), and salicylates (5, 6) appear to have a particular predilection for producing hypoprothrombinemia in newborn infants, when administered to their mothers late in pregnancy, probably because of a limited reserve for producing prothrombin. Severe, sometimes fatal, fetal or neonatal hemorrhages may occur when the maternal prothrombin activity is not excessively depressed. On the other hand, when heparin was administered during early labor, coagulation of cord blood was normal even when the maternal blood was incoagulable (131a), suggesting that heparin should be substituted for coumarins when anticoagulant therapy is deemed necessary during late pregnancy.

D. ALTERATIONS OF BILIRUBIN DISTRIBUTION

The possibility that a drug could produce deleterious effects by altering the distribution of endogenous bilirubin was brought to light by the report of a greatly increased mortality rate, due principally to kernicterus, among premature infants who received sulfisoxazole prophylactically (39). The increment in incidence of this complication could not be attributed to enhancement of hyperbilirubinemia, since the infants actually had significantly lower levels of serum bilirubin than did a group of control infants who were not so treated (132). Subsequent experimental studies (133, 134) suggested that various drugs including sulfisoxazole were capable of competing with bilirubin for binding to serum albumin, thereby increasing the amount of bilirubin which was free to pass through semipermeable membranes. *In vivo* studies employing the Gunn rat (inherited deficiency of bilirubin glucuronidation) indicated that kernicterus could be potentiated by other drugs as well (38), and a number of *in vivo* and *in vitro* procedures have been used for testing the abilities of various drugs to accomplish similar alterations of bilirubin distribution (2). Table III lists these drugs in descending order of potency (i.e., potency as displacers of bilirubin from albumin-binding).

Although sulfisoxazole is the only drug which has definitely been implicated in the potentiation of kernicterus in human infants, it can be seen in Table III that several drugs are even more potent in this regard. From the data summarized in the Table and from the knowledge that a vast number of drugs are bound to serum proteins, it is apparent that the full story of

TABLE III

DRUG UNCOUPLING OF BILIRUBIN-ALBUMIN BINDING[a]

Potency						
High	Moderate		Slight or equivocal		Inactive	
Novobiocin	Salicylate[b]	Sulfisoxazole[b]	Acetazolamide	Epinephrine	Chloramphenicol[b]	Phenobarbital
Indomethacin	Caffeine Na benzoate		Menadione Na bisulfite		Oleandomycin	Metrazol
Sulfadimethoxine[b]	Lobelin	Strophanthidin	Sulfathiazole	Penicillin G	Tetracycline[b]	Isoniazid
Lanatoside C	Tolbutamide	Sulfadiazine[b]	Erythromycin[b]	Prednisolone	Oxytetracycline	Coramine
Menadiol Na diphosphate	Sulfamethoxypyridazine		Kanamycin	Chlorpromazine	Versenate	
			Promazine			

[a] References are in Table V of review article (2).

[b] In addition to *in vitro* studies, tested for effects on kernicterus incidence in congenitally jaundiced infant rats (Gunn).

drug potentiation of kernicterus is far from written. Certainly, careful clinical observations and additional experimental studies relative to this possibility are warranted. Perhaps more important are attempts to evaluate accurately a drug's potential in this regard; such efforts are currently underway in this laboratory.

E. DEVELOPMENT EFFECTS

Influences of therapeutic agents upon the process of normal development beyond the period of organogenesis are far more subtle than are gross teratologic effects or adverse reactions which are associated with structural pathology. As a result, few examples of drug effects on a development process have been identified. There is every reason, however, to believe that the problem extends far beyond these few isolated examples and that additional studies which search for functional as well as morphologic abnormalities are badly needed.

1. Physical Growth and Development

The best known iatrogenic effects upon growth are those exerted by hormonal agents. Prolonged therapy with adrenocortical hormones may lead to significant inhibition of linear growth and skeletal maturation in growing children (67, 68). The pre- or postnatal administration of androgens or the antepartum administration of progestins may result in advanced skeletal maturation (53–57) which, if sufficiently severe and protracted, could result in a dimunition of ultimate stature as the result of early cessation of growth (53, 68, 135). More unexpected and less well-known are the growth effects of certain nonhormonal agents. The known examples are few in number and usually of unclear significance, but they do indicate that materials having effects which are entirely foreign to the body can influence its growth and differentiation. Most importantly, they open up the possibility that this is an area of developmental pharmacology about which we must be concerned, at least until considerable additional information dictates otherwise.

Tetracyclines.—The administration of therapeutic doses of tetracyclines was demonstrated to produce a striking inhibition of linear growth both in premature human infants and in the fetal rat (41, 42, 136). This growth effect is related to inhibition of skeletal development subsequent to the deposition of tetracycline fluorophores in the skeleton, a phenomenon which has been observed in several experimental situations (2, 137). Because the effect upon skeletal growth is apparently reversible, its long-term significance to the individual, if any, is in question; however, these findings indicate, as mentioned above, that growth can be affected adversely by nonhormonal agents. As a corollary of the foregoing, tetracyclines acquired transplacentally or postnatally may produce a defect of dentition which similarly results from the deposition of metabolites of the drug in calcifying tissues (9a, 43, 44, 45). The result is permanent discoloration of the

teeth, and enamel hypoplasia, caused by diminished calcification in the affected areas. This can occur either in the primary or permanent dentition. The extent to which this reaction is shared by the various tetracyclines is unclear at present, but there are at least suggestive evidences that it may occur with demethylchlortetracycline (43, 44) and perhaps oxytetracycline (44), as well as tetracycline.

Deserving of further investigation is the report (33) that the administration of a single, not extraordinary, dose of penicillin given to the pregnant mouse on the fourteenth day of gestation resulted in ultimate retardation of growth of the offspring. The mechanism and significance of the effect remain to be determined, and there is no information as to whether administration of the drug later in pregnancy would produce similar effects.

Hormones and sexual development.—The production of genital changes in the female infant ranging from mild enlargement of the clitoris to full-blown female pseudohermaphrodism has resulted from the administration of androgens, progestins, and stilbestrol during the first few weeks of gestation. Malformations sufficient to produce ambiguous genitalia would not occur, of course, after differentiation of the genitourinary system is complete; however, the possibility must be considered that more subtle virilization may take place when these agents are administered during later stages of pregnancy. In addition, the possibility of feminizing the male fetus by the antenatal administration of estrogens must be considered, although this has been found to be extremely rare (53, 138).

2. Mental and Behavioral Development

Only recently has much attention been given to the nebulous, but potentially important, possibility that drugs may affect mental and behavioral development. Recent animal experiments indicate that rather startling aberrations can be induced by relatively meager amounts of certain drugs. The available data and their possible implications have been reviewed recently by others (60, 65). Throughout the present review, the question of relevance of animal studies to the human therapeutic situation has loomed large, but in no place as much as here. It is probable, actually, that none of these findings is transposable to humans, yet the uncertainty is sufficient to warrant further consideration and research.

Sedatives and psychotropic drugs.—Many of the early studies involved doses of depressants which were sufficient to produce high mortality rates among pregnant animals; consequently, it is not at all surprising that their offspring had great difficulties. With lower doses of barbiturates given just before delivery, a variety of mental, neurological, and learning deficits has been observed (65). Meprobamate administration to gravid rats has also been reported to produce persistent deleterious effects on emotionality and learning ability of the progeny (74, 139), but later work by others (140, 141) failed to reveal such an effect. The administration to pregnant rats of

drugs which affect serotonin levels (iproniazid, 5-hydroxytryptophane, reserpine, and a benzyl analogue of serotonin) resulted in persistent changes in the offspring, resembling those seen in hyperkinetic children (75). Among studies of human newborn infants whose mothers received depressant drugs immediately prior to delivery there was noted diminished attentiveness at two to four days of age (73), a prolongation of the usual period of disorganized activity, and slow adaptation to breast feeding (72).

Hormones and sexual behavior.—It has long been known that gonadal hormones have important influences upon the development of sexual behavior in subhuman species (60). Numerous data suggest that neural structures which determine adult sexual behavior may be adversely affected by heterotypical, and perhaps homotypical, hormones acting during a critical stage of their development. Thus, the administration either of androgens or estrogens to neonatal female rats resulted in permanent abolition of sexual receptivity (59, 61), and estrogen treatment of the male rat resulted in failure of development of normal sexual behavior (64). The behavioral changes secondary to the administration of heterotypical hormones were associated in the female with constant vaginal estrus, small ovaries devoid of corpora lutea, and permanent sterility (62, 63), and in the male by testicular underdevelopment (62, 64). In both instances the changes persisted into adult life. Great doubt has been expressed regarding a role of sex hormones in determining the direction or content of erotic inclination in human beings (142, 143), but the final answer with regard to a possible iatrogenic effect upon the development of human sexual behavior must await further data.

GENERAL CONCLUSIONS

It is inevitable that any review concerned with deleterious effects of drugs will malign some agents which ultimately will prove not to be deserving of such a fate, while ignoring or "whitewashing" others which actually pose more serious threats. However, it was intended that this necessarily sketchy presentation be looked upon as reflecting only the status of the available information at this moment. Thus, the only defensible justification for undertaking this task was to reiterate the few answers which are available and to attempt to stimulate interest in the far more numerous questions which remain unanswered. It is fully apparent that our knowledge of developmental pharmacology has not kept pace with pharmaceutical advances. If and when the former overtakes the latter, we may find that the problem of drug injury to the immature is either more or less serious than is implied by the data presented herein, but there is no doubt that such a list as is presented in Table I will be quite different.

Before anyone draws lasting conclusions about the extent, possible solutions, and possibilities for further investigation of this problem, it is important to remember how and when the known perinatal drug hazards came to light. Without exception, these were discovered only after widespread use

when tragic consequences focused attention upon the drug. This will continue to be the case until we are able to improve and extend our means for experimental and clinical investigation of drugs intended for perinatal use. The difficulties of interpolating the results among species cannot be underestimated, yet we should not abandon the possibility of obtaining animal data which are relevant to human beings; certain of the known perinatal drug hazards would have been predicted in this manner, and others would not. Certainly, the final proving ground must be the human infant and fetus. Clinical trials not involving essential treatment of serious illness in infants are difficult to justify, especially with our present paucity of knowledge of the therapeutic implications of immaturity. However, we can take optimal advantage of legitimate therapeutic experiences by determining the long-term effects of therapeutic procedures and reporting instances of otherwise inexplicable morbidity or mortality to appropriate agencies in the hope that similar reports from elsewhere will result in recognition of a hazard prior to its eruption into an epidemic. Until more information is available it would, in my opinion, behoove all physicians who treat children or pregnant women to adopt an attitude of relative therapeutic nihilism. This is not to suggest that necessary medications be denied to such individuals but rather that measures of questionable value should be avoided and any therapy be weighed carefully against the known or inapparent hazards which may be involved.

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