DEVELOPMENTAL PHARMACOLOGY[1,2]

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Introduction

A review of the field of developmental pharmacology should cover at least two areas. The first area is that of metabolism of drugs administered to subjects of different maturity, e.g. differences in rate of absorption, body distribution, rates of catabolism, inactivation and elimination of the drug or its intermediates. The second area is chiefly devoted to the investigation of the possible interference of drugs and chemicals with the normal biochemical and physiologic development of the growing organisms.

Such a review can only be general and the selection of the material reported arbitrary. This article will delineate the more pertinent contributions to the field of developmental pharmacology. We refer the reader to two recent comprehensive publications concerning this subject (1, 2).

Differences in Response to Pharmacological Stimuli By Subjects of Different Ages

For comparable therapeutic effect, the dose of a drug administered to subjects of different ages and sizes depends on two principal factors: (*a*) concentration and distribution of the drug in the biological fluids and tissues; and (*b*) the response of the target organ to the pharmacological stimulus.

A review of adverse effects of drugs administered to newborn infants was recently compiled by Done (1). Some of these toxic effects are probably related to the greater sensitivity of immature tissues to drugs.

Studies on experimental animals.—For some time the CNS of very young subjects has been considered more sensitive to depressants and the explanation of this phenomenon varies with the different types of drugs used. In a few cases, the greater sensitivity of immature brain was a result of a different response of the CNS to the pharmacological stimulus.

Equivalent doses of barbiturates induce a much longer sleeping time in newborn animals than in adult animals. This is due to either an accumulation of the drug in body fluids of the newborn as a result of decreased metabolism (3), or to an increased permeability of the blood-brain barrier (4). Bianchine & Ferguson (5) have shown that the cerebral tissue of newborn rats is more sensitive to the depressant effect of pentobarbital than is the

[1] The survey of the literature pertaining to this review was concluded in June 1967.

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tissue of adult rats. The LD_{50} for newborn rats was approximately one-third that for adults. At death, the concentration of pentobarbital found in the brain of newborn rats was about one-third that found in brain of animals 20 days of age.

Bagdon & Mann (6–8) recently studied the change in body temperature of young albino mice following administration of phenothiazines. When chlorpromazine hydrochloride was given intraperitoneally, its effect on body temperature varied with the age of the animal. The expected depression in body temperature was found in mice 38 days of age, but in mice 10 days old the drug caused an elevation in the orally measured body temperature (6). The dechlorinated analogue of chlorpromazine (promazine) elicited a similar but less pronounced response in accordance with the age of the animals (7). The exact mechanism for the hyperthermic effect of chlorpromazine encountered in young animals is unknown (8). Muscle tone did not play a significant role, since simultaneous administration of tubocurarine did not prevent the hyperthermic activity of chlorpromazine. Chlorpromazine sulfoxide also produces hyperthermia in newborn mice, probably because the immature hypothalamic thermoregulatory centers respond differently to chlorpromazine and its metabolites than do those of the adult. This hypothesis is based mainly on the fact that some centrally acting drugs, such as lysergic acid, antagonize the effect of chlorpromazine (8).

A few years ago, Buchsbaum & Buchsbaum (9) conducted an interesting study which correlated the age of mice with their response to ether anesthesia. Mice, 15 days old, resisted ether anesthesia for a shorter period than adults and elderly animals. From 30 days of age, females were more resistant to ether than males. On the other hand, recovery time was longer for young and old mice, than for normal adults. The authors concluded that the more rapid intoxication of young mice is probably due to hyperventilation, tachycardia, and greater pulmonary diffusion. The slower recovery of young subjects may be a consequence of a more severe depression of the respiratory centers of the immature animals. The differences in sensitivity to ether anesthesia exemplify participation of multiple physiologic and tissue factors in different responses to the same drug at different ages.

Another temporal demonstration of the variable sensitivity of the CNS to a pharmacological stimulus was recently reported by Kulkarni & Shideman who demonstrated that depletion of catecholamines by reserpine and tetrabenazine is much greater in rats 11 days of age than in adult animals (10). A single dose of either drug produced a more pronounced and persistant fall in catecholamine concentration in the brains of newborn rats. Furthermore, when reserpine was administered for a prolonged period, maximal depletion of brain catecholamines was attained in one day in suckling animals, whereas it took about 15 days in adults. The reasons for the differences between immature and mature subjects in the sensitivity of the brain to reserpine were not determined. The concentration of catecholamine per gram of fresh tissue is lower in brains of immature subjects than in adults (11).

This is presumed to be related to the lack of full development of catecholamine storage sites in the brains of young subjects (12). The Kulkarni & Shideman hypothesis (10) is that the greater sensitivity to reserpine of immature brain is the result of more complete interference of the drug with the catecholamine storage sites in young animals.

Examples of different sensitivity of immature tissues to pharmacological stimuli are not confined to the CNS. Schlesinger & Mark reported that large doses of cortisol acetate induce a wasting disease in young mice (13). When a single dose of 0.1 to 0.5 mg of steroid per gram of body weight is injected into rats less than 10 days of age, a very high percentage of the animals sustain a fatal disease similar to that usually observed in animals thymectomized at birth, e.g. diarrhea, impairment of hair growth, ruffled and scarce fur. When the same amount of hydrocortisone was injected into animals older than 10 days, this syndrome was observed only in a small percentage of the cases.

Investigations on humans.—In a few instances, the response to drugs of humans at different stages of development has been evaluated quantitatively.

The sensitivity of newborn animals to morphine is well established. Way and coworkers (14) evaluated the respiratory depressant effect of morphine and meperidine in human infants, using a technique based upon body plethysmography and sampling of end tidal CO_2. In infants given one-third the dose of morphine necessary to induce respiratory depression in adults, a greater depressant effect was induced than with a similar dose of meperidine. These observations, and others which show in animals little or no age difference in heroin toxicity (14), do not support the hypothesis that receptors of the immature brain are more sensitive to morphine-like drugs. Since neither impaired conjugation or excretion of these compounds appears to play a role (15), the increased toxicity of morphine in immaturity may be related to a higher concentration of the drug in the CNS (14) of the young animal, e.g. the result of increased permeability or decreased flux.

The response of newborn and premature infants to muscle relaxants differs from that of adults. Newborns tolerate relatively high doses of depolarizing relaxants such as succinylcholine, but they are sensitive to nondepolarizing drugs such as tubocurarine. Churchill-Davidson & Wise (16) investigated the influence of the depolarizing drug decamethonium upon neuromuscular transmission, and the influence of the anticholinesterase drugs, neostigmine and edrophonium, on the neuromuscular block produced by decamethonium. The results indicated that the resistance of the infant to depolarizing drugs is two to three times that of the adult on a weight basis. Decamethonium block in the first few weeks of life strongly resembles that produced in patients with myasthenia gravis. The same authors also studied the response of the infant to *d*-tubocurarine (17). They concluded that except for a possible increased susceptibility of the respiratory musculature the newborn infant responds to nondepolarizing relaxant drugs similarly to adult subjects. Finally, Nightingale et al. (18) investigated the effects of neuro-

muscular blockade by succinylcholine in subjects four months to 13 years of age. When the drug was administered in moderate doses and on the basis of body weight, the duration of neuromuscular block increased with advancing age. Factors which might determine the resistance of younger subjects to succinylcholine are: a higher rate of succinylcholine metabolism; a relatively higher number of motor end plates per kilogram of body weight; or a larger space in which the drug is distributed.

Von Harnack (19) has recently shown that no matter which parameter is chosen to calculate dosage at different ages, the minimum amount of epinephrine necessary to significantly increased blood pressure is much higher in immature subjects than in full-term infants and children. This finding may be related to a difference in response of the immature vascular system to the drug.

Although previous clinical observations indicated that proportionally higher therapeutic doses of digitalis were necessary in young infants than in older children, two recent reports, by Levine & Blumenthal (20) and Marini and co-workers (21), indicate that when digitalis is given on the basis of body weight, toxic effects are produced at lower doses in premature and newborn infants.

Marini and co-workers (21), using the isolated and perfused atrium of newborn rabbits, demonstrated that the younger the infant, the lower the concentration of digitalis required to induce an effective depression of contractility of the heart muscle. From these *in vitro* data, one of the factors in determining the higher toxicity of digitalis in premature and newborn infants might be an increased sensitivity of cardiac muscle.

Marini and co-workers (22) have also shown that newborn infants are more sensitive than older infants to volatile anesthetics, especially fluothane. This is probably a result of the greater susceptibility of the myocardial tissue and of inadequate control of peripheral vascular tonus in immature subjects.

Pharmacokinetics and Developmental Pharmacology

Placental transfer of antibiotics.—The rate of transfer of antibiotics across the placenta has some very interesting clinical implications. Table I summarizes some of the data collected from humans. The transfer of substances across the placenta is a very complicated process, and the data cited must be viewed with caution.

Chloramphenicol passes freely across the human placenta. Penicillin, tetracyclines, ampicillin, and streptomycin pass in smaller amounts, but they have a tendency to accumulate in fetal fluids. Erythromycin and rifomycin do not cross the placenta in significant amounts. The importance of an exact evaluation of the rate of transfer of antibiotics through the placenta is stressed by a series of papers which indicate that certain drugs are toxic to the fetus.

The toxic effect of streptomycin on the fetal ear was demonstrated many years ago (30). This was recently confirmed by Conway & Birt (31), who

TABLE I

PLACENTAL TRANSFER OF ANTIBIOTICS

Antibiotic	Route of administration	Time elapsed after administration	Maternal / fetal ratio	Author
Chloramphenicol	Oral	1 hr	1	(23)
Penicillin G	i.m.	1 hr	3	(24)
		2 hr	2	
		6 hr	1.4	
Long-acting Penicillin	i.m.	1 hr	2	(24)
		2 hr	2	
		6	0.8	
Tetracyclines	i.m.	1 hr	4	(25)
		2 hr	2	
Ampicillin	i.m.	½ hr	2	(26)
		1 hr	1	
		2 hr	0.33	
Streptomycin	i.m.	1 hr	4	(27)
Eyrthromycin	Oral	1 hr	Not detectable in fetal blood	(28)
Rifomycin	i.m.	1 hr	20	(29)

studied audiograms of a group of children 6 to 13 years of age whose mothers received streptomycin during pregnancy. Boecher & Delost (32) found that penicillin and streptomycin given to mother mice induced a depression in the rate of growth of offspring, which was correlated with the amount of drug administered. Many authors (33–36) have reported discoloration of decidual teeth associated with antepartum administration of tetracycline. Hughes and co-workers (37) studied the growth of chick embryos injected with six different types of tetracyclines, and reported that large amounts of the drug inhibited bone growth.

Pharmacokinetics of antibiotics in infants.—Table II summarizes the most recent data on the serum half life of 11 different antibiotics. The rate of disappearance of antibiotics from plasma (T 50 per cent) is greater in premature and full-term infants than in later periods of life. In newborns less than 48 hours old, a particularly long half life was invariably found for tetracycline (38), streptomycin (39), kanamycin (30), chloramphenicol (40), ampicillin (41, 42), methicillin (41, 42), colistin (41, 43) and cephaloridin (44). Antibiotics have a longer half life in premature infants than in full-term infants of the same age. The persistence of relatively high concentrations of antibiotics in the plasma of very young subjects is related to low urinary excretion of the compounds. Some of the most important characteristics of urinary excre-

TABLE II

SERUM HALF LIFE OF ANTIBIOTICS IN NEWBORN, PREMATURE, AND FULL-TERM INFANTS

Antibiotic	Subject	Age	Half Life of Drug (hours)	Author
Chloramphenicol	Premature infants	1 da	15–22	Hodgman & Burns (1960)
emisuccinate	Premature infants	13–23 da	8–15	Hodgman & Burns (1960)
	Children	5 yr	4	Hodgman & Burns (1960)
Streptomycin	Premature infants	1–3 da	7.0	Axline & Simon (1964)
	Adults	—	2.7	Axline & Simon (1964)
Kanamycin	Premature infants	<48 hr	18	Axline & Simon (1964)
	Premature infants	5–22 da	6	Axline & Simon (1964)
	Adults	—	2	Axline & Simon (1965)
Tetracycline-1-methyl-	Newborn infants	1–2 da	16.2	Sereni et al. (1965)
enelsine	Infants	3–7 mo	9.8	Sereni et al (1965)
	Children	5–11 yr	6.8	Sereni et al. (1965)
Ampicillin	Premature infants	3–6 da	3.6	Axline et al. (1967)
	Premature infants	21–39 da	1.9	Axline et al. (1967)
	Term infants	<24 hr	3.4	Boe et al. (1967)
	Term infants	4–5 da	2.2	Boe et al. (1967)
Methicillin	Premature infants	4–5 da	3.3	Boe et al. (1967)
	Premature infants	4–7 da	2.4	Axline et al. (1967)
	Premature infants	13–15 da	2.0	Boe et al. (1967)
	Premature infants	17–33 da	1.4	Axline et al. (1967)
	Premature infants	26–30 da	1.4	Boe et al. (1963)
	Term infants	<24 hr	3.3	Boe et al. (1967)
	Term infants	4–5 da	1.3	Boe et al. (1967)
	Term infants	8–30 da	0.9	Boe et al. (1967)
Oxacillin	Premature infants	8–15 da	1.6	Axline et al. (1967)
	Premature infants	20–21 da	1.2	Axline et al. (1967)
	Term infants	1–6 da	1.5	von Harnack et al. (1964)
	Children	1 yr	1.1	von Harnack et al. (1964)
	Adults	—	0.7	von Harnack et al. (1964)
Neomycin	Premature infants	4–10 da	5.4	Axline et al. (1967)
	Premature infants	13–21 da	3.7	Axline et al. (1967)
Colistin methansulfonate	Premature infants	4 da	2.6	Axline et al. (1967)
	Premature infants	12–51 da	2.3	Axline et al. (1967)
	Term infants	1 da	9.0	Muratore et al. (1967)
	Term infants	3–4 da	2.6	Muratore et al (1967)
Cephaloridin	Term infants	1 da	5.4	Orzalesi et al. (1967)
	Term infants	4 da	3.7	Orzalesi et al. (1967)
	Term infants	10–14 da	2.1	Orzalesi et al. (1967)
	Term infants	2–4 mo	1.1	Orzalesi et al. (1967)
Oleandomycin	Term infants	2–4 da	3.2	Colarizi et al. (1967)
	Term infants	10–15 da	3.0	Colarizi et al. (1967)

tion of antibiotics in premature and newborn infants are summarized on Table III.

The findings were not surprising since glomerular filtration rate and some aspects of tubular function of these young infants are comparatively lower than in children and adults (45). Barnett et al. (46) showed that the clearance and tubular excretion rate of penicillin G is much less in premature infants than in children. A few other recent studies attempted to correlate renal function with values for excretion of antibiotics.

Axline & Simon (39) have shown in seven premature infants that the serum half life of kanamycin declined as glomerular filtration rate increased.

Sereni et al. (38) found that the ratio of clearance of tetracycline to endogenous creatinine clearance was much the same in newborns one-day-old, as in infants and in children suggesting that the low urinary excretion values of tetracyline in newborn infants is a consequence of the low glomerular filtration rate encountered at this age.

Little is known about other kinetic constants for the antibiotics most commonly employed in newborns and older infants. No quantitative data are available for the rate of intestinal absorption. Colarizi et al. (47) recently reported delayed plasma concentration curves of oleandomycin in two-to-four-

TABLE III

EXCRETION OF ANTIBIOTICS AT DIFFERENT AGES

Antibiotic	Excretion of Antibiotic in Urine	Author
Streptomycin	12 hours after a single i.m.* administration, premature infants 1 to 3 days old excrete 29%; whereas adults excrete 70% of the dose.	Axline & Simon (1964)
Kanamycin	12 hours after a single i.m. administration, premature infants less than 48 hours old excrete 20% of the dose; whereas premature infants 5 to 22 days old excrete 66% and adults excrete 65%.	Axline & Simon (1964)
Ampicillin	12 hours after a single i.m. administration, premature infants 2 to 7 days old excrete 22% of the dose; whereas premature infants 15 to 40 days old excrete 32%.	Axline et al. (1967)
Methicillin	6 hours after a single i.m. administration, premature infants 4 to 7 days old excrete 31% of the dose; whereas premature infants 17 to 33 days old excrete 42%.	Axline et al. (1967)
Oxacillin	6 hours after a single i.m. administration, premature infants 8 to 14 days old excrete 17% of the dose; whereas premature infants 20 to 21 days old excrete 34%.	Axline et al. (1967)
Tetracycline-1-methylenlysine	At comparable plasma levels urinary excretion of tetracycline in newborns 1 day old was 20% of that found in older infants (10 to 105 days old).	Sereni et al. (1965)

* Intramuscular.

day-old newborns, suggesting a slow transport of this antibiotic through the intestinal wall shortly after birth. The same results were found many years ago for a sulfonamide mixture, by Fichter & Curtis (48) who compared premature infants to full-term infants. A few published data have suggested that the volume of distribution of some antibiotics differs in young immature subjects and adults compared on the basis of body weight. Sereni et al. (38) found that the per cent volume of distribution per kilo body weight of a tetracycline derivative is definitely less in newborn infants, but intermediate in infants and higher in children. When tissue concentrations of tetracycline were examined in newborn and adult rabbits after comparable amounts of tetracycline were given intravenously, the concentration of drug was much higher in plasma and brain of the newborn. No significant differences in concentration of the drug were obtained in lungs, liver, and kidneys. Though the abnormally high accumulation of drugs in the CNS of immature subjects is well known (14), it is still uncertain whether this finding is a result of increased permeability of the blood-brain barrier or impairment of excretion from cerebrospinal fluid. In addition, tetracycline concentrates in particularly high amounts in bones and decidual teeth during development (33).

In contrast with these data for tetracycline, no significant differences were found by Axline et al. (39) in the apparent volume of distribution of ampicillin and methicillin in two groups of premature infants one less than eight days old and the other more than 15 days old.

TABLE IV

PHARMACOKINETIC CONSTANTS, PLASMA PROTEIN BINDING CONSTANTS AND OPTIMAL DRUG DOSAGE OF A LONG-ACTING SULFONAMIDE (2-SULPHA-3-METHOXY-PYRAZINE) IN SUBJECTS OF VARIOUS AGES

	Newborns	Infants	Children	Adults	Older Subjects
Drug concentration in plasma water at half saturation binding (μmol/L)	513	294	200	348	508
Maximum specific binding capacity of plasma proteins (μmol/L)	10.6	12.0	10.1	12.5	17.3
Minimum % of free sulfonamide in plasma	43.4	27.6	21.8	27.4	28.5
Rate constant of absorption (h^{-1})	1.47	1.96	1.85	0.70	2.42
Rate constant of elimination (h^{-1})	0.0061	0.0146	0.0169	0.0111	0.0073
Biological half life (hr)	135.6	53.9	51.0	63.3	98.2
Coefficient of distribution (ml/g)	0.47	0.36	0.20	0.22	0.26
Relative maintenance dose* (mg/Kg)	0.68	1.93	1.70	0.98	0.70
Initial maintenance dose ratio (hr)	8.67	3.77	3.00	4.33	6.42

* Interval between doses = 24 hr.

Pharmacokinetics of sulfonamides in animals of different ages.—Boger (49) had demonstrated that the same dose of sulphamethoxypyridazine results in an approximately threefold higher concentration in plasma of an 87-year-old person than in a 37-year-old man. Vest (50) has shown that plasma levels, biological half life, and urinary excretion of the same amounts of 4-sulphanilamido-5,6 dimethoxypyrimidine are very different in newborn infants and children.

Starting with these preliminary observations, a complete pharmacokinetic study was recently performed by Sereni et al. (51) using a long acting sulphonamide (2-sulpha-3-methoxy-pyrazine) in various groups of subjects of different size and age (newborns, infants, children, adults and elderly subjects). From pharmacokinetic and plasma protein binding constants, the optimal dosage regimen was derived using the method of Kruger-Thiemer (52). Average values are reported in Table IV. The minimum per cent of free sulphonamide in plasma was significantly higher in newborn infants than in any other age group. Marked differences have been observed in rate of elimination, biological half life, and coefficient of distribution. Consequently, the optimal dosage given varied considerably with the age of the subject. The maintenance dose was very low in newborns, higher in infants and children, lower in adults and even lower in older subjects. The practical value of this type of study was checked by giving the calculated optimal dosage of the sulphonamide to all subjects of different ages for prolonged periods of time. In every instance, a constant and satisfactory minimum plasma level of the compound was observed.

Interference of Drugs with Normal Biochemical and Morphological Development

Developmental pharmacology is concerned not only with the toxic and teratologic effects of many drugs on the fetus and the newborn, but also with the possibility of alteration in the normal developmental pattern of a tissue or organ. Some selected examples of this possible interference are discussed below.

Influence of steroids on the development of intestinal mucosa.—Many investigations have demonstrated the role of the adrenal cortex on normal development of intestinal mucosa, and have proved that exogeous glucocorticoids influence some important aspects of the maturation of this tissue. Moog reported that hydrocortisone given to newborn mice increases the alkaline phosphatase activity of the duodenum (53). Subsequently, Hinni & Watterson (54) showed that if adrenal hypofunction is established in chick embryos (by decapitation and interruption of the hypophyseal-adrenal axis), an inhibition of developmental increase of this enzyme may readily be obtained. Under the same experimental conditions, the morphogenesis of duodenal mucosa is also impaired.

Increased alkaline phosphatase activity of duodenum mucosa was induced in tissue cultures by Moog (55). Hayes (56, 57), working with duodenal mucosa explants of chick embryos, confirmed these preliminary observations,

and showed that if the explants are incubated before differentiation was initiated, no *in vitro* increase of alkaline phosphatase activity occurs even after a prolonged period. However, the addition of cortisone acetate to the culture induces a very significant increase of the enzyme activity when tissue from embryos older than 12 days was used. The sensitivity of tissue cultures to cortisone varies with the age and the degree of maturity of the mucosa. A lower concentration of steroid is needed to elicit a maximal enzymatic response in older tissue; moreover when the concentration of cortisone in the medium greatly exceeds the optimal dose, the activation capacity of the steroid is lost.

These experiments with duodenal alkaline phosphatase show the dependence of the normal developmental curve upon an efficient adrenal function, and prove that the administration of glucocorticoids to immature subjects may strikingly alter the normal maturation of intestinal function.

Two investigations dealing with intestinal invertase, have shown that the low enzyme activity characteristic of the immature stage *in vivo* (58) and *in vitro* (59) may be increased with glucocorticoids. Hijmans & McCarty (59) have demonstrated, that if the incubation is sufficiently prolonged, invertase activity is always increased even without adding steroids to the medium.

Corticosteroids not only interfere with intestinal maturation by activating enzyme activities which are depressed in early stages of development, but they also play a fundamental role in determining the physiologic decrease of enzyme activities which sometime occurs when a certain degree of maturity is attained. Koldowsky and co-workers (60), have found that in the rat, normal adrenal function is necessary for the physiologic decrease of β-glucuronidase activity at the initiation of weaning. When rats were adrenalectomized at 15 days of age, elevated enzymatic activities persisted for a long time. The administration of both corticosterone and aldosterone to operated animals was effective in restoring the developmental curve to normal. The final example of interference by corticosteroids with the development of intestinal function is the promotion of decreased intestinal permeability to macromolecules in newborn animals which received corticosteroids (61). Although it is commonly assumed that man is born with an intestinal barrier to macromolecules, these observations may have a clinical significance.

The activation of liver microsomal enzyme systems by administration of drug to fetus and newborn animals.—Remmer (62), Gillette (63), Fouts (64), and Conney & Burns (65) demonstrated increased activity of detoxication systems in liver microsomes following *in vivo* administration of a relatively large number of drugs and chemicals.

The practical implications of these studies for developmental pharmacology are obvious. An understanding of the mechanism might aid in comprehension of the differences in metabolism of many drugs and also endogenous compounds in immature subjects. Some of these investigations were recently reviewed in detail by Yaffe (2). Inscoe & Axelrod (66) have shown that benzpyrene injected into newborn rats causes a significant increase in hepatic

microsomal glucuronyl transferase as compared with untreated litter mates.

Hart and co-workers (67) injected phenobarbital into newborn rabbits and to pregnant does; the treatments resulted in a significant increase, both in newborn and fetal rabbits, of the microsomal enzyme activities which are of great importance in the rate of metabolism and inactivation of hexobarbital, *p*-nitrobenzoic acid, and aminopyrine. This increase, however, was not observed in livers from fetuses taken four to eight days prior to term, suggesting that such stimulation can be induced only when some enzyme activity is already present.

Catz & Yaffe (68) reported an increase in liver glucuronyl transferase activity in newborn mice treated with barbital before or just after birth. Finally, Careddu and co-workers (69) have shown that the same enzyme activity is significantly increased in newborn rabbits treated with both Coramine® and Gardenale®.

In a subsequent study conducted with newborn twins, Sereni and co-workers (70) have shown that the same type of drug activation of liver microsomal enzyme activities can be induced in humans. In every instance in which an infant was treated shortly after birth with Coramine®, a significantly lower serum bilirubin concentration than in the untreated twin was found, suggesting a more efficient process of bilirubin metabolism or clearance in the treated infant.

Investigations concerning the influence of certain drugs or chemicals injected into fetuses or infants on the activity of detoxication enzyme systems are better understood if some recent data on cytoplasmic ultrastructure of immature hepatic cells are considered.

In early stages of fetal development, liver cell cytoplasm contains very little smooth endoplasmic reticulum and comparatively few ribosomes (71). Fouts (72) has demonstrated the possibility of correlating the degree of activity of detoxication enzyme systems, which are located in ribosomes, with histologic evaluation of the smooth endoplasmic reticulum. The low capacity of fetal and neonatal liver to metabolize many drugs is not surprising. Soon after birth, the amount of smooth endoplasmic reticulum increases sharply (71); concomitantly, the activity of detoxication enzyme systems rapidly reaches adult levels (73).

Interference with somatic growth of children by steroids and other drugs.— High doses of corticosteroids given to children for prolonged periods of time induce a significant impairment in the skeletal growth rate (74). This growth retardation is often temporary and when the steroid therapy is withdrawn, a catch-up phenomenon is usually observed and lost growth is regained (75). In severe chronic diseases, such as juvenile rheumatoid arthritis or intractable asthma, steroid therapy cannot be interrupted for a prolonged period of time, and the children may be permanently stunted. In view of these important clinical observations, the recent publication by Friedman & Strang is particularly worth noting (76). Ten children were treated at different times with prednisone, corticotropin, or a combination of both drugs. The

effect of therapy on linear growth was determined by computing the rate of increase in height when different drugs were administered to the same child. Corticosteroids induced considerable stunting, but when corticotropin was given in a dose sufficient to control clinical symptoms, little or no growth impairment was observed. The reason for the difference in growth between the corticotropin and steroid-treated children is debatable, but may be related to the more physiologic role of corticotropin. The possibility that corticosteroids interfere with release of growth hormone (GH) was investigated by Hartog and co-workers (77) and by Morris and co-workers (78). Hartog and co-workers measured serum growth hormone during insulin-induced hypoglycemia in ten adults (three patients with Cushing's disease, and seven patients during steroid therapy). In seven of these cases, they found a significant low GH response in the patients given insulin. The hypothesis that GH release can be inhibited by glucocorticoids in chronically ill children is doubtful, if the results of Morris and co-workers are accepted. These authors did not find a significant difference in concentration of serum GH between control and steroid treated patients during fasting or induced hypoglycemia. Exogenous growth hormone failed to produce a significant anabolic response in the children treated with corticosteroids. These studies suggest an abnormality at the peripheral tissue level as a mechanism responsible for growth retardation by corticosteroids, although Soyka (79) has shown that corticosteroids are peripheral antagonists of GH.

In contrast with previous reports (80), it is possible that in special cases low continuous doses of testosterone derivatives can produce a significant increase in height of short children. This observation was reported from many sources in recent years (81–83). Principi (84) has recently shown that the association of small doses of an anabolic steroid to glucocorticoids in a group of nephrotic children was very effective in preventing growth retardation, but this type of therapy must be used with caution.

Finally, Limbeck and co-workers (85) have demonstrated a significant growth inhibition of immature rats treated for prolonged periods of time with therapeutic doses of salicylates. Although the mechanism of the growth inhibition remains unexplained, these observations may at least in part explain the growth retardation which is often observed in children with severe rheumatism treated with salicylates.

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