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Present Status of Drugs as Teratogens in Man [1,2,3]

JAMES G. WILSON
Children's Hospital Research Foundation and Departments of Pediatrics and Anatomy, University of Cincinnati, Cincinnati, Ohio 45229

ABSTRACT The literature pertaining to the effects of drugs on human intrauterine development has been reviewed. As far as quality and quantity of reported evidence permits, four categories of drugs were established, namely, those: (1) positively implicated as teratogenic, (2) suspected of having some teratogenic potential, (3) possibly teratogenic under some conditions, and (4) having little or no teratogenic potential under usual conditions of usage. Although a few compounds were judged to belong in each of the first three categories, it was concluded that drugs taken during pregnancy appear in total to make only a small contribution to the causation of human developmental defects.

Current concern about adverse effects of many aspects of the changing environment on human development prompts a further look at the possible role of drugs in this regard. The subject has been reviewed on previous occasions (Cahen, '66; Cohlan, '64; Lenz, '64; Nishimura, '64; Palmisano and Polhill, '72; Slater, '65; Tuchmann-Duplessis, '65, and others), but until more effective systems of surveillance for environmental teratogens are in operation, frequent scrutiny in the form of surveys and reviews may serve to maintain a degree of alertness, if not provide the needed safeguard.

A logical place to begin a survey of this type is to indicate the relative role of drugs in the total causation of human congenital disease. Table 1 estimates the known causes in man; and it is evident that, based on present information, drugs account for only a small percentage of the total burden of human developmental defects. Such percentages, however, must not be taken literally because they are crude estimates and altogether represent only the presently visible part of a mostly submerged iceberg. Certainly a majority of infants born with, or later diagnosed as having, developmental defects cannot be positively assigned to any single category of causation listed here.

Several investigators concerned with the problem have suggested that much of the presently unknown category (table 1) may eventually be explainable in terms of *combinations and interactions* of agents, either within and among categories listed in the table, or involving factors not now suspected. Whether or not this is true, and I am inclined to guess that it may be, there is strong likelihood that chemicals, including drugs, will be ranked high in the lists of interacting substances. Support for this opinion is found in the tremendous numbers of drugs and chemicals already known to be teratogenic in laboratory animals (table 2). Striking degrees of potentiative interactions have been demonstrated to occur in laboratory animals when two or more compounds, some included in the accompanying list, were given simultaneously at near threshold level for teratogenicity (Wilson, '64). It should be emphasized that most of the substances listed in table 2 were teratogenic only at doses far above human therapeutic or exposure levels. One can only guess at the extent to which pregnant women are exposed simultaneously to more than one of these agents.

The implications of the thalidomide catastrophe notwithstanding, drugs are still taken in appreciable numbers for more or less legitimate reasons during human pregnancy. A prospective study of 240 pregnancies revealed that a mean of 3.7 drugs regarded by the authors (Nora et al., '67b) as potentially teratogenic were taken dur-

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TABLE 1

Causes of developmental defects in man — estimates based on past experience

Known genetic transmission	20%
Chromosomal aberration	5
Environmental causes	
Radiations	<1
Therapeutic	
Nuclear	
Infections	2–3
Rubella virus	
cytomegalovirus	
Herpesvirus hominis	
Toxoplasma	
syphilis	
Maternal metabolic imbalance	1–2
endemic cretinism	
diabetes	
phenylketonuria	
virilizing tumors	
Drugs and environmental chemicals	2–3
androgenic hormone	
folic antagonists	
thalidomide	
organic mercury	
some hypoglycemics (?)	
some anticonvulsants (?)	
Combinations and interactions	?
Unknown	65–70%

From Wilson ('72a).

ing the first trimester. A survey in Scotland showed that over 97% of 1369 mothers took prescribed drugs and 65% self-administered drugs during pregnancy (Nelson and Forfar, '71). It was found that significantly more of the mothers in the latter study who gave birth to infants with developmental abnormality took aspirin, antacid, dextroamphetamine, phenobarbitone, sodium amytal, other barbiturates, cough medicines, iron sulphonamides, and nicotinamide than did mothers in the control group. The real meaning of such data is uncertain because, for one thing, it is impossible without appropriate controls to separate influences on development caused by the drug and by the condition for which the drug was taken. Furthermore, the time during gestation when a drug is taken, particularly when it is first taken, may determine whether and what type of embryotoxicity will result.

Available literature has been surveyed for information on the effects on the offspring of drugs known to have been taken in the first 2 or 3 months of pregnancy. The reviewer has tried to be mindful of the quality of documentation in weighing the evidence for or against implicating a particular drug, but the scope of this review does not permit critical evaluation of the individual reports cited. This judgment is reflected, however, in the classification of drugs into one of four categories. Relatively few drugs can be *positively implicated as teratogenic*. Others are *suspected of having teratogenic potential* because of several more or less well-documented case reports but are yet to be clearly established in this regard. Still others must be regarded as *possibly teratogenic* on the basis of scattered, usually not-well-documented evidence. Some drugs, however, have been used widely enough in suitably controlled situations to warrant the conclusion that under usual conditions of usage they *involve little or no teratogenic risk*.

I. DRUGS POSITIVELY IMPLICATED AS TERATOGENIC

1. *Thalidomide.* In the 10 years since the recognition of its devastating effect on the human embryo, thalidomide has assumed the status of a classic teratogenic agent (Lenz, '64). It proved to be almost invariably effective if taken in adequate dosage on a very few days or even a single day during the susceptible period of the human embryo, from the 20th to the 35th day postconception. It produced a well-defined pattern of musculoskeletal deformities, affecting mainly the extremities and face, not precisely duplicated in any other syndrome, although infrequently some of the characteristic defects may occur spontaneously. It was virtually nontoxic to young adults and consequently carried no risk of overdosage. Thus, at the expense of several thousand crippled children, and the loss of an otherwise safe and effective sedative, teratologists have learned several valuable lessons. The most important one is that the human embryo may be inordinately sensitive to a substance that causes little or no toxicity in human adults or in test animals. It is a disquieting fact that the animals most widely used in the testing of teratogenic effects of drugs, i.e., mouse, rat, rabbit, are relatively insensitive to this most potent human teratogen.

The only animals known to react teratogenically to thalidomide as does man are several species of macaque monkeys and baboons (Wilson, '72b). This has resulted

TABLE 2

Types of drugs and environmental chemicals that have been shown to be teratogenic [1] in one or more species of mammals

Type of agent	Examples
Salicylates	Aspirin, oil of wintergreen
Certain alkaloids	Caffeine, nicotine, colchicine
Tranquilizers	Meprobamate, chlorpromazine, reserpine
Antihistamines	Buclizine, meclizine, cyclizine
Antibiotics	Chloramphenicol, streptonigrin, penicillin
Hypoglycemics	Carbutamide, tolbutamide, hypoglycin B
Corticoids	Triamcinolone, cortisone
Alkylating agents	Busulfan, chlorambucil, cyclophosphamide, TEM
Antimalarials	Chloroquine, quinacrine, pyrimethamine
Anesthetics	Halothane, urethan, nitrous oxide, pentobarbital
Antimetabolites	Folic acid, purine and pyrimidine analogues
Solvents	Benzene, dimethylsulfoxide, propylene glycol
Pesticides	2,4,5-T, carbaryl, captan, folpet

[1] Teratogenic effects were usually seen only at doses well above therapeutic levels for the drugs, or above likely exposure levels for the environmental chemicals.
From Wilson ('72a).

TABLE 3

Embryotoxic effects of diphenylhydantoin as seen in 100-day rhesus monkey fetuses from dams given large doses early in pregnancy

Fetus Number	Maternal treatment		Condition of fetus			
	Daily dose	Gest. days treated	Wt.	External	Autopsy	Skeleton
	mg/kg		*g*			
♂3a	25 id	22–24	145	Normal	Normal	Normal
29c	50 id	19–21		aborted on day 29		
♀11c	25 bid	22–24	118	Normal	Normal	Small talus
♀90a	5 bid	25–45	141	Normal	Normal	Normal
♂13f	5 bid	25–45	129	Normal	Retrocaval rt. ureter [1]	Normal
♀73b	5 bid	25–45	141	Normal	Normal	Normal
♀71b	5 bid	25–45	136	Normal	Retrocaval rt. ureter	Normal
♀83b	10 bid	24–44	132	Normal	Normal	Normal
♀59d	10 bid	25–45	121	Normal	Normal	Normal
♂29f	10 bid	23–43	152	Normal	Normal	Normal
♂38d	10 bid	20–40	134	? neck webbing	Normal	Normal
♂33e	20 bid	22–42	122	Normal	Retrocaval rt. ureter	Absent talus
♀50d	20 bid	24–44	144	Normal	3 cusps on mitral valve	Normal
♂13g	20 bid	20–40	146	Normal	Normal	Cervical ribs
81c	20 bid	23–43		aborted on day 44		
12 controls	Vehicle or none	—	142 ± 12[2]	Normal	Normal	Several skeletal variations [3]

[1] Retrocaval right ureter has not been previously seen in rhesus monkeys.
[2] ± Standard deviation.
[3] Skeletal variants include 1 with no ossification of talus, 2 with extra pr. ribs, 2 with extra rudimentary ribs, 1 with "knobby" ribs.

in an increasing tendency to consider the simian primates as more valid test animals for the evaluation of human teratological risk than are the currently used rodents and rabbits, but it must be emphasized that the close parallel between man and monkey as regards the teratogenicity of thalidomide has not been demonstrated for other drugs except those with androgenic properties.

2. *Steroid hormones.* It has been known for almost 30 years that treatment of preg-

nant mammals including monkeys (van Wagenen and Hamilton, '43) with male sex hormones produced pseudohermaphroditism in the female offspring similar to that occurring spontaneously in human infants. The injection of androgenic hormones per se as treatment for breast cancer has resulted in the masculinization of a number of female fetuses when such treatment was commenced prior to the 12th week of gestation (Grumback and Ducharme, '60). The accepted practice of using progesterone from natural sources for treatment of threatened abortion led to the widespread use between 1950 and 1960 of synthetic progestins for the same purpose. More than 600 female babies with equivocal or frankly masculinized external genitalia were born before it was realized that some of these synthetic compounds had appreciable androgenic activity (Wilkins, '60; Cahen, '66; Voorhess, '67).

Estrogenic hormones given at higher than physiologic levels are generally regarded as incompatible with pregnancy, and therefore of little teratogenic risk. Their tendency to stimulate uterine contraction is thought sufficient usually to dislodge the conceptus, but this is not invariably the case (Bačič et al., '70). Three cases of malformed newborns have been attributed to maternal treatment with large doses of estrogen early in pregnancy (Uhlig, '59), although no instances of feminization of genetic males is known. Paradoxically, treatment with the nonsteroidal estrogenic substance diethylstilbesterol during pregnancy has been associated with masculinization of the female fetus in four instances (Bongiovanni et al., '59). Another puzzling reaction to maternal treatment with diethylstilbesterol during pregnancy has recently been reported. A number of young women aged 16–22 years have developed adenocarcinoma of the vagina after a common history of having been exposed to this synthetic estogen in utero when their mothers were treated for threatened abortion during the first trimester of pregnancy (Greenwald et al., '71; Herbst et al., '71). Although these neoplasms do not appear to represent deviations of normal developmental processes, and accordingly are not strictly teratic in origin, they seem to have been induced during early differentiation of the vagina, possibly as a somatic mutation. In any event, they raise interesting questions about the relation between carcinogenesis and teratogenesis.

The ease with which corticosteroids given during pregnancy to mice produced cleft palate (Fraser and Fainstat, '51) has caused some concern about their use during human pregnancy. Published reports on the administration of these substances to pregnant women indicate some increase in abortion, stillbirth, and prematurity above background levels (Reilly, '58), but only five cases of cleft palate were observed in infants from more than 300 women treated for a variety of reasons (Bongiovanni and McFadden, '60, and others). Considering their extensive use and the failure of any recent epidemiologic surveys to show statistical correlation these steroids must be regarded as having little if any teratogenic potential (DeCosta and Abelman, '52).

3. *Folic acid antagonists.* Early reports of the use of folic acid antagonists in laboratory animals indicated that such compounds were almost invariably embryolethal, which was taken as justification for their use as abortifacients in human pregnancies scheduled for therapeutic abortion (Thiersch, '52, '56). Of 24 pregnancies so treated, eight failed to abort and two of these yielded malformed infants. In addition, two of those that died in utero also appear to have been malformed. In another series of 20 cases treated with aminopterin during pregnancy (Goetsch, '62), there was subsequent abortion in 15 and malformation in one of the five survivors. Combining these reports, 70% of treated pregnancies aborted and 23% of the surviving infants were malformed. Seven additional cases of malformed liveborn infants, making a total of 10, have now been attributed to antifolic compounds, mainly aminopterin (Meltzer, '56; Warkany et al., '59; Milunsky et al., '68; Shaw and Steinbach, '68; de Alvarez, '62; Emerson, '62). Thus, although treatment with folic acid antagonists during the early months of human pregnancy usually resulted in intrauterine death, between 20 and 30% of the fetuses that reached term were malformed. The types of malformations observed in the infants were varied and no basic pattern or syndrome was recogniza-

ble, a fact in keeping with animal studies which have shown that almost any organ can be the site of abnormality depending on the time in gestation at which the antagonist is applied (Nelson, '63).

II. DRUGS SUSPECTED OF SOME TERATOGENIC POTENTIAL

Several drugs are suspected of having some teratogenic potential because they are occasionally associated with malformations in the offspring of women treated during early pregnancy. These reports, however, constitute only a low percentage of the total number of women known or thought to have been treated, and consequently are subject to varied interpretations: (1) as spontaneous occurrences coincidentally related to drug treatment, (2) as attributable in some part to the maternal disease for which the drug was given, or (3) as manifestation of a low order of teratogenic potential of the drug. Reliance on voluntary reporting of individual cases generally does not provide the type or quantity of data needed to choose among these alternatives. Prospective epidemiologic surveys are sometimes able to rule out the possibility of drug-related causation, as was the case with meclizine (Mellin and Katzenstein, '64), but more often such surveys provide suggestive rather than definitive data (Nelson and Forfar, '71).

1. *Anticonvulsants.* Some of these are prominent in the group of drugs suspected of being teratogenic in man under certain conditions. Meadow ('68, '70) reported a total of 38 cases of cleft lip and/or cleft palate in infants born to epileptic mothers on anticonvulsant drugs throughout pregnancy. Eight also had cardiac malformations. *Phenobarbitone* was most commonly used, but several other drugs were also taken singly or in combination. The incidence of these defects was substantially higher than would be expected in an otherwise similar population that had not taken these drugs; but in view of the unreliability of retrospective surveys of this type the author regarded the data as only suggestive. Mirkin ('71) prospectively followed three epileptic women on *phenylhydantoin* throughout pregnancy and reported that all gave birth to babies with cleft lip or palate. Five additional cases were noted by Pashayan ('71) and McMullin ('71). *Trimethadione*, another antiepileptic drug, has been associated with malformation in eight of 14 pregnancies of four women who received this compound during the early months of pregnancy (German et al., '70). Four of the defective children had facial clefts and four had cardiac defects, which, together with the above, strongly suggests a recurring pattern of malformations associated with these anticonvulsant drugs.

The Report (6th annual) of the Committee on Adverse Drug Reactions of New Zealand ('71) indicates that 11 of the 29 adverse effects attributed to anticonvulsants in 1 year involved birth of malformed children and that nine of the mothers were epileptic and were on continuous therapy throughout pregnancy. Seven of the children in the latter group had facial clefts and three had congenital heart disease. Kučera ('71) in a large survey in Czechoslavakia reported a marginally significant ($P = 0.05$) increase in facial clefts and congenital heart disease in infants born to epileptic women on anticonvulsant therapy, as compared with the general population. On the other hand, it has been pointed out that many women are on anticonvulsant therapy throughout pregnancy with no untoward effect (Bird, '69).

The foregoing data relate to use of several anticonvulsants, but they bring to a disturbing total the number of defective children attributed to the taking of drugs of this class during early pregnancy. It is noteworthy that a great majority of the children had facial clefts and not a few had cardiovascular defects. Of interest is the fact that diphenylhydantoin in single doses is highly teratogenic in mice (Harbison and Becker, '69). Because of the recurring suggestive reports in man the present author has undertaken to test the teratogenicity of Dilantin (diphenylhydantoin) in pregnant rhesus monkeys (table 3). Using doses several times larger than the recommended human dosage, the only embryotoxicity yet seen in this species was a minor urinary tract anomaly and possibly a slight increase in abortions. Nevertheless, this class of drugs must continue to be watched closely.

2. *Neurotropic-anorexogenic drugs.*

Such compounds as *dexamphetamine* and *phenmetrazine* have at times been held suspect, in part on the basis of results from animal experiments (Tuchmann-Duplessis and Mercier-Parot, '64). For example, dexamphetamine sulfate readily produced malformations when given during pregnancy to mice (Nora et al., '65), but retrospective analysis of 219 cases and prospective study of 52 cases involving use during human pregnancy yielded no teratogenic effects (Nora et al., '67a). The question was reconsidered, however, when a subsequent study of 184 mothers of infants with heart malformations showed a higher incidence of amphetamine ingestion than a control group (Nora et al., '70). Another study has found an elevated incidence of biliary tract atresia among offspring of mothers taking amphetamines (Levin, '71). A recent retrospective survey of 458 mothers of children with various malformations (Nelson and Forfar, '71) showed that a higher proportion of such mothers had taken dextroamphetamine for suppression of appetite during early pregnancy than had the control mothers of normal infants. Another neurotropic drug used as an appetite suppressant during pregnancy, phenmetrazine, was reported to have been associated with the birth of defective children in a few instances (Moss, '62; Powell and Johnstone, '62), but this was not confirmed by other reports (Notter and Delande, '62). Neurotropic substances sometimes mentioned as possibly teratogenic are Dominal (Tuchmann-Duplessis and Mercier-Parot, '64) and bromine-containing compounds (Opitz et al., '72) but supporting evidence is meager.

3. *Oral hypoglycemics.* Certain of these drugs must now be included in the suspect category. Since 1961 when two cases (Campbell, '61; Larsson and Sterky, '61) of malformed infants were reported as born to mothers who had taken *tolbutamide* or other sulfonylurea compounds throughout pregnancy to control diabetes at least 10 similar cases have been described (Coopersmith and Kerbel, '62; Campbell, '63; Dolger et al., '69; Caldera, '70; Schiff et al., '70). Generally, malformed infants have occurred in a ratio of about one in 20 among all births to women taking tolbutamide during pregnancy; but there have been other reports of fairly large series of cases in which no abnormality was observed (Sterne, '63). The low incidence together with the absence of a syndrome of defects leaves the teratogenic status of the sulfonylurea hypoglycemics in some doubt. There is, however, no doubt that these compounds are highly teratogenic in mice, rats, and rabbits (Tuchmann-Duplessis and Mercier-Parot, '63).

4. *Alkylating agents.* Because of their polyfunctional suppression of growth, alkylating agents would be immediately suspect as teratogens. They are radiomimetic, cytotoxic, and highly teratogenic in laboratory animals (Chaube and Murphy, '68). Nevertheless, very few instances of human maldevelopment have been attributed to use of these compounds during pregnancy (Sokal and Lessman, '60), although intrauterine death and abortion regularly occur with high dosage (Nickolson, '68). One woman given 6-mercaptopurine and busulfan gave birth to a baby with multiple malformations (Diamond et al., '60) and one given cyclophosphamide delivered a child with multiple musculoskeletal defects (Greenberg and Tanaka, '64). Various cytotoxic cancer chemotherapeutic agents have been administered to pregnant monkeys and found to produce high rates of intrauterine death but relatively few outright malformations (Wilson, '72b). The paucity of such cases in man may be attributed to all of three factors: (1) restricted use owing to high teratogenic risk as shown in laboratory animals, (2) easy justification of elective abortion in view of the life-saving role of these drugs for the mother, and (3) high rate of treatment-induced intrauterine death and abortion.

III. DRUGS POSSIBLY TERATOGENIC UNDER SOME CONDITIONS

This category includes drugs that have been used widely and have only rarely been implicated in human teratogenesis. Nevertheless they have demonstrated more or less teratogenic potential in laboratory animals and there is reason to believe that they possibly have such potential in man under some conditions.

1. *Aspirin.* Since Warkany and Takacs ('59) in rats, and Larsson et al. ('63) in mice demonstrated that large doses of

salicylates were teratogenic, questions occasionally arise about the possible teratogenicity of aspirin in man, both in view of its widespread use as an analgesic and the high dosage used in rheumatic disease. Recent studies in rhesus monkeys showed that when doses of aspirin equivalent to five or six times the teratogenic level in rats were used, definite embryotoxicity resulted (Wilson, '71). Of eight pregnant monkeys so treated, two aborted within three weeks of oral dosage, three produced malformed offspring, and two produced growth-retarded fetuses, of which one had unilateral cervical rib, and only one produced a normal fetus. It should be emphasized that the daily dose (500 mg/kg) was considerably in excess of that likely to be used therapeutically in pregnant women. This "margin of safety" has been made less secure, however, by the observation of Kimmel et al. ('71) that the teratogenic potential of a given dose of aspirin in rats can be appreciably increased by concurrent administration of benzoic acid, a widely used food preservative. Similar metabolic interaction of benzoic acid and salicylates is known to occur in man (Levy, '65).

There are no known instances of human teratogenicity traceable directly to the taking of large doses of aspirin during pregnancy, but there is some epidemiologic indication of a relation between the taking of aspirin during pregnancy and the delivery of defective babies. In a retrospective survey of 833 pregnancies that resulted in the birth of malformed infants (Richards, '69), it was found that a significantly greater ($P = <0.001$) percentage of women delivering defective babies had taken a salicylate preparation during the first trimester of pregnancy than had women delivering normal babies. Another retrospective study in which 458 mothers gave birth to malformed infants (Nelson and Forfar, '71) revealed that analgesics (mainly aspirin) were taken by a significantly higher proportion of mothers during the first 56 days of pregnancy than was the case in controls. Thus, although not proven to have teratogenic potential, it would seem unwise at this time to dismiss aspirin as involving no teratogenic risk for man.

2, *Antibiotics.* This diverse group of drugs has been implicated in human teratology mainly by the reports of Carter and Wilson ('65) who made a retrospective analysis of 85 women given antibiotics during the first 12 weeks of pregnancy. Twelve of the infants were malformed, as against two that would have been expected in untreated pregnancies, and 13 aborted, whereas the expected number was eight. An additional 67 cases of antibiotic administration during the first 12 weeks of gestation yielded approximately 25% pregnancy wastage (sum of abortion, malformation, stillbirth, and neonatal death) as compared with 14% in controls (Carter, '65). Deafness has occasionally been reported in young children after streptomycin therapy of the pregnant mother (Boletti and Croatto, '58; Robinson and Combon, '64) and one woman given chloramphenicol during pregnancy produced a fetus with urinary tract anomalies (Shotten and Monie, '63). However, in recent retrospective studies (Richards, '69; Nelson and Forfar, '71) no indication was found of an increase in malformations after antibiotics given during pregnancy. Several antibiotics have been shown to be teratogenic in laboratory animals. Nevertheless, in view of the considerable use of these agents during human pregnancy over the past 20 years it would seem likely that any appreciable teratogenicity for man would by now have been well documented. Their known teratogenicity in animals together with their general antimetabolic effects, however, suggests that some teratogenic potential in man under some conditions be regarded as a possibility.

3. *Antituberculous drugs.* Of this assorted group of drugs some have been questioned as regards adverse effects on pregnancy or its outcome but no strong evidence has been advanced to implicate any one or combination. *Ethionamide* was reported to be teratogenic in one study of 22 pregnant women who received the drug during pregnancy (Potworowska, '66). Only five were known to have taken the drug during the early months of pregnancy, but of these four produced malformed children. There was no common defect or syndrome but the central nervous system was involved in all. The simultaneous use of two or more antituberculous drugs (streptomycin, isoniazid, and paraaminosalicylic acid) in 123 women was reported (Var-

pela, '64) to have increased malformations by a factor of two or three compared with controls. Other studies of the use of isoniazid during pregnancy reported "harmful effects" but no malformations (Monnet et al., '67), and of various antituberculous drugs there was found "nothing to suggest that any of the drugs was teratogenic" (Lowe, '64). Again, the evidence is conflicting and too limited for a firm conclusion at this time.

4. *Quinine.* In high doses such as might be used in attempted abortion this antimalarial has at times been mentioned as a possible human teratogenic agent. Winckel ('48) was able to collect 17 cases in which visual or auditory defects in the offspring were associated with the taking of quinine during pregnancy, but the evidence for a causal relation was tenuous in several of these. Tanimura ('72) undertook to survey the literature and was able to find 20 cases of human malformation after the taking of quinine to induce abortion, but there is no indication of the sample size from which these were taken and the details of dosage given in such cases are usually not reliable. Animal experiments reviewed by the same author found death and growth retardation but very few malformations among offspring of treated females.

5. *Imipramine.* Early in 1972 reports from Australia stated that a positive correlation had been established between the taking of this antidepressant during the first third of pregnancy and the birth of a few infants with reduction deformities of the upper limb, resembling those seen after thalidomide ingestion (McBride, '72). Although press reports later indicated that these claims had been in part withdrawn the fact that this and related tricyclic antidepressants had been found to show a variable level of teratogenicity in rabbits and rats (Robson and Sullivan, '63; Aeppli, '69), requires that the possibility of human teratogenicity be thoroughly investigated. A search through current literature by the present author yielded 221 published cases in which one of these drugs was known or presumed to have been taken during the first trimester of pregnancy (Barson, '72; Crombie et al., '72; Kuenssberg and Knox, '72; Scanlon, '69; Sim, '72; Report of the New Zealand Committee on Adverse Drug Reactions, '71). A total of six children with various malformations was reported, and, interestingly, none had limb defects such as were characteristic of McBride's cases. (These data do not represent a true incidence because the total number of pregnancies treated is not known and the search for malformations was not exhaustive.) The Metropolitan Atlanta Congenital Defects Program report of Jan.-Feb., 1972 examined 120 cases involving reduction deformity of the limbs similar to those described by McBride, but was unable to establish that any of the mothers had taken imipramine or related antidepressants. Thus, if the tricyclic antidepressant drugs have teratogenic potential in man it is of a low order when used at recommended therapeutic doses, since there is no new evidence to support the original view that reduction deformities of the limbs are typically produced by these drugs.

6. *Insulin.* This widely used drug has at times been the basis for some concern. Of 14 women subjected to insulin coma in psychiatric therapy during the first 14 weeks of gestation four produced dead and two delivered malformed fetuses (Sobel, '60), and two mentally defective children were associated with similar maternal therapy during the third month of pregnancy (Wickes, '54). The occasional malformed infant born to a diabetic woman maintained on insulin is probably coincidental (Pettersson et al., '70).

IV. DRUGS INVOLVING LITTLE OR NO TERATOGENIC RISK

To state categorically that a particular drug or other environmental factor involves no risk to human development, in view of events over the last 12 years, would be foolhardy. In fact most teratologists accept the theoretical principle that all chemical agents could, under the right conditions of dosage, developmental stage, and species selection, be shown to have adverse effects on development (Karnofsky, '65), although the corollary that it is not always possible to prove this principle must also be accepted. Nevertheless, it can be stated with some assurance that certain agents are unlikely to cause adverse ef-

fects within the limits of dosage ordinarily encountered. The categories of drugs discussed here have, for one reason or another, at some time been suspect but then found after further investigation to pose little risk in human therapeutic use, despite the fact that at higher dosage they may be detrimental to development in laboratory animals.

1. *LSD.* There has been much controversy over the cytogenetic and teratogenic potential of lysergic acid diethylamide (LSD). A recent comprehensive review by Dishotsky et al. ('71) of more than 100 publications on the subject has done much to place it in perspective. In brief, the conclusions reached were: (1) when chromosomal damage has been found it was among illicit drug users and therefore appears to be related to drug abuse generally; (2) pure LSD ingested in moderate dosage does not produce chromosomal damage that can be detected by current methods; (3) LSD may be a weak mutagen, but it is unlikely to be mutagenic in concentrations used by human beings; (4) early reports of teratogenic effects in rats and hamsters have for the most part not been confirmed and results in mice have been highly inconsistent; (5) the several instances of malformations among infants born to women having ingested illicit LSD during pregnancy may either be coincidental or related to the general drug-abuse problem; (6) there is no reported instance of a woman delivering a malformed child after taking pure LSD during pregnancy. A further review by Long ('72) critically analyzed five instances of limb defects among 161 children from parents who took LSD and concluded that there was no strong evidence that LSD was causative.

Kato et al. ('70) injected four pregnant monkeys with massive doses of LSD (0.125–1.0 mg/kg, approximately 90 times the human hallucinogenic dose) repeatedly at times estimated to be in the third or fourth month of gestation. They observed one normal infant, two stillborn infants which "on gross inspection showed facial deformity," and one which died 1 month postnatally. In the present author's laboratory eight pregnant monkeys have been treated orally three times per week for four weeks between days 20 and 45 of gestation with doses of 200 μg (20 times the human "trip" dose on mg/kg basis). One female aborted, but seven produced normal 100-day fetuses at hysterotomy. Chromosomal abnormalities were not significantly increased in the mothers or the fetuses.

2. *Sulfonamides.* Although these bacteriostatic drugs would theoretically seem to be likely teratogens by the nature of their biological action, as a group they appear to have little effect on early human development, as indicated by lack of case reports or epidemiologic survey data that would suggest embryotoxicity after dosage during pregnancy.

3. *Meclizine.* This antihistamine was reported to have adverse effects on human development when taken during pregnancy in several scattered instances soon after thalidomide was first revealed to be teratogenic. Subsequently, however, several prospective studies involving large numbers of cases (Mellin, '63; Smithells and Chinn, '64; Yerushalmy and Milkovich, '65; Nelson and Forfar, '71) revealed that pregnant women having taken this and related drugs produced no more defective babies than did other women.

4. *Cortisone.* As already noted, cortisone is judged to have little or no teratogenic potential in man on the grounds that it has been widely used during human pregnancy and has rarely been shown, either in reported cases or in epidemiologic surveys, to have been associated with the birth of defective children. The well-known teratogenicity of this compound in some rodent species undoubtedly has insured that such associations have been looked for in man.

5. *Tranquilizers* and *antiemetics* generally. Like cortisone these classes of drugs are assumed to have little or no teratogenic potential in man because they also have been extensively used. Both of these classes have, nevertheless, been held suspect because of their categorical association with thalidomide, a known teratogen, and meclizine, a drug at one time suspected of being teratogenic.

The truism that when an association is looked for on a large scale and is not found it is safe to assume that such an association is infrequent in occurrence, applies to this category of drugs as regards their

teratogenicity. A small reservation must be held, however, because in the event of infrequent occurrence it is often impossible to distinguish between coincidence and a low level of cause-effect relation.

CONCLUDING REMARKS

Many drugs too numerous to name have never been mentioned in relation to teratogenesis. Prospective surveys have usually failed to indict any particular drug in association with developmental defects, and furthermore have failed to show that the taking of drugs in general during pregnancy predisposes to a higher incidence of defects. For example, Mellin ('64) made special effort to ascertain the drugs actually taken by 3200 women during the first 13 weeks of their pregnancies. A total of 266 (8.3%) of these yielded structurally or functionally defective offspring. When these were compared with equal numbers of pregnancies yielding normal offspring, born immediately before and immediately after those yielding abnormal infants, it was found that mothers producing abnormal children did not take more or significantly different drugs than the mothers in the two control groups. Although these numbers were limited the care with which this study was done strengthens the opinion that the mere taking of drugs during the first trimester does not predispose to abnormal development. In consideration of the findings in the foregoing review, one is inclined to agree with Mellin who concluded that ". . . drugs in general are not an important factor in congenital malformations in general." Barring teratological catastrophes such as thalidomide, the few drugs that have been identified as having some teratogenic potential in man represent only a very small fraction of either the drugs used or of the defects occurring.

To avert any complacency that may result from the views stated above, however, it should be noted that two lingering questions remain unanswered: (1) Is it possible to devise tests and surveillance systems that will prevent another teratological catastrophe such as thalidomide? (2) How are interactions between drugs and other environmental factors, or these and unstable genetic loci, to be identified, assuming that such interactions contribute significantly to the large "unknown" segment of causation in human teratology? These questions will not be definitively answered in the immediate future. In the meantime responsible clinical surveillance and reporting of cases, whether one-by-one or in organized surveys, are to be encouraged in view of their proven value in identifying human teratogens, although spontaneous reporting will continue to lack the consistency, completeness, and coordination needed to evaluate properly the embryotoxic risks from drugs.

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