Ann. Rev. Pharmacol. Toxicol. 1984. 24:483–500

MECHANISMS OF TERATOGENESIS

D. A. Beckman and R. L. Brent

Department of Pediatrics, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania 19107

MECHANISMS

The mechanisms of teratogenesis fall into two broad categories based on the etiology of the congenital malformations: (*a*) errors in genetic programming based on deviations in the genotype of the embryo or the low probability for error of a normal genotype; and (*b*) environmental agents or factors that interact with an embryo during the period of development (drugs, chemicals, radiation, hyperthermia, infections, abnormal maternal metabolic states, or mechanical factors).

The etiology of human malformations includes both genetic and environmental factors, but it also includes a large category labelled *unknown* (Table 1). Many geneticists believe that a significant proportion of congenital malformations of unknown etiology are polygenic (1, 2). Thus, malformations with an increased recurrent risk, such as cleft palate, anencephaly, spina bifida, congenital heart disease, pyloric stenosis, talipes equinovarus, and congenital dislocation of the hip, fit the criteria for polygenic inherited disease. They also happen to fit the criteria for multifactorial disease (1, 3). Included in the unknown category are malformations that occur spontaneously at a very low frequency simply on the basis of the probability of spontaneous errors of development. Thus, particular genotypes have an inherent malformation rate based on the fact that embryonic development is a very complicated process and has a variable but low probability of going awry just as DNA duplication, for example, is not an error-free process. The explanation for the etiology and mechanisms of teratogenesis for this large group of malformations with unknown etiology will depend upon identifying the genes involved in polygenic or plurogenic processes, identifying the interacting genetic and environmental

0362-1642/84/415-0483$02.00

Table 1 Etiology of human malformations observed during the first year of life[a]

Suspected cause	Percent of total
Genetic	
Autosomal genetic disease	15–20%
Cytogenetic (chromosomal abnormalities)	5%
Unknown	65%
Polygenic	
Multifactorial (genetic-environmental interactions)	
Spontaneous errors of development	
Synergistic interactions of teratogens	
Environmental	
Maternal conditions: diabetes, endocrinopathies, nutritional deficiencies, drug and substance addictions	4%
Maternal infections: rubella, toxoplasmosis, syphilis, herpes, cytomegalic inclusion disease	3%
Mechanical (deformations): abnormal uterus, amniotic bands, umbilical cord constrictions, disparity in uterine size and uterine contents	1–2%
Chemicals, drugs, radiation, hyperthermia	<1%

[a]References 4, 5

determinants of multifactorial traits, and identifying the mathematical risks for error during important embryonic processes of normal development. Until this can be accomplished, we will continue to label a large proportion of human malformations as having hypothetical etiologies.

The other two etiological categories of teratogenic agents, environmental and genetic, have different pathologic processes that result in embryopathology. Congenital malformations due to genetic etiology have a spectrum of pathologic processes that are the result of a gene deficiency, a gene abnormality, chromosome rearrangement, chromosome deletion, or chromosome excess that results in abnormal development. The pathologic nature of this process is determined before conception or at least before differentiation because of the presence of inherited or newly acquired genetic abnormalities. Although environmental factors may modify the development of the genetically abnormal embryo, the genetic abnormality is the predominant contributor to the pathologic process. Many genetic diseases in animals and man have been studied and we are able to determine the mechanism of teratogenesis of some hereditary malformations (i.e. T locus and Ah locus in the mouse and diaphragm aplasia and jejunal atresia in man). However, this review will not discuss the mechanisms involved in hereditary malformations but rather will discuss the mechanisms involved in malformations that are primarily environmentally produced.

Basic tenets of environmentally produced malformations are that teratogens or teratogenic milieus have certain characteristics in common:

1. *Stage sensitivity* indicates that susceptibility to teratogenesis varies during gestation so that the three stages of development have the following associated characteristics of teratogenesis: from fertilization through early post-implantation, the embryo has relatively few cells and a great capacity for the replacement of omnipotent cells. Thus, the effect of a teratogenic insult is typically an all-or-none phenomenon, because either the agent affects enough cells to result in embryolethality or so few cells are affected that the embryo is able to effectively repair itself. The second stage, the period of organogenesis (from day 18 through about day 60 of gestation in the human), is the period of greatest sensitivity to teratogenic insults and the period when anatomical malformations can be induced. The third stage, the fetal period, is characterized by cell depletion and growth retardation resulting from exposure to teratogenic agents after the major tissue and organ types have differentiated, although fetal death can be produced.

2. *Dose-response relationships* refer to the phenomenon that, as the exposure or dosage increases, frequency and severity of the teratogenic effects also increase.

3. *Threshold effects* refer to the dosage or level of exposure below which the incidence of death, malformation, growth retardation, or functional deficit is not statistically greater than that of controls (this is usually one to three orders of magnitude below the teratogenic dose).

4. *Genetic variability* in mammals determines differences in placental transport, absorption, metabolism, and distribution of an agent and accounts for variation in teratogenic effects among species and individuals.

5. *Infections* are exceptions to the basic tenets of teratogenesis. Infectious agents may not conform because the course of an infection is difficult to define in terms of period of exposure to the fetus and dose of the infectious agent to which the fetus is exposed at any one time. Therefore, dose-response relationships, threshold effects, and genetic variability have been impossible to demonstrate in the human.

Based on his review of the literature, Wilson (6, 7) proposed possible mechanisms of teratogenesis, summarized in Table 2. This list illustrates the many levels at which embryonic development is vulnerable to errors or disruptive influences. Unfortunately, this approach may generate some confusion when one attempts to determine etiology for the following two reasons: (*a*) the pathologic processes could result from genetic or environmental factors; and (*b*) the fact that an environmental agent can induce one of these pathologic processes does not guarantee that exposure will result in teratogenesis. Thus, while the listing summarized in Table 2 provides us with a format of theoretical teratogenic mechanisms, it does not relate these to known teratogens nor does it enable us to predict teratogenesis in the human if an agent exhibits one of these characteristics in an experimental test system.

We will first briefly discuss some of Wilson's proposed mechanisms to

Table 2 Mechanisms of teratogenesis as suggested by J. G. Wilson[a]

1. Mutation: changes in the nucleotide sequence in DNA.
2. Chromosomal aberations: alterations in the amount of DNA.
3. Mitotic interference: a disturbance in the cell cycle.
4. Altered nucleic acid synthesis and function: a disturbance in translation, transcription or DNA synthesis.
5. Lack of precursors, substrates and coenzymes for biosynthesis: a general or specific nutritional deficiency.
6. Altered energy sources: interference with the citric acid cycle or the terminal electron transport system.
7. Enzyme inhibition: limited or specific enzyme inhibition.
8. Osmolar imbalance: alterations in fluid pressures, viscosities, and osmotic pressures.
9. Altered membrane characteristics: a disruption in membrane transport and permeability.
10. Other mechanisms: an extensive list of possible mechanisms for which there is little scientific support.

[a]References 6, 7

illustrate the difficulty in using them to determine etiology and then we will discuss our current understanding of the mechanisms of teratogenesis of selected agents known to be teratogenic in man.

MUTATIONS, CHROMOSOMAL ABERRATIONS The mutagenic effects listed in Table 2 are unlikely to play a role in the production of malformations following in utero exposure. Mutagens are more likely teratogenic due to their cytotoxic effects, which are related to cell destruction, and not to genetic changes that persist and affect embryonic development for many cell cycles in the developing embryo. While gene changes or chromosome abnormalities produced in eggs or sperm could result in embryopathology, they play little or no role when induced in somatic cells of the developing embryo except as they may cause cell death, retardation of differentiation, or mitotic delay.

ALTERED NUCLEIC ACID SYNTHESIS OR FUNCTION Although there are no examples of subtle changes in the expression of genetic information due to exposures to environmental agents, the disruption of protein synthesis that must ensue from any significant disturbance in RNA or DNA synthesis or function would be of such great magnitude as to be incompatible with life.

The other proposed mechanisms listed in Table 2 similarly describe effects that may be attributable to an agent under defined experimental conditions. However, it is improbable that a drug, chemical, or other agent will have only one effect on a biological system. It is also improbable, even assuming that the mechanisms of action of a particular agent may be known, that an in utero exposure to that agent will result in congenital malformations without taking into consideration developmental state or dose. Rather than picking possible

mechanisms of action from a list to test which fit the agent, a more useful approach is to study the effects of the agents in question to determine their mechanisms of action.

The following section briefly discusses what is known concerning the mechanisms of action of agents that have been proven to cause congenital malformations in man, summarized in Table 3.

TERATOGENIC AGENTS OF MAN

Alcohol

Jones et al (8) described fetal alcohol syndrome (FAS) in children with intrauterine growth retardation, microcephaly, maxillary hypoplasia, and reduction in the width of palpebral fissures (cardiac abnormalities were also seen). Approximately one-third of the children of alcoholic mothers had FAS (9, 10) and all of the affected children evidenced developmental delay (11).

A period of greatest susceptibility and a dose-response relationship have not yet been established (12). While consumption of six ounces of alcohol per day constitutes a high risk, FAS is not likely when the mother drinks less than two drinks (equivalent to two ounces of alcohol) per day (13). The human syndrome is likely to involve the direct effects of alcohol and its metabolite, acetaldehyde (14), and the indirect effects of genetic predisposition and poor nutrition. Alcoholism is also associated with smoking and the use of other drugs.

Aminopterin and Methotrexate

Aminopterin-induced therapeutic abortions have been shown to result in malformations (hydrocephalus, cleft palate, meningomyelocele) in some of the abortuses (15, 16). Three case reports of children receiving in utero exposure to aminopterin included observations of growth retardation, abnormal cranial ossification, high-arched palate, and reduction in derivatives of the first branchial arch (17, 18, 19).

Methotrexate (methylaminopterin) ingestion during the first two months (20) or for 5 days between the 8th and 10th weeks (21) resulted in the absence of the frontal bones, craniosynostosis, rib defects, and the absence of digits.

Both compounds are folic acid antagonists that inhibit dihydrofolate reductase, resulting in cell death during the S phase of the cell cycle (22). The clinical literature has been reviewed by Warkany (23).

Androgens

Masculinization of the external genitalia of the female has been reported following in utero exposure to large doses of testosterone (24), methyltestosterone (25), and testosterone enanthate (26). The masculinization is characterized by clitoromegaly with or without fusion of the labia minora.

Table 3 Teratogenic agents of man

Agents	Reported effects and/or associations	Comments
Alcohol	Fetal alcohol syndrome: intrauterine growth retardation, microcephaly; maxillary hypoplasia, reduction in width of palpebral fissure, mental retardation.	Direct cytotoxic effects of alcohol and acetaldehyde and indirect effects of alcoholism (poor nutrition, smoking, use of other drugs). Consumption of six ounces of alcohol or more per day constitutes a high risk.
Aminopterin, methotrexate	Hydrocephalus, cleft palate, meningomyelocele, intrauterine growth retardation, abnormal cranial ossification, reduction in derivatives of first branchial arch.	Folic acid antagonists that inhibit dihydrofolate reductase, resulting in cell death.
Androgens	Masculinization of female embryo: clitoromegaly with or without fusion of labia minora.	Effects are dose dependent; stimulates growth and differentiation of receptor containing tissue.
Coumarin derivates	Nasal hypoplasia, stippling of secondary epiphysis; intrauterine growth retardation, anomalies of eyes, hands, neck, variable CNS effects in gestation.	Metabolic inhibitor; bleeding is an unlikely explanation for effects. 10–25% risk from exposure during 8th–14th week of pregnancy.
Diethylstilbesterol	Masculinization of female, vaginal adenocarcinoma, anomalies of cervix and uterus. Affected males show hypotrophic testes, epidymal cysts, abnormal spermatozoa. Effects are dose-dependent.	Stimulates estrogen receptor-containing tissue, may cause misplaced tissue. 75% risk for vaginal adenosis for exposures before 9th week of pregnancy; risk of vaginal adenocarcinoma is low (1 in 10,000). 25% risk for anomalies in males (including minor variations).
Diphenylhydantoin	Hydantoin syndrome: hypoplastic nails and distal phalanges, cleft lip/palate, microcephaly, mental retardation.	Direct effect on cell membranes, folate and vitamin K metabolism. Wide variation in reported risk. Associations documented only with chronic exposure.
Methylmercury	Minamata disease: cerebral palsy, microcephaly, mental retardation, blindness.	Cell death due to inhibition of enzymes, especially sulfhydryl enzymes.

Table 3 *(continued)*

Agents	Reported effects and/or associations	Comments
Oxazolidine-2,4-diones	Fetal trimethadione syndrome: V-shaped eyebrows, low-set ears with anteriorly folded helix, high-arched palate, irregular teeth, central nervous system anomalies, developmental delay.	Affects cell membrane permeability. Wide variation in reported risk. Associations documented only with chronic exposure.
Polychlorinated biphenyls	Cola-colored children: pigmentation of gums, nails, and groin, hypoplastic deformed nails, intrauterine growth retardation.	Polychlorinated biphenyls and commonly occurring contaminants are cytotoxic.
Progestins	Masculinization of female embryo exposed to high doses.	Stimulates growth and differentiation of receptor-containing tissue.
Radiation	Microcephaly, mental retardation, eye anomalies, intrauterine growth retardation, visceral malformations depend on dose and stage of exposure.	Cell death and mitotic delay. Little or no risk with exposures of 5 rads or less of x-rays.
Tetracycline	Hypoplastic tooth enamel, tooth and bone staining	Effects seen only if exposure is during second or third trimester.
Thalidomide	Bilateral limb reduction defects (preaxial preferential effects, phocomelia), facial hemangioma, esophageal or duodenal atresia, anomalies of external ears, kidneys, and heart	Increased programmed cell death in the early limb bud causing retarded growth in the apical ectodermal ridge, especially in the preaxial border. Primary mechanism unknown. Very high risk of major malformations during critical periods.
Thyroid: Iodides, radioiodine, antithyroid drugs (propylthiouracil)	Hypothyroidism, goiter	Fetopathic effect specific for the thyroid. Metabolic block resulting in decreased thyroid hormone synthesis and gland development. Maternal intake of 12 mg of iodide per day or more increases the risk of fetal goiter.

To illustrate that androgens can only affect tissues with androgen receptors, inherited male pseudohermaphroditism is a syndrome in which the testes secrete normal amounts of testosterone but receptor binding in the target tissues is defective. The result is that genotypic males undergo feminine development (27). This is the same result that a lack of androgens has on the development of sex structures in the male (28). Thus, it can be seen that either an excess or a deficiency in androgens can have an effect only on those tissues with androgen receptors.

Coumarin Derivatives

Nasal hypoplasia following exposure to several drugs, including warfarin, during pregnancy was reported by DiSaia (29). Kerber et al (30) were the first to suggest warfarin as the teratogenic agent. Coumarin anticoagulants have since been associated with nasal hypoplasia, calcific stippling of the secondary epiphysis, and central nervous system abnormalities (31–33). Barr & Burdi (34) have described warfarin embryopathy and Warkany (35, 36), besides summarizing the clinical data, provides an excellent overview of the difficulties in relating a congenital malformation to an environmental cause. There is an estimated 25% risk for affected infants following exposure during the period from the 8th through the 14th week of pregnancy.

Coumarin has been shown to inhibit the formation of γ-carboxyglutamyl residues from glutamyl residues, decreasing the ability of proteins to bind calcium (37). The inhibition of calcium binding by proteins during embryonic/fetal development, especially during a critical period of ossification, could explain the nasal hypoplasia, stippled calcification, and skeletal abnormalities of warfarin embryopathy (33).

Diethylstilbestrol (DES)

The first abnormality reported following exposure to diethylstilbestrol during the first trimester was clitoromegaly in female newborns (38). Much later, Herbst et al (39, 40) and Greenwald et al (41) reported an increased incidence of vaginal adenocarcinoma in female offspring following first-trimester exposures. Further studies revealed that almost all of the cancers occurred after 14 years of age and only in those exposed before the 18th week of gestation (42, 43). There is a 75% risk for vaginal adenosis for exposures occurring before the 9th week of pregnancy; however, the risk of developing the adenocarcinoma is extremely low (44).

Twenty-five percent of males exposed to DES in utero exhibited genital lesions and abnormal spermatozoa, but no malignancies have been observed (45). A review of the syndrome has been presented by Ulfelder (46).

DES is a very potent nonsteroidal estrogen and, as in the case of steroidal estrogens, must interact with the receptor proteins present only in estrogen-

responsive tissues before exerting its effects by stimulating RNA, protein, and DNA synthesis. The alleged carcinogenic effect of DES is most likely indirect: DES exposure results in the presence of columnar epithelium in the vagina and this "misplaced tissue" may have a greater susceptibility to developing the adenocarcinoma.

Diphenylhydantoin

Exposure to diphenylhydantoin may involve a 10% risk for full syndrome and a 30% risk for some anomalies (47–49). While cleft lip and palate, congenital heart disease, and microcephaly have been reported, hypoplasia of the nails and distal phalanges are possibly specific malformations in up to 18% of the exposed fetuses (50, 51). Hanson et al (52) noted that, although the hydantoin syndrome is observed in 11% in their study, three times as many exhibit mental deficits. The hydantoin syndrome has been reviewed by Hanson et al (52). It should be mentioned that prospective studies demonstrate a much lower frequency of effects and some do not demonstrate any effect.

Factors associated with epilepsy may contribute to the etiology of these malformations: based on the United States Collaborative Perinatal Project and a large Finnish registry, the incidence of malformations was 10.5% when the mother was epileptic, 8.3% when the father was epileptic, and 6.4 when neither parent was affected (53).

Diphenylhydantoin affects ion movements to exert a stabilizing effect on cell membranes. There may also be some effect on folate and vitamin K metabolism (54).

Methylmercury

Mercury inactivates sulfhydryl enzymes by forming covalent bonds with sulfur present in sulfhydryl groups or divalent mercury can replace the hydrogen atom to form mercaptides. Mercury can further interfere with metabolism and function by combining with phosphoryl, carboxyl, amide, and amine groups to inhibit enzymes and precipitate proteins.

There have been several incidences of human exposures to methylmercury as an environmental pollutant or as a fungicide present on seed grain consumed by humans. In Minamata, Japan, the local population was exposed by ingesting fish caught in a bay heavily polluted by methylmercury. Cerebral palsy and associated microcephaly were the common features, with few other congenital defects (55, 56). Snyder (57) described the severe damage to the central nervous system in the offspring following ingestion by the pregnant mother of meat from a pig fed seed grain containing a mercurial fungicide. Seed grain containing a methylmercury fungicide was responsible for fetal exposures in Iraq, when pregnant women consumed bread inadvertantly prepared using the

seed grain (58, 59). Cerebral palsy and motor and mental impairments were reported.

Harada (60) has reviewed the clinical aspects of congenital Minamata disease.

Oxazolidine-2, 4-Diones

Trimethadione and paramethadione are antiepileptic oxazolidine-2, 4-diones that distribute uniformly throughout body tissues and exert their effects via the actions of their metabolites. These drugs affect cell membrane permeability and vitamin K-dependent clotting factors, but their primary mode of action is not known.

Zackai et al (61) described the fetal trimethadione syndrome characterized by developmental delay, V-shaped eyebrows, low-set ears with anteriorly folded helix, high-arched palate, and irregular teeth. German et al (62) reported similar findings plus cardiac anomalies. Feldman et al (63) and Goldman & Yaffe (64) have reviewed the clinical findings in the literature and from their own observations. There are wide variations in reported risk, with estimates as high as 80% for major or minor defects.

Polychlorinated Biphenyls

First identified in Japan in 1968 (65), then in Taiwan in 1979 (66), polychlorinated biphenyls (PCBs) consumed in contaminated cooking oil by pregnant women resulted in pigmented children (cola-colored) with low birth weight, pigmentation of the gums, nails, and groin, hypoplastic deformed nails, and conjunctivitis with an enlargement of the sebaceous glands of the eyelid (66).

Several circumstances have inhibited a full evaluation of PCB teratogenicity in the human: there are technical difficulties in measuring PCB concentrations; there are no dose-response data for the human; and PCBs are present in mixtures containing highly toxic products of degradation.

Rogan (66) has recently reviewed the effects of PCBs on human development.

Progestins

A few patients have an inadequate luteal response (deficient progesterone secretion) and it has been suggested that women with repeated abortions might benefit from progestins during the first trimester. The effects of progesterone on the human fetus are not well documented: there are only two case reports of masculinized female infants (67) and a few reports suggesting that progesterone may be associated with a low risk of hypospadias (68, 69).

In contrast to progesterone, some of the synthetic progestins have been reported to cause virilizing effects in the human. Exposure during the first trimester to large doses of 17-α-ethinyl-testosterone has been associated with

masculinization of the external genitalia of female fetuses (70, 71). Similar associations result from exposure to large doses of 17-α-ethinyl-19-nortestosterone (norethadrone) (72) and 17-α-enthinyl-17-OH-5(10)estren-3-one (Enovid-R) (73). The synthetic progestins, like progesterone, can influence only those tissues with the appropriate steroid-receptor proteins. The preparations with androgenic properties will cause abnormalities in the genital development of females only if present in sufficient amounts during critical periods of development (70, 72). In 1959, Grumbach et al (73) pointed out that labio-scrotal fusion could be produced with large doses if the fetuses were exposed before the 13th week of pregnancy, while clitoromegaly could be produced after this period, illustrating that a specific form of maldevelopment can be induced only when the susceptible embryonic tissues are in a limited range of development. In a recent review, Wilson & Brent (74) presented evidence against the involvement of female sex hormones in nongenital teratogenesis.

Radiation

The effects of radiation are due to direct damage to the cell chromatin; they result in cell death or damage that is partially or completely repaired by the cell. The classical triad of effects of radiation are gross malformations, intrauterine growth retardation, and embryonic death, with each of these effects having a dose-response relationship and a threshold exposure below which no difference between an exposed and an unexposed control population can be demonstrated (75). Offspring born to patients receiving radiation therapy for various conditions exhibited growth retardation, eye malformations, and central nervous system defects (76–78). Microcephaly is probably the most common manifestation observed following in utero exposure to high levels of radiation in the human (79). Fetal exposure to radiation at Hiroshima resulted in microcephaly, growth retardation, and mental retardation (80–82). In his recent review of radiation teratogenesis, Brent (75) pointed out that no malformation of the limb, viscera, or other tissue has been observed unless the child also exhibits intrauterine growth retardation, microcephaly, or eye malformations.

The risk of major malformations is not increased by in utero exposure of 5 rads or less (75).

Tetracycline

The antimicrobial tetracyclines inhibit bacterial protein synthesis by preventing access of aminoacyl tRNA to the mRNA-ribosome complex (83).

Tetracycline crosses the placenta but is not concentrated by the fetus. Although tetracycline has been shown to discolor teeth (84), very high doses may depress skeletal bone growth and result in hypoplasia of tooth enamel (85).

Tetracylines complex with calcium and the organic matrix of newly forming bone without altering the crystalline structure of hydroxyapatite (85).

Thalidomide

Lenz & Knapp (86) and McBride (87) were the first to describe thalidomide-induced phocomelia. Limb defects resulted from exposure limited to a two-week period from the 27th to the 40th day of gestation: exposures from the 27th–30th days most often affected only the arms, while exposures from the 30th–33rd days (lower limb buds appear on about the 30th day) resulted in both leg and arm abnormalities (88). Although there was no association of central nervous system defects, other abnormalities included facial hemangioma, esophageal or duodenal atresia, and anomalies of the kidneys, heart, and external ears (86, 88, 89). A high proportion of the fetuses exposed during the critical period were affected.

McCredie & McBride (90) suggested that the limb-reduction defects exhibited a segmental pattern. McCredie (91) proposed that the segmental pattern was determined by the periperal nerves derived from the neural crest. McBride (92, 93) and Stokes et al (94) presented experimental evidence supporting an alternative proposal that the quantity of nerves was important: damage to the peripheral sensory nerves results in pre-axial abnormalities and greater damage results in amelia.

Stephens & McNulty (95) have confirmed that limb development exhibits a segmental pattern. However, recent studies by Streker & Stephens (96) have refuted the proposed role of peripheral nerve damage in thalidomide-induced embryopathy. A foil barrier was placed lateral to the chick neural tube to block the innervation of the wing field by the brachial plexus. A reduced source of innervation from spinal nerves anterior or posterior to the brachial plexus resulted in muscular atrophy but not in reductions or malformations of the skeleton of the wing. Therefore, both the proposal that the segmental pattern of the limb is determined by level-specific nerves and the proposal that diminished levels of innervation will result in skeletal malformations are untenable.

Lash & Saxen have postulated that thalidomide indirectly exerts its effects on limb chondrogenesis by acting upon the kidney primordia (97). Based upon an association between nephric tissue and limb development (98–100), Lash & Saxen (97) have in vitro evidence suggesting that thalidomide inhibits an interaction between metanephric tissue and associated mesenchymal tissue necessary for normal limb chondrogenesis.

The mechanism of thalidomide embryopathy is still controversial.

Thyroid: Iodides, Radioiodine, Antithyroid Drugs

Several drugs used to treat maternal hyperthyroidism (^{131}I and antithyroid drugs) and nonthyroid conditions (especially iodide-containing compounds for

bronchitis and asthma) affect thyroid function. In utero exposure to these drugs may result in congenitally hypothyroid infants who will not reach their potential for physical or mental development unless treated very early following birth with thyroid hormone.

There are several case reports of congenital goiter due to in utero exposures to iodide-containing drugs (101, 102). Maternal intake of as low as 12 mg/day may result in fetal goiter (102). Iodinated contrast agents used for amniofetography have been reported to adversely affect fetal thyroid function (103).

Propylthiouracil and methimazole, used to treat thyrotoxicosis, readily cross the placenta (104). Methimazole has been associated with aplasia cutis (105, 106). Propylthiouracil is safer since the incidence of fetal goiter is low (107, 108) and there have been no observed detrimental effects on mental development (109, 110).

Radioactive iodine, ^{131}I, is a potential risk to the fetal thyroid, especially once the fetal thyroid begins to concentrate iodide at 10–12 weeks of gestation. In a retrospective study of fetuses accidentally exposed to ^{131}I during the first or first and second trimesters, six neonates out of 178 live births had hypothyroidism, while other anomalies were not statistically increased above the general population (111). Although there are few case reports in the literature, there is a definite risk of neonatal thyroid dysfunction.

Other

Although they are beyond the scope of this article, several infectious agents and maternal conditions have been associated with congenital malformations.

Rubella (112, 113), cytomegalovirus (114), toxoplasmosis (115), and syphilis (116) have all been shown to cause maldevelopment in the human. Similarly, maternal conditions such as starvation (117–119) and diabetes mellitus (120, 121) have been associated with an increased incidence of abnormalities. However, it may be difficult to determine whether a condition or a treatment for that condition during pregnancy is responsible for the malformed infant.

CONCLUSION

An estimate of the congenital malformations in man resulting from exposures to environmental agents as a single cause is 5–8% (4, 5, 122) and in combination with genetic components (multifactorial causes) is about 20% (123). We must continue to increase our knowledge of both the etiology and the mechanisms of teratogenesis so that avoidable exposures to known and possibly unrecognized environmental teratogens can be prevented in the future.

ACKNOWLEDGEMENTS

We thank Mrs. Yvonne G. Edney for secretarial assistance in the preparation of this manuscript. This work was supported in part by funds from the Foerderer Foundation, Harry Bock Charities, and NIH CA 29628.

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