Robert L. Brent

Environmental causes of human congenital malformations

When I had completed medical school and graduate school, the scientific world did not even have the correct figure for the number of human chromosomes. Gregg[1] had recently described the teratogenicity of rubella virus infection during pregnancy. The teratogenic risk of the folic acid antagonists was established[2,3] and there were experimental studies indicating that nutritional deficiencies could produce birth defects in animals.[4]

What have we learned and accomplished in the past 50 years? Thousands of previously unknown genetic diseases have been described and many of their genes have been identified since the 1950s.[5,6] The fields of prenatal intrauterine diagnoses, intervention and treatment have been created. Metabolic and biochemical screening have become standard care for pregnant women and newborns. Over 50 teratogenic environmental drugs, chemicals and physical agents have been described[7–10] using modern epidemiological tools and the talents of clinical dysmorphologists.[11–17] The basic science and clinical rules for evaluating teratogenic risks have been established (Table 1).[18] The development of the rubella vaccine and the recognition of the importance of adequate folic acid intake in women of reproductive age are forerunners for the prevention of birth defects from teratogenic infectious agents and nutritional components that are important for normal development. The completion of the first stage of the Human Genome Project in the year 2000 offers the geneticist and teratologist immense opportunities to evaluate the concepts of polygenic and multifactorial etiologies[19,20] of congenital malformations.

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Table 1 Evaluation of the allegation that a particular environmental agent causes congenital malformations or is responsible for malformations in an individual patient

Epidemiological studies	Controlled epidemiological studies consistently demonstrate an increased incidence of a particular spectrum of embryonic and/or fetal effects in exposed human populations
Secular trend data	Secular trends demonstrate a positive relationship between the changing exposures to a common environmental agent in human populations and the incidence of a particular embryonic and/or fetal effect
Animal developmental toxicity studies	An animal model can be developed which mimics the human developmental effect at clinically comparable exposures. Since mimicry may not occur in all animal species, animal models are more likely to be developed once there is good evidence for the embryotoxic effects reported in the human. Developmental toxicity studies in animals are indicative of a potential hazard in general rather than the potential for a specific adverse effect on the fetus when there are no human data on which to base the animal experiments
Dose–response relationship (pharmacokinetics and toxicokinetics)	Developmental toxicity in the human increases with dose (exposure) and the developmental toxicity in animal occur at a dose that is pharmacokinetically (quantitatively) equivalent to the human exposure
Biological plausibility	The mechanisms of developmental toxicity are understood and the effects are biologically plausible: • Mechanisms of action (MOA) • Receptor studies • Nature of the malformations • Teratology principles

Modified from several references.[7,8,18,26,36–38,41]

EMOTIONAL IMPACT OF CONGENITAL MALFORMATIONS

Reproductive problems encompass a multiplicity of diseases including sterility, infertility, abortion (miscarriage), stillbirth, congenital malformations (due to environmental or hereditary etiologies), fetal growth retardation and prematurity.[7–10,13] These clinical problems occur commonly in the general population and, therefore, environmental causes are not always easy to corroborate (Table 2). Severe congenital malformations occur in 3% of births. According to the Centers for Disease Control, severe congenital malformations (including those birth defects that cause death, hospitalization, and mental retardation) necessitate significant or repeated surgical procedures, are disfiguring, or interfere with physical performance. That means that each year in the US, 120,000 newborns are born with severe birth defects. Genetic diseases occur in about 11% of births. Spontaneous mutations account for less than 2–3% of genetic disease. Therefore, mutations induced from preconception exposures of environmental mutagens are difficult end-points to document (Table 2). It may surprise the reader to know that birth defects

Table 2 Background reproductive risks per million pregnancies

Reproductive risk	Frequency
Immunologically and clinically diagnosed spontaneous abortions per million conceptions	350,000
Clinically recognized spontaneous abortions per million clinically recognized pregnancies	150,000
Genetic diseases per million births	110,000
Multifactorial or polygenic genetic environmental interactions (*i.e. neural tube defects, cleft lip, hypospadius, hyperlipidemia, diabetes*)	90,000
Dominantly inherited disease (*i.e. achondroplasia, Huntington's chorea, neurofibromatosis*)	10,000
Autosomal and sex-linked genetic disease (*i.e. cystic fibrosis, hemophilia, sickle-cell disease, thalassemia*)	1200
Cytogenetic (chromosomal abnormalities) *i.e. Down's syndrome (trisomy 21), trisomy 13, trisomy 18, Turner's syndrome, 22q deletion, etc.*	5000
New mutations*	3000
Severe congenital malformations# (*due to all causes of birth defects: genetic, unknown, environmental per million births*)	30,000
Prematurity/million births	40,000
Fetal growth retardation/million births	30,000
Stillbirths (> 20 weeks)/million births	2000–20,900
Infertility	7% of couples

*The mutation rate for many genetic diseases can be calculated. This can be readily performed with dominantly inherited diseases when offspring are born with a dominant genetic disease and neither parent has the disease.

#Congenital malformations have multiple etiologies including a significant proportion that are genetic.

account for 440,000 children's deaths each year in the low- and middle-income nations from congenital malformations. That represents 3.7% of the deaths in children. In the high-income countries, congenital malformations are the second highest cause of death in children, accounting for 20% of the deaths.

DISEASES OF AFFLICTION

Along with cancer, psychiatric illness, and hereditary diseases, reproductive problems have been viewed throughout history as diseases of affliction. Inherent in the reactions of most cultures is that these diseases have been viewed as punishments for misdeeds.[21–24] Regardless of the irrationality of this viewpoint, these feelings do exist. Ancient Babylonian writings recount tales of mothers being put to death because they delivered malformed infants. One George Spencer was slain by the Puritans in New Haven in the 17th century,

having been convicted of fathering a cyclopean pig, since the Puritans were unable to differentiate between George Spencer's cataract and the malformed pigs cloudy cornea.[21] In modern times, some individuals with reproductive problems reverse the historical perspective, and blame others for the occurrence of their congenital malformations, infertility, abortions and hereditary diseases. They place the responsibility of their illness on environmental agents dispensed by their healthcare provider or utilized by their employer.[21–24]

Reproductive problems alarm the public, the press and some scientists to a greater degree than most other diseases. In fact, severely malformed children are disquieting to healthcare providers, especially if they are not experienced in dealing with these problems. No physician will be comfortable informing a family that their child was born without arms and legs. The objective evaluation of environmental causes of reproductive diseases is clouded by the emotional climate that surrounds these diseases, resulting in the expression of partisan positions that either diminish or magnify the environmental risks. These non-objective opinions can be expressed by scientists, the laity or the press.[23,24] It is the responsibility of every physician to be aware of the emotionally charged situation when a family has a child with a birth defect. The inadvertent comment by the physician, nurse, resident or student in attendance at the time of the child's delivery can have grave consequences for the physician and the family. Comments such as, 'Oh, you had an X-ray during your pregnancy', or 'You did not tell me that you were prescribed tetracycline while you were pregnant', can direct the patient's family to an attorney rather than to a teratology or genetic counselor.

BASIC PRINCIPLES OF TERATOLOGY

Labeling an environmental exposure as teratogenic is inappropriate unless one characterizes the exposure with regard to the dose, route of exposure and the stage of pregnancy when the exposure occurred. Labeling an agent as teratogenic only indicates that it may have the potential for producing congenital malformations. A 50-mg dose of thalidomide administered on the 26th day post-conception has a significant risk of malforming the embryo. That same dose taken during the 10th week of gestation will not result in congenital malformations.[25] One milligram of thalidomide taken at any time during pregnancy will have no effect on the developing embryo. We know that X-irradiation can be teratogenic.[26–30] However, if the dose is too low or the X-ray does not directly expose the embryo, there is no increased risk of congenital malformations (Fig. 1).[7,8,26] So a list of teratogens only indicates teratogenic potential. Evaluation of the dose and time of exposure could indicate that there is no teratogenic risk or that the risk is significant.

When evaluating studies dealing with the reproductive effects of any environmental agent, important principles should guide the analysis of human and animal reproductive studies. Paramount to this evaluation is the application of the basic science principles of teratology and developmental biology.[7,8,26] These principles are as follows:

1. *Exposure to teratogens follows a toxicological dose–response curve. There is a threshold below which no teratogenic effect will be observed; as the dose of the*

teratogen is increased, both the severity and frequency of reproductive effects will increase (Fig. 1; Table 3).

2. *The embryonic stage of exposure is critical in determining what deleterious effects will be produced and whether any of these effects can be produced by a known teratogen. Some teratogenic effects have a broad, and others a very narrow, period of sensitivity. The most sensitive stage for the induction of mental retardation from ionizing radiation is from the 8th to 15th week of pregnancy, a lengthy period. Thalidomide's period of sensitivity is about 2 weeks (Table 4).*[25]

3. *Even the most potent teratogenic agent cannot produce every malformation.*

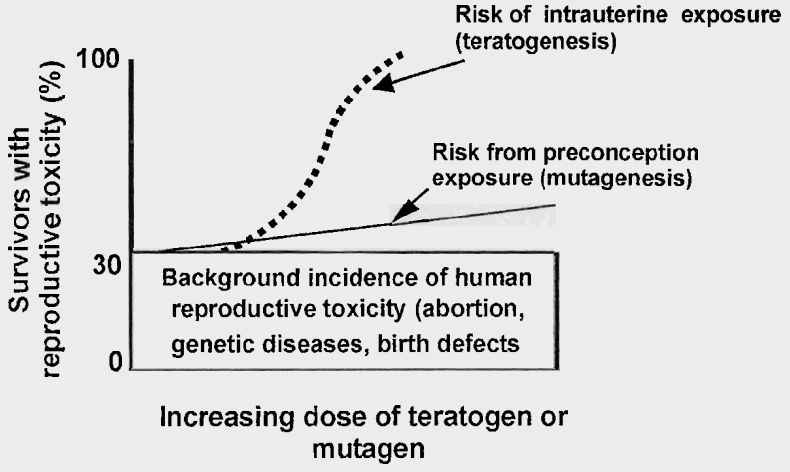

Fig. 1. Dose–response relationship of reproductive toxins comparing preconception and post-conception risks. Reprouced with permission of Wiley-Liss Inc © 1999 from Brent[26]

Table 3 Stochastic and threshold dose–response relationships of diseases produced by environmental agents

Relationship	Stochastic phenomena	Threshold phenomena
Pathology	Damage to a single cell may result in disease	Multicellular injury
Site	DNA	High variation in etiology, affecting many cells and organ processes
Diseases	Cancer, mutation	Malformation, growth retardation, death, chemical toxicity, *etc.*
Risk	Some risk exists at all dosages; at low exposures, the hypothetical risk is below the spontaneous risk	No increased risk below the threshold dose
Effect	The incidence of the disease increases with the dose but the severity and nature of the disease remain the same	Both the severity and incidence of the disease increase with dose

Modified from Brent.[26]

Table 4 Developmental stage sensitivity to thalidomide-induced limb reduction defects in the human

Days from conception for induction of defects	Limb reduction defects
21–26 days	Thumb aplasia
22–23 days	Microtia, deafness
23–34 days	Hip dislocation
24–29 days	Amelia, upper limbs
24–33 days	Phocomelia, upper limbs
25–31 days	Pre-axial aplasia, upper limbs
27–31 days	Amelia, lower limbs
28–33 days	Pre-axial aplasia, lower limbs; phocomelia, lower limbs; femoral hypoplasia; girdle hypoplasia
33–36 days	Triphalangeal thumb

Modified from Brent and Holmes.[24]

4. *Most teratogens have a confined group of congenital malformations that result after exposure during a critical period of embryonic development. This confined group of malformations is referred to as the syndrome that describes the agent's teratogenic effects.*

5. *While a group of malformations may suggest the possibility of certain teratogens, they cannot definitively confirm the causal agent because some teratogenic syndromes mimic genetic syndromes. On the other hand, the presence of certain malformations can eliminate the possibility that a particular teratogenic agent was responsible because those malformations have not been demonstrated to be part of the syndrome or because the production of that malformation is not biologically plausible for that particular alleged teratogen.*

ETIOLOGY OF CONGENITAL MALFORMATIONS

The etiology of congenital malformations can be divided into three categories – unknown, genetic, and environmental (Table 5). The etiology of a majority of human malformations is unknown. A significant proportion of congenital malformations of unknown etiology is likely to have an important genetic component. In fact, newly published findings are describing genetic causes for malformations or syndromes whose etiology were previously listed as unknown. Malformations with an increased recurrent risk, such as cleft lip and palate, anencephaly, spina bifida, certain congenital heart diseases (pyloric stenosis, hypospadias, inguinal hernia, talipes equinovarus, and congenital dislocation of the hip) fit in the category of multifactorial disease as well as in the category of polygenic inherited disease.[19,20] The multifactorial/threshold hypothesis postulates the modulation of a continuum of genetic characteristics by intrinsic and extrinsic (environmental) factors.

Spontaneous errors of development may account for some of the malformations that occur without apparent abnormalities of the genome or

Table 5 Etiology of human congenital malformations observed during the first year of life*

Suspected cause	Percentage of total
Unknown	65–75
Polygenic	
Multifactorial (gene-environment interactions)	
Spontaneous errors of development	
Synergistic interactions of teratogens	
Genetic	15–25
Autosomal and sex-linked inherited genetic disease	
Cytogenetic (chromosomal abnormalities)	
New mutations	
Environmental	10
Maternal conditions: alcoholism, diabetes, endocrinopathies, phenylketonuria, smoking and nicotine, starvation, nutritional deficits	4
Infectious agents: rubella, toxoplasmosis, syphilis, herpes simplex, cytomegalovirus, varicella-zoster, Venezuelan equine encephalitis, parvovirus B19	3
Mechanical problems (deformations): amniotic band constrictions, umbilical cord constraint, disparity in uterine size and uterine contents	1–2
Chemicals, prescription drugs, high-dose ionizing radiation, hyperthermia	<1

*Modified from several references.[7,8,26,36–38,41]

environmental influence. Spontaneous errors of development may indicate that we may never achieve our goal of eliminating all birth defects because a significant percentage of birth defects are due to the statistical probability of errors in the developmental process, similar to the concept of spontaneous mutation. It is estimated that 30–40% of all conceptions are lost before term, many within the first 3 weeks of development. The World Health Organization estimated that 15% of all clinically recognizable pregnancies end in a spontaneous abortion, 50–60% of which are due to chromosomal abnormalities.[31–34] Finally, 3–6% of offspring are malformed, which represents the background risk for human maldevelopment (Table 2).

FACTORS AFFECTING SUSCEPTIBILITY TO DEVELOPMENTAL TOXICANTS

A basic tenet of environmentally produced malformations is that teratogens or a teratogenic milieu have certain characteristics in common and follow certain basic principles. These principles determine the quantitative and qualitative aspects of environmentally produced malformations.

Embryonic stage

The types and risk of malformations caused by teratogenic agents usually results in a spectrum of malformations that varies depending on the stage of

exposure and the dose. The developmental period at which an exposure occurs will determine which structures are most susceptible to the deleterious effects of the drug or chemical and to what extent the embryo can repair the damage. This period of sensitivity may be narrow or broad, depending on the environmental agent and the malformation in question. The period of susceptibility to thalidomide-induced limb defects is very narrow (Table 4),[25] while susceptibility period for radiation-induced microcephaly is very broad.[26]

Dose or magnitude of the exposure

The quantitative correlation of the magnitude of the embryopathic effects to the dose of a drug, chemical or other agent is referred to as the dose–response relationship. This is extremely important when comparing effects among different species because the use of mg/kg doses is ,at most, a rough approximation. Dose equivalence among species for drugs and chemicals can only be accomplished by performing pharmacokinetic studies, metabolic studies and dose–response investigations in the human and the species being studied, while ionizing radiation exposures in rads or Sieverts (Sv) are comparable in most mammalian species.[26]

Threshold dose

The threshold dose (no-adverse-effect-level, NOAEL) is the dosage below which the incidence of death, malformation, growth retardation, or functional deficit is not statistically greater than that of controls (Fig. 1; Table 3). The threshold level of exposure is usually from less than one to two orders of magnitude below the teratogenic or embryopathic dose for drugs and chemicals that kill or malform half the embryos. An exogenous teratogenic agent, therefore, has a no-effect dose as compared to mutagens or carcinogens that have a stochastic dose response curve (Fig. 1; Table 3). Stochastic phenomena, namely mutation and oncogenesis, are hypothesized not to have a threshold. Therefore, there is no exposure that does not have a theoretical risk. The severity and incidence of malformations produced by every exogenous teratogenic agent that has been appropriately studied have exhibited threshold phenomena during organogenesis.

Pharmacokinetics and metabolism of the drug or chemical

The physiological alterations in pregnancy and the bioconversion of compounds can significantly influence the teratogenic effects of drugs and chemicals by affecting absorption, body distribution, active form(s) and excretion of the compound.

Physiological alterations in the mother during pregnancy affect the pharmacokinetics of drugs:

1. Decreased gastrointestinal motility and increased intestinal transit time resulting in delayed absorption of drugs absorbed in the small intestine due to increased stomach retention and enhanced absorption of slowly absorbed drugs.

2. Decreased plasma albumin concentration which alters the kinetics of compound normally bound to albumin.
3. Increased plasma and extracellular fluid volumes that affect concentration-dependent transfer of compounds.
4. Renal elimination, which is generally increased but is influenced by body position during late pregnancy.
5. Inhibition of metabolic inactivation in the maternal liver.
6. Variations in uterine blood flow, although little is known about how this affects transfer across the placenta.

The fetus also undergoes physiological alterations that affect the pharmacokinetics of drugs:

1. The amount and distribution of fat varies with development and affects the distribution of lipid-soluble drugs and chemicals.
2. The fetal circulation contains a higher concentration of unbound drug largely because the plasma fetal protein concentrations are lower than in the adult.
3. The functional development of pharmacological receptors is likely to proceed at different rates in the various tissues.
4. Drugs excreted by the fetal kidneys may be recycled via amniotic fluid swallowing by the fetus.

The role the placenta plays in drug pharmacokinetics has been reviewed by Juchau and Rettie[35] and involves: (i) transport; (ii) the presence of receptors sites for a number of endogenous and xenobiotic compounds (β-adrenergic, glucocorticoid, epidermal growth factor, IgG-Fc, insulin, low-density lipoproteins, opiates, somatomedin, testosterone, transcobalamin II, transferrin, folate, retinoid); and (iii) the bioconversion of xenobiotics. Bioconversion of xenobiotics has been shown to be important in the teratogenic activity of several xenobiotics. There is strong evidence that reactive metabolites of cyclophosphamide, 2-acetylaminofluorene, and nitroheterocycles (niridazole) are the proximal teratogens. There is also experimental evidence that suggests that other chemicals undergo conversion to intermediates that have deleterious effects on embryonic development including phenytoin, procarbazine, rifampicin, diethylstilbestrol, some benzhydrylpiperazine antihistamines, adriamycin, testosterone, benzo(a)pyrene, methoxyethanol, caffeine, and paraquat.

The major site of bioconversion of chemicals *in vivo* is likely to be the maternal liver. Placental cytochrome P450-dependent monooxygenation of xenobiotics will occur at low rates unless induced by such compounds as those found in tobacco smoke. However, the rodent embryo and yolk sac have been shown to possess functional cytochrome P450 oxidative isozymes capable of converting pro-teratogens to active metabolites during early organogenesis. In addition, cytochrome P450-independent bioactivation has been suggested: for example, there is strong evidence that the rat embryo can reductively convert niridazole to an embryotoxic metabolite.

As defined by Juchau and Rettie,[35] there are several experimental criteria that would suggest that a suspected metabolite is responsible for the *in vivo*

teratogenic effects of a chemical or drug: (i) the chemical must be convertible to the intermediate; (ii) the intermediate must be found in or have access to the tissue(s) affected; (iii) the embryotoxic effect should increase with the concentration of the metabolite; (iv) inhibiting the conversion should reduce the embryotoxic effect of the agent; (v) promoting the conversion should increase the embryotoxicity of the agent; (vi) inhibiting or promoting the conversion should not alter the target tissues; and (vii) inhibition of biochemical inactivation should increase the embryotoxicity of the agent. It is readily apparent why there may exist marked qualitative and quantitative differences in the species' response to a teratogenic agent.

Placental transport

The placenta controls the exchange between the embryo and the maternal organism. The placenta varies in structure and function among species and for each stage of gestation. Thus, differences in placental function and structure may affect our ability to apply teratogenic data developed in one species directly to other species, including the human. Yet, as pharmacokinetic techniques and the actual measurement of metabolic products in the embryo become more sophisticated, the appropriateness of utilizing animal data to project human effects may improve.[35]

While it has been alleged that the placental barrier was protective and, therefore, harmful substances did not reach the embryo, it is now clear that there is no 'placental barrier' *per se*. Yet the package inserts on many drugs state that: 'this drug crosses the placental barrier'.[26] The uninitiated may infer from this statement that this characteristic of a drug is both unusual and hazardous. The fact is that most drugs and chemicals cross the placenta. It will be a rare chemical that will cross the placental barrier in one species and be unable to reach the fetus in another. No such chemical exists except for selected proteins whose actions are species-specific.

Genetic differences

The genetic constitution of an organism is an important factor in the susceptibility of a species to a drug or chemical. More than 30 disorders of increased sensitivity to drug toxicity or effects in the human are due to an inherited trait.

ENVIRONMENTAL AGENT EXPOSURE DURING PREGNANCY RESULTING IN REPRODUCTIVE TOXICITY[7–9]

Table 6 lists environmental agents that have resulted in reproductive toxicity and or congenital malformations in human populations. The list cannot be used in isolation because so many other parameters must be considered in analyzing the risks in individual patients. Many of these agents represent a very small risk while others may represent substantial risk. The risks will vary with the magnitude, timing and length of exposure. More information can be obtained from more extensive reviews or summary articles. Table 7 includes agents that have had concerns raised about their reproductive risks but, after

Table 6 Proven human teratogens or embryotoxins: drugs, chemicals, milieu and physical agents that have resulted in human congenital malformations

REPRODUCTIVE TOXIN AND ALLEGED EFFECTS
Aminopterin, methotrexate – growth retardation, microcephaly, meningomyelocele mental retardation, hydrocephalus, and cleft palate
Androgens – masculinization of the developing fetus can occur from androgens and high doses of some male-derived progestins
Angiotensin converting enzyme (ACE) inhibitors – fetal hypotension syndrome in 2nd and 3rd trimester resulting in fetal kidney hypoperfusion, and anuria, oligohydramnios, pulmonary hypoplasia and cranial bone hypoplasia. No teratogenic effect in the first trimester **although** a recent publication[54] contests this conclusion
Angiotensin II receptor blocking agents – the effects of this group of drugs is very similar to the ACE inhibitors
Antituberculous therapy – INH, PAS has an increased risk for some CNS abnormalities
Caffeine – moderate caffeine exposure is not associated with birth defects; high exposures are associated with an increased risk of abortion but the data are inconsistent
Chorionic villous sampling (CVS) – vascular disruption malformations, *i.e.* limb reduction defects
Cobalt in hematemic multivitamins – fetal goiter
Cocaine – vascular disruptive type malformations in very low incidence, pregnancy loss. Inconsistent reports of decrease in cognitive function
Corticosteroids – high exposures administered systemically have a low risk for cleft palate in some studies, but the epidemiological studies are not consistent
Coumarin derivatives – early exposure during pregnancy can result in nasal hypoplasia, stippling of secondary epiphysis, intrauterine growth retardation. CNS malformations can occur in late pregnancy exposure due to bleeding
Cyclophosphamide and other chemotherapeutic agents and immunosuppressive agents like cyclosporine or leflunomide – many chemotherapeutic agents used to treat cancer have a theoretical risk for producing malformations in the fetus when administered to pregnant women, especially since most of these drugs are teratogenic in animals, but the clinical data are not consistent. Many of these drugs have not been shown to be teratogenic, but the numbers of cases in the studies are small. Caution is the byword
Diethylstilbestrol – administration during pregnancy produces genital abnormalities, adenosis, clear cell adenocarcinoma of vagina in adolescents. The latter has a risk of 1:1000 to 1:10,000, but the other effects, such as adenosis can be quite high
Ethyl alcohol – fetal alcohol syndrome consists of microcephaly, mental retardation, growth retardation, typical facial dysmorphogenesis, abnormal ears, small palpebral fissures. It is the most common environmental cause of a decrease in intellectual performance
Ionizing radiation – the threshold for major birth defects is greater than 20 rad (0.2 Gy) at the most sensitive stage of embryogenesis (18–35 days post-conception). Radiation can increased the risk for some fetal effects such as micocephaly or growth retardation at mid-gestation, but the threshold for these effects is higher
Insulin shock therapy – this therapeutic modality when administered to pregnant women resulted in microcephaly, mental retardation. This therapy is no longer used
Lithium therapy – continuous exposure during pregnancy for the treatment of manic-depressive illness has an increased risk for Ebstein's anomaly and other malformations, but the risks appear to be very low

Table 6 *(continued)* Proven human teratogens or embryotoxins: drugs, chemicals, milieu and physical agents that have resulted in human congenital malformations

Minoxidil – the effect of the growth promotion of fetal hair was discovered for this drug because administration during pregnancy resulted in hirsutism in newborns

Methimazole – aplasia cutis has been reported to be increased in mothers administered this drug during pregnancy*

Methylene blue intra-amniotic instillation – fetal intestinal atresia, hemolytic anemia and jaundice in neonatal period. This procedure is no longer utilized to identify one twin

Misoprostol – a low incidence of vascular disruptive phenomena, such as limb reduction defects and Mobius syndrome have been reported in pregnancies in which this drug was used to induce an abortion. Autism has also been associated with *in utero* exposure[55]

Penicillamine (D-penicillamine) – this drug results in the physical effects referred to as lathyrism, the results of poisoning by the seeds of the genus Lathyrus. It causes collagen disruption, cutis laxa, and hyperflexibility of joints. The condition appears to be reversible and the risk is low

Progestin therapy – very high doses of androgen hormone derived progestins can produce masculinization. Many drugs with progestational activity do not have masculinizing potential. None of the commonly used progestational drugs have the potential for producing non-genital malformations

Propylthiouracil – this drug and other antithyroid medications administered during pregnancy can result in an infant born with a goiter

Radioactive isotopes – tissue- and organ-specific damage is dependent on the radioisotope element and distribution, *i.e.* high doses of ^{131}I administered to a pregnant woman can cause fetal thyroid hypoplasia after the 8th week of development

Retinoids (Acutane) – systemic retinoic acid, isotretinoin, Etretinate can cause increased risk of central nervous system, cardio-aortic, ear and clefting defects. Microtia, anotia, thymic aplasia and other branchial arch, aortic arch abnormalities and certain congenital heart malformations

Retinoids, topical – topical administration is very unlikely to have teratogenic potential because one cannot attain a teratogenic serum level from topical exposure to retinoids

Streptomycin – streptomycin and a group of ototoxic drugs can affect the eighth nerve and interfere with hearing; it is a relatively low-risk phenomenon. Even children are less sensitive to the ototoxic effects of these drugs when compared to adults

Sulfa drug and vitamin K – these drugs can produce hemolysis in some subpopulations of fetuses

Tetracycline – this drug produces bone and teeth staining, No other malformations are at increased risk

Thalidomide – this drug results in an increased incidence of deafness, anotia, pre-axial limb reduction defects, phocomelia, ventricular septal defects and GI atresias. The susceptible period is from the 22nd to the 36th day post-conception. Autism has also been associated with *in utero* exposure[55]

Trimethorpin – this drug was frequently used to treat urinary tract infections and has been linked to an increased incidence of neural tube defects. The risk is not high, but it is biologically plausible because of the drug's effect on lowering folic acid levels. This has resulted in neurological symptoms in adults taking this drug

Vitamin A – the same malformations that have been reported with the retinoids have been reported with very high doses of vitamin A (retinol). Dosages to produce birth defects would have to be in excess of 25,000–50,000 units per day

Vitamin D* – large doses given in vitamin D prophylaxis are possibly involved in the etiology of supravalvular aortic stenosis, elfin faces, and mental retardation

Table 6 *(continued)* Proven human teratogens or embryotoxins: drugs, chemicals, milieu and physical agents that have resulted in human congenital malformations

Warfarin (Coumarin) – early exposure during pregnancy can result in nasal hypoplasia, stippling of secondary epiphysis, intrauterine growth retardation. CNS malformations can occur in late pregnancy exposure due to bleeding

ANTICONVULSANTS

Diphenylhydantoin – treatment of convulsive disorders increases the risk of the fetal hydantoin syndrome, consisting of facial dysmorphology, cleft palate, VSD, growth and mental retardation

Trimethadione and paramethadione – treatment of convulsive disorders increases the risk of characteristic facial dysmorphology, mental retardation, V-shaped eye brows, low-set ears with anteriorly folded helix, high-arched palate, irregular teeth, CNS anomalies, severe developmental delay

Valproic acid – treatment of convulsive disorders increases the risk of spina bifida, facial dysmorphology and autism.[55] A threshold (NOAEL) has been suggested for exposures below 1000 mg/day and a serum level below 70 µg%

Carbamazepine – treatment of convulsive disorders increases the risk facial dysmorphology

Primidone, phenobarbital, Lamotrigine and other anticonvulsants – anticonvulsants all have **real or hypothetical risks for a** group of malformations and reduction in cognitive function. The actual risks are difficult to determine, but most authorities are of the opinion that some type of regimen must be utilized to prevent or decrease convulsive episodes during pregnancy. Anticonvulsant polytherapy increases the risk of developmental effects

CHEMICALS

Carbon monoxide poisoning – CNS damage has been reported with very high exposures, but the risk appears to be low*

Lead – very high exposures can cause pregnancy loss; intrauterine teratogenesis is not established at very low exposures below 20 µg% in the serum of pregnant mothers

Gasoline addiction embryopathy – facial dysmorphology, mental retardation

Methyl mercury – Minamata disease consists of cerebral palsy, microcephaly, mental retardation, blindness, cerebellum hypoplasia. Other endemics have occurred from adulteration of wheat with mercury containing chemicals that are used to prevent grain spoilage. Present environmental levels of mercury are unlikely to represent a teratogenic risk, but reducing or limiting the consumption of carnivorous fish has been suggested in order not to exceed the EPA's MPE (maximum permissible exposure), which is far below the toxic effects of mercury

Polychlorinated biphenyls – poisoning has occurred from adulteration of food products (Cola-colored babies, CNS effects, pigmentation of gums, nails, teeth and groin; hypoplastic deformed nails; intrauterine growth retardation; abnormal skull calcification). The threshold exposure has not been determined, but it is unlikely to be teratogenic at the present environmental exposures

Toluene and gasoline addiction – facial dysmorphology, mental retardation

EMBRYONIC AND FETAL INFECTIONS

Cytomegalovirus infection – retinopathy, CNS calcification, microcephaly, mental retardation

Rubella – deafness, congenital heart disease, microcephaly, cataracts, mental retardation

Table 6 *(continued)* Proven human teratogens or embryotoxins: drugs, chemicals, milieu and physical agents that have resulted in human congenital malformations

Herpes simplex – fetal infection, liver disease, death

Human immunodeficiency virus – perinatal HIV infection

Parvovirus infection, B19 – stillbirth, hydrops

Syphilis – maculopapular rash, hepatosplenomegaly, deformed nails, osteochondritis at joints of extremities, congenital neurosyphilis, abnormal epiphyses, chorioretinitis

Toxoplasmosis – hydrocephaly, microphthalmia, chorioretinitis, mental retardation

Varicella Zoster – skin and muscle defects, intrauterine growth retardation, limb reduction defects, CNS damage (very low increase risk)

Venezuelan equine encephalitis – hydranencephaly, microphthalmia, central nervous system destructive lesions, luxation of the hip.

Rubeola (wild-type measles) – the measles virus can infect the placenta and this severe infection can cause pregnancy loss, which is uncommon

Malaria – pregnancy loss by miscarriage or stillbirth. Maternal demise

MATERNAL DISEASE STATES

Corticosteroid secreting endocrinopathy – mothers with Cushing's disease can have infants with hyperadrenocortism, but anatomical malformations do not appear to be increased

Iodine deficiency – can result in embryonic goiter and mental retardation

Intrauterine problems of constraint and vascular disruption – these types of defects are more common in multiple-birth pregnancies, pregnancies with anatomical defects of the uterus, placental emboli, amniotic bands; birth defects such as club feet, limb reduction defects, aplasia cutis, cranial asymmetry, external ear malformations, mid-line closure defects, cleft palate and muscle aplasia, limb reduction defects, cleft lip, omphalocele, encephalocele)

Maternal androgen endocrinopathy (adrenal tumors) – masculinization

Maternal depression and the use of antidepressants – at the present time, there is a controversy as to whether the SSRI exposures during pregnancy represent a risk for congenital malformations. The data are inconsistent and more studies and well-performed animal studies are necessary.[55–62] There is data indicating the presence of fetal growth retardation and postnatal hyperactivity that is transient

Maternal diabetes – caudal and femoral hypoplasia, transposition of great vessels and other malformations

Maternal folic acid in reduced amounts – an increased incidence of neural tube defects (NTDs) and possibly other mid-line malformations

Maternal phenylketonuria – abortion, microcephaly, and mental retardation. Very high risk in untreated patients

Maternal starvation – IUGR, abortion, NTDs

Tobacco smoking – abortion, IUGR, and stillbirth. Question of decrease in cognitive function a possibly and increase in some birth defects, although this is controversial

Zinc deficiency – neural tube defects*

*Controversial.

careful and complete evaluation, the agents were found not to represent an increased reproductive risk.[36–41]

References for the environmental agents can be found in review articles and texts dealing with teratogenesis.[5,6,11,16,34,42–47]

Table 7 Agents erroneously alleged to have caused human malformations

Bendectin	Alleged to cause numerous types of birth defects including limb reduction defects, heart malformations and many other malformations
Diagnostic ultrasonography	No significant hyperthermia, therefore no reproductive effects. Newer ultrasound equipment and lengthy procedures could raise the intrauterine temperature. This can be monitored to make certain that the fetal temperature is not significantly increased
Electromagnetic fields (EMFs)	Alleged to cause abortion, cancer, and birth defects
Progestational drugs	Alleged to cause numerous types of non-genital birth defects, including limb reduction defects, heart malformations and many other malformations)

ROLE OF THE PHYSICIAN IN COUNSELING FAMILIES

The clinician must be cognizant of the fact that many patients believe that most congenital malformations are caused by a drug or medication taken during pregnancy. Counseling patients about reproductive risks requires a significant degree of both knowledge and skill. Physicians must also realize that erroneous counseling by inexperienced health professionals may be a stimulus to non-meritorious litigation.[22]

Unfortunately, some individuals have assumed that if a drug or chemical causes birth defects in an animal model or *in vitro* system at a high dose, then it has the potential for producing birth defects at any dose.[48,49] This may be reinforced by the fact that many teratology studies reported in the literature using several doses do not determine the no-effect dose.

Ignoring the basic tenets of teratology appears to occur most commonly in the evaluation of environmental toxic exposures where the exposure was very low or unknown and the agent has been reported to be teratogenic at a very high dose or a maternally toxic dose in animal models.[48,49] In most instances, but of course not all instances, the actual population exposure is revealed to be orders of magnitude below the threshold dose and the doses that were used in animal studies or toxic exposures in the population. This has occurred with 2,4,5-T, PCBs, Pb, Cd, pesticides, herbicides, veterinary hormones and some industrial exposures.

Unfortunately, we do have examples where environmental disasters have been responsible for birth defects or pregnancy loss in exposed populations (methyl mercury in Japan, PCBs in the Orient, organic mercury in the Middle East, lead poisoning in the 19th and early 20th centuries) and we do have many examples of the introduction of teratogenic drugs (Table 6). Therefore, we can never generalize as to whether a chemical or drug is safe or hazardous unless we know the magnitude of the exposure.

Before their baby is born, parents may be concerned about the risks of various environmental exposures. If the child is born with congenital malformations they may question whether there was a causal relationship

with an environmental exposure:

1. *Has the environmental agent been proven to increase the risk of congenital malformations in exposed human populations? In other words, is the agent a proven human teratogen?*
2. *Should a woman of reproductive age or who is pregnant be concerned about increased risks of reproductive effects from exposure to a particular environmental agent?*
3. *If a child is born with congenital malformations and the mother was exposed during her pregnancy to a particular environmental agent, was the agent responsible for the child's birth defects?*
4. *Should a physician report or publish a case of a patient or cluster of patients who were born with congenital malformations and whose mother was exposed to an environmental agent?*[50]

Scholarly evaluation

When a physician responds to a parent's inquiry ('What caused my child's birth defect?'), the physician should respond in the same scholarly manner that would be utilized in performing a differential diagnosis for any clinical problem. Physicians have a protocol for evaluating complex clinical problems; *i.e.* 'fever of unknown origin', 'failure to thrive', 'congestive heart failure', or 'respiratory distress'. If a mother of a malformed infant had some type of exposure during pregnancy, such as a diagnostic radiological examination or medication during pregnancy, the consulting physician should not support or suggest the possibility of a causal relationship before performing a complete evaluation. Likewise, if a pregnant woman who had not yet delivered had some type of exposure during pregnancy, the consulting physician should not support or suggest the possibility that the fetus is at increased risk before performing a complete evaluation. As mentioned previously, only a small percentage of birth defects are due to prescribed drugs, chemicals and physical agents (Table 5).[9,36,51] Even when the drug is listed as a teratogen, it has to have been administered during the sensitive period of development for that drug and above the threshold dose for producing teratogenesis. Furthermore, the malformations in the child should be the malformations that are included in the teratogenic syndrome produced by that drug. It should be emphasized that a recent analysis pointed out that there are no drugs with measurable teratogenic potential in the list of the 200 most prescribed drugs in the US.[51]

After a complete examination of the child and a review of the genetic and teratology medical literature, the clinician must decide on whether the child's malformations are due to a genetic cause or an environmental toxin or agent. The clinician may not be able to conclude, definitively or presumptively, the etiology of the child's birth defects. This information must then be conveyed to the patient in an objective and compassionate manner. A similar situation exists if a pregnant women has been exposed to a drug, chemical or physical agent, since the mother will want to know the risk of that exposure to her unborn child. If one wishes to answer the generic question, 'Is a particular environmental drug, chemical or physical agent a reproductive toxicant?' then a formal approach is recommended that includes a 5-part evaluation as described in Table 1.[18]

Some typical analyses of the risks of reproductive effects for Bendectin, sex steroids, diagnostic ultrasound, and electromagnetic fields demonstrate the usefulness of an organized approach to determine whether an environmental agent has been demonstrated to be a reproductive toxin.[36–41]

There are resources that can assist the physician with the medical literature evaluation and the clinical evaluation of the patient.[5,6,11,16,34,42–47]

Clinical evaluation

There are many articles and books that can assist the physician with the clinical evaluation, although physician training programs do not usually prepare generalists to perform sophisticated genetic counseling or teratology counseling.[11,16] Besides the usual history and physical evaluation, the physician has to obtain information about the nature, magnitude and timing of the exposure. The physical examination should include descriptive and quantitative information about the physical characteristics of the child. While some growth measurements are routine, many measurements utilized by these specialized counselors are not part of the usual physical examination, *i.e.* palpebral fissure size, ear length, intercanthal distances, total height-to-trunk ratio, and many others. Important physical variations in facial, hand and foot structure as well as other anatomical structures may be suggestive of known syndromes, either teratologic or genetic.

Evaluation of the reproductive risk of an environmental exposure that occurred during pregnancy or the cause of a child's malformation in which an exposure occurred during pregnancy

The vast majority of consultations involving pregnancy exposures conclude that the exposure does not change the reproductive risks in that pregnancy. In many instances, the information that is available is so vague that the counselor cannot reach a definitive conclusion about the magnitude of the risk. Information that is necessary for this evaluation is:

1. What was the nature of the exposure?
2. Is the exposure agent identifiable? If the agent is identifiable, has it been definitively identified as a reproductive toxin with a recognized constellation of malformations or other reproductive effects?
3. When did the exposure occur during embryonic and fetal development?
4. If the agent is known to produce reproductive toxic effects, was the exposure above or below the threshold for these effects?
5. Were there other significant environmental exposures or medical problems during the pregnancy?
6. Is this is a wanted pregnancy or is the family ambivalent about carrying this baby to term?
7. What is the medical and reproductive history of this mother with regard to prior pregnancies and the reproductive history of the family lineage?

Evaluation of the reproductive risk of an environmental exposure that occurred during pregnancy

After obtaining all this information, the counselor is in a position to provide the family with an estimate of the reproductive risks of the exposure. Here are some examples of consultations that have been referred to our clinical teratology service:

Patient 1

A 26-year-old pregnant woman was in an automobile accident in her 10th week of pregnancy and sustained a severe concussion. Although she did not convulse post-injury, the treating neurosurgeon prescribed 300 mg of diphenylhydantoin during her first 24 hours in the hospital. Fortunately, she recovered from the injury without any sequelae but her primary physician was concerned that she had received an anticonvulsant associated with a teratogenic syndrome. No other exposure to reproductive toxins occurred in this pregnancy and the family history for congenital malformations was negative, except for an uncle with neurofibromatosis. The primary physician requested a consultation with regard to the teratogenic risk. While diphenylhydantoin administered chronically throughout pregnancy has been associated with a low incidence of characteristic facial dysmorphogenesis, reduced mentation, cleft palate and digital hypoplasia, there are no data to indicate that one day of therapy would cause any of the features of this syndrome. Furthermore, the lip and palate have completed their development by the 10th week. This was a wanted pregnancy and the mother chose to continue her pregnancy. She delivered a normal 3370-g boy at term.

Patient 2

A 25-year-old woman was seen in the emergency service of her local hospital with nausea, vomiting and diarrhea. She had just returned from a cruise on which a number of the passengers became ill on the last day of the trip with similar symptoms. The emergency ward physician ordered a pregnancy test followed by a flat plate of the abdomen because there was evidence of peritoneal irritation. Both of these studies were negative. But 1 week later, she missed her menstrual period and a week later her pregnancy test was positive. Her obstetrician was concerned because she had been exposed to a radiological procedure at a time when she was pregnant. The obstetrician referred the patient for counseling after obtaining an ultrasound that indicated that the embryo was approximately 7 days post-conception at the time of the radiological examination. The patient advised the counselor that she was ambivalent about the pregnancy because of the 'dangers' of the X-rays to her embryo. The estimated exposure to the embryo was less than 500 mrad (0.005 Sv). This exposure is far below the exposure that is known to affect the developing embryo. Just as important is the fact that the embryo was exposed during the first 2 weeks post-conception, a time that is less likely to increase the risk of teratogenesis, even if the exposure was much higher.[26,52] After evaluation of the family history and after she received counseling about the risks of the X-ray, the prospective mother decided to continue the pregnancy. She delivered a 3150-g normal baby.

Evaluation of whether a child born with congenital malformations was caused by an environmental exposure during pregnancy, has a genetic etiology or whose cause cannot be determined

Patient 3

A mother of a 30-year-old man born in the Azores in 1960 with congenital absence of the right leg below the knee had pursued compensation for her son because she was certain that she must have received thalidomide during her pregnancy.[24] The German manufacturer of thalidomide refused compensation claiming that thalidomide had never been distributed in the Azores. The mother fervently believed that thalidomide was responsible for her son's malformations and I received a letter from her asking for my opinion. I requested her son's medical records, X-rays and photographs of the malformations. She sent me the X-ray studies of his hips and legs and his complete evaluation performed at the local hospital in the Azores. He had none of the other stigmata of thalidomide embryopathy (pre-axial limb defects, phocomelia, facial hemangioma, ear malformations, deafness, crocodile tears, ventricular septal defect, intestinal or gall bladder atresia, kidney malformations). Most importantly, his limb malformations were not of the thalidomide type. He had a unilateral congenital amputation, with no digital remnants at the end of the limb. His pelvic girdle was completely normal which would be unusual in a thalidomide malformed limb. Finally, his limb defect involved only one leg; the other leg was completely normal. This would be very unusual in a true thalidomide embryopathy. In this particular case, the young man had a congenital amputation, probably due to vascular disruption, etiology unknown. Known causes of vascular disruptive malformations are cocaine, misoprostol and chorionic villous sampling. It is difficult to determine whether any amount of appropriate counseling will put closure on this problem for this mother.

Patient 4

A family claimed that the anti-nausea medication, Bendectin,[36,37,53] taken by the mother of a malformed boy, was responsible for her son's congenital limb reduction defects. Bendectin was taken during the mother's pregnancy after the period of limb organogenesis, but some limb malformations can be produced by teratogens later in pregnancy. The malformation was unaccompanied by any other dysmorphogenetic effects. The boy's malformations were the classical split-hand, split-foot syndrome, which is dominantly inherited. This malformation has a significant portion of cases that are due to a new mutation. Since neither parent manifested the malformation, the conclusion had to be that a new mutation had occurred in the sex cells of one of the parents. Therefore, the risk of this malformation occurring in the offspring of this boy would be 50%. Obviously, Bendectin was not responsible for this child's malformations. In spite of the obvious genetic etiology of the malformed child's birth defects, a legal suit was filed. A jury decided for the defendant – namely, that Bendectin was not responsible for the child's birth defects.

It should be apparent that determining the reproductive risks of an exposure during pregnancy or the etiology of a child's congenital malformations is not a

simple process. It involves a careful analysis of the medical and scientific literature pertaining to the reproductive toxic effects of exogenous agents in humans and animals, as well as an evaluation of the exposure and biological plausibility of an increased risk or a causal connection between the exposure and a child's congenital malformation. It also involves a careful physical examination, a review of the scientific literature pertaining to genetic and environmental causes of the malformations in question. Abridged counseling based on superficial and incomplete analyses is a dis-service to the family.

CONCLUSIONS

There have been significant advances in embryology, teratology, reproductive biology, genetics and epidemiology in the last 50 years that have provided scientists and clinicians with a better perspective on the causes of congenital malformations. We still cannot provide the families of children with malformations a definitive diagnosis and etiology for every malformed child. However, there are numerous environmental drugs, chemicals and physical agents that have been documented to produce congenital malformations and reproductive effects. While this multitude of teratogenic agents (agents that produce congenital malformations from exposures during pregnancy) account for only a small proportion of malformations, it is important to remember that all these environmentally produced birth defects are potentially preventable. The most common known cause of congenital malformations is genetic, but the largest group, unfortunately, is unknown. There are a number of important clinical rules that are important for clinicians to utilize when determining the cause of their patient's congenital malformations.

1. No teratogenic agent should be described qualitatively as a teratogen (an agent that causes birth defects), since a teratogenic exposure includes not only the agent, but also the dose and the time in pregnancy when the exposure occurs.
2. Even agents that have been demonstrated to result in malformations cannot produce every type of malformation. Known teratogens may be presumptively implicated by the spectrum of malformations they produce (the syndrome that describes the clinical manifestations of the teratogenic agent). It is easier to exclude an agent as a cause of birth defects than to definitively conclude that it was responsible for birth defects, because of the existence of genocopies of some teratogenic syndromes.
3. When evaluating the risk of exposures, the dose is a crucial component in determining the risk. Teratogenic agents follow a toxicological dose–response curve. This means that each teratogen has a threshold dose, below which, there is no risk of teratogenesis, no matter when in pregnancy the exposure occurred.
4. The evaluation of a child with congenital malformations cannot be adequately performed unless it is approached with the same scholarship and intensity as the evaluation of any other complicated medical problem.
5. Each physician must recognize the consequences of providing erroneous reproductive risks to pregnant women exposed to drugs and chemicals

during pregnancy or alleging that a child's malformations are due to an environmental agent without performing a complete and scholarly evaluation.

6. Unfortunately, clinical teratology and clinical genetics are not emphasized in medical school and residency education programs. But physicians have a multitude of educational aids to assist them in their evaluations, which include consultations with clinical teratologists and geneticists, the medical literature and the OMIM website.

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