Environmental Causes of Human Congenital Malformations: The Pediatrician's Role in Dealing With These Complex Clinical Problems Caused by a Multiplicity of Environmental and Genetic Factors

Robert L. Brent, MD, PhD

ABSTRACT. There have been amazing advances in embryology, teratology, reproductive biology, genetics, and epidemiology in the past 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 cause in every instance. The purpose of this article is to inform pediatricians about environmental drugs, chemicals, and physical agents that have been documented to produce congenital malformations and reproductive effects and to indicate that the multitude of teratogenic agents account for only a small proportion of malformations. The most common known cause is genetic, but the largest group, unfortunately, is unknown. There are a number of important clinical rules that are important for clinicians to use when determining the cause of their patient's congenital malformations:

1. **No teratogenic agent should be described qualitatively as a teratogen, because a teratogenic exposure includes not only the agent but also the dose and the time in pregnancy when the exposure has to occur.**
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 that they produce. It is easier to exclude an agent as a cause of birth defects than to conclude definitively 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 toxicologic 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 performed adequately 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 who are exposed to drugs and chemicals during pregnancy or alleging that a child's malformations are attributable to an environmental agent without performing a complete and scholarly evaluation.**
6. **Unfortunately, clinical teratology and clinical genetics is not emphasized in medical school and residency education programs, but pediatricians have a multitude of educational aids to assist them in their evaluations, which includes consultations with clinical teratologists and geneticists, the medical literature, and the OMIM web site. *Pediatrics* 2004;113:957–968; *etiology of congenital malformations, birth defects, threshold exposure, teratogenic syndrome, method of evaluation of etiology, stochastic and deterministic effects.***

From the Thomas Jefferson University, Alfred I. duPont Hospital for Children, Laboratory of Clinical and Environmental Teratology, Wilmington, Delaware.

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Reprint requests to (R.L.B.) Rm 308, R/A, Alfred I. duPont Hospital for Children, Box 269, Wilmington, DE 19899. E-mail rbrent@nemours.org

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When I was a medical student at the University of Rochester, I was fortunate to have James G. Wilson, an embryologist, as one of my teachers in the anatomy course. He was working on the effects of radiation on the embryo, and that is how I became interested in congenital malformations. Many of the faculty members discouraged me from pursuing the study of the causes of birth defects as an academic goal, "Because we are never going to solve that problem." In 1955, 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. More than 50 teratogenic environmental drugs, chemicals, and physical agents have been described[7–10] using modern epidemiologic tools and the talents of clinical dysmorphologists.[11–17] The basic science and clinical rules for evaluating teratogenic risks have been established[18] (Table 1). 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

TABLE 1. Evaluation of the Allegation That a Particular Environmental Agent Causes Congenital Malformations or Is Responsible for Malformations in an Individual Patient

Epidemiologic studies. Controlled epidemiologic 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 that mimics the human developmental effect at clinically comparable exposures can be developed. Because 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 occurs 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.
1. MOA
2. Receptor studies
3. Nature of the malformations
4. Teratology principles

Modified from Brent. 1976, 1986, 1991, 1995.[7,8,18,36,37,39–41,53]

Human Genome Project in 2000 offers the geneticist and the teratologist immense opportunities to evaluate the concepts of polygenic and multifactorial causes[19,20] of congenital malformations.

EMOTIONAL IMPACT OF CONGENITAL MALFORMATIONS

Reproductive problems encompass a multiplicity of diseases, including sterility, infertility, abortion (miscarriage), stillbirth, congenital malformations (as a result of environmental or hereditary causes), fetal growth retardation, and prematurity. 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 and Prevention, severe congenital malformations include birth defects that cause death, hospitalization, mental retardation; necessitate significant or repeated surgical procedures; are disfiguring; or interfere with physical performance. That means that each year in the United States, 120 000 newborns are born with severe birth defects. Genetic diseases occur in approximately 11% of births. Spontaneous mutations account for <2% to 3% of genetic disease. Therefore, mutations induced from preconception exposures of environmental mutagens are difficult endpoints to document (Table 3).

Along with cancer, psychiatric illness, and hereditary diseases, reproductive problems have been viewed throughout history as diseases of affliction (Fig 1). Inherent in the reactions of most cultures is that these diseases have been viewed as punishments for misdeeds[21–24] (Fig 1). 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. George Spencer was slain by the Puritans in New Haven in the 17th century, having been convicted of fathering a cyclopean pig, because 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 health care provider or used by their employer.[21,22]

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 health care providers, espe-

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) (eg, neural tube defects, cleft lip, hypospadius, hyperlipidemia, diabetes)	90 000
Dominantly inherited disease (eg, achondroplasia, Huntingtons chorea, neurofibromatosis)	10 000
Autosomal and sex-linked genetic disease (eg, cystic fibrosis, hemophilia, sickle-cell disease, thalassemia)	1200
Cytogenetic (chromosomal abnormalities) (eg, Down syndrome [Trisomy 21]; Trisomy 13, 18; Turner syndrome; 22q deletion)	5000
New mutations*	3000
Severe congenital malformations† (as a result of 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 wk)/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 (reference).
† Congenital malformations have multiple causes, including a significant proportion that are genetic.

TABLE 3. Cause of Human Congenital Malformations Observed During the First Year of Life

Suspected Cause	% 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 contrictions, umbilical cord constraint, disparity in uterine size and uterine contents	1–2
Chemicals, prescription drugs, high-dose ionizing radiation, hyperthermia	<1

Modified from Brent.[7–9,14,23,26,36,37,39,40]

cially when 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 nonobjective opinions can be expressed by scientists, the laity, or the press.[25,26] 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 a radiograph 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 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 postconception has a significant risk of malforming the embryo. That same dose taken during the 10th week of gestation will not result in congenital malformations. 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,[27–29] but if the dose is too low or the radiograph does not directly expose the embryo, then there is no risk of congenital malformations.[23] So a list of teratogens only indicates teratogenic potential. Evaluation of the dose and the time of exposure could indicate that there is no teratogenic risk or that the risk is significant.

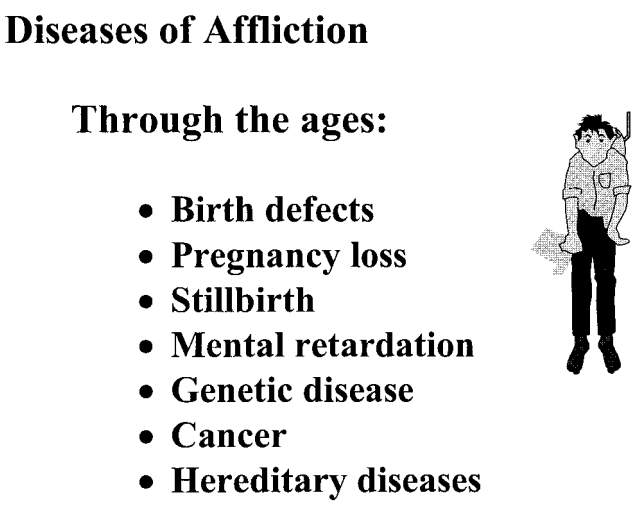

Fig 1. Through the ages these diseases have been interpreted or considered by multiple cultures to be stigmatizing; punishments for misdeeds or sins. In modern times, these are the diseases whose causation is thought to be due to environmental factors—thus converting the guilt of the past into anger that is projected onto others in our society and sometimes leads to litigation.

When evaluating studies that deal 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.[23] These principles are as follows:

1. Exposure to teratogens follows a toxicologic dose–response curve. There is a threshold below which no teratogenic effect will be observed, and as the dose of the teratogen is increased, both the severity and the frequency of reproductive effects will increase (Fig 2).
2. The embryonic stage of exposure is critical in determining which 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

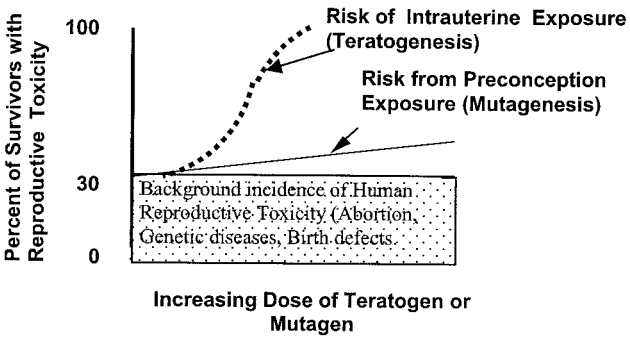

Fig 2. The dose response curve of environmental toxicants (drugs, chemicals, and physical agents) can have deterministic (threshold) and/or stochastic effects. Mutagenic and carcinogenic events are stochastic phenomena and theoretically do not have a threshold exposure below which no risk exists. At low exposures the risk still exists, but it is usually below the spontaneous risk of cancer and mutations. Whether the curve is linear or curvilinear for stochastic phenomena can be debated, but from a theoretical point, it traverses zero. Toxicological phenomena, such as teratogenesis, that do not involve mutagenic and carcinogenic effects usually follow an S-shaped curve, with a threshold below which no effects are expected.

the induction of mental retardation from ionizing radiation is from the 8th to the 15th week of pregnancy, a lengthy period. Thalidomide's period of sensitivity is approximately 2 weeks[24] (Table 4).

3. Even the most potent teratogenic agent cannot produce every malformation.
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. Although 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. However, 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.[30]

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	Thumb aplasia
22–23	Microtia, deafness
23–34	Hip dislocation
24–29	Amelia, upper limbs
24–33	Phocomelia, upper limbs
25–31	Preaxial aplasia, upper limbs
27–31	Amelia, lower limbs
28–33	Preaxial aplasia, lower limbs; phocomelia, lower limbs; femoral hypoplasia; girdle hypoplasia
33–36	Triphalangeal thymb

Modified from Brent and Holmes.[24]

CAUSE OF CONGENITAL MALFORMATIONS

The cause of congenital malformations can be divided into 3 categories: unknown, genetic, and environmental (Table 3). The cause of a majority of human malformations is unknown. A significant proportion of congenital malformations of unknown cause is likely to have an important genetic component. 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 environmental influence. Spontaneous errors of development may indicate that we never achieve our goal of eliminating birth defects because a significant percentage of birth defects are attributable to the statistical probability of errors in the developmental process, similar to the concept of spontaneous mutation. It is estimated that the majority 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% to 60% of which are attributable to chromosomal abnormalities.[31–34] Finally, 3T to 6% of offspring are malformed, which represents the background risk for human maldevelopment (Table 2).

FACTORS THAT AFFECT THE 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 result in a spectrum of malformations that vary 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 the 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[24] (Table 4), whereas the susceptibility period for radiation-induced microcephaly is very broad.[23]

TABLE 5. Stochastic and Threshold Dose–Response Relationships of Diseases Produced by Environmental Agents

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

Modified from Brent.[23]

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 are, at most, rough approximations. Dose equivalence among species for drugs and chemicals can be accomplished only by performing pharmacokinetic studies, metabolic studies, and dose–response investigations in the human and the species being studied, whereas ionizing radiation exposures in rads or Sieverts (Sv) are comparable in most mammalian species.[23]

Threshold Dose

The threshold dose is the dosage below which the incidence of death, malformation, growth retardation, or functional deficit is not statistically greater than that of controls (Fig 2). The threshold level of exposure is usually from <1 to 2 orders of magnitude below the teratogenic or embryopathic dose for drugs and chemicals that kill or malform half of the embryos. An exogenous teratogenic agent, therefore, has a no-effect dose as compared with mutagens or carcinogens, which have a stochastic dose–response curve (Table 5, Fig 2). The severity and the incidence of malformations produced by every exogenous teratogenic agent that has been studied appropriately have exhibited threshold phenomena during organogenesis.

Pharmacokinetics and Metabolism of the Drug or the Chemical

The physiologic 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. Physiologic 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 as a result of 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. Variation in uterine blood flow, although little is known about how this affects transfer across the placenta

The fetus also undergoes physiologic 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 pharmacologic receptors is likely to proceed at different rates in the various tissues
4. Drugs that are excreted by the fetal kidneys may be recycled via amniotic fluid swallowing by the fetus

The role that the placenta plays in drug pharmacokinetics has been reviewed by Juchau and Rettie[35] and involves 1) transport, 2) the presence of receptor sites for a number of endogenous and xenobiotic compounds (β-adrenergic, glucocorticoid, epidermal growth factor, immunoglobulin G Fc, insulin, low-density lipoproteins, opiates, somatomedin, testosterone, transcobalamin II, transferrin, folate, and retinoid), and 3) 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.

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 effect in the first trimester.
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 is 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**.**
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 quire high.
Ethyl Alcohol: Fetal Alcohol Syndrome consists of microcephaly, mental retardation, growth retardation, typical facial dysmorphogenesis, abnormal ears, small palpebral fissures.
Ionizing Radiation: The threshold is greater than 20 rad (0.2 Gy) can increased the risk for some fetal effects such as micocephaly or growth retardation, but the threshold for mental retardation is higher.
Insulin Shock Therapy: This therapeutic modality when administered to pregnant women resulted in microcephaly, mental retardation.
Lithium Therapy: Chronic sage for the treatment of manic depressive illness has an increased risk for Ebstein's Anomaly and other malformations, but the risk appears to be very low.
Minoxidil: The discovery of the growth promotion of 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 intramniotic 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 phenomenon, such as limb reduction defects and Mobius syndrome have been reported in pregnancies in which this drug was used to induce an abortion.
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 these 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, preaxial limb reduction defects, phocomelia, ventricular septal defects and GI atresias. The susceptible period is from the 22nd to the 36th day postconception.
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 to 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.
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.

The major site of bioconversion of chemicals in vivo is likely to be the maternal liver. Placental P450-dependent mono-oxygenation 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 P450 oxidative isozymes capable of converting pro-teratogens to active metabolites dur-

TABLE 6. Continued

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.
Carbamazepine: Treatment of convulsive disorders increases the risk facial dysmorphology.
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 ugm% 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 Addiction Embryopathy: 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).
Herpes Simplex: Fetal infection, liver disease, death.
Human Immunodeficiency Virus: Perinatal HIV infection.
Parvovirus Infection, B 19: 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 hip.
Maternal Disease States
Corticosteroid Secreting Endocrinopathy: Mothers with Cushings Disease can have infants with hyperadrenocortism, but anatomical malfromations 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, midline closure defects, cleft palate and muscle aplasia, limb reduction defects, cleft lip, omphalocele, encephalocele).
Maternal Androgen Endocrinopathy (Adrenal tumors): Masculinization.
Maternal Diabetes: Caudal and femoral hypoplasia, transposition of great vessels.
Maternal Folic Acid in reduced amounts: An increased incidence of neural tube defects (NTDs).
Maternal Phenylketonuria: Abortion, microcephaly, and mental retardation. Very high risk in untreated patients.
Maternal Starvation: IUGR, abortion, NTDs.
Tobacco Smoking: Abortion, IUGR, and stillbirth.
Zinc Deficiency*: Neural Tube Defects*

* Controversial

ing early organogenesis. In addition, 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: 1) the chemical must be convertible to the intermediate, 2) the intermediate must be found in or have access to the tissue(s) affected, 3) the embryotoxic effect should increase with the concentration of the metabolite, 4) inhibiting the conversion should reduce the embryotoxic effect of the agent, 5) promoting the conversion should increase the embryotoxicity of the agent, 6) inhibiting or promoting the conversion should not alter the target tissues, and 7) 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 exchange between the embryo and the maternal organism is controlled by the placenta. 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 spe-

cies 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 using animal data to project human effects may improve.

Although 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 a chemical. More than 30 disorders of increased sensitivity to drug toxicity or effects in the human are attributable to an inherited trait.

ENVIRONMENTAL AGENTS WHOSE EXPOSURE DURING PREGNANCY HAS BEEN DEMONSTRATED TO RESULT IN REPRODUCTIVE TOXICITY

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 used in any analysis of the risks in individual patients. Many of these agents represent a very small risk, whereas others may represent substantial risks. The risks will vary with the magnitude, timing, and length of exposure. More information can be obtained from more extensive reviews or summary articles. You will also note that Table 7 includes agents that have had concerns raised about their reproductive risks, but after 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 that deal 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.
Electromagnetic Fields (EMF): Alleged to cause abortion, cancer, and birth defects.
Progestational drugs: Alleged to cause numerous types of nongenital birth defects, including limb reduction defects, heart malformations and many other malformations).

ROLE OF THE PEDIATRICIAN IN COUNSELING FAMILIES CONCERNING THE CAUSE OF THEIR CHILD'S CONGENITAL MALFORMATIONS

The clinician must be cognizant 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 nonmeritorious 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 seems to occur most commonly in the evaluation of environmental toxic exposures in which 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 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-trichlorophenoxyacetic acid, polychlorinated biphenyls, lead, cadmium, arsenic, pesticides, herbicides, veterinary hormones, and industrial exposures.

Unfortunately, we do have examples in which environmental disasters have been responsible for birth defects or pregnancy loss in exposed populations (methyl mercury in Japan, polychlorinated biphenyls in Asia, 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 a drug is safe or hazardous unless we know the magnitude of the exposure.

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

1. Has the environmental agent been proved 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, then 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 pediatrician responds to a parent's inquiry, "What caused my child's birth defect?" the pediatrician should respond in the same scholarly manner that would be used in performing a differential diagnosis for any clinical problem. Pediatricians have a protocol for evaluating complex clinical problems (eg, "fever of unknown origin," "failure to thrive," "congestive heart failure," "respiratory distress"). If a mother of a malformed infant had some type of exposure during pregnancy, such as a diagnostic radiologic examination or medication, then 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, then 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 attributable to prescribed drugs, chemicals, and physical agents[9,36,51] (Table 3). 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 in a recent analysis, it was pointed out that there are no drugs with measurable teratogenic potential in the list of the 200 most prescribed drugs in the United States.[51]

After a complete examination of the child and a review of the genetic and teratology medical literature, the clinician must decide whether the child's malformations are attributable to a genetic cause or an environmental toxin or agent. He may not be able to conclude definitively or presumptively the cause 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 woman has been exposed to a drug, chemical, or physical agent, because 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 that includes a 5-part evaluation is recommended as described in Table 1[18] and is summarized as follows:

1. Consistency of epidemiologic studies
2. Secular trend analysis
3. Animal reproductive studies
4. Dose–response relationships and pharmacokinetic studies comparing human and animal metabolism
5. Biological plausibility

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 general pediatric 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. Although some growth measurements are routine, many measurements used by these specialized counselors are not part of the usual physical examination (eg, palpebral fissure size, ear length, intercanthal distances, total height-to-trunk ratio). Important physical variations in facial, hand, and foot structure as well as other anatomic 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 the 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 as follows:

1. What was the nature of the exposure?
2. Is the exposure agent identifiable? If the agent is identifiable, then has it been identified definitively 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, then 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 infant to term?
7. What is the medical and reproductive history of this mother with regard to previous 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 of 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 34-year-old pregnant laboratory worker dropped and broke a reaction vessel that contained a mixture of chemical reagents. She proceeded to clean the floor with paper towels. Later she became concerned about the potential harmful effects of the exposure. She was in the sixth week of her pregnancy, which means that the embryo was in the period of early organogenesis. The chemicals in the spill were tetrahydrofuran (70%), pyridine (20%), and iodine (1%). It was not possible to estimate quantitatively the exposure to these agents, but the laboratory worker experienced no symptoms from the exposure. This was a planned, wanted pregnancy. Although iodine can interfere with thyroid development, the exposure in this situation would be inconsequential, because the thyroid is not yet present. The other 2 compounds have not been studied in epidemiologic studies of pregnant women. No other exposure to reproductive toxins occurred in this pregnancy, and the family history for congenital malformations was negative. The woman was advised that it would be very unlikely that this exposure would increase her teratogenic risk because the exposures to the embryo would be extremely low. She was also told that she still was faced with the background risks for birth defects and miscarriage. Therefore, her reproductive risks should be the same as the risks for the general population (Table 2).

Patient 2

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 postinjury, 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. Although 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 1 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 3

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 department 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 radiologic 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 postconception at the time of the radiologic examination. The patient advised the counselor that she was ambivalent about the pregnancy because of the "dangers" of the radiographs to her embryo. The estimated exposure to the embryo was <500 mrad (0.005 Sv). This exposure is far below the exposure that is known to affect the developing embryo. Just as important is that the embryo was exposed during the first 2 weeks postconception, a time that is less likely to increase the risk of teratogenesis, even if the exposure was much higher.[23,52] After evaluation of the family history and after she received counseling about the risks of the radiograph, the prospective mother decided to continue the pregnancy. She delivered a 3150-g normal infant.

Evaluation of Whether the Cause of Congenital Malformations Was an Environmental Exposure During Pregnancy, Is Genetic, or Cannot Be Determined

Patient 4

The mother of a 30-year-old man who was 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, radiographs, and photographs of the malformations. She sent me the radiograph 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 (preaxial limb defects, phocomelia, facial hemangioma, ear malformations, deafness, crocodile tears, ventricular septal defect, intestinal or gall bladder atresia, kidney malformations). Most important, 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 1 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 as a result of vascular disruption, cause 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 5

A family claimed that the antinausea 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 boys malformations were the classical split-hand, split-foot syndrome, which is dominantly inherited. This malformation has a significant portion of cases that are attributable to a new mutation. Because neither parent manifested the malformation, the conclusion had to be that a new mutation had occurred in the sex cells of 1 of the parents. Therefore, the risk of this malformation's occurring in the offspring of this boy would be 50%. Obviously, Bendectin was not responsible for this child's malformations. Despite the obvious genetic cause 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.

Patient 6

A woman visited the emergency department of an excellent university hospital complaining of severe lower abdominal pain. An obstetric resident saw her because she informed the staff that she had a previous ectopic pregnancy that necessitated the removal of her ovary and tube. A pregnancy test was positive, and she was scheduled to return to the obstetric clinic in 1 week. At that time, her chorionic gonadotropin level was repeated and had not changed from its previous level. Without performing an ultrasound, a diagnosis of ectopic pregnancy was made. To preserve the patient's reproductive potential, it was decided to treat the ectopic pregnancy with methotrexate rather than remove the remaining tube and ovary. After the administration of methotrexate, the patient was sent home, but a laboratory report indicated that the gonadotropin level had increased 5-fold. The laboratory report received earlier in the day was a copy of the original report performed a week earlier. The patient was called back to the hospital, and an ultrasound revealed a normally implanted embryo. The senior obstetric staff counseled the mother that the infant was at increased risk for having congenital malformations because of the exposure. The patient refused to abort the pregnancy. The obstetric department offered to provide care for the pregnancy and delivery that included a number of ultrasound examinations. At 28 weeks, the patient went into labor and delivered a live-born premature infant. During infancy, a diagnosis of hydrocephalus, developmental delay, and spastic cerebral symptoms was made. A lawsuit was filed by the family against the doctors and the university hospital. The attorney representing the child called me and asked me to evaluate the allegation that the abnormalities in the child were attributable to the administration of the methotrexate. Methotrexate has been reported to cause growth retardation, microcephaly, developmental delay, and hydrocephalus, but not prematurity. The clinical care provided by the resident doctor was unfortunate, but the offer of providing care by the senior obstetricians turned out to be fortunate for the defendants in this case. Review of the records revealed 2 important findings. First, an ultrasound examination taken 1 week before the premature delivery revealed that there was no evidence of hydrocephalus. Second, the birth weight was appropriate for the gestational stage. The exposure to methotrexate was not responsible for the serious problems in this infant, because the hydrocephalus and neurologic symptoms were attributable to a central nervous system bleed in the postnatal period as a complication of the prematurity.

It should be apparent that determining the reproductive risks of an exposure during pregnancy or the cause of a child's congenital malformations is not a simple process. It involves a careful analyses 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 and a review of the scientific literature pertaining to genetic and environmental causes of the malformations in question. Abridged counseling on the basis of superficial and incomplete analyses is a disservice to the family.

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