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The Role of the Pediatrician in Preventing Congenital Malformations

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Objectives After completing this article, readers should be able to:

1. Review the discoveries and advances in teratology, genetics, toxicology, and clinical teratology counseling in the past 50 years.
2. Explain the changes that have occurred in some basic principles of teratology.
3. List the drugs, chemicals, infections, and other environmental agents that may harm the developing embryo.
4. Explain how congenital malformations can be prevented and how to manage pregnancies in which the embryo has a congenital malformation.
5. Delineate the principles involved in evaluating the risks and effects of environmental toxicants and know how to evaluate the potential risks of a specific exposure.
6. Discuss how to evaluate whether a child's congenital malformation is caused by an environmental exposure or other mechanism.

Introduction

During the first half of the 20th century, the field of teratology (the study of birth defects) was represented sparsely in the medical literature. Pediatricians who graduated from medical school in the 1950s were taught that the correct number of human chromosomes was 48, until the number was reported accurately as 46 by Tijo and Levan in 1956. (1) Gregg had described the teratogenicity of rubella virus infection during pregnancy in 1941. (2) The teratogenic risk of the folic acid antagonists (aminopterin) was established in humans, (3)(4) and experimental studies indicated that nutritional deficiencies could produce congenital malformations (CMs) in animals. (5)(6)(7)

In the 1950s, teratologists were aware that only a small percentage of birth defects were caused by drugs, chemicals, and physical agents. (5) By 2007, further information confirmed the viewpoint that birth defects caused by drugs, chemicals, and physical agents account for a small but significant percentage of total birth defects (Table 1). (6)(7)(8)(9) However, avoiding teratogenic drugs and chemicals or reducing teratogenic maternal disease states has a major impact on an individual pregnancy and family.

Reproductive problems encompass a multiplicity of diseases, including sterility, infertility, spontaneous abortion (miscarriage), stillbirth, congenital malformations (due to environmental or hereditary causes), fetal growth restriction, and prematurity. (6)(7)(8)(9) Because these clinical problems occur commonly in the general population, environmental causes are not always easy to corroborate (Table 2). Severe CMs occur in 3% of births.

According to the Centers for Disease Control and Prevention (CDC), severe CMs include those birth defects that cause death, hospitalization, or intellectual disability; necessitate significant or repeated surgical procedures; are disfiguring; or interfere with physical performance. Each year in the United States, 120,000 infants are born with severe birth defects. Genetic diseases occur in approximately 11% of births. Spontaneous mutations account for less than 2% to 3% of genetic diseases (Table 1). Therefore, mutations induced from preconception exposures to environmental mutagens are difficult endpoints to document (Table 2). Birth defects account for 440,000 deaths among children each year in developing nations, representing 3.7% of the deaths in children. In the United States, 25% of infant deaths are due to lethal CMs.

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Table 1. Reproductive and Developmental Effects

Condition	Frequency
Immunologically and clinically diagnosed spontaneous abortions per million conceptions (20% have lethal malformations or chromosome abnormalities that cause spontaneous abortion before the first month of gestation [first missed menstrual period])	350,000
Clinically recognized spontaneous abortions per million clinically recognized pregnancies	150,000
Spontaneous abortion after the first missed menstrual period	
Genetic diseases per million births	110,000
Multifactorial or polygenic genetic environmental interactions	90,000
Dominantly inherited disease	10,000
Autosomal recessive and sex-linked genetic disease	1,200
Cytogenetic (chromosomal abnormalities)	5,000
New mutations in the developing ova or sperm before conception	3,000
Major malformations (genetic, unknown, environmental)	30,000
Prematurity (Ireland, 55,000; United States, 124,000)	69,000
Fetal growth restriction	30,000
Stillbirths (>20 wk)	4,000 to 20,900
Infertility	7% of couples
Modified from Brent. (7)	

Pediatricians and pediatric subspecialists cannot ignore the medical problems associated with CMs because they are the leading cause of death in infancy (1 to 12 months of age). (6)(7) They are the fifth leading cause of death from disease in the entire population and are responsible for a large number of hospitalizations. Although clinicians who care for pregnant women play a very important role in the effort to prevent CMs, pediatricians also can contribute to the preventive effort and counseling of families in their practices who have a child born with a CM.

Advances in Teratology and Genetics During the Last Half of the 20th Century

During the past 50 years, substantial discoveries and advances have been made in teratology, genetics, toxicology, and clinical teratology counseling (Table 3). The number of genetic diseases catalogued in the post-World War II period was approximately 1,500. (10)(11) In the year 2006, the Human Genome Project identified more than 6,000 single-gene genetic abnormalities, many of which manifest as CMs. (12) Also, a large number of chromosome abnormalities and complex or polygenic genetic diseases involve multiple genetic loci (eg, diabetes and obesity).

The field of prenatal diagnosis, using ultrasonography, karyotyping, biochemical studies, and molecular biology studies, has expanded the ability to diagnose anatomic malformations, metabolic diseases, and genetic diseases in the embryo and to determine the cause of many birth defects that previously were listed in the unknown category (Tables 1 and 2). The ability to determine the cause of a child's birth defect has improved, as well as the ability to inform the family about the risk of recurrence. (11)(13)(14)(15)(16)(17)(18)

The topic of interruption of pregnancy is controversial in many countries and continues to be debated both politically and ethically, but it offers the opportunity to eliminate nonviable or severely malformed embryos early in pregnancy. Physicians should understand that the family makes the decision on how to manage pregnancies affected with serious abnormalities; the physician's role is as an educator who defines the problem and prognosis. Nature frequently preempts politics and ethics, with most early spontaneous abortions occurring in embryos that have either karyotype abnormalities or serious anatomic malformations. Another reason that interruption of pregnancy is controversial is because the procedure does not prevent CMs; rather, it eliminates severely malformed embryos very early in pregnancy. Abnormal pregnancies can be diagnosed early in gestation through maternal serum biochemical markers, and ultrasonography, amniocentesis, and chorionic villous sampling can aid in the diagnosis of very serious or fatal abnormalities early in pregnancy.

Discovery of new teratogens, such as the angiotensin-converting enzyme inhibitors and misoprostol, have taught clinicians to be prepared to accept new principles in teratology that are discovered when new teratogens are identified that do not follow the "old" rules, such as the belief that severe anatomic CMs can be induced only during early organogenesis. (19)(20)(21)(22)(23)(24)(25)(26)(27)(28)(29)(30) Microcephaly, intellectual disability, growth restriction, and vascular disruptive phenomena can be induced by embryotoxic exposures in the second and third trimesters (Table 4).

Table 2. **Causes of Congenital Malformations Observed During the First Year After Birth**

Suspected Cause	Percent of Total
Unknown	65
Polygenic	
Multifactorial (gene–environment interactions)	
Spontaneous errors of development	
Synergistic interactions of teratogens?	
Genetic	15 to 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 to 2
Chemicals, prescription drugs, high-dose ionizing radiation, hyperthermia	2 to 3

Modified from Brent. (7)

Environmental Causes of Developmental and Reproductive Effects

Obstetricians and perinatologists obviously must be familiar with drugs, chemicals, infections, and other environmental agents (Table 4) that may harm the developing embryos of their pregnant patients, but this an area of importance to pediatricians as well. A comprehensive textbook chapter on the environmental causes of birth defects may be helpful to pediatricians who wish to have more extensive information about teratogenic agents. (14) Pediatricians may encounter several specific situations related to birth defects:

- Because teenagers under the care of a pediatrician do get pregnant, it is important to consider the possibility of pregnancy when prescribing medications for teenage patients. In particular, the administration of retinoids (isotretinoin), anticonvulsants, and vaccines may place the pediatrician at legal risk. (31)
- Some of pediatric patients have CMs or other developmental effects and the parents may ask the pediatrician about the cause of their child's medical problems. The pediatrician should be prepared to answer the questions or refer the family to a clinical teratologist or geneticist.

- The pediatrician may attend a delivery of a malformed child and subsequently be involved in litigation as a fact witness or defendant.
- Mothers of pediatric patients may become pregnant and ask their child's pediatrician about the risk of medications, immunizations, or other environmental exposures that may be prescribed during pregnancy.
- Pediatricians should encourage teenagers to receive the human papillomavirus vaccine and encourage all women of reproductive age to take 400 μg of folic acid and 6 μg of vitamin B-12 each day to reduce the risk of neural tube defects. (15)

Pediatricians have a multitude of educational aids to assist in their evaluations, including consultations with clinical teratologists

and geneticists, the medical literature, OMIM (the web site for the Online Mendelian Inheritance of Man supported by the National Institutes of Health) (11) and TERIS (the web site of the Teratogen Information Services located at the University of Washington), (17) and publications that review the field of CMs. (12)(13)(14)(16)(18)(19)(20)(21)(22)(23)(24)(25)(26)(27)(28)(29)(30)

Prevention of Congenital Malformations and Management of Affected Pregnancies

Some of the discoveries pertaining to the causes of in utero developmental problems have been translated into preventive measures (Table 5) The implementation of all of these measures could reduce the prevalence of birth defects and other developmental problems. The Centers for Disease Control and Prevention (CDC) has initiated a campaign to emphasize that some birth defects can be prevented. (32) A fact sheet from this campaign is published in the online version of this article (see data supplement). The National Academy of Sciences has published a report addressing the problem of reducing birth defects in developing nations. (33) Individual teratologists have been attempting to accomplish this goal for years with regard to the prevention of neural tube

Table 3. Advances in Teratology, Molecular Biology, Epidemiology, Clinical Teratology, and Genetics

- Correct number of chromosomes: 46 (1)
- Karyotyping and the discovery of chromosomal diseases
- Advances in molecular biology
- Development of the principles of teratology
- Improvement in the techniques of counseling parents about causes and risks
- Increasing number of identified genetic diseases that are responsible for congenital malformations and developmental problems
- Continuing discovery of new teratogens (3 in 1950 to more than 52 in 2008)
- Invention and application of computed tomography scans, magnetic resonance imaging, and diagnostic ultrasonography
- Development and implementation of the administration of rubella vaccination
- Folic acid supplementation to wheat grains and the prevention of folic acid-preventable neural tube defects
- Creation of the Online Mendelian Inheritance in Man program on the internet for diagnosing genetic diseases (10)(11)
- Introduction of fetal therapy and accompanying controversies
- Improvement in the control and management of diabetes during pregnancy
- The Human Genome Project (12)
- Determination of the vulnerability of the embryo at different stages of development
- Fetal therapy and intervention based on the wishes of the parents after thorough discussion of the risks and benefits

defects (NTDs) through folic acid supplementation. (15)(34)(35)(36)(37)(38)(39)(40)

Folic Acid

Folic acid supplementation of grain was recommended following the 1991 publication of the controlled study performed by the Medical Research Council that demonstrated that folic acid could prevent NTDs. (35) Based on this and other publications, the United States Food and Drug Administration (FDA) recommended that folic acid be added to grains, and the grain industry complied. Although only 50% of the amount recommended by the Institute of Medicine was added to the grain supply, the incidence of NTDs was reduced. Proponents of doubling the amount of folic acid in the grains claimed that all the preventable NTDs were not being prevented. (15)(36)(37)(38)(39)(40) The situation is worse in the rest of the world because only 10% of the world's population is receiving additional folic acid in the grain supply, which suggests that 90% of the populations in the developing nations are not receiving adequate amounts of folic acid. Only a small proportion of women take 400 μg of folic acid and 6 to 8 μg of vitamin B-12 in a multivitamin each day. Because of inadequate supplementation of grains, especially corn meal, even in the United States,

a significant proportion of the population is not receiving adequate folic acid and vitamin B-12 to prevent all folic acid-preventable NTDs.

Tens of thousands of children are born each year with folic acid-preventable NTDs. The United States spends \$200,000,000 each year to eradicate poliomyelitis through an excellent program of polio immunization, and frequent epidemiologic monitoring of the incidence of poliomyelitis provides data on the changing incidence of the disease (personal communication, G.P. Oakley Jr, 2010). The program has reduced the incidence of polio to 1,000 cases per year. Polio may never be eliminated because of subclinical infections and the possibility of new mutated strains, in contrast with smallpox. The CDC has been provided with a budget of \$5,000,000 for the prevention of the approximate 200,000

folic acid-preventable NTDs worldwide. Thus, the United States is spending \$200,000 for each case of polio prevented and \$25 for each NTD case prevented.

Iodine Deficiencies

Iodine deficiency as a cause of intellectual disability and goiter was recognized by a Swiss physician almost 200 years ago, (41) but the Swiss Academy rejected the findings. One hundred years elapsed before iodine deficiency as a clinical entity was supported by other scientists. (41) In many parts of the world, the soil is deficient in iodine, and goiters, hypothyroidism, and cretinism have been endemic. (42)(43) In 2007, the World Health Organization estimated that 2 billion individuals had insufficient iodine intake. Iodine deficiency is considered the single greatest preventable cause of intellectual disability. These problems were reduced or eliminated in the United States with the addition of sodium iodide to salt, referred to as "iodized salt." However, iodide deficiency may return to the United States with the emphasis on reducing salt intake to reduce the incidence of hypertension, especially if restaurants and prepared food product manufacturers also reduce the amount of salt in their products. The FDA and some pharmaceutical companies are considering the addition of potassium iodide or so-

Table 4. Environmental Agents or Milieus That May Increase the Risk or Be Associated With an Increased Risk of Reproductive or Developmental Effects

Agents

- Alcohol (ethyl alcohol)
- Aminopterin, methotrexate
- Androgens
- Angiotensin-converting enzyme inhibitors
- Angiotensin II receptor blocker (sartans)
- Antidepressants (selective serotonin reuptake inhibitors)
- Antituberculosis therapy
- Caffeine
- Carbamazepine
- Cocaine
- Cobalt used in hematinic vitamin preparation
- Coumarin derivatives
- Cyclophosphamide
- Diethylstilbestrol
- Diphenylhydantoin
- Lithium carbonate (salts)
- Methimazole
- Minoxidil
- Misoprostol
- Mycophenolate mofetil
- Penicillamine (D-penicillamine)
- Phenobarbital
- Progestational drugs
- Retinoids administered systemically (isotretinoin, etretinate)
- Retinoids administered topically
- Streptomycin
- Tetracyclines
- Thalidomide
- Trimethoprim
- Valproic acid
- Vitamin D

Procedures

- Chorionic villous sampling
- Insulin shock therapy
- Methylene blue intrauterine instillation
- Radiation: radioactive isotopes (radionuclides)
- Radiation: external diagnostic or therapeutic ionizing radiation
- Ultrasonography

Environmental Exposures

- Carbon monoxide (maternal) poisoning
- Electromagnetic fields
- Environmental chemicals (eg, dioxin, Agent Orange, phthalates, bisphenol A)
- Lead
- Methyl and ethyl mercury "poisoning"
- Polychlorinated biphenyls
- Smoking tobacco and absorption of nicotine and other products contained in tobacco
- Toluene and gasoline inhalation addiction

Environmental Conditions

- Diabetes
- Endocrinopathy
- Hyperthermia
- Folic acid and vitamin B-12 (risk of deficiency)
- Iodide deficiency
- Phenylketonuria (maternal)
- Mechanical problems in utero
- Nutritional deprivation
- Obesity
- Thyroid hypofunction (iodine deficiency, I-131 administration, antithyroid drugs)
- Vitamin A excess and deficiency

Infectious Diseases

- Fetal infections
- Cytomegalovirus
- Herpes simplex 1 and 2
- Human immunodeficiency virus
- Parvovirus B19
- Rubella virus
- Rubella vaccine
- Syphilis
- *Toxoplasma*
- Varicella-zoster
- Venezuelan equine virus encephalitis

Reproductive or developmental effects include congenital malformations, miscarriage, growth restriction, and neurobehavioral effects. Published articles addressing these reproductive or developmental agents can be found on the TERIS web site, (17) which provides the risk estimate for each agent and the quality of the available literature. Other drugs, chemicals, and environmental situations (eg, obesity) that may affect the embryo/fetus can be obtained from the TERIS web site and Shepard (now on the TERIS web site).

Table 5. Prevention of Congenital Malformation and Perinatal Disease

1. Rubella vaccination
2. Folic acid (400 $\mu\text{g}/\text{day}$), vitamin B-12 supplementation (6 $\mu\text{g}/\text{day}$)
3. Supplementation of iodine to deficient populations
4. Diagnosis and management of maternal hypothyroidism
5. Meticulous diabetic control and eventually the prevention or cure of diabetes
6. Obesity control (reduces the risk of birth defects and decreases the risk of developing diabetes)
7. Human immunodeficiency virus screening and treatment
8. Vaccination with group B *Streptococcus* vaccine
9. Maternal phenylalanine management for phenylketonuria
10. Management or discontinuation of oral anticoagulants, anticonvulsants, retinoids, thalidomide, and all known teratogens
11. Recognition that that new teratogens can be represented in the next new drug or chemical: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, mycophenolate
12. Cessation of maternal smoking and alcohol ingestion
13. Immunization against known teratogenic infections (botulin toxin vaccine for the pregnant mother to prevent infant botulism)
14. Reducing the incidence of multiple births following in vitro fertilization
15. Counseling older women and men about the increased risk of Down syndrome and other genetically determined diseases in older couples contemplating pregnancy
16. Screening for chromosome abnormalities and genetic disease: amniocentesis, chorionic villous sampling, maternal serum monitoring, and ultrasonographic monitoring to diagnose identifiable genetic diseases, karyotype abnormalities, and serious birth defects to inform the parents about their risks and options

dium iodide to multivitamin preparations. Young infants should ingest 40 $\mu\text{g}/\text{day}$ of iodine, and women require 150 $\mu\text{g}/\text{day}$ during pregnancy. (44)

Down Syndrome

The incidence of Down syndrome in the United States has increased significantly since 1980. In 1980, the prevalence was 0.99 per 1,000 births, with 3,579 affected newborns in the United States. In 2003, the prevalence of Down syndrome was 1.5 per 1,000 births, with 6,134 affected newborns, reflecting a 71% increase in numbers and 52% increase in prevalence. (45) In 1980, 4.57% births were in women older than 35 years. In 2003, 14.04% of births occurred in women older than 35 years. The increase in pregnancies in older women related to women postponing marriage and pregnancy for education or professional reasons make this a difficult problem to solve.

Clinical Evaluation

The physician responding to the question, "What caused my child's birth defect?" should perform the same schol-

arly analysis required for a differential diagnosis of any complicated clinical problem. If the mother of a malformed infant had some type of exposure during pregnancy, such as a diagnostic radiologic examination or medication, the consulting physician should not support or suggest the possibility of a causal relationship before performing a complete evaluation. Similarly, if a pregnant woman who has 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.

Many articles and books can assist the physician with the clinical evaluation, although general pediatric training programs do not usually prepare generalists to perform sophisticated genetic or teratology counseling. (11)(24)(25)(26)(27)(28)(29)(30) In addition to performing the usual history and

physical evaluation, the physician must 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 specialized counselors are not part of the usual physical examination, such as palpebral fissure size, ear length, intercanthal distances, total height-to-trunk ratio, and many other findings. 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.

Evaluating the Potential Risks of Environmental Exposure

Most consultations involving pregnancy exposures conclude that the exposure does not change the reproductive risks in that pregnancy. In many instances, the available information is so vague that the counselor cannot reach a definitive conclusion about the magnitude of the

risk. Information that is necessary for this evaluation includes:

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

Teratology Principles

A number of important clinical rules are important when determining the cause of a patient's congenital malformations. (6)(7)(9)(14)

- 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 the potential for causing CMs and other developmental effects.
- Even agents that have been demonstrated to result in malformations cannot produce every type of malformation. Known teratogens may be implicated presumptively by the spectrum of malformations they produce (the syndrome that describes the clinical manifestations of the teratogenic agent). However, different teratogenic agents may affect the fetus with a similar spectrum of malformations, thus preventing the physician from providing the family with a definitive diagnosis. Some teratogenic syndromes mimic genetic syndromes, such as thalidomide effects mimicking Holt-Oran syndrome. 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.
- The dose is a crucial component when evaluating the risk of exposures. Teratogenic agents follow a toxicologic dose-response curve, which means that each teratogen has a threshold dose, below which there is no risk

of teratogenesis, no matter when in pregnancy the exposure occurred.

- The evaluation of a child born with CMs cannot be performed adequately unless it is approached with the same scholarship and intensity as the evaluation of any other complicated medical problem.
- Each physician must recognize the consequences of providing erroneous information on 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.
- 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 clinicians, especially those inexperienced in dealing with these problems. No physician is 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. Such nonobjective opinions can be expressed by scientists, the public, or the press. (31) Every physician must be aware of the emotionally charged situation when a family has a child born with a birth defect.

Environmental Exposures Occurring 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. Following are some examples of consultations that have been referred to our clinical teratology service:

Patient 1. A 33-year-old mother of two was diagnosed with breast cancer, and her only treatment was radiation therapy to the left breast. She had a very good prognosis because the disease was only in the breast and there were no positive axillary lymph nodes. She underwent 6 weeks of radiation therapy. In the third week of therapy, it was determined that she was 8 weeks postconception. The oncologist and radiation therapist suggested that the pregnancy should be interrupted. The woman continued her radiation therapy to her breast but refused the interruption of her pregnancy and requested another opinion. The radiation therapist informed our office that the mother was receiving 2.25 Gy/day to her left breast. The health physicist calculated the fetal exposure to be 0.017 Gy for each therapy

session, which indicated that the fetus would receive 0.425 Gy (42.5 rads) during 25 radiation sessions over a period of 5 weeks. The mother asked to speak with the physician directly because she wanted the answers to several questions: 1) "Could the child be malformed?" Answer: The fetus had a 3% risk of malformation and a 15% of miscarriage because that is the background risk for all women. The risks would not be increased by the radiation exposure because of the protracted exposure over a 5-week period. 2) "Could the child have growth restriction?" Answer: Approximately 4% to 10% of children experience growth restriction, and it is unlikely that the protracted radiation exposure would have a marked effect on growth, but it is possible. 3) "Could my child be normal?" There is a greater than 90% chance that the child will be normal. This mother told her physicians that she was not interrupting the pregnancy. She delivered a 6 lb 11oz boy who was physically healthy after a careful evaluation.

Patient 2. A 34-year-old pregnant laboratory worker dropped and broke a reaction vessel containing a mixture of chemical reagents. After cleaning the floor with paper towels, 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 organogenesis. The chemicals in the spill were tetrahydrofuran (70%), pyridine (20%), and iodine (1%). It was not possible to estimate the quantitative exposure to the agents, but the laboratory worker experienced no symptoms from the exposure. The pregnancy was planned and wanted. Although iodine can interfere with thyroid development, the exposure in this situation would be inconsequential because the thyroid gland is not yet present in the fetus. The other two compounds have not been evaluated in epidemiologic studies of pregnant women. No other exposure to reproductive toxins occurred in this pregnancy, and the family history for CMs was negative. The woman was advised that this exposure was very unlikely to increase her teratogenic risk because the exposures to the embryo would be extremely low. She was also told that she still faced the background risks for birth defects and miscarriage. Therefore, her reproductive risks should be the same as the risks for the general population. The infant was healthy at birth and weighed 3,170 g.

Patient 3. A 26-year-old woman was in an automobile crash in her tenth 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. She recovered from the injury without any sequelae, but her primary physician was concerned that she had received an anticonvulsant associated with a tera-

toxic syndrome. No other exposure to reproductive toxins occurred in this pregnancy, and the family history for CMs was negative, except for an uncle who was born with neurofibromatosis. The primary physician requested a consultation about 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, no data 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 of gestation. The mother chose to continue her wanted pregnancy and delivered a healthy 3,370-g boy at term.

Patient 4. A 25-year-old woman was seen in the emergency service of her local hospital because of nausea, vomiting, and diarrhea. She had just returned from a cruise on which a number of the passengers became ill with similar symptoms. The emergency department physician ordered a pregnancy test followed by a radiograph of the abdomen because there was evidence of peritoneal irritation. Results of both studies were negative. However, 1 week later, the woman missed her menstrual period, and 2 weeks 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 and referred her for counseling after obtaining ultrasonography 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 less than 500 mrad (0.005 Sv), which is far below the exposure known to affect the developing embryo. Further, the embryo was exposed during the first 2 weeks postconception (all or none period), a time that is less likely to increase the risk of teratogenesis, even if the exposure had been much higher. 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 3,150-g healthy baby.

Evaluating the Cause of a Congenital Malformation

Patient 5. A mother of a 30-year-old man born in the Azores in 1960 who had 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. 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 asked for a further opinion. Review of the radiographs of his hips and legs and reports of his complete evaluation performed at the local hospital in the Azores revealed no 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 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 pelvis 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, a finding that is very unusual in a true thalidomide embryopathy. The young man had a congenital amputation, probably due to vascular disruption, cause unknown. Known causes of vascular disruptive malformations are placental emboli, cocaine or misoprostol exposure, and chorionic villous sampling.

Patient 6. A family claimed that the anti-nausea medication bendeclin, taken by the mother of a malformed boy, was responsible for her son's congenital limb reduction defects. The mother took the medication after the period of limb organogenesis, but some limb malformations can be produced by environmental insults later in pregnancy. The malformation was unaccompanied by any other dysmorphic effects. The boy's malformation was the classic split-hand, split-foot syndrome, which is inherited dominantly. In a significant portion of cases, this malformation is due to a new mutation. Because neither parent manifested the malformation, the logical conclusion was that a new mutation had occurred in the sex cell of one of the parents. Therefore, the risk of this malformation occurring in the offspring of this boy would be 50%. Bendeclin obviously was not responsible for this child's malformations. In spite of the obvious genetic cause of the malformed child's birth defects, a legal suit was filed, and a jury decided that bendeclin was not responsible for the child's birth defects.

Patient 7. A woman visited the emergency department of a university hospital complaining of severe lower abdominal pain. An obstetric resident saw her because she informed the staff that she had experienced a previous ectopic pregnancy that necessitated the removal of one 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 assessment was repeated and had not changed from its previous value.

Without performing ultrasonography, ectopic pregnancy was diagnosed. 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. Following the administration of methotrexate, the patient was sent home, but a laboratory report subsequently was received that indicated that the gonadotropin value had increased fivefold; 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 ultrasonography revealed a normally implanted embryo. The senior obstetric staff counseled the mother that the baby was at increased risk for CMs 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 serial ultrasonography. At 28 weeks' gestation, the patient went into labor and delivered a liveborn preterm infant. During infancy, hydrocephalus, developmental delay, and spastic cerebral palsy were diagnosed. The family filed a lawsuit against the doctors and the university hospital. The attorney representing the child requested an evaluation of the allegation that the child's abnormalities were due to the administration of the methotrexate. Methotrexate has been reported to cause growth restriction, microcephaly, developmental delay, and hydrocephalus but not prematurity. Review of the records revealed that ultrasonography performed 1 week before the preterm delivery showed no evidence of hydrocephalus and that the birthweight was appropriate for the gestational stage. The exposure to methotrexate was not responsible for the serious problems in this infant; the hydrocephalus and neurologic symptoms were due to an intracranial hemorrhage in the postnatal period as a complication of the prematurity.

As these case reports indicate, determining the reproductive risks of an exposure during pregnancy or the cause of a child's CM 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 biologic plausibility of an increased risk or a causal connection between the exposure and a child's CM. Evaluation must include a careful physical examination in addition to 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 disservice to the family.

Summary

- The development of new knowledge and new diagnostic techniques and technology as well as the sophistication of epidemiology studies and maturation of the fields of clinical genetics and clinical teratology have revolutionized the field of reproductive and developmental biology.
- Advances have enabled physicians and scientists to determine the causes of developmental abnormalities and, therefore, discover methods of prevention. The process of evaluation is based on the knowledge base developed over the past 50 years.
- Although genetic abnormalities are responsible for a significant proportion of reproductive and developmental deleterious effects, a larger proportion of these effects are due to unknown causes.
- Environmental causes are less frequent, although many of the environmental effects as well as many of the genetic effects can be prevented through genetic counseling and preconceptual planning. Effective treatment and amelioration of developmental effects also have improved.
- More than 50 environmental drugs, chemicals, maternal diseases, infections, nutritional abnormalities, and physical agents can affect reproduction deleteriously and result in CMs. Theoretically, all these causes are preventable.
- Throughout the developing world, the addition of folic acid and iodine could prevent tens of thousands of birth defects and developmental abnormalities.
- In the United States, the opportunity for prevention can be introduced at the population level and by addressing individual patients' clinical problems.
- If a mother of a malformed infant had some type of exposure during pregnancy, such as a diagnostic radiologic examination or medication, the consulting physician should not support or suggest the possibility of a causal relationship before performing a complete evaluation. If a pregnant woman who has 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. (11)(25)(26)(27)(28)(29)(30)
- Every patient deserves a complete, scholarly evaluation that uses the basic principles of teratology and risk analysis. (13)(14)(24)

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1. One of the principal advances in teratology over the past five decades is the discovery that:
 - A. Exposure to teratogenic agents late in the second trimester may mar fetal development.
 - B. Most congenital malformations can be explained by exposure to teratogens.
 - C. Teratogenic syndromes cannot be confused with genetic mimics.
 - D. The effects of exposure to a teratogenic are independent of timing.
 - E. The effects of teratogenic agents are independent of dose.
2. Which of the following is a drug that has established teratogenic potential?
 - A. Amlodipine.
 - B. Clonidine.
 - C. Hydrochlorothiazide.
 - D. Misoprostol.
 - E. Metoprolol.
3. Neural tube defects can be prevented *best* by assuring adequate folic acid and vitamin B-12 intake:
 - A. Before pregnancy.
 - B. In pregnant women who have a family history of neural tube defects.
 - C. No later than the beginning of the second trimester.
 - D. Throughout the third trimester.
 - E. Upon diagnosis of pregnancy.
4. A fetus was exposed to radiation via radiotherapy of the mother's breast cancer over a 5-week period beginning at the 8th week of gestation. The infant at term is *most likely* to be:
 - A. Deformed.
 - B. Large for age but otherwise normal.
 - C. Malformed.
 - D. Normal in all respects.
 - E. Small for age but otherwise normal.
5. An embryo was exposed at 7 days of gestation to radiation when the mother received a single abdominal flat plate radiographic study to evaluate severe abdominal tenderness. The infant at term is *most likely* to be:
 - A. Deformed.
 - B. Large for age but otherwise normal.
 - C. Malformed.
 - D. Normal in all respects.
 - E. Small for age but otherwise normal.

The Role of the Pediatrician in Preventing Congenital Malformations

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The following material is available online only for “The Role of the Pediatrician in Preventing Congenital Malformations.”



Things You Need To Know About Birth Defects

1. Did you know that birth defects are common?

- ▶ **Fact:** Birth defects affect 1 in 33 babies every year and cause 1 in 5 infant deaths. For many babies born with a birth defect, there is no family history of the condition.

2. Did you know that a woman should take folic acid during her teens and throughout her life?

- ▶ **Fact:** Because half of all pregnancies in the United States are not planned, all women who can become pregnant should take a vitamin with folic acid every day. Folic acid helps a baby's brain and spine develop very early in the first month of pregnancy when a woman might not know she is pregnant.

3. Did you know that many birth defects are diagnosed after a baby leaves the hospital?

- ▶ **Fact:** Many birth defects are not found immediately at birth. A birth defect can affect how the body looks, how it works, or both. Some birth defects like cleft lip or spina bifida are easy to see. Others, like heart defects, are not.

4. Did you know that some birth defects can be diagnosed before birth?

- ▶ **Fact:** Tests like an ultrasound and amniocentesis can detect birth defects such as spina bifida, heart defects, or Down syndrome before a baby is born. Prenatal care and screening are important because early diagnosis allows families to make decisions and plan for the future.

5. Did you know that birth defects can greatly affect the finances not only of the families involved, but of everyone?

- ▶ **Fact:** In the United States, birth defects have accounted for over 139,000 hospital stays during a single year, resulting in \$2.5 billion in hospital costs alone. Families and the government share the burden of these costs. Additional costs due to lost wages or occupational limitations can affect families as well.



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Things You Need To Know About Birth Defects

6. Did you know that birth defects can be caused by many different things, not just genetics?

▶ **Fact:** The cause of most birth defects is unknown. Use of cigarettes, alcohol, and other drugs, taking of some medicines; and exposure to chemicals and infectious diseases during pregnancy have been linked to birth defects. Researchers are studying the role of these factors, as well as genetics, as causes of birth defects.

7. Did you know that some birth defects can be prevented?

▶ **Fact:** A woman can take some important steps before and during pregnancy to help prevent birth defects. She can take folic acid; have regular medical checkups; make sure medical conditions, such as diabetes, are under control; have tests for infectious diseases and get necessary vaccinations; and not use cigarettes, alcohol, or other drugs.

8. Did you know there are ways a pregnant woman can keep her unborn baby safe from infections?

▶ **Fact:** The best way to keep an unborn baby safe from infections is for a pregnant woman to wash her hands often, especially after using the bathroom; touching raw meat, uncooked eggs, or unwashed vegetables; handling pets; gardening; or caring for small children.

9. Did you know there is no known safe amount of alcohol or safe time to drink during pregnancy?

▶ **Fact:** Fetal alcohol spectrum disorders (FASDs) are a group of conditions that can occur in a person whose mother drank alcohol during pregnancy. These effects can include physical problems and problems with behavior and learning which can last a lifetime. There is no known safe amount, no safe time, and no safe type of alcohol to drink during pregnancy. FASDs are 100% preventable if a woman does not drink alcohol while pregnant.

10. Did you know that an unborn child is not always protected from the outside world?

▶ **Fact:** The placenta, which attaches a baby to the mother, is not a strong barrier. When a mother uses cigarettes, alcohol, or other drugs, or is exposed to infectious diseases, her baby is exposed also. Healthy habits like taking folic acid daily and eating nutritious foods can help ensure that a child is born healthy.



To find out more about birth defects and healthy pregnancies, please visit the Centers for Disease Control and Prevention website www.cdc.gov/pregnancy or call your state or local health department.



This fact sheet was developed in partnership with the National Birth Defects Prevention Network (NBDPN).