Effects of Environmental Exposures on the Cardiovascular System: Prenatal Period Through Adolescence

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ABSTRACT. Exposures to drugs, chemical and biological agents, therapeutic radiation, and other factors before and after birth can lead to pediatric or adult cardiovascular anomalies. Furthermore, nutritional deficiencies in the perinatal period can cause cardiovascular anomalies. These anomalies may affect heart structure, the conduction system, the myocardium, blood pressure, or cholesterol metabolism. Developmental periods before and after birth are associated with different types of risks. The embryonic period is the critical window of vulnerability for congenital malformations. The fetal period seems to have lifelong effects on coronary heart disease and its precursors. During the weeks immediately after birth, susceptibility to myocardial damage seems to be high. Exposure to cancer chemotherapy or radiotherapy in childhood raises the risk of long-term progressive left ventricular dysfunction and other cardiovascular problems. In childhood and adolescence, use of recreational drugs such as cocaine and tobacco poses cardiovascular dangers as well. Where evidence about environmental exposures is limited, we have included models of disease and other exposures that are suggestive of the potential impact of environmental exposures. Pediatrics 2004;113: 1058–1069; environmental exposures, cardiovascular system, pediatric, fetal.

ABBREVIATIONS. HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval; TCE, trichloroethylene; DCE, dichloroethylene; AV, atrioventricular; NSAID, nonsteroidal anti-inflammatory drug; LV, left ventricular; HDL, high-density lipoprotein.

Evidence has been mounting that the cardiovascular system is susceptible to external influences throughout gestation and after birth. Fetal, early childhood, and adolescent environmental exposures can impair cardiovascular health and function. In addition, biological and lifestyle factors can strongly affect cardiovascular health, sometimes by interacting with the effects of environmental exposures.

Among the cardiovascular problems that may be caused by environmental exposures are abnormal anatomic development, dysrhythmias, conduction system defects, myocardial abnormalities, and derangements in blood pressure and cholesterol metabolism. Depending on when the exposure occurs and the magnitude of the exposure, it may cause transient or permanent effects, and the effects may change over time.

In areas in which direct evidence about environmental exposures is limited, models of disease and other types of exposures are often suggestive about the potential impact of environmental exposures. For example, cause for concern about the role of the environment in the development of congenital cardiovascular malformations is found in the fact that such malformations are associated with exposure to maternal human immunodeficiency virus (HIV) infection, regardless of whether the child is infected.1,2 Malformations such as tetralogy of Fallot, truncus arteriosus, and double-outlet right ventricle are associated with maternal nongestational diabetes existing before and during pregnancy, but not with maternal diabetes, further suggesting that the cause is within the uterine environment. A recent prospective case-control study confirmed that maternal diabetes was associated with an increased risk for cardiovascular malformations (odds ratio [OR]: 2.38; 95% confidence interval [CI]: 1.36–4.15).3 Heart failure and transient asymmetric septal hypertrophy, which can manifest as hypertrophic cardiomyopathy, can occur secondary to maternal diabetes.4 In contrast, gestational diabetes, which generally develops after organogenesis is complete, is not associated with cardiovascular abnormalities.6,7 In this article, we provide a sampling of exposures and deficiencies that highlight known and potential effects on the cardiovascular system, rather than a comprehensive review of all environmental cardiac exposures.

ENVIRONMENTAL EXPOSURES DURING THE FETAL PERIOD

Fetal Exposures That May Cause Congenital Cardiovascular Malformations

Cell division makes the developing cardiovascular system vulnerable to exposure from an adverse intrauterine environment. The heart and the vascular system are almost fully formed by midgestation, so
the early months of pregnancy are a critical window of exposure for cardiovascular malformations. Congenital cardiovascular malformations remain a major public health problem despite the dramatic advances that have been made in surgical repair, and they account for a large proportion of the infant mortality rate. Many surgical survivors are not completely cured and continue to be susceptible to increased morbidity and mortality.

Drugs that are known to be teratogenic to the fetal cardiovascular system when ingested by the mother include busulfan, lithium, retinoids, thalidomide, and trimethadione.8 Busulfan is an animal teratogen, and there are not definitive data that exposures have resulted in birth defects in humans. The other drugs are proven human teratogens, depending on the dose. The teratogenic risk of lithium is low and controversial. Some teratologists do not believe that lithium is a teratogen, but others do. Because patients with manic depressive illness may not respond to a second course if lithium therapy is stopped, many therapists continue lithium even though there is a teratogenic risk, because they consider the psychiatric risk to be greater. Knowledge about the teratogenic effects of these drugs is now widespread, and these drugs are usually neither used nor knowingly prescribed in pregnant women except as noted above. However, some pregnant women continue to receive these medications because of lack of pregnancy awareness or inadequate counseling.9

Exposure to solvents during pregnancy are human cardiac teratogens and should also be avoided. A recent study of cardiovascular defects without known chromosomal anomalies in 577,730 live births in Sweden from 1995 to 2001 found associations with maternal use of insulin, antihypertensives, fertility drugs, erythromycin, naproxen, anticonvulsants, nitrofurantoin, clomipramine, and budesonide in nasal preparations.10 The authors noted that some associations may relate to confounding from underlying disease or complaint or multiple testing, but some may be true drug effects. The Organization of Teratogen Information Services (866-626-OTIS, www.otispregnancy.org) is a resource for prenatal exposure risk information.

Maternal febrile illness (a 40%–80% increased risk with first-trimester febrile illness11–13), black race (6.5-fold risk elevation14), and obesity (OR for a body mass index >29 kg/m²: 1.4 in 1 study15 and 1.46; 95% CI: 1.12–1.90 in another15) may also be risk factors for overall congenital cardiovascular malformations in their offspring. Obesity may be confounded by diabetes.

Women who use cocaine while pregnant are more likely to give birth to children with congenital cardiovascular malformations.16 Cardiovascular abnormalities, which include congenital cardiovascular malformations, abnormalities of ventricular structure and function, arrhythmias, and intracardiac conduction abnormalities, persist beyond the period of exposure to cocaine. In some children, they are associated with congestive heart failure, cardiopulmonary arrest, and death.17

Experimental studies suggest that cocaine may exert direct toxic effects on fetal myocytes. Exposure of primary cultures of myocardial cells, from near-term fetal rats, to cocaine resulted in apoptotic cell death.18 Maternal administration of cocaine to the pregnant rat also caused a dose-dependent apoptotic myocyte cell death in the fetal rat heart.11 Both an upregulation of the Bax/Bcl-2 ratio and an increase in caspase activities were observed in the affected cells.19

Cardiac abnormalities are present in an increased number of neonates with fetal alcohol syndrome.20,21 Atrial septal defects were the most frequent cardiac anomalies found in these neonates. The variety of cardiac abnormalities tends to vary with the extent of intrauterine exposure and the resulting severity of the fetal alcohol syndrome.21 Maternal use of alcohol during the first trimester of pregnancy was reported to double the risk of atrial septal defect.22 Animal studies have examined the effect of dose on the occurrence of specific abnormalities. Incubation of the chick embryo with a low concentration of ethanol (0.20 mL of 50% ethanol/egg) caused a 43% incidence of ventricular septal defects; at a higher dose (0.4 mL of 50% ethanol/egg), a 74% frequency of aortic and ventricular septal abnormalities was seen.23

Various sympathomimetic amines (isoproterenol, epinephrine, and norepinephrine) have been reported to cause cardiovascular anomalies in the chick embryo preparation.24–26 Abnormalities observed included persistence of vessels that normally obliterate (left fourth aortic arch), obliteration of vessels that should remain patent (right third aortic arch), incomplete formation of the interventricular septum, or any combination of these. Such alterations are thought to result from sympathetic β-1 receptor-mediated changes in flow patterns within the embryonic heart and great vessels.27 It was assumed that stimulation of the β-1 receptor was responsible for the observed teratogenic activity. However, both terbutaline and ritodrine have been found to cause cardiovascular abnormalities in the chick embryo.28,29 The preferential β-2 activity of these 2 agents and the reported presence of β-2 receptors in the embryonic chick heart suggest that this receptor also plays a role in the teratogenic effect of terbutaline and ritodrine in the chick.

Because of cross-species differences, it is not clear whether the effects noted in these studies would also occur in human fetal myocardial tissue. There are case reports indicating that terbutaline tocolysis caused fetal heart alterations. Bohm et al30 examined the hearts of 25 newborns whose mothers had been treated with β-sympathomimetics for 24 hours to 8 weeks. They found 3 cases of focal subendocardial necrosis, 3 cases of diffuse myocyte fatty degeneration, and 14 cases of right ventricular subendocardial nuclear polypliodization. Fletcher et al31 reported a case of myocardial necrosis in a newborn whose mother was treated with long-term subcutaneous terbutaline. Altered myocardial function and ventricular septal hypertrophy have been detected in human fetal hearts after long-term in utero exposure to ritodrine (mean duration: 16.2 ± 13.2 days).32

Maternal exposure to chemicals has been implicated in damaging the fetal heart and may be ame-
Exposure to certain chemicals (dyes, lacquers, and paints) during the first trimester of pregnancy was found to be associated with a slightly higher incidence of congenital heart disease than occurred in a nonexposed control group. These investigators also determined that the risk of ventricular septal defect was increased with exposure to organic solvents during the first trimester. However, this study did not include critical exposure levels. An increased risk of congenital heart disease has been demonstrated with exposure to solvents and paints, with organic solvents being associated with ventricular septal defects; dyes, lacquers, and paints with cardiac malformations; and mineral oil products with coarctation of the aorta.

Halogenated hydrocarbons may constitute a potential serious water supply contaminant problem. A recent Centers for Disease Control and Prevention review of the literature on drinking water contaminants and adverse pregnancy outcomes, however, concluded that the findings of excess cardiac defects in 5 studies that evaluated trichloroethylene (TCE)-contaminated drinking water deserve follow-up. Goldberg et al. noted an association between TCE-contaminated drinking water and an increase in occurrence of cardiac malformations in children who were born to mothers who resided in the areas of contamination. Experimental studies found that both TCE and dichloroethylene (DCE) caused general and cardiac teratogenic effects in the developing chick embryo. In pregnant rats, uterine application of TCE and DCE caused increased frequency of fetal cardiac abnormalities. An increased frequency of cardiac malformations was also noted when TCE or DCE was given to the pregnant rat via the drinking water during the critical days of fetal organogenesis. Of the various TCE or DCE metabolites, only trichloroacetic acid seems to be a fetal cardiac teratogen when consumed by the pregnant mother. These studies identified a variety of cardiac abnormalities. It is not clear whether the results of these types of experimental studies can be extrapolated to humans; however, it should be noted that the pathways of cell division, migration, and differentiation are common to all mammals during pregnancy.

There seems to be a TCE dose effect on cardiovascular malformations that inhibits the development of embryonic heart valve precursors in vitro and leads to ventricular septal defects and levocardia. In Milwaukee from 1997 to 1999, the risk of congenital heart defects in offspring of older mothers who lived within 1.32 miles of a TCE-emitting site was 3.2-fold higher (OR: 3.2; 95% CI: 1.2–8.7) in multivariate analyses than similar mothers who did not live near a TCE-emitting site. Other public drinking water contaminants have been significantly associated with major cardiac birth defects. In northern New Jersey from 1985 to 1988, total trihalomethanes, benzene, and 1,2-dichloroethane monthly exposures during pregnancy for >81 000 pregnancies using tap water sample data were associated with major congenital heart defects. Similarly, for 58 669 Swedish women, chloride dioxide in municipal drinking water seems to be an independent risk factor for congenital heart defects (adjusted OR: 1.61; 95% CI: 1.00–2.59), and the risk for cardiac defects increases with increasing trihalomethane concentrations (P = .0005). Despite the findings of these studies, a recent review noted that several published studies that have examined the relation between cardiac and other defects and maternal exposure to chlorine by-products in municipal water supplies “have been inconsistent and may reflect differences in study population and methods, including completeness of case ascertainment, specificity of exposure assessment, information on covariates, and adequate consideration of potential underlying pathogenic mechanisms. Further studies addressing such methodological challenges will help this issue of chemical water quality.”

Another potential environmental contamination is nitrofen (2,4-dichloro-4′-nitrodiphenyl ether), which results in abnormal heart development that is uniquely different from the mode of adult toxicity by this agent. This herbicide has been found to cause congenital heart (ventricular septal defect, double-outlet right ventricle, and transposition of the great arteries), diaphragm, and kidney abnormalities when given to pregnant rats. Kim et al studied the characteristics of nitrofen-induced cardiovascular anomalies. The frequency of congenital cardiovascular abnormalities was dose related and highest when nitrofen was given on day 11 of gestation. The most common anomalies were ventricular septal defects, tetralogy of Fallot, and an anomalous right subclavian artery with left aortic arch. These investigators believed that the rat model of congenital cardiovascular abnormalities had meaningful analogies to the human situation. Nitrofen-exposed fetal rats have heart hypoplasia associated with reduced endothelin-1, reduced total DNA and percentage of proliferating cells, and reduced cardiac atrial natriuretic peptide. This nitrofen-associated cardiotoxic hypoplastic effect during cardiogenesis can be minimized or reversed by therapy with prenatal corticosteroids and vitamin A, which stimulates myogenesis.

### Fetal Exposures That May Cause Arrhythmias and Conduction System Defects

Electrocardiographic abnormalities, including sustained arrhythmias, have been documented in infants and children who were exposed prenatally to cocaine. These arrhythmias manifest as widely varied rhythms and are markedly resistant to conventional therapy. Arrhythmias, including ventricular tachycardia, and conduction disturbances are also frequent among HIV-infected children.

Maternal lupus provides a model to illustrate the importance of the fetal environment in the development of arrhythmias. Immune-mediated damage to fetal atrioventricular (AV) nodal tissue is strongly associated with transplacental passage of specific maternal autoantibodies. Damage becomes evident at 16 to 30 weeks’ gestation, usually at 22 to 24 weeks. By that time, an intrauterine myocarditis has damaged the AV node, resulting in destruction of the
node and replacement of normal nodal tissue with fibrotic tissue. The resulting AV block causes fetal bradyarrhythmia that may be accompanied by congestive heart failure, hydrops fetalis, and pericarditis.

Defects that predispose to sinoatrial node or AV node dysfunction include atrial septal defect, AV septal defects, and abnormalities in AV situs or AV concordance.\textsuperscript{72} Ebstein’s anomaly is associated with a variety of rhythm disturbances. In the setting of anatomic anomalies, these rhythm disturbances can have long-term effects on the health of the myocardium.

Arrhythmias have been induced in fetal and newborn rats after prenatal exposure to the organochlorine insecticide mirex. Exposure of pregnant rats to moderate amounts of mirex caused a high incidence of fetal deaths without evidence of serious malformations.\textsuperscript{73} Fetuses from pregnant rats that were fed 5 to 6 mg/kg/day mirex were found to have a variety of cardiac conduction problems (first-, second-, and third-degree heart blocks; bradycardia; tachycardia; atrial and ventricular premature contractions; and atrial fibrillation).\textsuperscript{74} These arrhythmias seemed to be specific for the fetus as they were not associated with any cardiac morphologic alterations and were not observed in the mother. Electrocardiograms monitored in neonates (exposed to mirex in utero) within 5 minutes of birth and subsequently up to 2 days of age showed a high incidence of arrhythmias. Some of the arrhythmias were transient, some persisted for days, and others did not appear until some period after birth.\textsuperscript{75} The characteristics of the arrhythmias suggested that the atrium and/or the conducting bundles of the immature hearts were most affected by prenatal exposure to mirex. The period before birth rather than the period of organogenesis was found to be more sensitive to the arrhythmogenic effects of mirex.

**Fetal Deficiencies and Excesses of Micronutrients That May Cause Congenital Cardiovascular Malformations**

Maternal nutrient deficiencies and excesses during pregnancy may have profound effects on fetal cardiovascular formations. These deficiencies are in essence exposures to poor maternal nutrition during pregnancy. Folic acid and vitamin A are 2 representative nutritional factors that can influence cardiac morphogenesis.

Animal experimental studies of maternal folate deficiency and cardiovascular abnormalities are pervasive, prominent, and persistent.\textsuperscript{76–78} Transient folate deficiency resulted in 29\% to 58\% of embryos with congenital cardiovascular malformations in 1 study.\textsuperscript{76} In another study of rats, deficient folate levels at days 9 to 11 were associated with anomalies such as a single pulmonary artery, absence of the ductus arteriosus, single coronary artery, pulmonary stenosis, truncus arteriosus, and total anomalous pulmonary venous return.\textsuperscript{77} Another study confirmed these findings in the 9- to 11-day fetal rat exposed to transient folate deficiency, in which 57\% had cardiovascular abnormalities.\textsuperscript{78}

Self-reporting of folate-containing vitamin supple-ments from 1 month before conception through 2 months after conception was associated with a reduced risk (OR: 0.65; 95\% CI: 0.44–0.96) for conotruncal heart defects among a 1987–1988 cohort of births (N = 341 839) ascertained by the California Birth Defects Monitoring Program.\textsuperscript{79} In a study from Hungary, the relationship between periconceptional multivitamin supplementation containing folic acid (0.8 mg daily) and congenital heart defects was examined in an intervention study of 4156 pregnancies with known outcomes and 3713 infants evaluated in the eighth month of life by physical examination.\textsuperscript{80–84} Congenital malformations were significantly elevated in the offspring of mothers who did not receive folate supplementation, compared with those who did. The rate of congenital heart defects was lower in the folate group, but the difference was not significant (10 vs 17; \( P = .16 \)). In western Australia, a case-control study of dietary folate and nonneural midline birth defects found 20 children with conotruncal heart defects but no evidence of an association.\textsuperscript{85} Other case-control studies were mixed.\textsuperscript{86–90}

A prospective study of 49 pregnancies involving mothers who took phenytoin or phenobarbital found 10 (20.4\%) abnormal outcomes including 4 (8.2\%) spontaneous abortions and 6 (12.2\%) major congenital malformations including ventricular septal defects, hypertrophic cardiomyopathy with endocardial fibroelastosis, and conduction defects.\textsuperscript{91} Blood folate levels were significantly lower in pregnancies with an abnormal outcome than in those with a normal outcome. This was supported by a Japanese study that demonstrated that reduced maternal serum folate levels were associated with an increased risk of congenital malformations, including cardiovascular defects, compared with higher folate levels.\textsuperscript{92}

Retinoic acid (all trans) and related vitamin A derivatives (retinoids) trigger and modulate morphogenic events during development and maintain homeostasis in adults. The heart and cardiac neural crest–derived tissues are prominent target tissues for teratogenic effects of retinoic acid during development. Paradoxical and perhaps more important, vitamin A deficiency leads to an overlapping spectrum of defects, indicating a requirement for retinoids during normal development. Vitamin A deficiency can lead to defects in ventricular chamber morphogenesis, including hypoplasia of the ventricular compact zone, and defects of the ventricular muscular septum, suggesting a defect in the proliferative capacity of fully differentiated ventricular myocytes or a defect in sequential maturation of ventricular myocyte lineages. In heart muscle, retinoic acid binds to the nuclear receptor RXRa, and this serves as a transcription-regulating factor that binds to DNA. Homozygous RXRa gene knockouts in mice show profound cardiac defects, including ventricular hypoplasia (100\% of embryos), trabecular disorganization, and muscular ventricular septal defects (90\% of embryos), and midgestational lethality from what seems to be an inability of the defective hearts to provide sufficient blood flow resulting in congestive heart failure and edema.\textsuperscript{93–95} Thus, it seems that retinoic
acid affects cardiac growth and development by affecting the expression of cardiac muscle–specific genes involved in specification, proliferation, maturation, trabeculation, and septation.

Experimental work in the past 50 years has confirmed in a variety of species the importance of retinoic acid and vitamin A derivatives on cardiovascular development. Maternal vitamin A deficiency is associated with cardiovascular abnormalities in 75% of neonatal rats, including 50% with retarded development and thin ventricular walls, 33% with ventricular septal defects, and 33% with aortic arch abnormalities. When retinol deprivation occurs early enough, there is a failure of mesenchymal development that dramatically prevents the circulatory system from developing. However, normal cardiac development can occur in vitamin A–deprived animals by the administration of retinoids, in particular all-trans-retinoic acid, during critical time points in heart development. Retinoic acid promotes ventricular specification and maturation in mouse cardiac stem cells.

Excessive vitamin A or its derivatives also affect normal cardiac mesodermal development and also result in defects in derivatives of the cardiac neural crest. The timing of retinoic acid administration determines the consequence to the developing heart. In Xenopus, retinoic acid administration at the primitive streak stage results in no heart development, administration after specification but before migration of myocardiocytes alters the curvature of the heart tube by inducing a secondary axis to the migration of myocardiocytes altering the curvature of the heart tube, and administration after initial development determines the consequence to the developing heart.

In the mouse, all-trans-retinoic acid at day 6 results in visceral heterotaxy in 36% of embryos (during the period of time when laterality is determined); by day 8, 91% of embryos develop either transposition of the great arteries or double-outlet right ventricle (suggestive of decreased endocardial cushion development); and by day 9, 67% of embryos develop tetralogy of Fallot, truncus arteriosus, ventricular septal defects, or interrupted aortic arch (defects in derivatives of cardiac neural crest).

The human cardiovascular teratogenicity of vitamin A and its derivatives is described in a number of reports and seems to be associated with an early, postimplantation exposure that may impair migration of cranial neural crest cells. Tetralogy of Fallot, transposition of the great arteries and a ventricular septal defect, interrupted aortic arch with a ventricular septal defect, and ventricular septal defect with dysplastic pulmonary and aortic valves all have been reported in infants who were exposed to isotretinoin in utero. These cardiac defects frequently occurred after isotretinoin exposure, with central nervous system, ear, and craniofacial defects also present in many cases. A number of spontaneous abortions have occurred as well. The Food and Drug Administration reported adverse pregnancy outcomes and birth defects after maternal isotretinoin use during pregnancy. The Centers for Disease Control and Prevention noted that there was a significantly increased risk of having a child born with a major malformation after isotretinoin exposure during fetal development (relative risk: 25.6; 95% CI: 11.4–57.5) after examining 154 pregnancies.

The Food and Drug Administration reference daily intake for vitamin A for food labeling purposes is 5000 IU, and reports suggest that vitamin A may be teratogenic in humans when consumed in amounts greatly in excess of the US National Research Council recommended dietary allowance during pregnancy of 2670 IU/day. Results of the small number of case-control studies in which there were comparisons of dose exposures in control subjects with those in selected birth defect categories have shown that children who were born to women who consumed supplemental vitamin A at levels found in multivitamin preparations were not at increased risk for birth defects. Higher-dose vitamin A exposure (>40 000 IU/day) during organogenesis has been shown in some case-control studies to be non-statistically significantly associated with malformations but not in others. Methodologic limitations have been noted for some of these case-control studies. A recent population-based case-control study of liveborn infants from 1987 through 1989 enrolled in the Baltimore-Washington Infant Study found that a retinol (preformed vitamin A) intake of ≥10 000 IU/day from supplements was associated with a 9-fold increased risk for transposition of the great arteries (OR: 9.2; 95% CI: 4.0–21.2) compared with an average daily intake of <10 000 IU. Two prospective studies, with comparisons of defect outcomes in high-dose to low-dose vitamin A–exposed women and vitamin A information collection before birth to reduce recall bias, have been performed. Recent reviews raised methodologic questions about these studies. Vitamin A may be teratogenic; however, the teratogenic threshold in humans has not yet been determined. Additional research is needed to determine whether excess consumption of vitamin A from supplements or foods, as well as diets deficient in vitamin A, or the therapeutic use of retinoids constitutes a public health problem.

Fetal Exposures That May Damage Myocardium

Cardiomyocytes are highly differentiated cells that rarely replicate after birth; thus, any agent that harms them during the fetal period can cause lasting damage. Loss of cardiomyocytes before birth may permanently reduce the number of functioning units in the heart, predisposing the myocardium to cardiomyopathic alterations that can lead to heart failure. In the fetal rat heart, cocaine has a direct cytotoxic effect, inducing apoptosis (commonly called “cell suicide”) in myocardial cells in a time- and dose-dependent manner. No similar data are available from humans; however, findings in rats suggest that maternal cocaine use might permanently impair heart function even in children who do not develop frank anomalies.

Prenatal agents may also affect the myocardium by inducing hypertrophy. For the neonate, antenatal corticosteroids have been beneficial, decreasing mor-
tality and morbidity from respiratory distress and interventricular hemorrhage. However, exposure of the fetus to maternal corticosteroids can also lead to hypertrophic changes in the myocardium that are related to both dose and duration of use. Most of these changes but not all are reversible. No data are available on the possible long-term effects of the myocardial remodeling that takes place.

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) during pregnancy poses another potential threat to the myocardium. Fetal exposure to maternally ingested naproxen, ibuprofen, and aspirin is associated with persistent pulmonary hypertension of the newborn and with subsequent treatment with inhaled nitric oxide or extracorporeal membrane oxygenation. Although persistent pulmonary hypertension of the newborn is clinically transient, it is possible that it may be associated with long-term effects on the ultrastructural level of the myocardium. The potential hazards of NSAID use during pregnancy have not been well publicized, and meconium analysis shows that NSAID use is significantly underestimated by maternal self-report.

Prenatal exposure to tobacco smoke inhibits cardiac DNA synthesis and impairs vascular smooth muscle function. A case-control study in California from 1987 to 1988 found a modestly elevated risk for conotruncal heart defects in newborns that was associated with both parents smoking (OR: 1.9; 95% CI: 1.2–3.1) compared with neither parent smoking. In newborns, cardiac cell damage is a consequence of concurrent, repeated exposures to nicotine and hypoxia. Studies of umbilical vessels (artery, vein, and placental villi) detected severe wall damage associated with maternal tobacco use during pregnancy.

The effects of such agents may be offset by other factors in the maternal and uterine environment. For example, the cardiotoxic effects of isoprenaline in rats are less severe in the offspring of rats that are exercised regularly than in the offspring of inactive mothers.

**Effects of Fetal Exposures on Blood Pressure, Cholesterol Metabolism, and the Vascular System**

Stimuli or insults during sensitive periods of development produce lifelong consequences in a mechanism known as programming, which is well established in developmental biology. Thus, even transient or low-dose exposures in the fetus may have long-term sequelae.

Epidemiologic data now show convincingly that lower birth weight (probably by restricting fetal growth and not by reducing the length of gestation) is associated with higher risks of hypertension, type 2 diabetes, coronary heart disease, and stroke in later life. Lower birth weight also seems to be associated with increased endothelial cell dysfunction, not only in childhood but also into the third decade of life. Endothelial cell dysfunction is an early event in experimental studies of atherogenesis, preceding plaque formation. These have led to new hypotheses about which alterations in the fetal environment could underlie them.

Fetal “nutrition” is an amalgam of several different determinants, including maternal diet, uterine blood flow, placental function, and the fetal genome. Animal models have taken advantage of the ability to alter maternal diet or uterine blood flow experimentally but may or may not be directly relevant to humans. Nevertheless, they provide insight into several possible mechanisms.

Early maternal nutritional deficiency may affect adaptive clonal selection or differential cellular proliferation, permanently changing the quantity or proportion of cell populations in a tissue. “Memories” of dietary restriction may include modifications in the distribution of placental or fetal cell types, in patterns of hormonal secretion (resetting the endocrine axes that control growth), in metabolic activity, and in organ structure. Animal studies involving short periods of maternal protein or energy restriction have produced persisting alterations in blood pressure; cholesterol metabolism; insulin responses to glucose; and other metabolic, endocrine, and immune variables in the offspring. Manipulating nutrition during pregnancy in animals produces many of the physiologic effects that are observed in human epidemiologic studies. Altered maternal diet may cause its effects not by directly stunting growth but instead by signaling directed activity via coupling mechanisms on receptors in sensitive tissues and by causing adaptive effects on gene expression.

A maternal diet high in saturated fat may affect fetal cardiovascular status. Offspring of rats on high-saturated-fat diets had mesenteric small artery dysfunction, and function further deteriorated in offspring of diabetic rats. In hypercholesterolemic rabbits, maternal therapy with cholestyramine and vitamin E decreased the aortic lesion size in their offspring. Because human fetuses display precursors to atherosclerotic lesions in the aorta, these data raise the possibility that lipid and oxidation abnormalities during pregnancy could underlie atherosclerosis in the offspring. Atherosclerotic precursor lesions progress more rapidly in children of hypercholesterolemic mothers than in children of normcholesterolemic mothers, according to the Fate of Early Lesions in Children study.

Nicotine and its major metabolite, cotinine, seem to play a major role in the failure of vascular reconstruction. Both prenatal and neonatal exposure to second-hand smoke has a deleterious effect on vascular smooth muscle function in infant rabbits (abnormal vasoconstrictor and vasodilator responses). Abnormalities of endothelial cell function were found in adult rabbits that were exposed to second-hand smoke for 3 to 10 weeks. Exposure to second-hand smoke also caused left ventricular (LV) hypertrophy in rabbits. However, thus far, studies in humans have not shown this effect.

Adaptive vascular remodeling in utero leads to increased cardiac afterload that affects long-term cardiovascular health, according to studies of the twin-twin transfusion syndrome. In this syndrome, both fetuses have hemodynamic disturbances. The recipient develops hypervolemia, cardiomegaly, and in-
increased systemic vascular resistance, and the donor develops chronic hypovolemia. Arterial distensibility is lower in the donor twin during infancy.\textsuperscript{149}

Because the placenta is the conduit for oxygen and maternal nutrients to reach the fetus and is an endocrine organ in its own right, it is also a likely player in fetal programming.\textsuperscript{150} To date, however, few studies of placental abnormalities and offspring cardiovascular status exist. We have found that maternal age is directly related to blood pressure level in newborns.\textsuperscript{151} Maternal age seems to be a determinant of placental dysfunction.\textsuperscript{152}

ENVIRONMENTAL EXPOSURES DURING INFANCY AND CHILDHOOD

Effect of Maternal Factors on the Infant’s Myocardium

Animal studies suggest that another critical window of vulnerability for the developing cardiovascular system is the period immediately after birth. Recent work in a transgenic mouse model of dilated cardiomyopathy found that hypertrophy-associated marker alterations had developed by 2 weeks of age and progressed rapidly during the next 2 weeks.\textsuperscript{153} By 4 weeks, before the onset of cardiac dysfunction and chamber remodeling, the mice also had reduced levels of connexin 43. This protein is reduced in nearly all human patients with end-stage heart disease.

Exposure to tobacco smoke causes myocyte cell damage in newborns as a consequence of concurrent, repeated exposures to nicotine and hypoxia. In experimental models, LV hypertrophy is significantly associated with long-time passive smoking exposure.\textsuperscript{127} Passive smoking, like active smoking, is now categorized as a serious risk factor in the initiation and progression of cardiovascular disease.\textsuperscript{154–156}

We recently reported that the neonatal period is associated with the highest levels of myocardocyte injury, as measured by elevations in serum cardiac troponin-T, of any pediatric age.\textsuperscript{157} The extent of myocardial injury in the neonatal period correlated with perinatal environmental exposures.\textsuperscript{157} Persistent postnatal cardiomyopathy may relate to this perinatal myocardocyte injury.\textsuperscript{158} We have found that children who are born to mothers who are infected with HIV-1 have abnormal hearts that do not pump as effectively as hearts of healthy children who are born to healthy mothers.\textsuperscript{158} Even infants who have not contracted HIV from their mothers have hearts with potential problems that will require careful monitoring because, in general, the longer a child has mild persistent LV dysfunction the more likely it will become worse over time.\textsuperscript{158} Although the abnormalities initially seemed mild, they persisted and often worsened in HIV-infected children. These abnormalities can lead to an increased risk of heart failure and death. The environment in the womb and a mother’s nutritional habits are possible etiologic factors. If we are going to prevent symptomatic illnesses and heart disease in adulthood, then we need to be thinking about preventive strategies in the fetal and perinatal periods.

Effects of Anthracycline Chemotherapy, Therapeutic Radiation Exposure, and Infection on the Myocardium

By the year 2010, 1 of approximately every 500 young adults aged 20 to 45 years in the United States will be a survivor of childhood cancer.\textsuperscript{159} Many have been treated with anthracyclines or radiation therapy to fields that included the heart, both of which have oncologic efficacy but are also cardiotoxic. Survivors today often live a normal lifespan, and this long survival coupled with the need for normal growth of the pediatric myocardium may result in accelerated progressive LV dysfunction and inadequate LV hypertrophy. In particular, anthracycline therapy is associated with subsequent dilated cardiomyopathy, a term that describes cardiac dilation and depressed myocardial contractility and encompasses a number of heterogeneous myocardial diseases.\textsuperscript{160–170}

Younger age at treatment is associated with worse outcomes. Other risk factors for early toxicity (toxicity within 1 year) are black race, trisomy 21, and amascrine therapy with anthracycline therapy. Early toxicity and high-dose anthracycline therapy are the 2 strongest risk factors for the development of late cardiotoxicity (onset 1 year or more after therapy). Length of follow-up is also a risk factor for late-onset asymptomatic cardiotoxicity. Cumulative anthracycline dose, peak anthracycline dose, and higher rate of administration affect both early and late cardiotoxicity. Female gender is a significant risk factor for both early and late cardiac dysfunction. LV contractile impairment and increased afterload occur as a result of thinning of the LV walls. Early depressed contractility is likely to progress with time.

Although most cases of cardiomyopathy are idiopathic, radiation therapy to the heart and HIV are also associated with cardiomyopathy.\textsuperscript{69,158,171–177} More than 90% of HIV-infected children have echocardiographic abnormalities pertaining to LV dysfunction, yet only 10% develop chronic congestive heart failure, 10% transient congestive heart failure, and 10% cardiac arrest or sudden death.\textsuperscript{69} One third of HIV-infected children who died did so in the setting of severe LV dysfunction, which often manifests as clinically overt heart failure. The prognosis for dilated cardiomyopathy is generally very poor, with a reported 5-year mortality of up to 80%.

In the absence of radiation therapy, 65% of anthracycline-treated childhood leukemia survivors have echocardiographic abnormalities.\textsuperscript{162} Inappropriately reduced LV wall thickness in the setting of increased LV afterload was the leading cause of LV dysfunction.

Abnormalities of LV fractional shortening and contractility are independent predictors of mortality years before the onset of dysfunction.\textsuperscript{176} Inappropriately increased LV wall thickness and mass were also independent long-term predictors.

Effects of Childhood Anthracycline and Therapeutic Radiation Exposure on the Conduction System

Cardiomyopathy, whether idiopathic or induced, can manifest as congestive heart failure, which can result in arrhythmias and can disturb the myocardial
conduction system. Sinus node disease and AV block can be late problems after cardiac radiation therapy in childhood cancer patients.

Both dilated and hypertrophic cardiomyopathies are associated with atrial or ventricular arrhythmias that are linked to sudden death in these populations. Chronic valvar insufficiency in these settings can predispose patients to primary atrial and ventricular arrhythmias.

Tobacco Smoking

The deleterious effects of both passive and active smoking on the heart include reduced platelet activation, increased resting sympathetic nerve activity, and hypertension. Alterations in vascular smooth muscle function, alteration of cardiac muscle cell DNA synthesis, and cell damage can occur as well.\textsuperscript{127,154–156,178} Multiple lines of evidence suggest that the effect is attributable to numerous smoke constituents, rather than a single component.\textsuperscript{179,180}

ENVIRONMENTAL EXPOSURES DURING ADOLESCENCE

Effects of Drugs and Therapeutic Radiation Exposure on the Conduction System

Cocaine, which is commonly abused by young adults, has profound cardiovascular effects. Rhythm disturbances, characteristically ventricular tachycardia, can occur in young adults.\textsuperscript{181}

Cardiovascular abnormalities related to anthracycline therapy and HIV infection persist into adolescence. Sinus node disease and AV block can be late problems after radiation therapy in childhood cancer patients.\textsuperscript{182,183}

Effects of Drugs, Therapeutic Radiation Exposure, Infection, Disease, and Lifestyle on the Myocardium

Cardiovascular complications related to cocaine abuse include myocardial ischemia and infarction, myocarditis, cardiomyopathy, and sudden death.\textsuperscript{181} Long-term studies of childhood cancer patients who were treated with mediastinal radiation have found aberrations in cardiac function, notably diastolic dysfunction in the setting of a restrictive cardiomyopathy.\textsuperscript{184} Radiation therapy significantly increases the risk of death from subsequent coronary artery disease.\textsuperscript{185} Other detrimental effects of mediastinal therapeutic radiation include hypothyroidism, which can adversely affect cardiac contractility, diastolic function, peripheral circulation, heart rate, blood pressure, and cholesterol metabolism and foster arrhythmias, coronary artery disease, congestive heart failure, and disturbances in the sympathetic nervous system. Sclerosis as well as impairment in soft tissue, muscle, and bone growth can have an impact on cardiac function.

Anorexia nervosa in the adolescent may cause cardiac degeneration that is manifested as bradycardia. Long-term investigations of recovered anorexia nervosa patients may provide insight into additional effects of undernutrition on growth, into catch-up growth, and into any resultant effects on the myocardium.

Effects of Lifestyle and Cardiovascular Risk Factors on Blood Pressure and Cholesterol

Second-hand smoke is estimated to contribute to 37,000 deaths from heart disease of the total 53,000 annual deaths.\textsuperscript{179} This makes passive smoking the third leading preventable cause of death, after smoking and alcohol.

The effect of passive smoking may be more serious in young people than in older ones. Second-hand smoke exposure in children seems to reduce the levels of high-density lipoprotein (HDL).\textsuperscript{186} Likewise, endothelium-dependent relaxation is impaired in teenagers and young adults who are exposed to second-hand smoke.\textsuperscript{187} Passive smoking has also been found to affect the rat myocardium. Cigarette smoke exposure during the neonatal to adolescent periods was associated with increased myocardial infarct size in a rat model of ischemia/reperfusion.\textsuperscript{188}

Active smoking, of course, is also dangerous. An autopsy investigation of 12- to 34-year-old individuals found that smoking (as well as low HDL cholesterol and high non-HDL cholesterol) was associated with more extensive fatty streaks and raised lesions in the aorta.\textsuperscript{189}

It is important to note that traditional risk factors such as overweight and obesity, dyslipidemia, and elevated blood pressure are extremely important for adolescent cardiovascular health. Many of these risk factors are becoming more prevalent and are associated with long-term cardiovascular problems.\textsuperscript{189–194}

DISCUSSION AND CONCLUSION

Numerous environmental exposures from the prenatal through adolescent time periods adversely affect the cardiovascular system at multiple levels. The maternofetoplacental unit plays a critical role in the foundations of cardiovascular disease. The impact of fetal and infant exposures on the heart may be worsened or modified by the childhood and adolescent environment. Research into the timing of environmental insults and their impact on the developing cardiovascular system will likely provide important information for treating and preventing disease.

Given the potential effects on the growing myocardium, it would be prudent for clinical trials to test pediatric drugs in pediatric populations. The use of medicines that are tested only among adults may have unknown deleterious effects on the growing myocardium. The teratogenic risk in human pregnancy has not been determined for 91.2% of 511 drugs approved in the United States from 1980 to 2000, according to an analysis of 468 commonly used drugs, including albuterol, atenolol, azithromycin, clarithromycin, loratadine, and zolpidem.\textsuperscript{195} Studies need to be performed to assess the outcomes of pregnancies in women who are treated with drugs to determine teratogenic risk in humans.

The American Academy of Pediatrics has argued that the new Best Pharmaceuticals for Children Act, passed in January 2002, which allows manufacturers who voluntarily conduct drug studies in children to obtain an additional 6 months of marketing exclusivity, does not extend far enough to support pediatric drug development and testing as it is a voluntary...
program. However, the Food and Drug Administration has also enacted a rule to mandate that pharmaceutical companies test more drugs in children to assess safety and effectiveness. The rule will remain in effect indefinitely, whereas the exclusivity program will end in 2007 unless it is extended by Congress. In 1994, the National Institutes of Health formed a network of 7 pediatric pharmacology research units at academic centers. By 1999, the network had expanded to 13 units. The network has conducted many of the studies in accordance with the pediatric exclusivity and the pediatric rules. This is a step in the right direction because adverse reactions to drug therapy are a significant cause of death and injury in infants and children.

In addition to being the leading cause of death in adults, heart disease is among the 5 most common causes of death in childhood. The impact of pre-natal and post-natal exposures on the heart, including those that manifest in childhood and adolescence, will be 1 of the greatest public health challenges in the years ahead. Long-term clinical investigations of the environmental impact on the developing cardiovascular system are essential to provide the knowledge necessary for an evidence-based approach to treating and preventing cardiovascular disease.

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REFERENCES

80. Zhu BQ, Parmiter WW. Hemodynamic and vascular effects of active and passive smoking. Am Heart J. 1995;130:1270–1275
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