MARCH OF DIMES

GLOBAL REPORT ON BIRTH DEFECTS

THE HIDDEN TOLL OF DYING AND DISABLED CHILDREN

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PREFACE

President Franklin Roosevelt established the March of Dimes Foundation in 1938 to defeat polio. He created a partnership of volunteers and researchers that led to the development of the polio vaccines. Today the March of Dimes mission is improving infant health by preventing birth defects, premature birth and infant mortality. A birth defect is defined as any abnormality affecting body structure or function that is present from birth. The March of Dimes mission is carried out through research, community services, education and advocacy.

In 1998, the March of Dimes broadened its mission beyond the United States and established its office of Global Programs. Global Programs conducts its work through mission alliances—close working partnerships with private and public organizations in countries—to improve perinatal health and prevent birth defects. In the past six years, March of Dimes has helped implement effective, affordable and feasible programs on four continents.

In 2000, Global Programs initiated a process to document the global toll of birth defects and provide policy makers, funding organizations and health care providers with feasible, cost-effective recommendations for reducing this toll. In 2004, it commissioned the current report from Professors Arnold Christianson of the National Health Laboratory Service and University of the Witwatersrand, Johannesburg, South Africa, and Bernadette Modell of the Royal Free and University College Medical School, London, England.

Professor Modell compiled the data presented in Appendix B. The methods she used are detailed in Appendix A. The data in this report represent the culmination of work that Professor Modell began in the early 1980s for the World Health Organization on hemoglobin disorders, which ultimately expanded to encompass all serious birth defects of genetic or partially genetic origin. This work draws on data from a range of existing databases and the authors would like to express their appreciation of those experts whose meticulous work and scientific dedication have contributed so much to the development of this global overview. Professor Christianson provided a first draft of the report based on his expertise as a clinical geneticist, experience in implementing medical services for the care and prevention of birth defects in South Africa and years of consulting on this topic with experts from other middle- and low-income countries. Dr. Christopher Howson of the March of Dimes drafted additional sections of the report and contributed his analytic and programmatic perspective as an epidemiologist and program manager with many years of experience in conducting joint programs with international partners to improve newborn health in middle- and low-income countries.

How The Data In This Report Were Derived

There is a paucity of data on the birth prevalence of birth defects in middle- and low-income countries. Constrained diagnostic capability, poor health-related statistics, lack of birth defect surveillance and registries and reliance on hospital-based rather than population-based studies have contributed to this situation and led to a systematic underestimation of the toll of birth defects in these regions (Christianson and Modell, 2004; Penchaszadeh, 2000; WHO, 1985, 1999).

This report is the first to provide global estimates of birth prevalence for serious birth defects of genetic or partially genetic origin. The estimates in this report (presented by country in Appendix B)

were derived from extrapolation of pooled data from a variety of sources. These include (1) birth prevalence rates of selected birth defects in populations of northern European origin from two birth defects registries, one located in western Canada (Baird et al., 1988) and the other in Hungary (Czeizel and Sankaranarayanan, 1984); (2) global data on carrier rates for common recessive conditions (WHO, 1989, 1994); (3) data on national prevalence rates of pregnant women of advanced maternal age (United Nations, 2003); (4) national rates of consanguineous marriage—i.e. marriage between close relatives, usually cousin-cousin but including uncle–niece (Bittles, 1990; Murdock, 1967) and; (5) national demographic profiles (UNICEF, 2003).

Additional description of how the country-specific estimates in Appendix B were derived is provided in Appendix A.

Report Structure

The report has three major parts. The first is the main body, with a stand-alone Executive Summary, which summarizes the report's main points, including its conclusions and recommendations. Subsequent sections deal with the definition, early knowledge and causes of birth defects; the global impact and epidemiology of major birth defects; the importance of medical genetic services for care and prevention; the nature of recommended services; the promotion of equity through overcoming barriers to medical genetic services; and the reference list.

Appendices A and B comprise the second major part and contain the data that underlie the report. Appendix A explains how the data were derived and Appendix B provides the raw data by country in accordion format. These include selected demographic indices, annual birth prevalence rates for categories of birth defects (e.g., total dominant, total recessive, total X-linked) and annual prevalence rates for specific birth defects. The third part of the report is a stand-alone wall chart that summarizes key data and depicts the global distribution of birth defects graphically.

Readers interested in an overview of the report's findings, conclusions and recommendations may choose to focus on the Executive Summary and wall chart. Those wishing to learn more about the content of the report are encouraged to read the main narrative. Readers interested in country-specific rates of birth defects will find these in Appendix B.

Acknowledgments

The authors are indebted to many colleagues who contributed to this report. In particular, they thank Dr. Michael Katz (March of Dimes) for his expert opinion on all aspects of the report and Ms. Shelley Grim (Division of Human Genetics, University of the Witwatersrand) for her substantive research and editing assistance and her contribution to formatting the database and wall chart. The authors also thank Mrs. Mary Hager for her expert help in editing the report, Ms. Jo-Anne Richards for her initial edit of the manuscript, and Ms. Wendy Scott-Williams for her assistance in finding and checking references. In addition, the authors acknowledge with gratitude the creative contribution of Mr. Michael Kristof to the design of the report, its database, and wall chart, and they thank Mr. Marshall Hoffman and his staff at Hoffman & Hoffman Worldwide for their substantive input into the presentation of the report. In particular, the authors thank Ms. Rachel Diamond for her vigilent oversight and many contributions throughout all the stages of report preparation.

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Finally, the authors thank Dr. Jennifer Howse, President of the March of Dimes, whose vision and support of the March of Dimes Global Programs made this report possible.

EXECUTIVE SUMMARY

Every year an estimated 7.9 million children—6 percent of total births worldwide—are born with a serious birth defect of genetic or partially genetic origin[1]. Additional hundreds of thousands more are born with serious birth defects of post-conception origin, including maternal exposure to environmental agents (teratogens) such as alcohol, rubella, syphilis and iodine deficiency that can harm a developing fetus.

Serious birth defects can be lethal. For those who survive, these disorders can cause lifelong mental, physical, auditory or visual disability. Data presented in this report show that at least 3.3 million children under five years of age die from birth defects each year and an estimated 3.2 million of those who survive may be disabled for life.

Birth defects are a global problem, but their impact is particularly severe in middle- and low-income countries where more than 94 percent of the births with serious birth defects and 95 percent of the deaths of these children occur[2]. The proportion of births with birth defects as well as the absolute number of births are much higher in middle- and low-income countries than in high-income countries because of sharp differences in maternal health and other significant risk factors, including poverty, a high percentage of older mothers, a greater frequency of consanguineous marriages and the survival advantage against malaria for carriers of sickle cell, thalassemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency genes.

This report identifies for the first time the severe, and previously hidden, toll of birth defects, highlighting the extent of this serious and vastly unappreciated public health problem. The accompanying database in Appendix B provides the first systematic, country-by-country summary of annual births of infants with specific serious birth defects of genetic or partially genetic origin.

The modeled estimates in Appendix B are based on the best statistics available, but they do not allow for the most precise comparisons of birth prevalence among countries. Such an analysis must await the collection of additional empirical data on birth prevalence. The data, however, do permit broad comparison of specific birth defects across countries. These analyses show that the birth prevalence of all genetic birth defects combined ranges from a high of 82 to a low of 39.7 per 1,000 live births worldwide. As the bar chart on pages 3-4 indicates, many of the highest birth prevalence rates are found among the world's poorest countries, while many of the lowest rates are found among the world's wealthier countries, with the exception of countries where common recessive disorders and marriages between first cousins and other close relatives are common.

According to the data in this report, five common serious birth defects of genetic or partially genetic origin in 2001 were: (1) congenital heart defects (1,040,835 births); (2) neural tube defects (323,904 births); (3) the hemoglobin disorders, thalassemia and sickle cell disease (307,897 births);

[1] Birth defects as defined in this report are abnormalities of structure or function, including metabolism, which are present from birth. Serious birth defects are life threatening or have the potential to result in disability (physical, intellectual, visual or hearing impairment or epilepsy). More than seven thousand different birth defects have been identified to date. Some birth defects are clinically obvious at birth; others may only be diagnosed later in life. Spina bifida is one example of a structural defect that is obvious at birth. The bleeding disorder hemophilia is a functional defect usually not clinically obvious until infancy or childhood. The authors accept that the term 'birth defect' is not considered appropriate by some, but it has been used extensively in medical literature over time and is widely understood by the broad audience of this report.

[2] This report refers to three categories of countries based on 2004 gross national income (GNI) per capita. These are high-income (industrialized) countries which have a GNI of >$10,065 and middle- and low-income countries (sometimes referred to as developing countries), which have GNIs of $826-10,065 and <$826, respectively (World Bank, 2005).

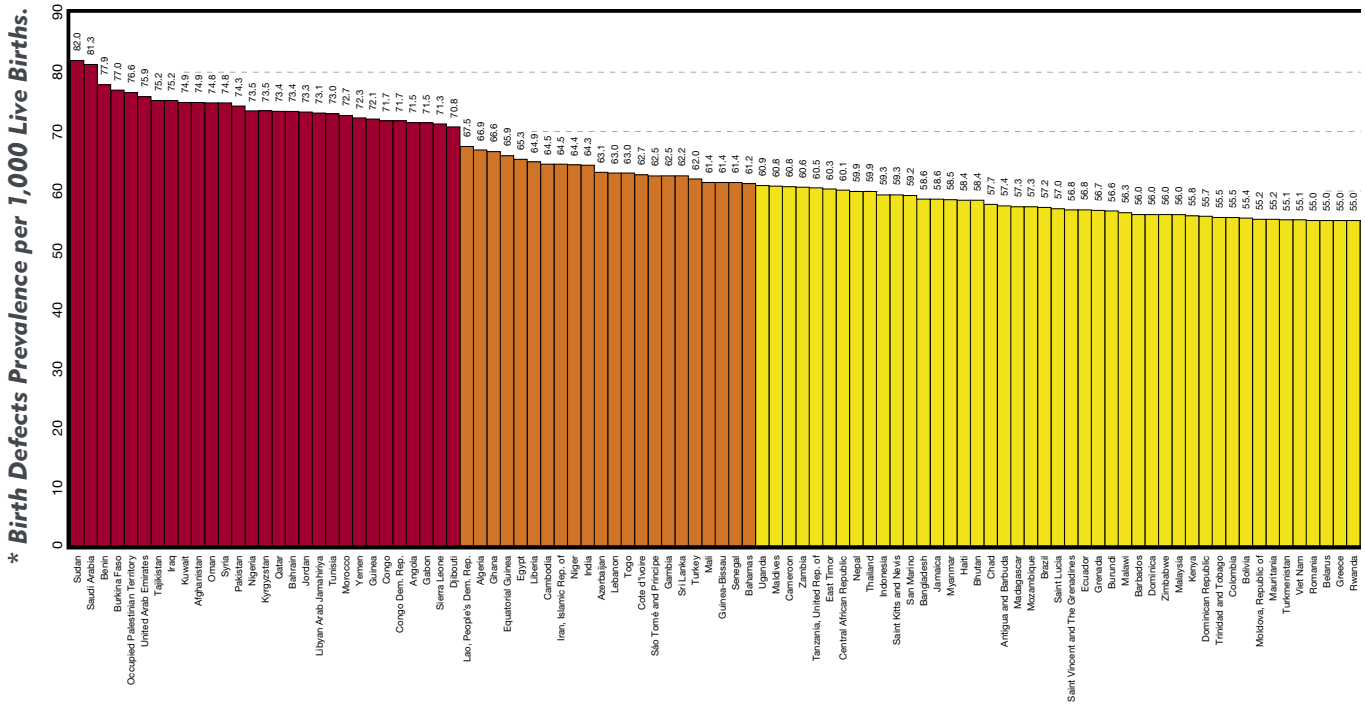
(4) Down syndrome (trisomy 21) (217,293 births); and (5) glucose-6-phosphate dehydrogenase (G6PD) deficiency (177,032 births). Combined, these five conditions account for about 25 percent of all of birth defects of genetic or partially genetic origin. To date, more than 7,000 different birth defects of genetic or partially genetic origin have been identified.

Comparable data could not be derived for birth defects due to post-conception damage caused by maternal exposure to teratogens, such as alcohol, drugs, some infections and a number of toxic environmental agents. What limited data do exist suggest the highest toll results from the following four post-conception birth defects: fetal alcohol spectrum disorder, iodine deficiency disorder, congenital rubella syndrome and congenital syphilis. Together, these disorders account for hundreds of thousands of affected births. As with birth defects of genetic or partially genetic origin, post-conception birth defects are more common in low- and middle-income countries, where the potential for exposure to teratogenic agents is greater and fewer preventive measures are in place than in high-income regions.

Experience from high-income countries shows that up to 70 percent of birth defects can either be prevented, or that affected children can be offered care that could be life saving or would reduce the severity of disability. These interventions include appropriate treatment, particularly surgery, and prevention, especially before conception or in very early pregnancy. For example, the United States reported a remarkable 46 percent decline in infant mortality rates from birth defects over the period 1980 to 2001, and much of this reduction can be attributed to improvements in diagnosis, care and prevention. Other high-income countries have reported similar declines.

On the other hand, limited data from low- and middle-income countries suggest that there has been little to no improvement in infant mortality rates from birth defects over the same general time period. The recommendations in this report are designed to address this disparity and reduce the unacceptably high rates of infant deaths from birth defects in low- and middle-income countries.

Most middle- and low-income countries currently lack the comprehensive health services needed to reduce their toll of birth defects. The report focuses

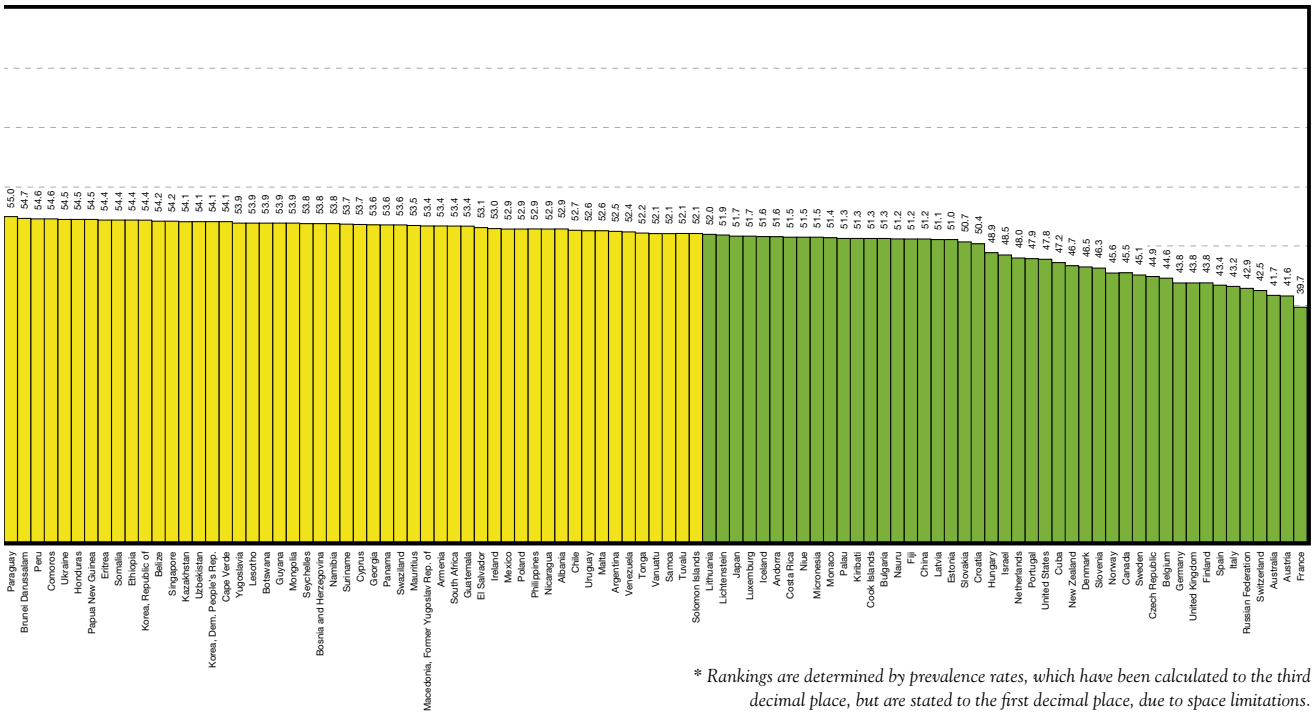


on both the prevention of birth defects as well as the care of those with birth defects and outlines simple and cost-efficient steps that must be taken to equip primary health care programs in less developed countries to focus on this problem.

The report gives numerous examples of successful strategies for care and prevention. For example, structural birth defects including congenital heart defects, congenital cataracts, cleft lip and palate and clubfoot, can be corrected with pediatric surgery. Children with functional problems, including thalassemia, sickle cell disorders and congenital hypothyroidism, also can survive with appropriate treatment. On the side of prevention, ongoing global efforts to fortify salt with iodine have led to a significant reduction in morbidity from iodine deficiency disorder, though an estimated 60,000 babies were born with severe congenital hypothyroidism in 1998 and about 28 million pregnancies still are at risk from maternal iodine deficiency. In the United States alone, fortification of the grain food supply with folic acid has produced a one-third decline in neural tube defects each year, with an overall cost savings calculated at $400 million annually.

Data compiled for this report constitute an important addition to the ongoing and extensive worldwide effort to reduce infant and child mortality. The United Nations Millennium Development Goals (MDGs) for 2015, set in 2000, included reducing child mortality by two-thirds from 1990 levels. By the beginning of 2004, efforts to achieve this goal fell well below United Nations projections.

The newborn was a focus of efforts to improve child health and survival in both the World Health Report 2005, *Make Every Mother and Child Count*, and the first *Lancet Neonatal Survival Series*. Despite this long overdue focus on newborn health, both reports failed to include birth defects as a major cause of childhood death and disability and, consequently, did not highlight care and prevention of birth defects as an essential and integral part of women's, maternal, newborn, and child health programs in all countries. Both concluded that the UN's MDG for reducing child mortality would not be met unless the international community did more to reduce neonatal deaths. The data presented in this report make a strong argument for recognizing and addressing the significant global contribution of birth defects to infant and childhood mortality if



** Rankings are determined by prevalence rates, which have been calculated to the third decimal place, but are stated to the first decimal place, due to space limitations.*

they are to succeed.

This report urges that efforts to promote healthy birth outcomes should target all women of childbearing age, in addition to mothers, newborns and children. The growing understanding of the importance of pre-conception health underscores the fact that good health practices, including regular access to health care, must be established before conception if the pregnancy and newborn are to be as healthy as possible.

Strategies for improving the health of women, mothers, newborns and children are essential for effective prevention and care of those with birth defects. Investing in the care and prevention of birth defects reduces child mortality and disability and, therefore, should be an integral component of any comprehensive women's maternal, newborn and child health program. This includes development of basic medical genetic services for both the prevention of birth defects and the care of affected children in middle- and low-income countries. This investment will ensure that all countries benefit from current knowledge and technology in medical genetics and genomics and that they also will benefit from future advances as they become available.

Several misperceptions identified in the report help to explain why care and prevention of birth defects have received little attention from international donors and health agencies. These misperceptions have been impediments to the development of appropriate programs, and need to be corrected.

The first is that health policy makers have not been aware of the immense global toll of birth defects, including the true extent of death and disabilities, a deficiency that should be corrected by the data presented in this report. In a few documented instances, where the burden of disease has been quantified, funding and corrective measures have usually followed. The implementation of rubella immunization in South America and the Caribbean following publication of the data on the high toll of congenital rubella syndrome in that region provides one such example.

A second misunderstanding is the belief that effective care and prevention of birth defects require costly high-technology interventions that are beyond the health budgets of low- and middle-income countries. In fact, most such efforts should be carried out in primary and secondary care settings. Effective interventions—including family planning, optimizing women's diets, managing maternal health problems and avoiding maternal infections—are both feasible and affordable, even for financially-constrained health systems, and have proven cost effective where implemented.

A third misperception is the belief that attention to birth defects will draw funding away from other high-priority maternal and child health efforts. Again, the reverse is true. Many risk factors for birth defects—including advanced maternal age, maternal medical complications, infection, poor nutrition, smoking, alcohol and drug use—are common to other maternal and child health problems. In fact, increasing efforts to reduce birth defects will also contribute to the overall health of women, mothers, newborns and children.

Recommendations

Experience shows that the care and prevention of birth defects are feasible and can be cost-effective. Such care and prevention requires comprehensive women's, maternal, newborn and child health programs and provision of basic medical genetic services to ensure that people with birth defects or at reproductive risk of having children with birth defects can live and reproduce as normally as possible.

The following steps should be taken to prevent

birth defects and improve the care of affected children in middle- and low-income countries. These steps can be implemented in two phases, according to the health needs and economic capacities of a given country.

Recommendations: Phase 1

- Educate the community, health professionals and workers, policy makers, the media, and other stakeholders about birth defects and the opportunities for effective care and prevention. To achieve this end, each ministry of health should designate an expert or an individual with responsibility for coordinating strategies for care and prevention. These strategies need to be woven into existing public health strategies. Ministries do not need to create a new position, but they should ensure that a knowledgeable, trained and effective person holds this responsibility.

- Promote family planning, allowing couples to space pregnancies, plan family size, define the ages at which they wish to complete their family and reduce the proportion of unintended pregnancies.

- Ensure a healthy, balanced diet during a woman's reproductive years through an adequate intake of macronutrients (protein, carbohydrates and fats) and a broad range of micronutrients. Special attention should be given to adding 400 micrograms of synthetic folic acid daily to the diet through fortification and/or supplementation, while also promoting a diet rich in food folates; correcting iodine and iron deficiencies; and removing teratogenic substances, the most important of which is alcohol, from the diet.

- Control infections in all women of reproductive age.

- Optimize maternal health through control of chronic illnesses associated with an increased risk of birth defects. These include insulin-dependent diabetes mellitus, epilepsy and its control with anti-epileptic drugs, and heart disorders for which sodium warfarin is prescribed.

- Train physicians, nurses, allied health professionals and workers in the fundamentals of the recognition of causes and care of children with birth defects.

- Conduct physical examinations of all newborns by a physician, nurse or allied health professional trained to recognize birth defects before hospital or clinic discharge.

- Establish appropriate child health services to care for infants with birth defects.

- Establish national capacity for surveillance and monitoring of common birth defects to inform policy and to allow for more robust evaluation of national interventions, such as fortification of the food supply with folic acid.

- Promote lay support organizations, including patient/parent support groups, to improve patient care and birth defect prevention by facilitating community and professional education and advocating for increased funding for research on the causes of birth defects.

Recommendations: Phase 2

- Train physicians, nurses and allied health professionals in the essentials of medical genetics. This training should include the recognition of birth defects; means of treatment where possible in the primary health care setting; knowing when to refer a patient for more specialized treatment; basic genetic counseling, including best practices in communicating unfavorable health information

to parents; and support for families who have a child or are at risk of having a child with a birth defect.

- Establish peri-conception medical services to assist women and their partners to attain optimal physical and mental health and well-being at the beginning of pregnancy to facilitate a normal pregnancy and delivery of a healthy infant. These include screening for the risk of genetic, partially genetic and teratogenic birth defects.

- Implement pre-conception or prenatal medical genetic screening to identify couples at risk of having a baby with hemoglobin disorders, Down syndrome, blood type incompatibility, congenital syphilis and congenital malformations, particularly neural tube defects.

- Establish newborn screening to identify congenital hypothyroidism, phenylketonuria, galactosemia, sickle cell disease, G6PD deficiency and other metabolic disorders.

- Educate the public about birth defects and the steps mothers and fathers can take with their health care provider to maximize the chances of a healthy pregnancy.

INTRODUCTION

Developing countries are a diverse assembly of nations with large differences in population size and level of development.[3] Contrary to perceptions in the industrialized world, most low- and middle-income countries have undergone gradual improvements in key national sectors over the past 40 years, including their economic and health sectors. These improvements have been most notable in the countries of Latin America and the Caribbean, East Asia, Pacific, Middle East and North Africa and underpin a gradual, consistent shift in the major causes of population mortality and morbidity, a shift referred to as the health transition. This positive health transition is marked by the decreasing occurrence of infectious diseases and malnutrition, mirrored by declining infant and under-age-five-year mortality rates and increased population life expectancy. The shift observed in these countries is similar to that experienced in industrialized countries in the first 60 years of the 20th Century (McKeown, 1976; UNICEF, 2003; WHO, 1999; IOM, 1997; World Bank, 1993).

Unfortunately, rates of birth defects and their associated developmental disabilities have not decreased in the same populations within the same time period. In fact, a growing body of data suggests that birth defects are a far more significant contributor to infant and childhood mortality and disability in low- and middle-income countries than previously estimated (IOM, 2003; WHO, 1999).

When disability is considered in addition to mortality, the global toll of birth defects reflects a particularly harsh reality. Many infants burdened with serious birth defects die early in life, particularly in middle- and low-income countries, and those who survive almost always have the potential to be disabled, either as a direct or indirect result of their condition. Improvements in patient care have contributed significantly to decreased levels of death and disability in individuals born in rich countries. However, application of this knowledge and technology has been limited in middle- and low-income countries, which currently do not have comprehensive services for care and prevention of birth defects and where 85 percent of the world's six billion people live (UNICEF, 2003). This is a tragedy because up to 70 percent of birth defects could either be prevented or the children affected offered care that would be life-saving or significantly reduce disability (Christianson and Modell, 2004; Czeizel et al, 1993). That is why this report focuses on care as well as prevention of birth defects.

In 2000, the United Nations announced its *Millennium Development Goals* for 2015, which included the health goal (MDG-4) of reducing child mortality by two-thirds from its 1990 base (WHO, 2005a). By the start of 2004, the UN had already noted that the world had fallen behind its projections of where it should have been in order to meet this goal. The recent Executive Summary of the *Lancet Neonatal Survival Series* concludes that MDG-4 goal cannot be met unless the international community does more to reduce neonatal deaths (Lawn et al, 2005). The data in this report show that such efforts must also recognize the global contribution of birth defects to infant and childhood mortality if they are to succeed (Howse et al., 2005).

Several misunderstandings underlie the reasons why care and prevention of birth defects have been accorded relatively low priority by international

[3] *Recognizing this fact, this report uses the World Bank classification of national economies on the basis of gross national income (GNI) per capita. Using 2004 GNI figures, the World Bank describes countries as low-income (<$826), middle-income (subdivided into lower-middle and upper-middle) ($826-10,065), or high-income (>$10,065) (World Bank, 2005). Low- and middle-income countries are sometimes referred to as developing countries and high-income economies as industrialized nations. Although convenient, these terms should not imply that all developing countries are experiencing similar development or that all industrialized countries have reached a preferred or final stage of development.*

donors, health agencies and national governments. The first is that health policy makers are generally unaware of the global toll of birth defects and associated disabilities because data documenting the extent of the problem have been lacking. In instances where the burden of disease has been quantified, health funding has usually followed. For example, widespread implementation of rubella immunization in South America and the Caribbean followed the publication of data on the high toll of congenital rubella syndrome in the region (Dr. Jon Andrus, Pan American Health Organization, Personal Communication, 2005).

A second misunderstanding is the widespread belief that effective care and prevention of birth defects require costly, high-technology interventions that are beyond the national health budgets of low- and middle-income countries. In fact, the bulk of care for and prevention of birth defects is most appropriately carried out routinely in primary and secondary care settings (Christianson and Modell, 2004; WHO, 1985, 1999). In low-income countries, the most effective interventions for prevention include family planning, optimizing women's diet, managing maternal health problems and avoiding maternal infections. These are feasible and affordable in financially-constrained environments and have a cascade of beneficial effects in addition to preventing birth defects. As low-income countries develop and move into and through the middle-income tier, the mix of interventions for care and prevention of birth defects can appropriately shift, taking advantage of the growing strengths in the health sectors of these countries. In middle-income countries which have successfully implemented basic reproductive health approaches, the development and strengthening of medical genetic services including establishing professional and academic networks is required. Professional education of nurses and physicians and developing their expertise in diagnosis, treatment and genetic counseling, wherein the simple basic principles of human inheritance are applied is key to building sustained capacity. Critical to the overall success throughout is building public awareness of these services and how they can be accessed. (Christianson et al., 2000; National Department of Health (South Africa) 2001; Penchaszadeh, 2000; WHO, 1999).

A third misunderstanding, which follows from the last, is that programmatic attention to care and prevention of birth defects will necessarily draw funding away from other high-priority interventions in maternal and child health. Because risk factors for birth defects—including advanced maternal age, poverty, maternal medical complications, infection, poor nutrition, smoking, alcohol and drug use to name a few—are common to other adverse maternal and child health outcomes, interventions to reduce birth defects will contribute to overall women's, maternal, neonatal and child health. Care and prevention of birth defects should be considered an integral and cost-effective arm of public health programs directed at saving the lives of and reducing disability among women, newborns and children. In fact, some interventions like fortification of food with micronutrients benefit the entire population.

DEFINITION, EARLY KNOWLEDGE AND CAUSES OF BIRTH DEFECTS

Definition

A birth defect is defined as any abnormality affecting body structure or function that is present from birth. It may be clinically obvious at birth or may be diagnosed only later in life. For example, spina bifida is a structural birth defect clinically obvious at birth and hemophilia is a functional birth defect that may present clinically only in infancy or childhood. A few birth defects, like Huntington disease, manifest only in adulthood. Serious birth defects are life-threatening or have the potential to cause lifelong disability (Christianson RE et al., 1981; WHO, 2000b).

Early Knowledge

Some evidence shows that birth defects were recognized as early as 6500 BC. A statue of conjoined twins, the Goddess of Anatolia, dated to this time, was found in 1962 in southern Turkey. The first written records were found on the Tablet of Nineveh, estimated to be 4,000 years old. Discovered in the ruins of Babylon the Tablet details 62 malformations (Warkany, 1979). Noah, as described by his great-grandfather the Prophet Enoch, was arguably the first person described with a birth defect, albinism (Sorsby, 1974). Subsequent historical evidence of birth defects has been found from as far afield as Peru, Mexico, Italy, Greece, Egypt, Sri Lanka and Australia (Warkany, 1979).

The risks of birth defects from alcohol intake and infectious diseases were also known very early in recorded history. The harmful effects of alcohol on the unborn child were suggested in the Old Testament: "Behold, thou shalt conceive, and bear a son: and now drink no wine or strong drink." (Judges 13:7). The first documentation of a birth defect caused by infection, congenital syphilis, was recorded during the epidemic of syphilis that occurred in Europe at the end of the 15th century. By the beginning of the 16th century, congenital syphilis had been recognized as a distinct entity (Warkany, 1979).

Causes

It was only in the 20th century that the causes of particular birth defects began to be recognized. The causes of birth defects are many and complex; even now, approximately 50 percent of birth defects cannot be ascribed to a specific cause (Nelson and Holmes, 1989; Turnpenny and Ellard, 2005). However, known causes can be divided broadly into two groups: (1) genetic and partially genetic causes, originating mostly before conception (preconception) and (2) causes developing after conception, but before birth (post-conception).

figure 1

The Goddess of Anatolia

Causes >

CAUSES ORIGINATING BEFORE CONCEPTION

Most birth defects originate before conception and are due to abnormalities of the genetic material—chromosomes and genes. Partially genetic birth defects are due to a combination of genes that puts the fetus at risk in the presence of specific environmental factors. Genetic abnormalities can be inherited, in which case they are found in families, or they can occur as an isolated event in a particular pregnancy. They include chromosomal abnormalities, single gene defects and conditions known as multifactorial disorders, which are caused by the interaction of genes and the environment.

Causes > Causes Originating Before Conception >

CHROMOSOMAL ABNORMALITIES

Chromosomal abnormalities are due to changes in the number or the structure of chromosomes from the normal state that result in a gain or loss of genetic material. Such abnormalities account for approximately 6 percent of birth defects in industrialized countries (Turnpenny and Ellard, 2005). Down syndrome, generally caused by an extra chromosome 21 (trisomy 21), is the most common chromosomal abnormality in man. Described clinically by Langdon Down in 1866, it became the first birth defect ascribed to a chromosomal disorder (Lejeune et al., 1959).

Causes > Causes Originating Before Conception >

SINGLE GENE DEFECTS

Single gene defects are caused by alterations in gene structure, called mutations, which result in abnormal cell functioning. More than 7,000 single gene defects have been described (OMIM, 2000). The first clinically documented single gene defect produced short hands and fingers (brachydactyly) in a large Pennsylvanian family (Farabee, 1903). All single gene defects combined account for an estimated 7.5 percent of all birth defects in industrialized countries (Turnpenny and Ellard, 2005).

Causes > Causes Originating Before Conception >

MULTIFACTORIAL DISORDERS

The concept of multifactorial inheritance (i.e., birth defects due to complex genetic and environmental interaction) was proposed by Boris Ephrussi in 1953 and is now broadly accepted (Passarge, 1995). Other terms to describe this etiological category—for example, non-Mendelian complex inheritance—have been used, but the term that remains in general use is multifactorial inheritance. This category accounts for an estimated 20-30 percent of all birth defects, a number of which are lethal (Turnpenny and Ellard, 2005). Examples of multifactorial birth defects are numerous, are usually malformations of a single organ system or limb, and include congenital heart disease, neural tube defects, cleft lip and/or cleft palate, clubfoot and developmental dysplasia of the hip.

Multifactorial inheritance is also the cause of the many common diseases with a genetic predisposition that present later in life, are usually systemic and do not involve malformations. Included among these disorders are hypertension, diabetes, stroke, mental disorders and cancer.

Causes >

CAUSES ORIGINATING AFTER CONCEPTION

Causes of birth defects originating after conception are primarily non-genetic. In these disorders, the genetic material inherited by the fetus is normal and the birth defect is caused by an intra-uterine environmental factor. These include teratogens that interefere with normal growth and development of the embryo or fetus, mechanical forces that deform the fetus, and vascular accidents that disrupt the normal growth of organs. This category accounts for an estimated 5-10 percent of all birth defects (Nelson and Holmes, 1989; Turnpenny and Ellard, 2005).

Teratogens are broadly categorized into five groups: (1) physical agents such as radiation, (2) environmental pollutants like methyl mercury; (3) maternal illness or disturbances of the mother's

metabolism such as maternal insulin-dependent diabetes mellitus or maternal iodine deficiency; (4) maternal infections, including rubella and toxoplasmosis; and (5) drugs, both medicinal and recreational (Seashore and Wappner, 1996).

Causes >

UNKNOWN CAUSES

As noted above, a specific cause cannot be designated in approximately 50 percent of all children born with birth defects. Some of these birth defects may be due to new autosomal dominant mutations, submicroscopic chromosome deletions or uniparental disomy (Turnpenny and Ellard, 2005). Causes for birth defects continue to be identified, so the percentage of birth defects of unknown cause can be expected to decrease in the future.

THE GLOBAL IMPACT OF BIRTH DEFECTS

The Health Transition

The decline in infant and childhood mortality rates that occurred in the populations of most countries in the 20th century is a public health triumph.[4] Improvements in socioeconomic, educational and health care conditions and the strengthening of infrastructure in high-income countries began in the first half of the last century and led to significant improvements in their population's health (Garret, 2000; Howson, 2000). The "health transition," is initially marked by a decline in infant and under-5-years mortality from infectious diseases and malnutrition, which predominate in the early years of life. At the same time, mortality from birth defects remains the same (*see Table 1*). Using countries in the Eastern Mediterranean region as an example, Figure 2 on page 19 shows that as overall infant mortality rates decrease, the proportionate contribution of birth defects to infant mortality in the country increases. Thus, birth defects increase in public health importance as a country moves through its health transition. This shift mobilized high-income countries in the 1960s to develop medical genetic services to control birth defects (Christianson and Modell, 2004; IOM, 2003; Penchaszadeh, 2000; WHO, 1964, 1999, 2002). The health transition is further marked by increasing life expectancy and, with this, the emergence of common diseases with a genetic predisposition, including heart disease, cancers, mental disorders, diabetes and stroke (Harper et al, 1996) (*see Table 1*).

Middle- and some low-income countries currently are following the high-income countries through the health transition about 40 years later. In 2001, most middle-income and a few low-income countries had achieved demographic profiles similar to the United States in 1960 (UNICEF, 2003). Should these counties begin to take the same steps to control birth defects that high-income countries did in the 1950s and 1960s, within the next 20 years, the health problems of the majority of the world's population should resemble those experienced in industrialized countries today (IOM, 1997; World Bank, 1993).

table 1

	1901	1971	% Reduction
INFECTIOUS DISEASES			
Airborne Diseases			
Respiratory Infection	2,747	603	78
Pulmonary Tuberculosis	1,268	13	99
Whooping Cough	312	1	100
Measles	278	0	100
Scarlet Fever and Diphtheria	407	0	100
Smallpox	10	0	100
Upper Respiratory Tract Infections	100	2	98
Sub Total:	5,122	619	88
Food and Water-Borne Diseases			
Cholera, Diarrhea, and Dysentery	1,232	33	97
Non Respiratory Tuberculosis	544	2	100
Typhus, Typhoid	155	0	100
Sub Total:	1,931	35	98
Other infections			
Sub Total:	1,415	60	96
90% Overall Reduction for Infectious Diseases			
NON-COMMUNICABLE DISEASES			
Birth Defects	126	127	0
Perinatal Problems	1,249	192	85
Heart Disease	1,186	1,688	-42
Rheumatic Heart Disease	487	88	92
Cancer	844	1,169	-39
Other Non-Communicable Diseases	4,598	1,406	69
Sub Total:	8,490	4,670	45
45% Overall Reduction for Non-Communicable Diseases			
TOTAL:	**16,958**	**5,384**	**68**
68% Overall Reduction in Death Rate of all Diseases			

Standardized death rates (per million) for England and Wales for 1901 and 1971

Standardized death rates per million population for England and Wales in 1901 and 1971. The data show an 88 and 96 percent drop in death rates for airborne and water-born infectious diseases, respectively. There was also a 68 percent drop in death rates for non-communicable diseases, although those for cancer and heart disease increased because of improved life s expectancy. Standardized death rates for birth defects did not change over this same time period. SOURCE: Adapted from McKeown, 1976.

[4] *There are notable exceptions where the drop in infant and child mortality rates has slowed or even reversed in recent years. These include many of the countries in sub-Saharan Africa and Afghanistan (Lancet, 2004; UNICEF, 2003). These countries are frequently affected by war, civil strife or poor governance. In the case of some, including South Africa and Botswana, the primary cause is the HIV/AIDS pandemic.*

The Heterogeneity of Developing Countries

To understand differences in the health transition across time and countries, developing countries cannot be viewed as a homogenous group of countries characterized by universal poverty, deficient infrastructure, and poor education and health care, with little or no hope of achieving the improvements experienced in the industrialized world. The reality is very different. Developing countries are a diverse assembly of nations with large differences in geographic size, population demographics, and level of development, with most having experienced continued improvements in socioeconomic progress, education, and health care over the last 40 years (UNICEF, 2003). That is why this report distinguishes among high-, middle- and low-income countries.

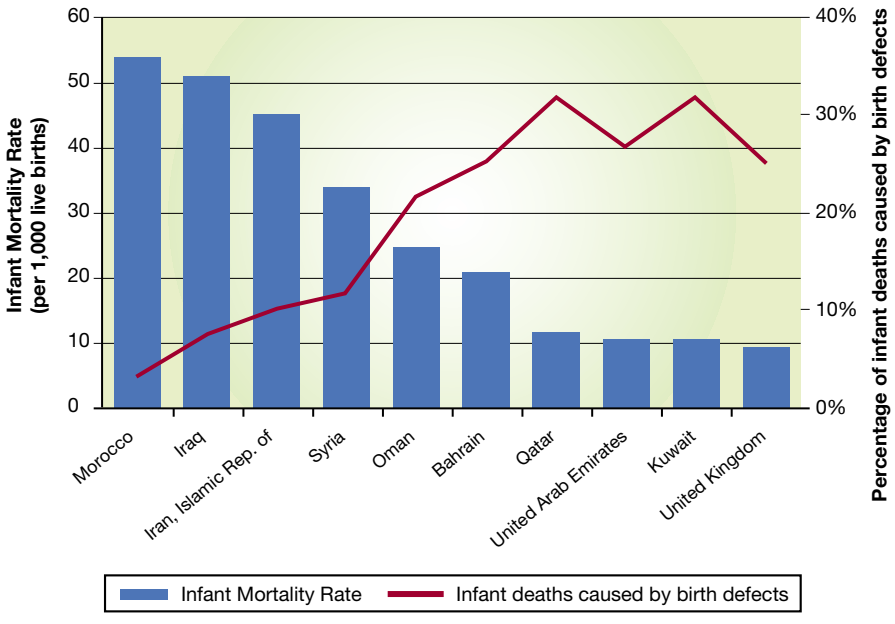
The greatest improvements in population health have occurred in middle-income countries, mainly in Latin America and the Caribbean, East Asia and the Pacific, and the Middle East and North Africa. Since 1960, many countries in these regions have experienced health transitions similar to those of industrialized countries in the first 60 years of the 20th century. Consequently, the toll of death and disability due to birth defects in these countries has attained public health significance and, thus, demands attention (UNICEF, 2003; WHO, 1999). A few low-income countries—including Indonesia, Nicaragua, Ukraine and Viet Nam—have lowered infant and under-five mortality rates beyond expectations and now more closely approximate wealthier countries in their demography and health profiles (UNICEF, 2003). These countries are worth closer study to understand the reasons for their success.

Birth Prevalence, Population Prevalence, Death and Disability

The global toll of birth defects is striking when measured as "birth prevalence" and "population prevalence." Birth prevalence is the number of infants affected in one or a defined collective group of birth defects per 1,000 live births. The use of birth prevalence allows birth defects rates to be compared across populations and time and provides a means for estimating the human and financial toll of birth defects.

figure 2

Relationship between Infant Mortality Rate and Percentage of Infant Deaths due to Birth Defects by Country



SOURCE: Adapted from WHO, 1997.

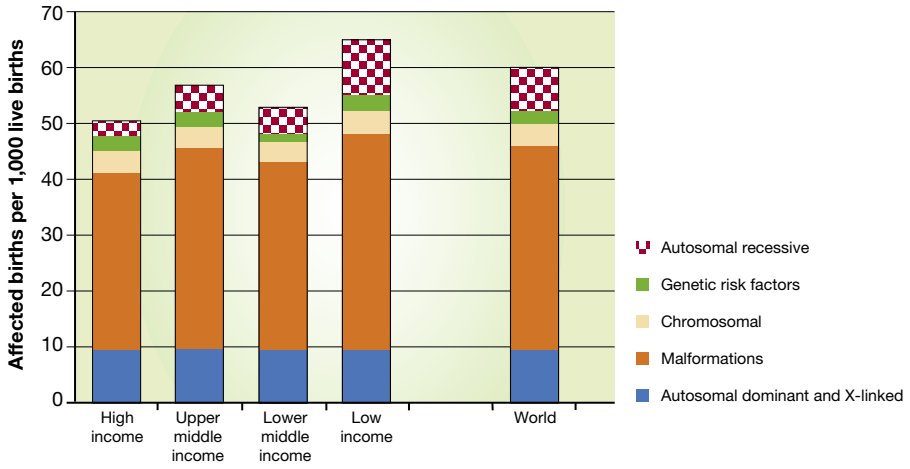
The birth prevalence of birth defects of genetic or partially genetic origin appears similar throughout the world. A few specific conditions, however, including the hemoglobin disorders, G6PD deficiency, oculocutaneous albinism, Down syndrome and neural tube defects have higher birth prevalence in middle- and low-income countries. The birth prevalence of birth defects is, therefore, about 20 percent higher in middle- and low-income countries than in high-income countries (*see Figure 3*) (Christianson and Modell, 2004).

An estimated 7.9 million children are born annually with a serious birth defect of genetic or partially genetic origin (Appendix B). The birth prevalence of post-conception birth defects due to teratogens differs widely but is generally higher in middle- and low-income countries. They are less likely to have systems to detect disorders arising from such exposure and quantification of such problems is limited. Thus, they tend to have few, if any, regulations governing the use of some of these substances and their health services are not directed towards identifying and controlling exposure (Christianson and Modell, 2004; Penchaszadeh, 2002). An undetermined number, but undoubtedly in the hundreds of thousands, of infants are born annually with serious birth defects of teratogenic origin.

Population prevalence refers to the number of affected individuals per 1,000 in a defined population. For birth defects, this number is usually far lower than birth prevalence, especially in middle- and low-income countries, because serious birth defects shorten life. In many of these countries, the difference between birth prevalence and population prevalence is so marked that studies may identify few or no living individuals with serious birth defects. In rural South Africa in the early and mid-1990s, for example, the birth prevalence of Down syndrome was reported to be 2.09 per 1,000 live births and the population prevalence to be only 0.75 per 1,000 children aged two to nine years (Christianson et al., 2002; Venter et al., 1995). This difference suggests that 65 percent of the infants and children with Down syndrome had died by the age of two. Experience has shown that as effective care becomes available, population prevalence rises gradually to approximate birth prevalence (Christianson and Modell, 2004).

More than 90 percent of all infants with a serious birth defect are born in middle- and low-income countries. Because most of these countries do not have adequate services to care for infants and children with birth defects, many of them will die young. In high-income countries, about 30 percent of all children born with a serious birth defect of genetic

figure 3



Minimum Global Estimates of Birth Prevalence of Birth Defects of Genetic or Partly Genetic Origin

SOURCE: Christianson and Modell, 2004.

or partially genetic origin die in infancy, another 30 percent can be treated and live with chronic disability, and the remaining 40 percent can have their condition cured or largely ameliorated with treatment, primarily surgery (Christianson and Modell, 2004; WHO, 1996) (*see Table 2*).

By conservative estimate, some 3.3 million deaths each year are associated with birth defects. This estimate includes approximately 30 percent of the children born with a serious birth defect of genetic or partially genetic origin who die early in high- and middle-income countries, and the 50 percent who die in low-income countries. It is also estimated that without appropriate care another 3.2 million children born with a serious birth defect are disabled each year (Christianson and Modell, 2004). The authors are continuing work to refine these figures.

Factors Influencing the Global Distribution of Birth Defects

Several factors contribute to the disparities in the global distribution of birth defects. These factors include:

Factors Influencing the Global Distribution of Birth Defects >

MALARIA

The presence of this protozoal parasitic disease, which has ravaged the tropics for centuries, was recorded as early as 2700 B.C. in the Chinese Canon of Medicine, the Nei Ching. Fevers that were undoubtedly malaria were recorded in the writings of Homer, Aristotle, Hippocrates, Plato, Socrates, Horace, Chaucer, Pepys and Shakespeare (Gilles and Warrell, 1993; IOM, 1991).

Compared to non-carriers, healthy carriers of recessive genes for sickle cell anemia, thalassemia, and G6PD deficiency have a well-documented survival advantage against the lethal effects of malaria. As a result, carriers are more likely to reach reproductive age. Over time, this has led to an increase in the population prevalence of these genes in tropical regions (Gilles and Warrell, 1993). Consequently the birth prevalence of thalassemia, sickle cell disease and G6PD deficiency is high in malaria endemic regions of the world like sub-Saharan Africa, the Eastern Mediterranean and North Africa, Southeast Asia and Western Pacific regions (Clegg and Weatherall, 1999; Modell and Kuliev, 1989; Mokenhaupt et al., 2004; WHO, 1996).

Factors Influencing the Global Distribution of Birth Defects >

CONSANGUINEOUS MARRIAGE

The social custom of consanguineous marriage is deeply entrenched in parts of the world and accepted by a minimum 20 percent of the world's population (*see Figure 4 page 22*). As a consequence, at least 8.4 percent of the world's children have related parents. Consanguineous marriage is especially common throughout the Eastern Mediterranean, North Africa and the Indian sub continent, where 25-70 percent of unions involve related family members. The practice is also accepted in South America and parts of sub-Saharan Africa. Parental consanguinity increases the birth prevalence of autosomal recessive birth defects. The risk for neonatal and childhood

table 2

Birth Prevalence and Outcomes of Birth Defects in Populations of North European Origin.

Group of Conditions	Birth Prevalence /1,000	% Early Mortality	% Chronic Problems	% Cure	Early Mortality /1,000	Chronic Problems /1,000	Cure /1,000
Congenital Malformations	36.5	22	24	54	8	8.8	19.7
Chromosomal Disorders	3.8	34	64	2	1.3	2.4	0.1
Genetic Risk Factor (Rhesus)	2.6	0	0	100	0	0	2.6
Single Gene Disorders	12.3	58	31	11	7.1	3.8	1.4
TOTAL:	**55.3**	**29.8**	**27.2**	**43.0**	**16.4**	**15.0**	**23.8**

The broad groups shown overlap considerably. Malformations due to chromosomal abnormailities or single gene defects are classed by cause, rather than with congential malformations. Figures apply for situations where enviromental risks are largely controlled. SOURCE: Christianson and Modell, 2004.

death, intellectual disability and serious birth defects is almost doubled for first cousin unions (*see Figure 5 page 23*) (Bittles, 1990; Bittles et al, 1991; Castilla et al., 1991; Christianson et al, 2000; Liascovich et al., 2001; Modell and Kuliev, 1989; Murdock, 1967; Rittler et al., 2001; WHO, 1996).

Factors Influencing the Global Distribution of Birth Defects >

PARENTAL AGE

Advancing maternal age increases the risk of certain chromosomal abnormalities, particularly Down syndrome. The percentage of women of advanced maternal age (greater than 35 years of age) delivering infants is high in middle- and low-income countries (average 11-18 percent), which do not have universal screening, prenatal diagnosis and associated services. The birth prevalence of Down syndrome can reach 2-3 per 1,000 live births in middle- and low-income countries, a rate approximately double that currently seen in high-income countries. Advanced paternal age (greater than 55 years of age), although associated with an increased rate of mutations and a slightly higher birth prevalence of autosomal dominant disorders, is not considered a significant influence on the overall birth prevalence of birth defects (WHO, 1996, 1999).

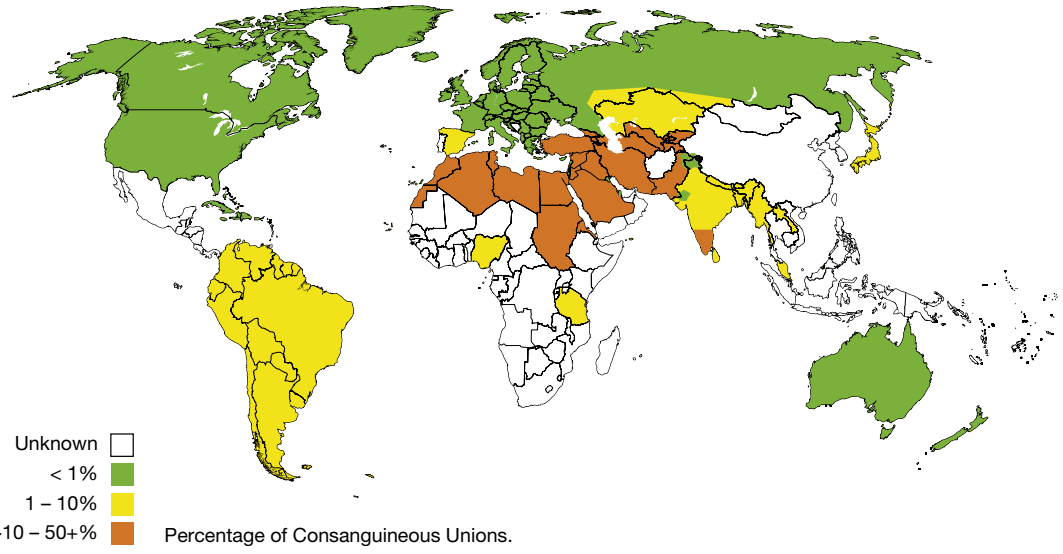
Factors Influencing the Global Distribution of Birth Defects >

MIGRATION

The migration of people who have or carry a single gene defect can introduce the gene into new populations. If those affected or those who are carriers reproduce (as happened with thalassemia and sickle cell disease) the gene can become embedded in the host population. The intercontinental spread of the hemoglobin disorders to the Americas, the Caribbean and Europe by the slave trade and later migrations typifies such gene migration. As a current example, sickle cell anemia, which was previously rare in South Africa, is being introduced through an influx of migrants from west and central Africa (*see Figure 6 page 24*) (Prof. A Krause, Division of Human Genetics, University of the Witwatersrand, personal communication, 2005). Other well-known examples of the introduction of single gene disorders into another continent or country by migration include Huntington disease to Venezuela, spinocerebellar atrophy to Cuba, and porphyria to South Africa (Auburger et al., 1990; Avila-Giron, 1973; Jenkins, 1990; WHO 1996, 1999)

Migration also occurs as a result of increased urbanization as people move from rural settings and

figure 4



Global Distribution of Consanguinity

SOURCE: Based on data from the World Health Organization attributed to A. Bittles (WHO, 1996).

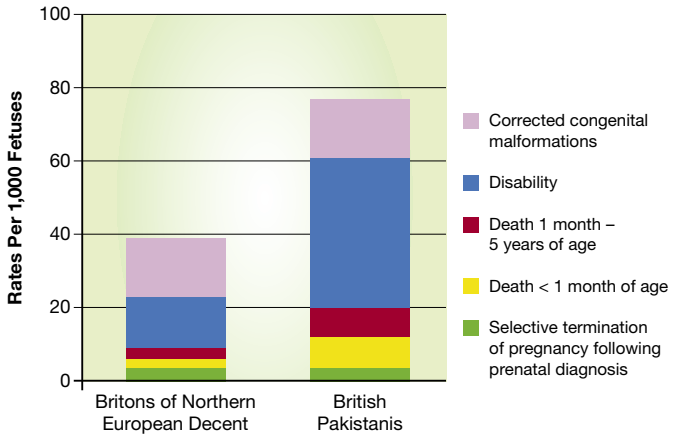
traditional lifestyles to towns and cities. In the years between 1990 and 2001, the average annual growth rate of urban populations in the developing world was 3.2 percent (UNICEF, 2003). The rapid growth of cities led to an increase in urban populations of common disorders with a genetic predisposition, such as hypertension, asthma and insulin-dependent diabetes mellitus. Etiologic factors involved include not only genetic predisposition, but also lifestyle and dietary changes (e.g. high-fat, high-caloric diets and lack of exercise leading to obesity, increased risk of diabetes and coronary artery disease) and exposure to occupational, recreational and environmental toxins and pollutants, particularly alcohol and smoke (WHO/ICBDMS/EUROCAT, 1998, WHO, 1999).

Factors Influencing the Global Distribution of Birth Defects >

POVERTY

Studies have shown families of low socioeconomic status have increased rates of birth defects. This finding has particular significance for middle- and low-income countries. The increased risk may be associated with many factors, including macronutrient and micronutrient malnutrition of the mother both before and during pregnancy and increased exposure to teratogens, particularly alcohol and infection (WHO/ICBDMS/EUROCAT, 1998).

figure 5



A comparison of pregnancy outcomes between Britons of Northern European decent and British Pakistani populations in Birmingham in 1993 illustrates the effects of intermarriage. More than 75 percent of British Pakistanis are married to a relative, 55 percent of them to a first cousin, while less than one percent of Britons of northern European decent have consanguineous unions. SOURCE: Christianson and Modell, 2004; based on data from Bundey and Aslam, 1993.

Factors Influencing the Global Distribution of Birth Defects >

NATIONAL LEVEL OF HEALTH CARE

Population prevalence of all birth defects is largely dependent on the level of available child health care in the target population. In middle- and low-income settings, most affected infants die undiagnosed. As services become available, though, the condition can be alleviated for an increasing proportion of children with birth defects. For example, structural birth defects including congenital heart defects, bowel atresia, congenital cataracts, cleft lip and palate and clubfoot, can be corrected with pediatric surgery. Children with functional problems, including thalassemia, sickle cell disorders and congenital hypothyroidism, also can survive with appropriate treatment. As the availability and level of health services in middle- and low-income countries approach those of high-income countries, many children with chronic disabilities due to birth defects, such as Down syndrome or neural tube defects, can be treated so they will live longer, more productive lives (Christianson and Modell, 2004).

The birth prevalence of birth defects is similarly influenced by the level of available reproductive, peri-conception and maternal health care services, and is lower in countries where women are more highly educated. The frequency of a number of birth defects, including neural tube defects, fetal alcohol syndrome, congenital syphilis and rubella and Down syndrome, decreases in the presence of preventative public health measures (Christianson and Modell, 2004; Penchaszadeh, 2000; WHO, 1999). Consequently, while the provision of health care services may extend the life of those affected with birth defects, it may decrease the birth prevalence of such individuals as well.

The Global Distribution of Specific Birth Defects

The global distribution of birth defects by category is presented below. The categories include birth defects of genetic or partially genetic origin, including single gene defects, chromosomal disorders, multifactorial disorders and birth defects caused by teratogens.

The Global Distribution of Specific Birth Defects >

SINGLE GENE DEFECTS

More than 7,000 single gene defects have been described worldwide (OMIM, 2000). In high-income countries, where a large proportion of the population is of northern European origin, single gene defects affect approximately one percent of the population. These countries have a cumulative birth prevalence of 3.6 per 1,000 live births and account for up to 7.5 percent of all birth defects in industrialized countries (Baird et al., 1988; Turnpenny and Ellard, 2005). The estimated birth prevalence of single gene defects in populations in many middle- and low-income countries is higher because of the high birth prevalence of common recessive disorders associated with a selective advantage for carriers to the lethal effects of malaria, and because of recessive disorders associated with the higher rates of consanguineous marriage (*see Table 3 page 25*).

Single gene defects fall into two broad groups: common recessive disorders and rare single gene defects.

The Global Distribution of Specific Birth Defects > Single Gene Defects

COMMON RECESSIVE DISORDERS

These include three major disorders: the hemoglobin disorders, sickle cell anemia and thalassemia; oculocutaneous albinism in sub-Saharan Africa; and cystic fibrosis.

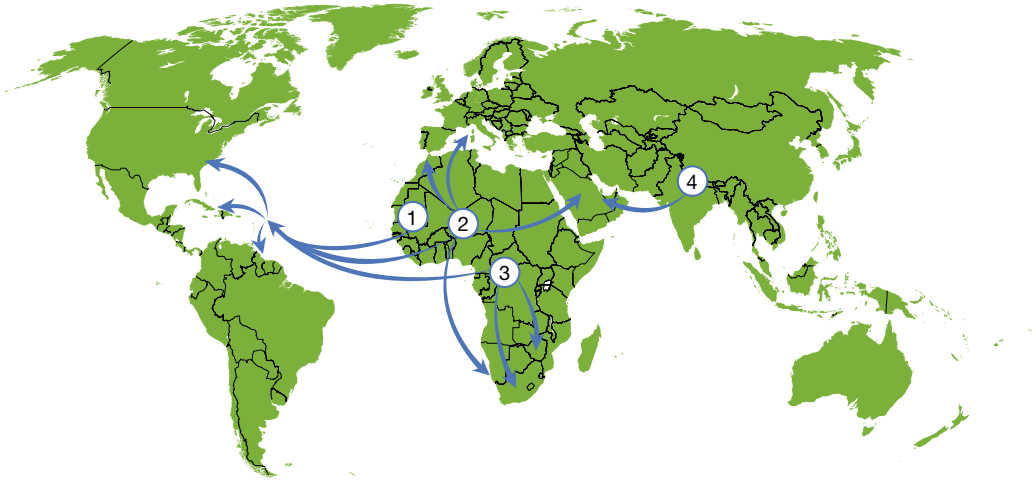
The Global Distribution of Specific Birth Defects > Single Gene Defects > Common Recessive Disorders

THE HEMOGLOBIN DISORDERS: SICKLE CELL ANEMIA AND THALASSEMIA

The most common lethal inherited disorders in humans, the hemoglobin disorders, originated in populations in tropical Africa, Asia and the Mediterranean region and have spread via migration throughout the world (Angastiniotis and Modell, 1998; Stuart and Nagel, 2004) (*see Figure 7 page 26*). Currently, an estimated 307,900 children are born annually with a severe hemoglobin disorder.

Sixty to 70 percent of affected births occur in sub-Saharan Africa. Sickle cell disorders account

figure 6



Migration of the Sickle Cell Gene

The mutations that cause sickle cell anemia had four independent origins. Three mutations arose in west and central Africa. The African mutations traveled with the slave trade to the Americas. The second mutation spread by trans-Saharan caravans to North Africa and the Mediterranean region and countries in southern Europe. The third mutation, originating in equatorial central Africa, spread east and south with inter-African population migration as far as the northern borders of South Africa. The fourth mutation, originating in the Indian sub-continent, spread through the Middle East by traders. Mutations two and three have been introduced into South Africa in the last decade by people from west and central Africa migrating for political and economic reasons. SOURCE: Stuart and Nagel, 2004; Krause A, University of the Witwatersrand, personal communication, 2004.

for 70 percent of hemoglobin disorders worldwide because of the high frequency of the gene in the tropical parts of sub-Saharan Africa. In Africa an estimated 224,200 infants are born each year with sickle cell disorder, the vast majority of whom die before the age of five (Akinyanju, 1989; Fleming et al., 1979). In North and South America and Western Europe, the birth prevalence of sickle cell disorder is related to the proportion of the population that originated from Africa.

Thalassemias are prevalent in the Mediterranean area, the Middle East, South and East Asia, and the Pacific, with carrier rates ranging from 2-19 percent in different populations. Studies in southern China report a 3-4 percent carrier rate for ß-thalassemia, and a 1-8 percent carrier rate for the severe form of alpha thalassemia (alpha zero (0)-thalassaemia).

The birth prevalence of hemoglobin disorders in industrialized countries, where only one percent of affected children are born, varies according to geographic location and the origins of their populations. It is currently estimated that 0.7 in 1,000 pregnancies are affected in the United Kingdom and 0.4 in 1,000 in North America (Angastiniotis and Modell, 1998; WHO, 1994).

OCULOCUTANEOUS ALBINISM

Oculocutaneous albinism is a hereditary disorder characterized by deficiency of the pigment melanin in the eyes, skin and hair. The lack of eye pigment causes photophobia (sensitivity to light), nystagmus, and decreased visual acuity. Oculocutaneous albinism is a common autosomal recessive birth defect found globally but with high birth prevalence in sub-Saharan Africa and in clusters in South America. Birth prevalence of 0.66 and 0.23 per 1,000 live births were recorded in rural and urban South Africa respectively (Delport et al., 1995; Venter et al., 1995). The rural rate was higher due to the greater acceptance of consanguineous marriage in the population surveyed. The population prevalence of oculocutaneous albinism is fairly uniform across countries in sub-Saharan Africa, ranging from one in 3,900 to one in 5,000 live births. The highest recorded prevalence is one in 1,000 live births in the geographically isolated Tonga people of Zimbabwe (Kromberg and Jenkins, 1982; Lund et al., 1997). In South America, the clusters described have been associated with geographic isolation and parental consanguinity (Baillet et al., 2001; Castilla and Adams, 1990; Castilla and Sod, 1990; Keeler, 1970).

Oculocutaneous albinism is a highly visible birth defect in dark-skinned people. As a consequence, people with oculocutaneous albinism are

table 3

Comparison of the global birth prevalence of different groups of single gene disorders among North European populations

Group of Disorder	North Europeans		World	
	Births / 1,000	% of Total	Births / 1,000	% of Total
Dominant	7	58.7	7	41.4
X-linked	1.3	10.9	1.3	7.9
Hemoglobin Disorders	0.5	4.2	2.3	13.8
Other Recessive Disorders	1.7	14.3	1.7	9.9
Recessive Disorders Related to Consanguinity	0.22	1.8	3.4	19.9
Total Recessive:	2.42	20.3	7.4	43.7
Genetic Type Unknown	1.2	10.1	1.2	7.1
TOTAL:	**11.92**	**100**	**16.9**	**100**

SOURCE: Christianson and Modell, 2004.

often socially stigmatized. In addition to visual problems, they also suffer from sun-induced skin disorders, including cancer. The susceptibility to skin cancer increases with age and proximity to the equator. As a result, oculocutaneous albinism is associated with early death. In Tanzania and Nigeria, for example, only 10 percent of those affected survive beyond 30 years of age (Kromberg, 1992; Kromberg et al., 1989; Luande et al., 1985).

The Global Distribution of Specific Birth Defects > Single Gene Defects > Common Recessive Disorders >

CYSTIC FIBROSIS

Cystic fibrosis is the most common single gene birth defect in Caucasian populations, with a birth prevalence of approximately one in 2,000 live births. The defect had been considered rare in other populations, but reports of birth prevalence of one in 2,560 and one in 2,608 live births in Jordan and Egypt, respectively, challenge that assumption. Carriers of a mutated cystic fibrosis gene are also more common than expected among black South Africans, in whom cystic fibrosis had been regarded as extremely rare (Padao et al., 1999).

The Global Distribution of Specific Birth Defects > Single Gene Defects >

RARE SINGLE GENE DEFECTS

The birth prevalence of rare single gene defects is generally one in 10,000, or more. However, in clusters of people in middle- and low-income countries, gene frequencies of rare single gene defects are greater than expected due to the founder effect, genetic drift and geographic or cultural isolation (WHO, 1999). Examples include porphyria in South Africa, spinocerebellar ataxia in Cuba, and Huntington disease in Venezuela (Auburger et al., 1990; Avila-Giron, 1973; Jenkins, 1990). In spite of their infrequency, certain rare single gene disorders for which treatment is available, for example hemophilia, are important in middle- and low-income countries because of the high costs associated with the care of affected individuals. Collectively, these rare disorders also add significantly to the infant and child health burden.

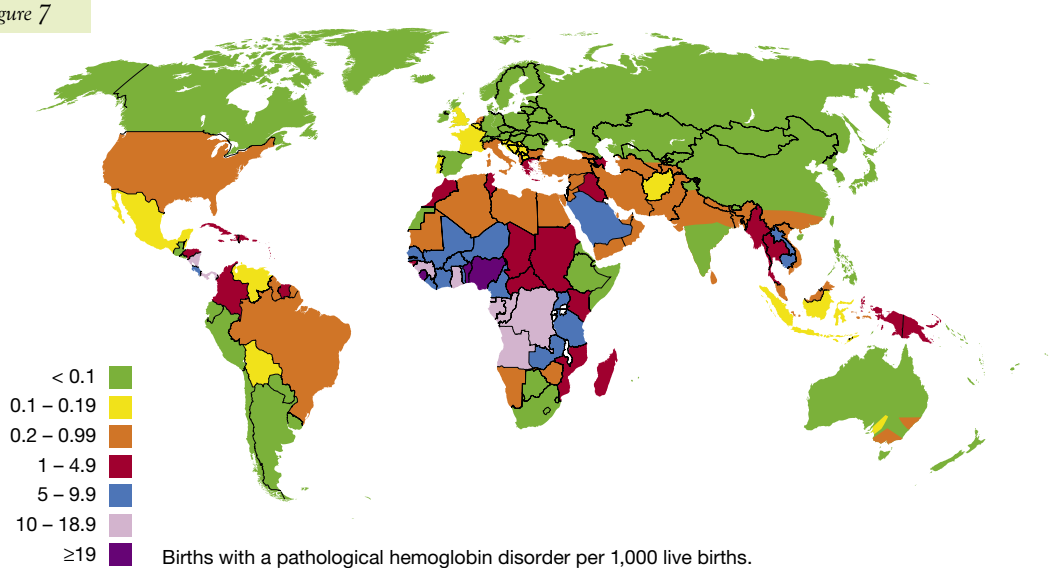
The Global Distribution of Specific Birth Defects > Single Gene Defects >

GENETIC PREDISPOSITION TO HEMOLYSIS AND NEONATAL JAUNDICE

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

G6PD deficiency, an X-linked recessive disorder, is the most common enzyme deficiency disease in humans. An estimated 7.5 percent of the world's population carries a G6PD deficiency gene. Hundreds of variants of the disorder, with differing clinical severity have been described, with approximately 90 percent of those affected being male. Individuals

figure 7



Global Distribution of Pathological Hemoglobin Disorders, 1996

SOURCE: WHO, 1996.

may be asymptomatic or may experience varying degrees of anemia caused by rapid breakdown of red blood cells. Acute crises can be induced by infection or the ingestion of drugs or certain foods, such as fava beans. In newborns with severe G6PD deficiency, neonatal jaundice due to the rapid breakdown of red blood cells may result in damage to the brain and auditory nerves, a condition called kernicterus. Kernicterus can lead to intellectual disability, cerebral palsy, deafness and death, and is a significant risk for affected infants in middle- and low-income countries where services for the detection and treatment of neonatal jaundice are limited (Luzzatto and Metha, 1989; Verjee, 1993; WHO, 1989). Prevention of these complications depends upon early diagnosis, phototherapy and exchange blood transfusions in severely jaundiced infants.

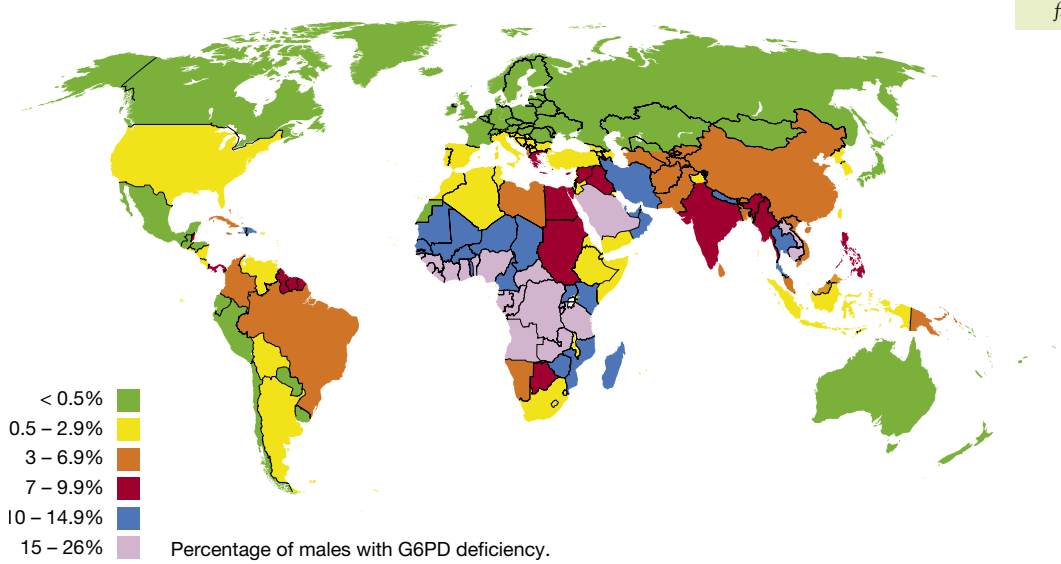
More than 5 million infants are born annually with G6PD deficiency of varying severity, mainly in tropical sub-Saharan Africa, the Eastern Mediterranean and North Africa, South and East Asia, and the Pacific (*see Figure 8*). However, only an estimated 177,000 of these infants are at risk for the severe adverse effects of G6PD deficiency including neonatal jaundice. Ninety-nine percent of these babies are born in middle- and low-income countries (see Appendix B).

RHESUS NEGATIVITY

Rhesus negativity confers a genetic predisposition to having children affected by Rhesus hemolytic disease of the newborn. When a Rhesus negative woman has a Rhesus positive partner, the fetus is often Rhesus positive. In such cases, fetal red cells may pass into the mother's circulation and stimulate the production of antibodies that cross the placenta and destroy fetal red cells, causing severe anemia. An affected fetus may be stillborn or become severely jaundiced soon after birth, with the risk of severe mental and neurological disability. Rhesus negativity is most common in women of Northern European origin. In the past, approximately two in 1,000 pregnancies in this population were affected, leading to stillbirth or severe disability. In addition, once a woman becomes immunized against fetal red cells, her future chances of successful pregnancy are severely jeopardized. In high-income countries, this problem has been almost completely eliminated by Rhesus blood grouping for all pregnant women, followed by injection of Anti-Rhesus antibody at delivery to destroy any fetal cells in the maternal circulation before anti-

figure 8

Global Distribution of Males with Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency, 1996*



*The incidence of female heterozygotes is approximately twice that of male hemizygotes.

Clinical severity of G6PD deficiency varies from minimal to severe depending on the mutation involved. SOURCE: WHO, 1996.

bodies develop.

This problem cannot be neglected in populations with lower prevalence of Rhesus negativity, however, because a Rhesus negative woman's chance of having a Rhesus positive partner is highest when prevalence is low. Avoidable fetal and neonatal death from Rhesus hemolytic disease will continue in any country that does not have a systematic prevention program, but the problem seems to have received relatively little attention in some lower-income countries.

The Global Distribution of Specific Birth Defects >

CHROMOSOMAL DISORDERS

The increasing risk of chromosomal abnormalities, particularly Down syndrome, with advancing maternal age is well recognized. Middle- and low-income countries have a high birth prevalence of Down syndrome for a number of reasons, including a high frequency of older women becoming pregnant, limited access to family planning, and deficient or absent prenatal screening, diagnosis and associated services. Birth prevalence may be as high as 2-3 per 1,000 live births in middle- and low-income countries and as low as 1.2 per 1,000 live births in high-income countries (Modell et al., 1992; WHO, 1996). An estimated 217,300 infants with Down syndrome are born each year. Early infant or childhood death from congenital heart disease and infection is common among infants and children with Down syndrome in middle- and low-income countries. In South America, 55 percent of infants with Down syndrome die prior to their first birthday, approximately 60 percent of them having congenital heart defects (Castilla et al., 1998). As a result, the population prevalence of chromosomal disorders is low (Christianson and Modell, 2004).

The Global Distribution of Specific Birth Defects >

MULTIFACTORIAL DISORDERS

Birth defects of multifactorial origin, most of which present as congenital malformations of single systems, organs or limbs, comprise the majority of birth defects. The birth prevalence of multifactorial disorders can vary with socio-economic status, ethnicity and geographic location, creating differences among and within regions and countries. Some of these birth defects are preventable, while many are amenable to treatment, mainly by pediatric surgery. In the absence of prevention, the toll from multifactorial disorders depends on the level of health care services in a country.

Key multifactorial disorders include congenital heart defects, neural tube defects, and cleft lip with or without cleft palate.

The Global Distribution of Specific Birth Defects > Multifactorial Disorders >

CONGENITAL HEART DEFECTS

Congenital heart defects are the most common form of birth defect, occurring in 4-8 per 1,000 live births. These defects result from disturbances as the heart and major vessels are formed during the third and eighth week after conception. The majority of congenital heart defects, about 90 percent, have a multifactorial cause (Rimion et al, 2002; Seashore and Wappner, 1996). The remaining congenital heart defects are associated with chromosome abnormalities (5-8 percent), single gene defects (3-5 percent) and teratogens (2-3 percent) (Seashore and Wappner, 1996). An estimated 1,040,800 infants are born each year with a multifactorial congenital heart defect.

The Global Distribution of Specific Birth Defects > Multifactorial Disorders >

NEURAL TUBE DEFECTS

Neural tube defects, including spina bifida, anencephaly and encephalocoele, occur when part of the neural tube, which forms the spine, spinal cord, skull and brain, fails to close between 21 and 28 days after conception—before women realize they are pregnant. These serious errors in the development of the central nervous system can cause death or permanent damage to the brain, spinal cord and spinal nerves. Many children affected by neural tube defects have multiple lifelong disabilities, including varying degrees of lower limb paralysis, bowel and bladder incontinence, hydrocephalus, intellectual and learning disabilities. Each year spina bifida and anencephaly, the two most common forms of neural

tube defects, occur in an estimated 300,000 newborns worldwide (CDC, 2005). Neural tube defects constitute one of the common forms of multifactorial congenital malformation, with recorded birth prevalence as high as six per 1,000 live births in China, but varying widely depending on genetic and environmental conditions (Berry et al, 1999; WHO/EURO, 2002).

Neural tube defects are occasionally caused by chromosomal abnormalities, single gene defects and teratogens.

The Global Distribution of Specific Birth Defects > Multifactorial Disorders >

CLEFT LIP WITH OR WITHOUT CLEFT PALATE

Cleft lip, with or without cleft palate, is a congenital malformation etiologically different from isolated cleft palate. It comprises a partial or complete cleft of the upper lip, with or without a cleft of the alveolar ridge (gum) or the palate. The cleft may be unilateral, mainly left sided, or bilateral, and results from the failure of face-building tissues to fuse by 10 weeks after conception. Multifactorial inheritance accounts for the majority of cleft lip, with or without cleft palate, with birth prevalence ranging from 0.3 per 1,000 live births in African American populations, one per 1,000 in Caucasians, two per 1,000 in Japanese to 3.6 per 1,000 live births in Native North Americans. A number of potentially causative genes are under investigation though certain drugs and maternal smoking are considered to play a role (Rimion et al, 2002; WHO, 2001b, 2002). Cleft lip with and without cleft palate is also associated with other syndromes caused by chromosomal abnormalities, single gene defects and teratogens.

Table 4 details the birth prevalence of congenital malformations, mostly of multifactorial origin, in Hungary in the 1980s, at a time when the country's demographic profile was that of a typical middle-income country (Czeizel and Sankaranarayanan, 1984; WHO, 1996).

The Global Distribution of Specific Birth Defects >

INDIVIDUAL TERATOGEN-ASSOCIATED BIRTH DEFECTS

Birth defects due to teratogens are among the more readily preventable. Pregnancies in middle- and low-income countries, by comparison to high-income countries, are more likely to be at risk from potential teratogens for several reasons, including increased frequency of intrauterine infection, poor maternal nutrition, low socioeconomic and educational levels, lack of environmental protection policies, and poorly regulated access to medication (Penchaszadeh, 2002). Broadly, three of the five causal groups of teratogens have the most significance: (1) congenital infections, (2) maternal illness and altered maternal metabolism

table 4

Birth prevalence and outcomes of congenital malformations, categorized by systems, in the absence of prevention in Hungary in 1980

Group of Congenital Malformation	Prevalence /1,000 Live Births	% of Total	Early Deaths /1,000 Live Births	Cure /1,000 Live Births	Chronic Problems /1,000 Live Births	% of Early Deaths Due to Malformation
Cardiovascular System	7.9	27.0	2.7	3.9	1.4	41.2
Central nervous System	2.2	7.5	1.7	0.1	0.4	26.5
Alimentary System	2.8	9.6	0.6	2.0	0.1	9.7
Skeletal System	2.1	7.2	0.4	1.3	0.4	6.0
Urinary Organs	1.6	5.5	0.3	0.7	0.6	4.4
Respiratory System	0.3	1.0	0.1	0.1	0.1	1.5
Eye	0.3	1.0	0.1	0.1	0.1	0.7
Cleft Palate, +/- Cleft Lip	1.4	4.7	0.0	1.1	0.3	0.5
Ear, Face, Neck	0.5	1.7	0.0	0.3	0.1	0.0
Genital Organs	7.5	25.6	0.0	6.5	1.0	0.0
Miscellaneous inc. Multiple.	2.7	9.2	0.6	1.6	0.6	9.5
TOTAL:	**29.3**	**100**	**6.5**	**17.7**	**5.1**	**100**
% of Malformations	100		22.2	60.4	17.4	

SOURCE: Christianson and Modell, 2004.

and (3) recreational and therapeutic drugs.

The Global Distribution of Specific Birth Defects > Individual Teratogen-Associated Birth Defects >

CONGENITAL INFECTIONS

Congenital means "present from birth." The baby acquires the infection in utero from the mother and is born with the sequelae of that infection. The TORCH organisms—Toxoplasmosis, Other (syphilis, varicella-zoster, human parvovirus B19), Rubella, Cytomegalovirus (CMV), and Herpes—account for the most common infections associated with birth defects (Stegman and Carrey, 2002).[5]

Most of the TORCH infections cause mild maternal morbidity, but have serious fetal consequences, and treatment of maternal infection, with the exceptions of syphilis and varicella zoster, has no impact on fetal outcome. Knowledge of these diseases can help health care providers counsel mothers on preventive measures needed to avoid these infections. Recognition of maternal disease and fetal monitoring once disease is recognized are important and will aid in counseling parents on the potential for adverse fetal outcomes and their options, when these infections are present.

The Global Distribution of Specific Birth Defects > Individual Teratogen-Associated Birth Defects > Congenital Infections >

TOXOPLASMOSIS

Toxoplasmosis is a relatively widespread parasitic infection. A pregnant woman who contracts toxoplasmosis for the first time has about a 40 percent chance of passing the infection to her fetus. However, the risk and severity of the baby's infection depend on the time in the pregnancy when a mother's infection occurs. When mothers are infected in the first trimester, about 15 percent of fetuses become infected, compared to about 30 percent in the second trimester and about 60 percent in the third. However, the consequences of the fetal infection are more severe when the infection occurs earlier in pregnancy (MOD, 2001c).

In about one in 10 infected fetuses, a severe toxoplasma infection is evident at birth. These newborns often have eye infections, an enlarged liver and spleen, jaundice and pneumonia. Some die within a few days of birth. Those who survive can have intellectual disability, severely impaired eyesight, cerebral palsy, seizures and other problems. Although up to 90 percent of infected babies appear normal at birth, between 55 and 85 percent of them develop problems months to years later, including eye manifestations that may affect sight, hearing loss, and learning disabilities. Toxoplasmosis during pregnancy also can result in miscarriage or stillbirth (MOD, 2001c).

Between one in 1,000 and one in 10,000 babies in the United States are born each year with toxoplasma infection (MOD, 2001c). An estimated four per 10,000 babies are born with this infection in middle- and low-income countries (Christianson and Modell, 2004).

The Global Distribution of Specific Birth Defects > Individual Teratogen-Associated Birth Defects > Congenital Infections >

CONGENITAL SYPHILIS

Syphilis is a common sexually transmitted infection. Over 11 million new infections occur each year worldwide. Population prevalence ranges from a low of 20.6 per 100,000 people in the United States to 3,500 per 100,000 people in Papua New Guinea. Syphilis can cross the placenta and infect the fetus. Congenital syphilis is a major cause of neonatal mortality, particularly in many middle- and low-income countries. In sub-Saharan Africa alone, 6-16 percent of pregnant women have active syphilis (Murray and Lopez, 1998). Unless the mother is treated with penicillin, as many as 40 percent of embryos or fetuses with syphilis die before or shortly after birth. In Haiti, 52 percent of infants with congenital syphilis die before their first birthday. Those who survive

[5] *Other infectious diseases, not ostensibly associated with birth defects, can be acquired by the fetus from the mother during pregnancy or at birth. The most important of these from a public health perspective is HIV/AIDS. Whether these congenital infections can be considered and managed as teratogenic disorders is debatable and not generally accepted (Christianson and Modell, 2004). Given the importance of HIV/AIDS, however, interested readers are directed to the following four websites: http://www.nih.gov/; http://www.aegis.com/; http://www.aidsmeds.com/Search.htm; http://www.acria.org/acria.html; http://my.webmd.com/medical_information/condition_centers/hiv_aids/default.htm?SRC=Google&Placement=hiv*

are at risk for brain damage, blindness, hearing loss, and bone and tooth problems if they are not treated with an antibiotic shortly after birth (Fitzgerald et al, 1998; MOD, 2002b; Murray and Lopez, 1998; WHO, 2005c).

The Global Distribution of Specific Birth Defects > Individual Teratogen-Associated Birth Defects > Congenital Infections >

VARICELLA-ZOSTER VIRUS

Primary infection with varicella-zoster virus (VZV) (chickenpox) can pose risks to the fetus if a mother is infected during pregnancy. A susceptible pregnant woman who is exposed to an infected household member has a 90 percent risk of contracting the illness. Maternal infection can lead to congenital varicella syndrome, a group of birth defects that can include defects of muscle and bone, malformed and paralyzed limbs, a smaller-than-normal head, blindness, seizures and intellectual disability. This syndrome affects about 2 percent of babies whose mothers are infected with varicella during the first 20 weeks of pregnancy, but is rare if infection occurs after 20 weeks (MOD, 2001a). The birth prevalence of VZV in middle- and low-income countries is unknown.

The Global Distribution of Specific Birth Defects > Individual Teratogen-Associated Birth Defects > Congenital Infections >

HUMAN PARVOVIRUS B19

Human parvovirus (HPV) B19 causes Fifth Disease (erythema infectosum), a mild viral illness usually seen in children. When the infection occurs in pregnant women, it acts as a teratogen and can cause fetal death. The virus disrupts the fetus's ability to produce red blood cells, leading to anemia, heart failure, and up to a 9 percent risk of miscarriage or stillbirth. Fetal deaths are more likely when a pregnant woman contracts the infection in the first twenty weeks of pregnancy. An estimated one per 3,333 newborns are infected in high-income countries (Markenson and Yancey, 1998). The fetal infection rate of HPV B19 infection in middle- and low-income countries is unknown.

The Global Distribution of Specific Birth Defects > Individual Teratogen-Associated Birth Defects > Congenital Infections >

CONGENITAL RUBELLA SYNDROME

Rubella poses a serious threat to the fetus if the mother contracts it during the first 16 weeks of pregnancy. The annual incidence of rubella worldwide is difficult to ascertain because the disease is often mild and overlooked, or, when it is more severe is often misdiagnosed as measles. About 25 percent of babies whose mothers contract rubella during the first trimester of pregnancy are born with one or more birth defects, which, together, are referred to as congenital rubella syndrome (CRS). These birth defects include blindness, hearing impairment, heart defects, intellectual disability and, less frequently, movement disorders. The infection occasionally causes miscarriage and stillbirth. Children with CRS also are at increased risk of diabetes, which may develop during childhood or adulthood (MOD, 2002a).

In high-income countries, successful rubella immunization programs have virtually eliminated CRS. By 1999, 105 (49 percent) of the countries and territories reporting to the WHO had introduced rubella vaccine programs. An analysis of countries, by WHO region, that introduced rubella vaccine programs indicates that those most in need of them had not introduced them. In the African region only 2 percent of countries had rubella vaccine programs, 20 percent in Southeast Asia, 50 percent in the Eastern Mediterranean region, 54 percent in the Western Pacific, 68 percent in the European region and 79 percent in the Americas. Although the situation is improving, more than 100,000 children are born annually with congenital rubella syndrome (WHO, 2000b).

The Global Distribution of Specific Birth Defects > Individual Teratogen-Associated Birth Defects > Congenital Infections >

CYTOMEGALO VIRUS

Cytomegalovirus (CMV) infection is the most common congenital infection in high-income countries. Intrauterine infections occur in mothers who have developed a first-time CMV infection during pregnancy. These women have a 30-40 percent risk

of passing the virus to their fetus (MOD, 2001b).

Most of the time, the infected infant shows no symptoms at birth, but 14 percent of asymptomatic newborns with infection develop serious disabilities over the next several years. These include neurological, growth and developmental problems; sight or hearing problems; and dental abnormalities. About 10 percent of infected newborns have symptomatic CMV disease. Of these, most who survive suffer from progressive deafness and/or intellectual disability. An estimated four per 10,000 newborns are affected in middle- and low-income countries (Christianson and Modell, 2004).

Recently, an increase in the frequency of congenital CMV has been observed among newborns in the academic hospitals in Johannesburg, South Africa. The mothers of many of these infants were HIV-positive, which suggests that pregnant mothers with an immune system compromised by HIV can contract CMV, despite previous CMV infection, thus affecting their fetus (Dr. M. Urban, Division of Human Genetics, University of the Witwatersrand, Johannesburg, personal communication, 2005).

The Global Distribution of Specific Birth Defects > Individual Teratogen-Associated Birth Defects > Congenital Infections >

HERPES SIMPLEX VIRUS

Herpes simplex virus type 2 (HSV-2) can cause genital infection and can be passed to the fetus by the mother in utero, during birth and postnatally. Fetal HSV infection is most commonly acquired during delivery in women who are newly infected (Brown et al., 1997). Unfortunately, many women are asymptomatic with no evidence of genital lesions at the time of primary infection complicating control efforts.

HSV infection in the newborn can present as isolated skin, eye, or mouth infection or as disseminated disease with CNS involvement that can result in in microcephaly, intellectual disability and seizures. Mortality rates as high as 25 percent have been reported for disseminated disease. Morbidity is also high. While 95 percent of newborns with isolated infection are normal at two years of age, only 60 percent of newborns who survive disseminated disease are normal at that age. (Whitley et al., 1991).

HSV infection in the form of genital herpes is of major public health importance in many lower-income countries (Carrey and Handsfield, 2000). Maternal HSV seroprevalences of greater than 50 percent have been documented in specific populations in Central America, Africa and Asia (Ghebrekidan et al., 1999; Kaur et al., 1999; Nahmias et al., 1990; Oberle et al., 1989).

The Global Distribution of Specific Birth Defects > Individual Teratogen-Associated Birth Defects >

MATERNAL ILLNESS AND ALTERED MATERNAL METABOLISM

MATERNAL INSULIN-DEPENDENT DIABETES MELLITUS

Maternal insulin-dependent diabetes mellitus (IDDM) during pregnancy can cause birth defects. It affects 0.5 percent of pregnancies in high-income countries (Khoury et al., 1989) and increases the risk of serious birth defects up to three-fold. The risk of fetal abnormalities due to maternal IDDM can be reduced by good peri-conception diabetic control. Unfortunately, poor control of diabetes is common in developing countries. A 1997 study in Libya showed that 13.8 percent of infants of mothers with insulin-dependent diabetes mellitus had easily recognizable birth defects, compared to three percent in the non-diabetic maternal population (Mir et al., 1992).

The Global Distribution of Specific Birth Defects > Individual Teratogen-Associated Birth Defects > Maternal Illness and Altered Maternal Metabolism >

MATERNAL EPILEPSY

Children of epileptic mothers have a greater risk for birth defects than is seen in the general population. Risk of major malformations, growth retardation and hypoplasia of the midface and fingers, known as anticonvulsant embryopathy, increases in infants exposed to anticonvulsant drugs in utero, including sodium valproate and phenytoin. In developing countries, the fetus of an epileptic mother is at even greater risk

because anti-epileptic therapy is less likely to be well-controlled, multiple drug therapy is more common, and cheaper drugs, more likely to cause fetal damage, are used in place of more expensive, less teratogenic anticonvulsant drugs (Shorvon and Farmer, 1988)

MATERNAL MALNUTRITION

Folic acid

Overwhelming evidence links an increased intake of synthetic folic acid (the more bioavailable form of folate) to a reduced risk of neural tube defects. Research indicates that at least half the cases of neural tube defects could be prevented if women consumed sufficient folic acid before conception and during early pregnancy (CDC, 2005). These and other findings lent support to the 1992 recommendation by the U.S. Public Health Service and 1998 recommendation of the Institute of Medicine of the U.S. National Academies that all women of childbearing age should consume 0.4 mg (400 μg) of synthetic folic acid daily, in addition to folate provided by a varied diet, in order to reduce their risk of a neural tube defect-affected pregnancy (DHHS, 1992; IOM, 1998).

Because neural tube defects result from early failure of neural tube closure, which occurs before pregnancy can be confirmed, women who are capable of becoming pregnant should consume folic acid daily to ensure that body levels are adequate before and after conception. If a woman has already had a baby with an neural tube defect, studies have shown that a larger daily dose of folic acid (4,000 μg or 4 mg), beginning at least one month before pregnancy and throughout the first trimester, reduces the risk of having another affected pregnancy by about 70 percent. Women with diabetes, epilepsy on treatment with sodium valproate and, possibly, obesity also are at increased risk of having a baby with a neural tube defect and should discuss the possibility of taking the higher level of folic acid with their primary care provider (MOD, 2004; MRC Vitamin Study Research Group, 1991).

An increasing body of evidence suggests that folic acid may help prevent other major malformations, including congenital heart defects as well as coronary heart disease, certain forms of cancer and possibly dementia (Canfield et al., 2005; La Vecchia et al., 2002; McIlroy et al., 2002; Wald et al., 2002).

Iodine

UNICEF considers iodine deficiency the single most important cause of preventable brain damage and intellectual disability, with most cases caused before birth (UNICEF, 1998). Iodine deficiency is common in inland, arid and mountainous regions. It causes spontaneous abortion, perinatal death and childhood intellectual, motor, and auditory disabilities (iodine deficiency disorder), with the severity depending on the level of maternal deficiency. Severe iodine deficiency through the second and third trimesters of pregnancy results in severe congenital hypothyroidism. Morbidity from iodine deficiency disorder has been significantly reduced since 1990 due to ongoing global efforts to fortify salt with iodine (IOM, 1998). Despite these efforts, though, in 1998 an estimated 60,000 babies were born worldwide with severe congenital hypothyroidism and an estimated 28 million pregnancies were still at risk from maternal iodine deficiency (UNICEF, 1998). In total, UNICEF estimates that 50 million people worldwide live with intellectual, motor and hearing disability due to iodine deficiency disorder (UNICEF, 2000).

RECREATIONAL AND THERAPEUTIC DRUGS

ALCOHOL

Fetal alcohol spectrum disorder

Fetal alcohol spectrum disorder (FASD) encompasses a range of effects that can occur in an individual whose mother drank alcohol during pregnancy (SAMHSA, 2005). These effects, which can

range from mild to severe, include physical, behavioral, mental and learning disabilities with lifelong implications for affected individuals. The only cause of FASD is alcohol use during pregnancy and no threshold for safety is known.

The following major conditions are included under FASD (Hoyme et al., 2005).

- Fetal alcohol syndrome (FAS)—the affected child has the characteristic pattern of facial anomalies (smooth philtrum, small palpebral fissures and thin upper lip), pre- and post-natal growth retardation and evidence of deficient brain growth or abnormal brain development (structural brain anomalies and/or circumference of head below the 10th percentile). The latter results in neurological, behavioral and cognitive deficits.

- Partial FAS—The child has the characteristic pattern of facial anomalies and evidence of one of three other complications: 1) pre-and/or postnatal growth retardation; 2) deficient brain growth or abnormal brain development; 3) a complex pattern of behavior and cognitive (learning) abnormalities.

- Alcohol-related neurodevelopmental disorder (ARND)—confirmed alcohol exposure and one of either evidence of deficient brain growth and abnormal brain development or evidence of a complex pattern of behavior and cognitive abnormalities.

- Alcohol-related birth defects (ARBD)—confirmed alcohol exposure and evidence of the characteristic pattern of facial anomalies and other minor dysmorphic anomalies, in addition to possibility of one or more of the congenital structural defects of the heart, skeleton, renal system, eyes or ears associated with alcohol exposure.

In Seattle, Washington, the prevalence of FAS/ARND for the period 1975-1981 was estimated to be 9.1 per 1,000 live births (Sampson et al., 1997). FAS, the most recognized condition in the spectrum, was estimated to occur in 0.5-2 per 1,000 live births in the United States in the 1980s and 1990s, outranking Down syndrome and autism in prevalence (May and Gossage, 2001; SAMHSA, 2005).

The prevalence of FAS appears to be much higher in certain other regions of the world. In the wine-growing Western Cape Province of South Africa, more than a quarter of pregnant women abuse alcohol during pregnancy and more than 4 percent of six to seven year-old school children had FAS (the highest rate ever reported for a stable community). Comparable studies in urban Johannesburg found 2.7 percent of children had fetal alcohol syndrome (Croxford and Viljoen, 1999; May et al., 2000; Viljoen et al., 2003). This finding has raised concern about the prevalence of FAS in other middle-and low-income countries where alcohol is available and used by women of reproductive age (Rosenthal et al., 2005).

THERAPEUTIC DRUGS

A number of therapeutic drugs have been implicated as teratogens and their adverse effects linked to the timing of use during pregnancy, dose, genetic susceptibility and other factors (IOM, 2003). These drugs include thalidomide (which causes severe limb reduction birth defects and was formerly used to combat morning sickness, but is also used to treat leprosy, macular degeneration in AIDS and psoriasis); misoprostal (an anti-gastric ulcer medication that is used illegally to induce early abortion, and is linked with several birth defects associated with vascular disruption); anticonvulsant drugs (associated with major malformations, including neural tube defects, microcephaly, intellectual disability, growth restriction, and malformations of the face and fingers); and anticoagulants (linked to nasal hypoplasia, stippling

of bones, optic atrophy, microcephaly, growth and intellectual disability, and fetal and neonatal hemorrhage) (Adab et al., 2001; Arpino et al., 2000; Castilla et al., 1996; Coelho et al., 2000; Gonzales et al., 1998; Grover et al., 2000; Hardman et al., 1996; Holmes et al., 2001; Koren et al., 1998; Orioli and Castilla, 2000; Samren et al., 1999; Vanchieri, 1997; Vargas et al., 2000).

These medications are cause for concern in middle- and low-income countries where use is less regulated. They are often readily available across the counter, multiple drug use is common, awareness of their teratogenic potential is lacking and most women are unaware of their pregnancy during the first few weeks. (Penchaszadeh, 2002). Recent research in South Africa revealed that 52 percent of women with heart valve replacements who received sodium warfarin anticoagulation had poor obstetric or fetal outcomes due to the poor coordination of the services needed to provide these women with appropriate information and care (Dr. N. Gregersen, Division of Human Genetics, University of the Witwatersrand, Johannesburg, personal communication, 2005).

The Latin American Collaborative Study of Congenital Malformations (ECLAMC) reported that 33 infants with limb defects due to thalidomide were diagnosed in its current network of 84 hospitals in South America and that, in Brazil alone, a third of mothers of infants with malformations due to disruption of blood flow to limbs and organs had used misoprostal during their pregnancy (Castilla et al., 1996). The true scale of such problems in middle- and low-income countries is currently unknown and will only become evident when additional birth defects surveillance systems like ECLAMC are in place.

SERVICES FOR CARE AND PREVENTION OF BIRTH DEFECTS

Medical Genetic Services

"Care is an Absolute. Prevention is the Ideal"
(Christianson et al., 2000)

The purpose of medical genetic services is to assist people with a genetic disadvantage, those with a birth defect or at risk of having children with one, to live and reproduce as normally as possible. Therein their objectives are to care for those with a disorder in order to reduce suffering and to improve health by prevention. The need for medical genetic services to integrate components for both the care and prevention of birth defects is clear and implicit in this purpose (Modell and Kuliev, 1998; WHO, 1985, 1999). Services for care and prevention of birth defects are often regarded as discrete entities and, when raised in the context of developing health policy for many middle- and low-income countries, the need for prevention is usually given priority over the requirement for patient care.

The first deep concern of patients, parents and primary health care providers is to acquire the best possible care. To achieve this has implications for the individuals and their families. These include the cost of care they may have to pay for, cost of transport to and from medical facilities for a disabled child, and the potential loss of earnings of a caregiver. The costs of care for patient and family are high in high-income countries, but they can be crushing to families and their communities in middle- and low-income countries where effective systems of care and social support are not yet in place (WHO, 1985).

Care for people with chronic disorders and disability is generally expensive for any country. The costs are due mainly to drugs, biological and technical products used in diagnosis and treatment. The patents for these products are almost exclusively held in high-income countries where many also are manufactured. Middle- and low-income countries are generally capable of providing, and funding at local prices, the human resources needed for these medical services, but they are inhibited by the cost of specialized materials, particularly medication, bought at international prices. This is epitomized by the current global crisis in patenting, producing and providing medication for those suffering from HIV/AIDS (WHO, 2000a).

Care for children with birth defects is no different. The cost of care of fetal alcohol syndrome in the United States is illustrative. In 2000, a child born with the syndrome was estimated to cost the health care system a total of $5 million over his or her lifetime. Overall, the U.S. government calculated the annual cost of fetal alcohol syndrome to be $3.3 billion, including $2.1 billion for treatment and $1.2 billion for special education and juvenile justice (Kellerman and Kellerman, 1995).

The societal costs for a child with spina bifida in the United States are estimated to be $760,000 per year, including $300,000 in medical expenditures. The cost of prevention by fortifying the food supply with folic acid is calculated to be about $10 million per year. Since fortification prevents an estimated 500-550 cases of spina bifida each year, the overall savings is approximately $400 million annually, including $158 million in direct medical expenditures (Waitzman et al., 1996).

The cost of care in middle- and low-income countries is illustrated by the example of Iran's thal-

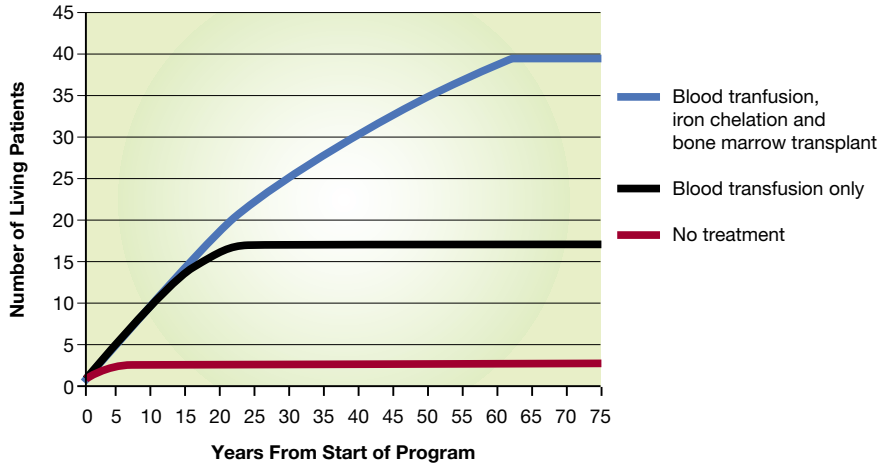
assemia treatment program before the implementation of a comprehensive prevention policy. As Figure 9 demonstrates, treatment for people with ß-thalassemia can be highly effective in extending life. The red line indicates the very limited survival expected with no treatment. These patients usually survive less than two years; thus, the cumulative number of living patients is twice the annual number born based on a theoretical birth prevalence of one affected birth per year. In the 1950s, regular blood transfusions, which were known to improve survival, were initiated as a treatment for ß-thalassemia. Because repeated blood transfusions lead to death from transfusion iron overload at a median age of 16 years, the cumulative number of living patients who received regular transfusions stabilized at 16 times the annual number born. This is indicated by the black line. Starting in the mid-1970s, treatment included nightly injections under the skin of the iron-chelating agent, desferrioxamine. Bone marrow transplantation (BMT) became available as a form of therapy in the mid-1980s. The addition of these two treatments improved survival to more than 40 years, with the result that the number of patients requiring treatment stabilizes at at least 40 times the annual number born. This is indicated by the blue line.

Figure 9 demonstrates that as treatments improve, the number of surviving patients and, as a result, the costs of treatment incurred by these patients increase. In the example of Iran, the cost of patient care with no treatment (red line) was small. Costs based on 1997 prices rose to $2,400 per patient per year for transfusion treatment alone (black line) and to $17,250 per patient per year for current conventional treatment (blue line). By 1992, 15,000 people with thalassemia were living in Iran, compared with the estimated 2,000 who were alive in the 1970s when no system of care was in place. By 2000, the costs of treatment of ß-thalassemia, including medication, were at least $17,250 per person annually or $259 million for the nation as a whole. The experience in Iran suggests that the cost of treatment for ß-thalassemia may be too high for many middle- and low-income countries with limited health budgets (Christianson and Modell 2004; WHO, 2000a).

For policy and health care planners considering medical genetic services, data like those in Figure 9 appear to favor prevention over care. This has led to the common belief that care services are expensive and beyond the resources of most low- and middle-income countries, while preventive services are comparatively low in cost and, if effectively applied, reduce the necessity for care (Christianson and Modell, 2004; WHO, 1999, 2000a). The authors believe that this unquestioned belief that prevention in low- and middle-income countries is feasible while

figure 9

Increasing patient survival with treatment for ß-thalassemia



Estimated increase in patient numbers with three treatment regimes for ß-thalassemia, based on a theoretical birth prevalence of one affected birth per year. SOURCE: Christianson and Modell, 2004.

care is not is unethical as it denies children with birth defects affordable and needed care. It is also unrealistic as experience has shown that unless prevention is offered in the context of care programs, it will likely be regarded with suspicion and rejected by target communities.

In addition, the concept that ignoring birth defects and not offering care for them has no cost is naive. Each year in South Africa, for example, about 2,300 infants with Down syndrome will enter the health care system. Only one-third (approximately 760) of these children will live beyond the age of two years. Assuming conservatively that these children live to an average age of five years, and given that the annual cost of basic care, without cardiac surgery, for a child with Down syndrome was approximately $3,000 in 2001 (National Department of Health, 2001), the estimated cost of caring for each annual cohort of these children totals $16 million—a substantial sum for just one birth defect in a financially-constrained health system.

Successful care does not negate the desire of individuals, communities and countries for programs to ensure the birth of healthy children without birth defects. It is the experience of the authors that when offered appropriate care for their child with a birth defect, parents will request strategies for birth defect prevention from health care providers. When developing clinical genetic services in South Africa's rural Northern Province, care was offered along with a counseling process that provided risk assessment and management. Once the service was accepted by the community, requests were received from the community for prenatal diagnosis. In Iran, a similar demand for prenatal diagnosis services from couples at risk of having a child with ß-thalassemia became clear when an audit of the ß-thalassemia screening program was undertaken (Christianson et al, 2000; Samavat and Modell, 2004).

The tension described between care and prevention is futile. Care must be balanced with prevention. The credibility of medical genetic services depends on commitment to care, both within the service and among the public. If care and prevention are provided simultaneously, the success of prevention can help counterbalance the cost consequences of care, and make it more available. People with disability, including those with congenital disability, are fellow human beings and one measure of our humanity, and the trust of the population in medical services, will depend on how well this situation is addressed.

Medical Genetic Services >

CARE

Most middle- and low-income countries do not have the robust tertiary services that high-income countries had in the 1960s when they began developing medical genetic services. Already within those services were the components needed to offer care for people with serious birth defects. That is not currently the situation in many middle- and low-income countries. They have yet to develop most of the services needed for care for birth defects, especially for common conditions, within their primary and secondary health care systems. Ironically, industrialized countries now also recognize the need to embed care for the more common birth defects in their primary health care systems. These countries do not have uniformly equitable, accessible medical genetic services since ethnicity, language, culture, religion, poverty and geographic location act as barriers to the universal provision of services. Thus, under-served populations in high-income countries also need an integrated, holistic approach to the introduction and development of services for the care and prevention of birth defects (Christianson and Modell, 2004; Paul and Kavanagh, 1990; WHO, 1985, 1999).

This recognition is spurred, in part, by a growing acceptance that the provision of care is the right of all people with disabilities, as well as an increased aware-

ness that such care is not necessarily expensive and beyond the reach of national economies. The best possible care available needs to be provided in the existing circumstances. This recognizes that, within and across countries, levels of available care differ, but that the best possible care must be offered. Once initiated, the level of care will improve as financial resources and education, training and capability of staff improve and, with audit and experience, the system upgrades. Experiences in a number of countries, including Cuba, Iran, Nigeria and South Africa, bear testimony to the success of this approach (Akinyanju et al., 2005; Christianson and Modell 2004; Christianson et al., 2000; Heredero, 1992; WHO, 1985, 2000a) (*see Box 1 on page 46*).

Medical Genetic Services >

PREVENTION

There are three levels of prevention.

Primary prevention seeks to ensure that individuals are born free of birth defects by being conceived normally and not being damaged in the early embryonic period—i.e., the first eight weeks after conception when the mother is not aware she is pregnant. Services for the primary prevention of birth defects include basic reproductive health approaches, which should be part of established women's, maternal, newborn and child health services in all middle- and low-income countries. These include: family planning; optimizing women's diets; detecting, treating and preventing maternal infections; optimizing women's health through the control of such diseases as insulin-dependent diabetes mellitus and epilepsy; and pre-conception screening for common recessive disorders. Examples of specific interventions include folic acid supplementation to prevent neural tube defects, rubella immunization to prevent congenital rubella syndrome, and programs to educate women of child-bearing age about the dangers of alcohol intake in early pregnancy. With its emphasis on ensuring normal conception and early pregnancy, primary prevention is the most important of all three levels.

Secondary prevention aims to reduce the number of children born with birth defects. This is achieved through medical genetic screening and prenatal diagnosis where birth defects are detected and the couple offered genetic counseling and therapeutic options. To make informed decisions affecting the outcome of pregnancy, parents need the best information available about their specific set of circumstances. This includes the diagnosis, if possible, affecting their fetus; the cause; the consequences for the fetus, available options for treatment and prognosis as far as this is available; and the risks for recurrence and whether this might be reduced. Secondary prevention requires prenatal diagnosis, which must be accompanied by genetic counseling that includes descriptions of the tests available, with their scope and attendant risks.

The March of Dimes maintains a policy of neutrality on the issue of abortion. If termination of pregnancy is discussed with parents in the course of prenatal care, this discussion must be within the limits of the legal terms of reference of the country. Health care providers must not give directive or coercive advice, are obliged to respect the religious and moral beliefs of the parents, and should abide by and support their decisions.

Tertiary prevention is directed toward the early detection and cure and amelioration of problems once a child with a birth defect is born. Interventions include early recognition and diagnosis, including newborn screening if available, medical treatment of complications, surgical repair of congenital malformations such as cleft lip and palate and heart defects, and offering neurodevelopmental therapy programs to infants and children with disability. It also includes palliative care for children dying from the consequences of their birth defects. In middle- and low-income countries, as much as possible of the medical treatment, neurodevelopmental therapy and palliative care needs to be managed in primary health

care settings (Christianson and Modell, 2004; Christianson et al., 2000; WHO, 1985, 1999).

Implementation of the recommendations in this report would strengthen all three levels of prevention. These recommendations include: training of physicians, nurses and allied health professionals in the causes and identification of birth defects and in medical genetics; promotion of parent/patient support groups to promote research and attention to care and prevention; and education of the public and of policy makers, the media and other stakeholders about birth defects and the means for effective care and prevention. As noted earlier, up to 70 percent of birth defects may be prevented, cured or ameliorated with the use of this full armamentarium of care and prevention (*see Table 5*).

Historical Aspects of the Development of Medical Genetic Services

In 1959, WHO initiated the world's first international study of the frequency and distribution of birth defects (Stevenson et al., 1966). Dr. Victor McKusick, the renown medical geneticist, also considered 1959 to be the birth-year of the discipline of clinical genetics (McKusick, 1975).

The period also provided a milestone in the industrialized world's health transition, as noted by the then Director General of WHO, Marcolino Gomes Candau, in an address in 1963. Candau stated that "with increasing control of infant mortality and infectious diseases, inherited abnormalities are assuming a proportionately greater importance in medical practice" (WHO, 1964). These beginnings heralded the emergence of medical genetic services.

Medical genetic services in high-income countries were initially developed in academic medical institutions within specialties like pediatrics, obstetrics, hematology and neurology. The growing need for accurate clinical and laboratory diagnosis of rare and complex birth defects led to the development of specialized medical genetic services. These focused primarily on diagnosis and genetic counseling for patients and their families, while treatment was largely left to clinicians from other medical disciplines. The result was a fragmented service with little

table 5 ***Relative contribution of different methods of prevention of birth defects***

Group of Disorders	Birth Prevalence (per 1,000 live births)	Intervention (Primary, Secondary, Tertiary)	Maximum Postnatal Lives Saved (per 1,000 live births)	Maximum Reduction %	Estimated Average Increase in Longevity Per Head of Population (Years)
Congenital Malformations	36.5	Pediatric Surgery (3°)**	17.70	48.5	1.24
		Folic Acid Supplement (1°)**	11.50	31.5	0.81
		Prenatal Diagnosis (2°)**	3.50	9.6	0.25
		Total Congenital Malformations:	**32.70**	**89.6**	**2.30**
Chromosomal Disorders	3.8	Family Planning (1°)**	0.75	19.7	0.05
		Prenatal Diagnosis (2°)**	0.50	13.2	0.04
		Total Chromosomal Disorders:	**1.25**	**32.9**	**0.09**
Genetic Risk Factors*	2.4	Routine Antenatal and Neonatal Care (3°)**	2.40	100.0	0.17
Inherited Disorders (severe, early onset)	11.5	Genetic Counseling (1°)**	1.73	15.0	0.12
		Neonatal Screening (3°)**	0.70	6.1	0.05
		Prenatal Diagnosis (2°)**	1.15	10.0	0.08
		Total Inherited:	**3.60**	**31.1**	**0.25**
TOTAL:	**54.2**		**39.9**	**73.7**	**2.80**

G6PD deficiency and Rhesus hemolytic disease of the newborn* * 1° = Primary prevention* *2° = Secondary prevention* *3° = Tertiary prevention*

SOURCE: Christianson and Modell, 2004.

contact with public health and community-based services, in which diagnosis resided in one department and care was either spread through a range of others or provided through disease-specific services, such as those for cystic fibrosis, hemoglobin disorders, hemophilia and metabolic disorders, in addition to medical genetic services for other birth defects (Christianson and Modell, 2004; Penchaszadeh, 1992; Pyeritz et al., 1987). Recently, however, it has been recognized that care and prevention of birth defects requires a more integrated approach. Together with advances in the field of common disorders with a genetic predisposition such as cancer genetics, increasing costs of medical genetic services and rising public demand for services, this recognition is leading to growing integration of medical genetics into all fields of medicine, including primary health care (Harper et al., 1996).

The role of medical genetic services, and their relationship to public health and primary health care, was initially examined by WHO in 1981. WHO recognized early that changes in national health profiles (the health transition) were beginning to occur in middle- and low-income countries and would eventually drive the need for medical genetic services in these countries. WHO also understood that the existing fragmented models for medical genetic services in high-income countries were not appropriate for middle- and low-income settings and that care and prevention of birth defects in these countries required a public health approach firmly rooted within the primary health care system (WHO, 1985).

Subsequent WHO initiatives further developed the concept of medical genetic services to include community genetic services and those for specific birth defects such as hemoglobin disorders and G6PD deficiency (Modell et al., 1992; WHO, 1989, 1994). In 1997, the Eastern Mediterranean Regional Office of the WHO published the results of their deliberations on developing medical genetic services in the region, and therein expanded the concepts of community genetics (Alwan and Modell, 1997). Subsequently, in 1999, WHO partnered with a March of Dimes affiliate, the World Alliance of Organizations for the Prevention of Birth Defects, to further address the problem of birth defects in developing countries. Together, they reviewed the known epidemiology of birth defects, the stage in development at which countries needed to introduce medical genetic services, the relative roles of care and prevention, the appropriate application of knowledge and technology to these purposes and the financial implications of medical genetic services. They identified the need to integrate medical genetic services into primary health care and to further integrate these with secondary and tertiary medical genetic services; reproductive; obstetric; pediatric and other medical and social services. WHO and the World Alliance also considered how this could be achieved within the limits of local circumstances, customs, available manpower and material resources (WHO, 1999).

WHO revisited the issue of medical genetic services in developing countries in 1999. These deliberations produced a document detailing how countries could develop a program to assist them in initiating and developing their services (WHO, 2000a).

One issue that remained unresolved despite these efforts was the appropriate time to initiate medical genetic services in middle- and low-income countries. The toll of birth defects in these countries, demonstrated for the first time systematically in this report, point to an immediate need, with each country carefully considering its requirements and resources and what services to implement. Thus, the time to act is now.

The Control of Birth Defects

In 1985, when WHO defined the aim of medical genetic services as helping people with a genetic dis-

advantage to live and reproduce as normally as possible, it recognized that to live normally, people with a genetic disadvantage require services for care and that to reproduce normally, they require services for prevention. Addressing care and prevention simultaneously, therefore, required "an integrated strategy combining best possible patient care, with prevention by community education, population screening, genetic counseling and the availability of prenatal diagnosis". The term used to define such an integrated strategy was the "control" of birth defects. (Modell and Kuliev, 1998; WHO, 1985).

Because multiple approaches are needed for care and prevention, these issues are difficult to conceptualize as part of the whole. Success is most likely, however, when integrated public health policies for care and prevention of birth defects are implemented, as they have been in Iran (*see Box 1 page 46*). Ministries of Health must include one or more trained personnel who can act as advocates for these services and facilitate their appropriate coordination with existing services—for example, women's and children's health, family planning, immunization, and nutrition.

The following section describes individual strategies. The process by which they can be developed into integrated policy adapted to current country situations was outlined in the 2000 WHO report on primary health care approaches for care and prevention of birth defects (WHO, 2000a).

Care of Patients with Birth Defects

The care of patients with birth defects is challenging. All people with birth defects, and their families, are entitled to expect the best possible patient care available to them in their circumstances (Modell and Kuliev, 1998; WHO, 1985, 1999). Currently, limited facilities make the provision of effective care particularly difficult in middle- and low-income settings.

RECOGNIZING BIRTH DEFECTS

Even in specialized tertiary centers, diagnosing birth defects is not always easy.

For primary health care workers, most of whom have little or no formal education or specialized training in medical genetics, the task is especially daunting. However, primary care practitioners can be trained to recognize birth defects using the tools of medical diagnosis—a full personal, family, birth and past medical history, physical examination and laboratory tests. With appropriate training, primary health care practitioners are capable of documenting and interpreting a three-generation family tree, a necessity for diagnosing birth defects. Many physical signs of birth defects (dysmorphic features) and malformations are externally obvious, so their detection and contribution to diagnosis can be demonstrated and taught. Laboratory testing may be expensive, so its use should be carefully regulated according to local guidelines (Christianson and Modell, 2004; Christianson et al., 2000).

With this rudimentary training, primary care practitioners will be able to:

- Suspect or recognize that a particular clinical problem is a birth defect

  Early recognition of birth defects is important. In the case of an infant born with an external malformation(s), obvious dysmorphic features or a family history of a disorder, the problem is obvious. It is more challenging when the infant or child has internal structural malformations such as a congenital heart defect, a functional abnormality such as congenital hypothyroidism or non-syndromic deafness, or few dysmorphic features.

- Suspect or identify any disabilities that their patient may have as a result of a birth defect

  This is important as treatment, genetic counseling and psychosocial support can be offered in many cases even without a definitive diagnosis.

- Make a definitive diagnosis when possible

  This should be possible for most common birth defects. Accurate diagnosis allows practitioners to plan further care, taking into account the circumstances of the family, community and medical services. The general principle is that as much care as possible should take place close to the patient's home and so should be undertaken in a primary health care setting. Referral should be contemplated only when a diagnosis is not possible or when further management, such as pediatric surgery, will improve the prognosis.

Care of Patients with Birth Defects >

TREATMENT

Availability of treatment for birth defects—both medical and surgical—depends on the level of health care in a country. It is important to stress however, that in middle- and low-income countries, basic cost-effective medical treatment is possible and within the scope and ability of primary health care (Christianson and Modell, 2004; WHO, 1999) (*see Box 1 page 46*).

Surgery can cure or lessen the effects of many potentially lethal or disabling birth defects, like cleft lip and palate, bowel atresia, squint, cataracts, club-foot and congenital heart defects (Czeizel and Sankanarayanan, 1984; WHO, 1996). The contribution to reducing mortality and morbidity of this aspect of the treatment is largely underestimated. Primary health care practitioners are capable of recognizing these problems and referring them appropriately. Secondary and tertiary services are responsible for ensuring that they have the equipment, facilities and staff trained to undertake the appropriate surgery and post operative care. More specialized surgery, like cardiac surgery for complex heart defects, may not be available. If it is, it may still not be offered to some children, such as those with Down syndrome, because of competing priorities.

Habilitation for people with birth defects through neurodevelopmental therapy—speech, occupational and physiotherapy—is an important component of treatment that can reduce levels of disability. Other specific forms of therapy, such as stomal therapy for the incontinent, may also be necessary. In middle- and low-income countries, availability of this expertise is often limited, but community-based habilitation may be substituted. With this strategy, parents and community members are trained and then use local resources to assist the disabled to integrate into society (Helander et al., 1989). The involvement of primary health care practitioners is inherent in this process.

Care of Patients with Birth Defects >

GENETIC COUNSELING WITH PSYCHOSOCIAL SUPPORT

Genetic counseling is an essential component of medical genetic care. It offers people with or at risk of developing a birth defect and their family members information on the nature, cause, available treatment and prognosis of the birth defect. It also provides information on the risk of recurrence and ways of reducing this risk (Harper, 2004). The aim of genetic counseling is to empower those who are counseled to make autonomous decisions regarding their health in ways that are consonant with their religious and ethical beliefs and circumstances, and to support them in their decisions. For this to happen, the correct information must be delivered in an empathetic manner that is non-directive and clearly understood by those counseled.

In high-income countries, genetic counseling usually is provided by medical specialists and spe-

box 1

The feasibility of care in middle- and low-income settings.

When considering care as a component of medical genetic services in middle- and low-income countries, cost is often cited as a rationale to apply resources elsewhere. However, there are examples that illustrate the feasibility of care to save or enhance the lives of people with birth defects in middle- and low-income settings, sometimes at limited cost.

Sickle Cell Care in Nigeria

Akinyanju and colleagues studied the effects of very basic comprehensive care on mortality and morbidity rates of patients with sickle cell anemia in Lagos, Nigeria, for the years 1988-1995. As a first step, nurses were trained in patient counseling and taught a broad range of therapies applicable to care. They were then encouraged to run a specialized Sickle Cell Clinic and an associated branch of a local support and advocacy group known as the Sickle Cell Club in the Apapa District of Lagos. Both sites provided an interactive, friendly environment for patients and their families. Therapies included preventive health and nutrition education, prompt treatment of illness and free supplies of vitamin supplements, antimalarial drugs and other necessary medications. One preventive health measure taught was to encourage patients to carry a water bottle to ensure they maintained adequate hydration at all times. Over the study period, the number of patients enrolled increased from 290 to 1,223. Mortality rates fell from 21 to 0.6 percent per year, the annual number of hospital admissions decreased from 350 to 25, and the number of patients transfused with blood fell from 260 to 25 for the years 1998 and 1995, respectively. The study demonstrated that the provision of comprehensive, well-organized and family-oriented care not only significantly reduces illness and deaths and improves the quality of the lives of people living with sickle cell disease, but also reduces demand for hospital care (Akinyanju et al., 2005).

Thalassemia Care in Iran

Another example involved the treatment of children with thalassemia using blood transfusions and iron chelating agents begun in Iran in the 1970s. Approximately 1,200 infants with thalassemia were being born annually at that time. By 1992, 15,000 people with thalassemia were living in Iran, in contrast to the approximate 2,000 projected to be alive if no care system were available. This success is testament to the program's effectiveness in extending healthy life. The success stimulated development of a bone marrow transplantation service for individuals with thalassemia and, as a spin-off benefit, for patients with other conditions requiring bone marrow transplantation. The initial costs were relatively low when there were few patients in the program, but costs rose with the increasing success of the program as more patients lived longer. This, in time, raised the profile of the disorder sufficiently to establish a national thalassemia prevention program (Samavat and Modell, 2004; WHO, 2000a).

cialist genetic counselors. Genetic counseling requires sensitivity to the ethical, social and legal situation in the country as well as to the social, religious and educational background of those being counseled. Primary health care practitioners, often nurses, live in close proximity to, speak the language and understand the customs of and are respected in the communities they serve. Thus, they are eminently suited, after appropriate training, to provide genetic counseling in middle- and low-income settings (Alwan and Modell, 1997; Christianson et al., 2000; WHO, 1998).

The serious lifelong implications of birth defects require continuing psychological, emotional and social support. Early death from birth defects is common in middle- and low-income countries, so primary health care practitioners undertake much of the terminal/palliative care including counseling and psychosocial support. Invaluable backing for this role can be available from patient/parent support groups and their participation should be actively sought in the process (Christianson and Modell, 2004; Penchaszadeh, 2000; WHO, 1999).

Prevention of Birth Defects

The control of infectious diseases in high-income countries occurred largely as a result of primary prevention through basic public health measures, such as improved sanitation, provision of clean water and education of the public (Garrett, 2000). The potential of primary prevention for reducing the birth prevalence of many birth defects is also great. Prevention of birth defects depends on risk identification and management through community and health service personnel education, population screening, genetic counseling and the availability of appropriate services. Elements of effective preventive services include basic reproductive health services and medical genetic screening (Christianson and Modell, 2004; Penchaszadeh, 2002; WHO, 2000a).

box 2

The Power of Prevention: Family planning and reducing the birth prevalence of Down syndrome.

In Western Europe in the early 1950s, an average 20 percent of pregnant women were over 35 years of age, and Down syndrome birth prevalence was close to 2.5 per 1,000 live births. With increasing user-friendly family planning, births to women of advanced maternal age fell to around five percent by 1980, with an associated fall in the birth prevalence of Down syndrome to less than 1.5 per 1,000 live births (Modell et al., 1992). As a result of social and economic change, the proportion of older mothers has subsequently risen to 11-18 percent depending on country. This would formerly have entailed a Down syndrome birth prevalence of 1.6-2.2 per 1,000 live births. However, in the years 1995-2000 in most of Western Europe, approximately 50 percent of affected pregnancies were terminated following prenatal diagnosis, and the prevalence of Down syndrome remains low at 0.8-1.1 per 1,000 live births (EUROCAT, 2002).

Prevention of Birth Defects >

BASIC REPRODUCTIVE HEALTH APPROACHES

Basic reproductive health approaches are primary prevention strategies to prevent birth defects. By their nature they have relatively few associated ethical, legal or social issues. They are integral to all functional health services for women. Thus, training of primary health care personnel and education of the community are essential.

Prevention of Birth Defects > Basic Reproductive Health Approaches >

FAMILY PLANNING

Available and accessible family planning can reduce the burden of birth defects. Enabling couples to space pregnancies and plan family size results in fewer children being born and, therefore, fewer children born with birth defects. In countries where fertility is high, reducing family size to two to three children can reduce the birth prevalence of single gene defects by 40–50 percent. Couples with one child with an inherited disorder who have been informed of the high recurrence risk have the choice of limiting their family size. Smaller family size is also usually associated with fewer babies born to women of advanced maternal age, which, in turn, reduces the birth prevalence of chromosomal disorders, particularly Down syndrome (*see Box 2*). In addition, family planning introduces women and their partners to the concept of reproductive choice, including the options of limiting family size or using prenatal diagnosis (Alwan and Modell, 1997; Penchaszadeh, 2002; WHO, 1999, 2000a).

Prevention of Birth Defects > Basic Reproductive Health Approaches >

OPTIMIZING WOMEN'S DIET

The serious consequence of maternal malnutrition on increased fetal loss and abnormality was documented in the study of the effects of the winter famine in Amsterdam and Rotterdam at the end of World War II (Smith, 1947). The recognition of the role of maternal nutrition in the prevention of birth defects such as neural tube defects and iodine deficiency disorder has confirmed the need for adequate women's peri-conception nutrition. The postulation

box 3

The Power of Prevention: Optimizing women's diet to prevent neural tube defects.

Supplementation with Folic Acid

The birth prevalence of neural tube defects in the northern provinces of China, approximately 6 per 1,000 births, has been among the highest recorded in the world. By comparison, the birth prevalence in provinces in southern China was about 1 per 1,000 births. Between 1993 and 1996, Beijing Medical University, in collaboration with the U.S. Centers for Disease Control and Prevention, conducted a large trial to assess the effectiveness of peri-conception folic acid supplementation on the birth prevalence of neural tube defects. A total of 247,831 pregnant women were registered in the trial. Women who took 400 mcg/day of folic acid had a significantly lower birth prevalence of neural tube defects. Rates were reduced from six to one per 1,000 births in the northern province and, from one to 0.6 per 1,000 births in the southern provinces (Berry et al., 1999; Moore et al., 1997).

Fortification of Wheat Flour with Folic Acid

Hertrampf and colleagues studied the impact of fortifying wheat flour, which is mainly consumed as bread, in the prevention of neural tube defects. Starting January 2000, the Chilean Ministry of Health legislated adding 2.2 mg of folic acid/kg of wheat flour at a national level to reduce the risk of NTD. This policy resulted in an estimated mean additional supply of folic acid of 427 mg/day and significant increases in serum folate and red cell folate of 3.8 and 2.4-fold, respectively, in women of fertile age one year after fortification (Hertrampf et al., 2003).

A prospective hospital-based study in Chile comparing birth prevalence of neural tube defects (anencephaly, encephalocele and spina bifida) between the time periods of January 1999 to December 2000 and January 2001 to June 2002 showed a 40 percent reduction in rates after the implementation of national folic acid fortification of flour in early 2000 (Hertramp and Cortés, 2004). Reduction of neural tube defect rates associated with folic acid food fortification in the region have also been reported by E. Castilla, J. Lopez-Carmelo and colleagues (Castilla et al., 2003; Lopez-Carmelo et al., 2005).

that fetal malnutrition can predispose to the development of disease in later life has caused significant recent interest in the long-term effects of fetal malnutrition (Barker, 1990; Godfrey and Barker, 2000).

Means of optimizing women's nutritional status include improving their general nutrition; ensuring they have adequate intake of specific micronutrients including folic acid, iodine and iron; and removing harmful substances from the diet, especially alcohol, which may damage the developing embryo or fetus. The peri-conception period (three months before and after conception) can be targeted by specific interventions such as folic acid supplementation for those planning a pregnancy. However, even in high-income countries, a large proportion of pregnancies are unplanned, making it impossible to target the peri-conception period. Therefore, all women need to be provided with adequate nutrition throughout their reproductive years. Policies including fortification of staple foods with folic acid, iodine and iron to prevent neural tube and other birth defects, iodine deficiency disorder and anemia, respectively, benefit the whole population and not just children and women of reproductive age.

FOLIC ACID

Consuming a daily multivitamin containing 400 μg of folic acid is the best way to ensure an adequate folic acid intake to prevent neural tube and other birth defects. However, providing folic acid supplementation to all women of childbearing age poses a major logistical challenge. In middle- and low-income countries, iron and folic acid supplementation reaches fewer than 30 percent of women (PAHO, 2004). Even in the United States, where there are aggressive promotional campaigns, only one in three (32

percent) women of childbearing age takes a vitamin with folic acid daily (MOD, 2003). For this reason, folic acid fortification of foods for mass consumption is considered an important strategy to increase folic acid levels in the population. Legislation for mandatory fortification of food staples exists in some, but not most, countries.

Box 3 provides two examples of successful programs to increase folic acid levels in target populations: one of supplementation in a high-risk population in China and one of a national fortification program in Chile.

Prevention of Birth Defects > Basic Reproductive Health Approaches > Optimizing Women's Diet >

IODINE

Iodine deficiency in pregnant women is a significant cause of miscarriage and impaired fetal neurological development. A global campaign by UNICEF to iodize salt has made significant inroads into this problem since 1990 (UNICEF, 1998) (*see Box 4*).

box 4

The Power of Prevention: Optimizing women's diet to prevent iodine deficiency disorder.

In 1990, UNICEF estimated that 120,000 infants were born with severe congenital hypothyroidism and that a further 40 million infants were born at risk of intellectual and auditory disability from maternal iodine deficiency. The means for preventing this had been available since 1922 when the Swiss, followed by other industrialized countries, introduced iodinated salt to prevent goiter. Sixty-eight years later, in 1990, UNICEF started a global campaign to introduce iodized salt. By 1997, when an estimated 67 percent of households globally consumed iodized salt, the number of infants born at risk from maternal iodine deficiency declined to 28 million and the number born with severe congenital hypothyroidism was halved. Further progress is needed, but the advances to date have been significant (UNICEF, 1998, 2003). This intervention is feasible in any country regardless of its economic level, and the campaign continues.

Prevention of Birth Defects > Basic Reproductive Health Approaches > Optimizing Women's Diet >

IRON

Iron deficiency is extremely common worldwide and is the most common cause of anemia among women and children. In response to increasing recognition of the importance of adequate iron nutrition for the health of women and children, WHO in 2001 produced a report summarizing recent evidence for the adverse effects of iron deficiency and iron deficiency anemia (WHO, 2001a). The iron balance of young infants is always precarious, and infants of iron deficient mothers often have inadequate iron stores and are at increased risk of morbidity due to iron deficiency. In young children, iron deficiency anemia is now known to delay psychomotor development and impair cognitive performance, effects that are not corrected by subsequent iron supplementation. There is also a direct relationship between iron deficiency anemia and physical energy. While the economic effects have been measured, little attention has been paid to the effects on the ability of women to carry out that most demanding of all physical tasks—to care for children effectively (IOM, 1998). Also practically no information exists on the effect of iron supplementation in pregnancy in developing countries on the subsequent physical and mental development and health of the child (WHO, 2000a). Together with UNICEF, WHO is currently mounting a global campaign promoting iron supplementation or food fortification in many lower-income countries; however, iron deficiency remains a neglected problem in many disadvantaged populations in high-income countries.

Prevention of Birth Defects > Basic Reproductive Health Approaches > Optimizing Women's Diet >

ALCOHOL

Improving pregnant women's diet must also include

removing exposure to teratogenic substances, the most important being alcohol. The scale of the problem caused by alcohol use and abuse in pregnancy is only now being recognized in many parts of the world.

Risk factors associated with maternal alcohol abuse include poor socioeconomic circumstances, poor education, malnutrition, advancing maternal age and gravidity, and binge drinking. These provide a starting point for identifying women at risk and offering intervention. Public and primary health care prevention programs to combat the use and abuse of alcohol during pregnancy are essential. They could be more effective and provide benefits beyond only preventing fetal alcohol spectrum disorder if combined with family planning and strategies for reducing sexually transmitted diseases, including HIV (May et al, 2000; Rosenthal et al., 2005).

Prevention of Birth Defects > Basic Reproductive Health Approaches >

PREVENTING, DETECTING AND TREATING MATERNAL INFECTIONS

Maternal infections likely to cause birth defects need to be avoided or prevented from occurring so that the woman and her fetus are not exposed to their consequences. If a pregnant woman does become infected, early detection and treatment, if possible, are the next priorities. If treatment and cure are not a possibility, counseling on the consequences of the infection for the pregnancy becomes mandatory. Syphilis and rubella have particular significance.

Congenital syphilis is entirely preventable by the use of penicillin, an inexpensive, effective drug that has been available for more than 50 years. Cost-effective means for the detection of syphilis are also available. The presence of congenital syphilis as a scourge in many middle- and low-income countries reflects the inadequate state of medical services in those countries. All countries should have services to control syphilis, especially its detection and treatment in women in the peri-conception and antenatal periods.

Congenital rubella syndrome (CRS) is wholly preventable by rubella immunization, which is cost-effective and should be a standard procedure within all primary health care services (*see Box 5 page 51*). Universal rubella immunization has resulted in virtual elimination of CRS in the United States, Canada, northern Europe and the English-speaking countries of the Caribbean. PAHO has slated CRS for elimination in the rest of the Americas by 2010 (Dr. Jon Andrus, Pan American Health Organization, personal communication, 2005). Other regional offices of WHO are addressing this issue and now we may expect rubella immunization to become routine in much of the world.

Prevention of Birth Defects > Basic Reproductive Health Approaches >

OPTIMIZING MATERNAL HEALTH

Other maternal health conditions and exposures known to increase the risk of birth defects should be identified and addressed. These include control of insulin-dependent diabetes mellitus during pregnancy and helping women to avoid therapeutic and recreational drugs, including alcohol. The training of primary health care providers in problem identification and steps that can be taken to reduce maternal and fetal risk should be given priority.

Prevention of Birth Defects >

PERI-CONCEPTION CARE

Many of the methods of primary prevention of birth defects can be incorporated into peri-conception care. This relatively new approach aims to ensure the optimal physical and mental wellbeing of women and their partners at the onset of and in early pregnancy in order to facilitate a normal pregnancy and delivery of a healthy infant (Wallace and Hurwitz, 1998). Peri-conception care encompasses basic reproductive health and medical genetic screening during the pre-conception period and first eight weeks of pregnancy. In Hungary, peri-conception care is offered by primary health care practitioners, mainly nurses, through family planning services and has proven successful in reducing pregnancy loss and birth defects (Czeizel, 2000).

box 5

The Power of Prevention: Immunization to prevent Congenital Rubella Syndrome

Rubella immunization is a highly effective and cost efficient method of primary prevention of congenital rubella syndrome. Hinman and colleagues conducted a MEDLINE search of articles published between 1970 and 2000 that dealt with economic analyses of rubella and rubella-containing vaccines. The Eastern Mediterranean, Southeast Asia and Africa regional Index Medicus databases and the LILACS database for Latin America and the Caribbean were also searched. For high-income countries, five cost-benefit analyses of rubella vaccine and five of measles-mumps-rubella vaccine as well as two cost-effectiveness analyses were found. For many middle- and low-income countries, five cost analyses and five cost-benefit analyses were found. All the cost-benefit analyses had a benefit: cost ratio greater than one and the cost-effectiveness studies indicated that rubella immunization was a cost-effective means of reducing the impact of congenital rubella syndrome. The authors concluded that the economic benefits of rubella immunization were similar to those associated with hepatitis B vaccine and Haemophilus influenzae type B vaccine and recommended inclusion of rubella vaccine in the immunization programs of high-, middle- and low-income countries (Hinman et al., 2002).

One of the studies considered by Hinman et al. was that of Irons and colleagues who compared estimated costs of rubella immunization to costs of rehabilitation and care of patients with congenital rubella syndrome in the English-speaking Caribbean and Suriname for the years 1997-2012. They calculated that if no further immunization programs were initiated in this time period, 1,500 preventable cases of congenital rubella syndrome would occur. The cost of care for these 1,500 cases, without even accounting for suffering, would amount to $60 million or $40,000 per CRS case. Implementing a strategy to interrupt rubella transmission and to prevent the occurrence of CRS over this time period, the cost of the immunization program would be approximately $4.5 million, resulting in an estimated savings of $3,000 per CRS case prevented (Irons et al., 2000). In other words, each CRS case prevented saved their health care system an estimated $37,000 ($40,000 minus $3,000).

Screening for Birth Defects

The implementation of basic reproductive health approaches results in a step-wise reduction in the birth prevalence of birth defects. To further reduce their birth prevalence, medical genetic screening and attendant services must be introduced. Medical genetic screening is the systematic offer of a test or inquiry to a defined population to identify those at increased risk for a specified disorder or at risk for passing one on to their children, in order that they can be informed of their risk and the options available for diagnosis to confirm or deny the risk. Screening for the risk of birth defects can be conducted in the preconception, antenatal and postnatal periods (Wald and Leck, 2000, WHO, 2000a).

Medical genetic screening can be expensive, so screening should be carefully considered, appropriately targeted, and should follow the principles and practices developed for these programs. (Wald and Leck, 2000; WHO, 2000a). However, many examples demonstrate that genetic screening is within the range of many lower-income countries (Alwan and Modell, 2003; Heredero, 1992; Samawat and Modell, 2004).

Screening for Birth Defects >

PRE-CONCEPTION SCREENING

This strategy has the advantage of identifying at-risk individuals when they have the widest range of personal and reproductive choices. Pre-conception medical genetic screening includes using family histories and carrier screening for common recessive disorders to identify those at risk of conceiving a child with a birth defect since inherited disorders tend to cluster within families.

A pictorial three-generation family tree is a powerful screening tool for detecting people who themselves have, or are at risk of having, children with inherited chromosomal abnormalities (translocations), multifactorial disorders or single gene disorders. Family clustering may be particularly marked in communities with a cultural preference for consanguineous marriage.

Primary health care practitioners can be taught to take and interpret a family tree. For example, starting from a single individual affected by thalassemia, an autosomal recessive birth defect (see Patient A in Figure 10), practitioners can use the family tree to trace family members at risk of being similarly affected or who may be carriers of the recessive gene. Alternately, unaffected family members (see Patients B and C in Figure 10) presenting in primary health care prior to their consanguineous marriage could have their risk of being a carrier and having an affected child assessed (WHO, 2000a).

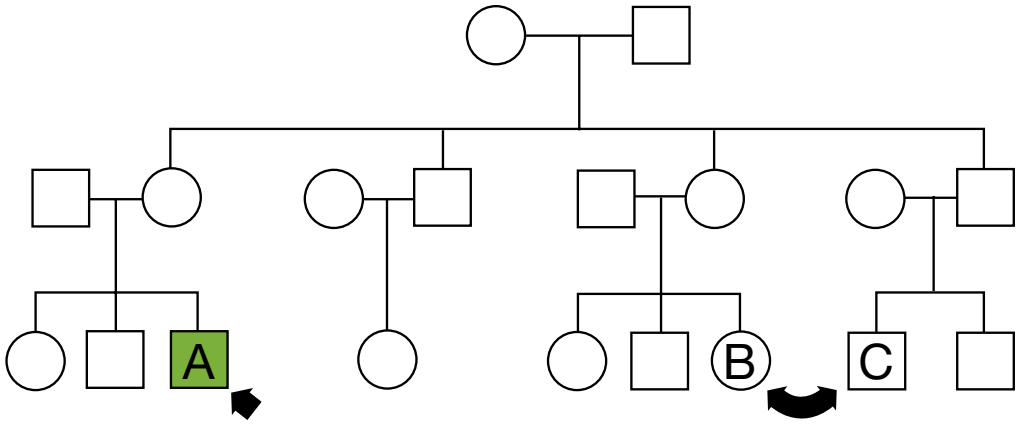
Population carrier screening for hemoglobin disorders and G6PD deficiency using conventional laboratory methods is well established in some middle- and low-income countries (Alwan and Modell, 2003; Heredero, 1992; Samavat and Modell, 2004). Identifying at-risk individuals in advance by combining the use of family trees with carrier testing rather than screening entire populations has been explored as a cost-effective approach to risk detection for recessive disorders in communities where consanguineous marriage is common. In Pakistan, one in 20 people carry ß-thalassemia, and consanguineous marriage is very common. Approximately half of the families with a child with thalassemia approached co-operated in extended family studies. These studies detected one at risk couple per 32 people tested, in contrast with an expected rate of one at-risk couple per 420 individuals screened using conventional population screening. This study shows how simple genetic testing using conventional laboratory methods may be used cost-effectively in many populations with very limited economic resources (Ahmed et al., 2002; WHO, 2000a). Those screened benefited by becoming aware of their risk of having a child with thalassemia, or of the absence of this risk, before marriage or before they had an affected child. In follow-up, all the carriers identified made sure they knew their partner's carrier status either before or soon after marriage. Numbers were small, but most at-risk couples requested prenatal diagnosis. For those that required and chose it, the option of prenatal diagnosis and associated services was available.

ANTENATAL SCREENING

ADVANCED MATERNAL AGE

Screening for advanced maternal age in pregnancy

figure 10



Use of Family History for Screening

Normal individuals (Patients B or C) can also have their family history explored as a routine process when they present to primary health care. This would be helpful in assessing their risks of having an infant with a birth defect or of developing a common disorder with a genetic predisposition. This, hopefully, will become accepted practice within future primary health care systems.

is applicable in middle- and low-income countries where prenatal diagnosis for Down syndrome is available and affordable. It involves asking the woman's age when the pregnancy is first diagnosed and offering genetic counseling to women 35 years or older. During genetic counseling, these women will be offered the option of prenatal diagnosis.

The role of the primary health care practitioner is to identify older mothers-to-be early and refer them appropriately. In middle- and low-income countries, this form of screening may be restricted by a number of factors: (1) some mothers do not seek antenatal care early enough to benefit from the screening; (2) the availability and capacity of cytogenetic services may be limited; (3) many women and primary health care workers are unaware of the availability of such services; (4) the financial cost of prenatal diagnosis may be too high for the patient or health care system; and (5) the possible consequences of prenatal diagnosis may be unacceptable (Christianson and Modell, 2004).

Recent experience in South Africa has shown some of the problems inherent in introducing antenatal advanced-maternal-age screening through primary health care in a middle- and low-income situation. Prenatal diagnostic services for Down syndrome have been available, at minimal cost to the individual, in the three academic hospitals in Johannesburg since the 1980s. At present, about 500 women of advanced maternal age deliver in these hospitals every month, but only about 20 of these women have had amniocentesis, apparently because women are referred to antenatal clinics too late to be offered genetic counseling and amniocentesis. Previous research showed that 80 percent of South African women of advanced maternal age will request amniocentesis after genetic counseling. Recent research has shown, though, that 70 percent of the women of advanced maternal age who presented in primary health care before 20 weeks' gestation, were not asked their age or offered genetic counseling. This finding emphasizes the importance of educating community and primary health care practitioners, if medical genetic screening programs are to succeed (Christianson and Modell, 2004).

Screening for Birth Defects > Antenatal Screening >

ULTRASOUND SCREENING

Ultrasonography is used as a screening tool in the first trimester for Down syndrome and in the second trimester for detecting serious fetal anomalies, including neural tube defects and chromosomal disorders. To be a reliable screening tool, ultrasonography is dependent on trained operators and on equipment that is initially expensive. However, the use of ultrasound is spreading rapidly in lower-income countries because of its general applications in obstetrics, and equipment costs are falling. If proper training can be offered, personnel from middle- and low-income countries can become as competent as those from high-income countries in the use of this screening tool. Ultrasonography screening in pregnancy is already being utilized in primary health care in countries in the Eastern Mediterranean region. Other countries could initially introduce it for high-risk groups of women and then expand its use as the situation allows.

Screening for Birth Defects > Antenatal Screening >

MATERNAL SERUM SCREENING FOR DOWN SYNDROME AND NEURAL TUBE DEFECTS

Maternal serum screening for Down syndrome in the first and second trimesters of pregnancy is available and is becoming increasingly sensitive. It is especially useful for younger mothers. The ability of this screening test to detect an affected fetus is further enhanced when combined with ultrasound screening. The technique can also be used to identify open neural tube defects in the second trimester. Gestational aging of the pregnancy by ultrasound is necessary for accurate maternal serum screening. The use of first and second trimester maternal serum screening in middle- and low-income countries is, therefore, limited by availability of antenatal ultrasound.

box 6

Power of prevention: Screening for thalassemia in Iran.

Iran's implementation of a national thalassemia prevention program in 1997 is a recent example of a successful implementation and development of a comprehensive thalassemia prevention program in a middle- or low-income country (Samavat and Modell, 2004). The program was initially designed to create a general infrastructure for primary prevention of genetic disorders. Screening was included as part of existing premarital care. Couples were screened for ß-thalassemia carrier status prior to marriage and the male was screened first. If positive, his partner was tested. Initially, couples who both screened positive were offered only information and genetic counseling about their situation, because termination of pregnancy after prenatal diagnosis was not available. After three years, an audit of the program indicated only about 20 percent of screen positive couples counseled had voluntarily separated. When asked, the remainder requested the option of prenatal diagnosis and selective termination of pregnancy. After inter-sectoral debate, a fatwa (law) was decreed recognizing the need for prenatal diagnosis and selective termination for serious birth defects. Thereafter the services needed to meet these needs for ß-thalassemia were developed.

Integration of the screening program into primary care in Iran required development of instruments and methods for educating health workers, the public and target groups, and establishment of professional networks to provide genetic diagnostic services, genetic counseling, and evaluation or surveillance. The Iranian health budget has covered planning, education, counseling and surveillance. Couples pay for their own screening tests, which cost about $5. The government health insurance companies cover DNA tests and prenatal diagnosis. The entire population is now insured (Dr. A. Samavat, Ministry of Health and Medical Education, Tehran, personal communication, 2005).

By the end of 2001, more than 2.7 million prospective couples had been screened and 10,298 at-risk couples had been identified and counseled about their risk and available options and services. Preliminary data from the national thalassemia register suggests that the affected birth rate had fallen to 30 percent of the expected rate by the year 2000.

The experience in Iran taught several lessons. First, so-called developing countries are capable of developing such services, including using the high technology needed and overcoming the implicit social, ethical and legal problems. The most difficult, expensive and time-consuming component of the program was establishing sustainable education for health workers and the community. Second, ongoing evaluation was important because it provided objective feedback that allowed the program to be adjusted to the needs of the target population. Third, primary care screening should be inclusive rather than focused on a single disorder. ß-thalassemia screening was simply a first step in the application of genetic knowledge for prevention in primary care. Currently, the national genetic program is being expanded to include screening for other birth defects, including sickle cell disease.

Screening for Birth Defects > Antenatal Screening >

CARRIER SCREENING FOR COMMON RECESSIVE DISORDERS

Carrier screening should be offered before conception as a tool of primary prevention of birth defects, but since this is not always possible, antenatal carrier screening should also be made available. This type of screening is now available with prenatal diagnosis in at least 25 middle- and low-income countries for detecting hemoglobin disorders and it is expected that other countries will follow (Alwan and Modell, 2003; *see Box* 6).

Screening for Birth Defects > Antenatal Screening >

SCREENING TO PREVENT SEVERE NEONATAL JAUNDICE AND KERNICTERUS

Antenatal screening is commonly used throughout the world to detect Rhesus blood group incompatibility. However, little current information exists on the residual prevalence of Rhesus hemolytic disease of the newborn in many low- and middle-income countries.

NEWBORN SCREENING

In middle- and low-income countries, the most obvious and inexpensive screening is clinical examination of all newborns by a trained primary health care practitioner. If the diagnoses of common disorders are carefully recorded and collated, this becomes birth defect surveillance. Ideally, stillbirths and neonatal deaths should be included. Full autopsies may not be possible, but non-invasive post-mortem examination can be undertaken and protocols for these examinations are available (Christianson et al., 1995; Mueller et al., 1984; WHO, 2000a).

Newborns can also be screened for certain hematological, metabolic and hormonal disorders. Most of the birth defects identified through newborn screening have no immediate visible effects on a baby but, unless detected and treated early, can cause death or physical, intellectual, visual, or auditory disability. Common conditions that may be considered for screening in middle- and low-income countries include congenital hypothyroidism, sickle cell disease, G6PD deficiency, phenylketonuria and galactosemia. The addition of other conditions to standard newborn screening protocols can be contemplated as resources become available (Note: the following website lists 29 conditions for which the March of Dimes recommends screening in the United States—http://www.marchofdimes.com/professionals/14332_15455.asp).

Such screening requires reliable systems to collect and transport samples, return reports, and trace patients in the community after discharge from the hospital or clinic. Screening has been initiated in countries in Latin America, the Middle East, parts of China, and the Philippines. Neonatal screening for G6PD deficiency is available in Sardinia, Singapore, and Malaysia and should be considered in other Middle Eastern and Southeast Asian countries where the birth prevalence of infants with the risk factor is high. Neonatal screening for sickle cell disorders is routine in parts of the United States and Western Europe, but would save tens of thousands of lives annually if introduced, in association with care and other prevention programs, in many sub-Saharan African countries (Alwan and Modell, 2003; Christianson and Modell, 2004).

As many as 3-4 in 1,000 newborns in the United States have significant hearing impairment. Without testing, most babies with hearing loss are not diagnosed until two or three years of age. By this time, they often have delayed speech and language development. Detection of hearing loss in the neonatal period is now possible with equipment that is relatively inexpensive and easily applied. Its use to diagnose auditory disability early is now routine in many high-income countries and can, with appropriate additional services, ensure improved outcome for speech and language development (March of Dimes—http://www.marchofdimes.com/professionals/14332_1232.asp). Its use in middle- and low-income settings is anticipated and expected to grow.

SURVEILLANCE OF BIRTH DEFECTS

Public health surveillance is the ongoing collection, analysis and interpretation of data essential to the planning, implementation and evaluation of public health interventions. Systematic collection of data on the background birth and population prevalence of birth defects is essential to initiating and developing care and prevention services at local, regional and national levels. Reliable data of the background toll of mortality and disability due to birth defects depend upon ongoing monitoring and surveillance on the types, prevalence, severity and outcome of birth defects. This can also provide a system of epidemic surveillance, alerting observers to geographic and temporal fluctuations in the frequencies of different birth defects that may shed light on possible causation and are needed to audit effectiveness of public health interventions and provide information on how these interventions might be improved (WHO, 2000a; WHO/ICBDMS/EUROCAT, 1998).

Birth defects surveillance is most often conducted at the local level—e.g. the California

box 7 **The Latin American Collaborative Study of Congenital Malformations (ECLAMC)**

There are few systems for monitoring the birth prevalence of birth defects in middle- and low-income countries. Consequently, good comprehensive data for most countries are limited. In Latin America, ECLAMC, a clinical-epidemiological research program initiated in Argentina in 1967, has performed regular monitoring of birth defects since 1974, registering over 100,000 newborns with birth defects and an equal number of matched controls. To date, about five million births have been examined in selected maternity hospitals across Latin America. Twelve countries are currently involved in the ECLAMC network (Castilla and Orioli, 2004).

Different methods are used to ensure accuracy of clinical diagnosis in the ECLAMC registry. All cases in which there is a question concerning the diagnosis are photographed and forwarded to a clinical review committee based in Rio de Janeiro. If the committee is unable to resolve uncertainties, the photographs are placed on a private website for the opinion of other clinical geneticists within the ECLAMC network. In addition, ECLAMC clinicians meet annually to discuss individual case studies and to train less experienced physicians from participating hospitals in the diagnosis of birth defects. As a final check, family histories, which often reveal the existence of consanguineous unions and other potential risk factors, are collected as part of the diagnostic procedures.

ECLAMC provides several valuable functions, in addition to routine monitoring of birth defects. It offers:

- A program of investigation. Its collection of cases and controls allows for investigation of potential risks factors for malformations, using the case-control methodology. Since more than half of all malformations have unknown causes, the identification of risk factors in Latin American populations is an important goal.
- Ongoing surveillance and monitoring. ECLAMC acts as a system of epidemic surveillance, systematically observing the fluctuations in the frequencies of different malformations and, in the cases of unusual increases in birth prevalence or clustering of a birth defect, providing a basis for mobilization around identification of possible causes.
- Voluntary cooperation. ECLAMC is a voluntary agreement among professionals dedicated to the study of congenital malformations in Latin American hospitals. It combines collaboration with uniformity of data collection and analysis, permitting comparison of data across hospitals and countries.

Birth Defects Registry. Regional networks—e.g. EUROCAT (European Concerted Action on Congenital Anomalies and Twins)—and international networks—e.g. International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS)—exist, but are far fewer in number. A good listing of surveillance networks may be obtained by visiting the **I**nternational **B**irth **D**efects **I**nformation **S**ystems (IBIS) website at http://www.ibis-birthdefects.org.

A major limitation of population-based surveillance systems is their relatively high cost. This has spurred development of alternative surveillance systems. The ECLAMC network in Latin America is an example of one that has been very successful (*see Box 7 page 58*).

PROMOTING EQUITY THROUGH OVERCOMING BARRIERS TO MEDICAL GENETIC SERVICES

A number of barriers restrict implementation of medical genetic services in middle- and low-income countries. As noted in the Introduction, one important constraint is the need of policy makers at the international, national and local levels for more information on the toll of birth defects and effective interventions available to reduce this toll. The use of such information to set priorities for equitable implementation of medical genetic services requires consideration of the often difficult ethical, legal and social issues (ELSI) surrounding these services. The absence of such dialogue increases the risk that provision of needed services will be delayed in at-risk populations and that preventable mortality and disability associated with birth defects will remain high. The lack of policies for care and prevention in populations where medical genetic services can be provided effectively and at affordable cost is unethical for it could result in the disenfranchisement of adversely affected women, newborns and children. Therefore, it is imperative to ensure an effective dialogue by all stakeholders on the ethical, legal and social issues associated with the equitable provision of medical genetic services in at-risk populations. This can best be provided through the enhancement of "genetic literacy" in key sectors of society and the promotion of "genetic citizenship" nationwide.

Genetic Literacy

Genetic literacy is the ability to communicate and understand genetic knowledge in ways that promote effective health decisions and health care (Jennings, 2003). Experience suggests that the cost-efficient delivery of genetic services depends on four things: (1) community education to create an informed health consumer base; (2) strengthening patient/parent support groups; (3) education and training of physicians and other health care providers; and (4) education of the broader constituency of stakeholders in society, including policy makers, legislators, students and the media.

In countries in the process of introducing medical genetic services, the first requirement is for advocacy by informed policy makers. Education and training of physicians and other health care providers are critical to increase genetic literacy among clinical staff and supporting laboratory personnel at all levels of health care. Primary care practitioners are key in this regard. In middle- and low-income countries, primary care providers take daily responsibility for tasks that would be undertaken by more trained personnel and specialists in high-income countries. Enabling them to take on the added responsibility for the care and prevention of birth defects will require education and training, as well as strengthening of the human and physical infrastructure around them (Christianson and Modell, 2004; WHO, 1999).

Community education is also critical for the success of medical genetic services. Experience in under-served populations in industrialized countries has shown that the public must be consulted, informed and helped to understand these services. People want to know how to access and use these services to their advantage. People also need to have confidence that discretion and confidentiality will be part of their care (MOD, 2005).

Strengthening of patient/parent support groups

is also vital. Such organizations, both individually and as national and international alliances, play a crucial role in supporting their members, educating health professionals and the public, and promoting relevant research. In 2003, the International Genetic Alliance, a confederation of patient/parent support groups, was initiated in Lyon, France with one of its aims being to raise awareness among international organizations and governments of the toll of disease and the plight of people with birth defects.

Finally, education of the broader constituency of society, including policy makers, legislators, students and the media about the benefits and limits of medical genetics is crucial to increasing the genetic literacy of the population. This can be accomplished through the strengthening of school curricula and the holding of conferences and workshops to inform legislators and the media.

Genetic Citizenship

Genetic literacy alone, however, is not sufficient to promote ethical provision of medical genetics services. It must be coupled with genetic citizenship, which is defined by Bruce Jennings as the capacity of a society to allow its individuals and communities to share information about genetics, to try to understand the meaning of that information in their lives, and to deliberate and debate with others how the application of genetics should be used and for what purposes. He notes "Genetic science—and the technologies it spawns—are increasingly important forms of power and domains of public policy. To be cut off from knowledge and information about the new genetics, and to be voiceless in the development of goals and regulations governing its use, is to be doubly disenfranchised. It is to be disenfranchised both in the political system in one's role as a democratic citizen, and in the health care system in one's role as a consumer of health care and a decision-maker, partner in the physician-patient relationship and increasingly in the future, as a subject or participant in genetic research." (Jennings, 2003).

Inherent in the concepts of genetic literacy and genetic citizenship is the respect for human rights and the belief that all stakeholders in society—medical care providers, their patients, government and the community—must be engaged in dialogue on how to achieve greater equity in the ways in which the toll of birth defects is distributed across racial, ethnic and socioeconomic groups and in which health for all people can be improved through equitable development of medical genetic services. It should be noted, though, that each community needs to decide for itself how to implement services for care and prevention of birth defects, since what is appropriate for high-income countries may not necessarily be so for middle- and low-income countries. Middle- and low-income countries must develop medical genetic services appropriate to their circumstances, with the benefit of experience from the industrialized countries where needed. Understanding and respecting each country's process and experience will hopefully allow for a WISER (Worldwide Insight in Social and Ethical Reasoning) view of medical genetics and its services (Christianson and Modell, 2004).

Currently, implementation of effective medical genetic services is being impeded in some countries by a lack of appropriately trained human resources, including policy makers, and by barriers related to infrastructure, language, culture, religion, geography, laws and unwritten antipathy to confronting the issues. Many middle- and low-income countries, however, including Brazil, Bahrain, China, Cuba, Cyprus, Egypt, India, Iran, Jordan, Maldives, Mexico, the Philippines, Sri Lanka, South Africa, Thailand and the Ukraine are accepting the challenge (Alwan and Modell, 2003; Penchaszadeh, 2000; Samavat and Modell, 2004; WHO, 1999, 2000a).

Achieving equity in medical genetic health care requires education. Adherence to the belief in the

importance of genetic literacy and genetic citizenship can, thus, serve to promote productive national discussion about important ethical, legal and social issues associated with equitable establishment of medical genetic services about how the health of all people in the population can be improved. Without this broad discussion and the political will and financial commitment that will be required, progress will be limited.

Genetic Counseling in Middle- and Low-income Countries

Ethical principles, developed in high-income countries and often held as universal truths, may be inappropriate in some non-Western settings. For example, advice about genetic counseling technique is largely intended to reduce interpersonal distance and promote an open exchange of information between counselor and counselee. In the primary health care settings of many middle- and low-income countries, however, the primary care practitioner often is a member of the village community and, as such, may find it difficult to share intimate information with someone he or she knows well. In this situation, it may prove necessary to train counselors in techniques for increasing formality and distance to ensure a feeling of confidentiality and trust.

In high-income countries, where the emphasis is on maintaining confidentiality, counseling is usually restricted to the individual or couple concerned. In societies with different kinship patterns, however, it may be best to offer counseling for the whole family, depending on the preference of those being counseled. In Iran for example, prospective at-risk couples usually bring all four parents along (Dr. A. Samavat, Ministry of Health and Medical Education, personal communication, 2003).

In the West, there is resistance to providing genetic testing for children and young adults. While this may be inappropriate for carriers of recessive disorders under most circumstances, families may need the information much earlier in countries where teenage pregnancy is frequent or arranged marriages are common and the choice of couples made during childhood.

In summary, the authors believe that each community needs to consider these matters for itself and then work out a pattern that provides for maximum benefit and minimum harm within the framework of the three WHO core principles: (1) the autonomy of the individual or couple; (2) their right to full information; and (3) confidentiality (WHO, 2001c). Policy makers and donor organizations in the West should remain open-minded and flexible, and not try to impose personal values or ethics on others without consultation and careful thought.

The Role of Lay Advocacy Groups

Lay advocacy groups, also commonly known as patient/parent support organizations, play an important role in helping ensure the effectiveness and equitability of medical genetic services for the care and prevention of birth defects. Lay advocacy groups support patients and their families through education and fundraising for research in high-income countries. In middle- and low-income countries their priority is usually service provision.

Lay support groups also lobby for increased investment in research and development of genetic and other health services for care and prevention of birth defects. These groups are, therefore, a critical component of national and international strategies to promote care and prevention.

The past 40 years have witnessed a remarkable growth of lay support groups in high-income countries and the beginnings of similar advances in middle- and low-income countries. The International Genetic Alliance (IGA), for example, represents more than 2,000 parent and patient organiza-

tions in the Americas (e.g. the Genetic Alliance), Europe (e.g. the European Genetic Alliances Network), Australasian, Middle East, India and South Africa. The IGA is currently reaching out to developing countries to foster a foundation of parent and patient support groups at local, regional and national levels. Such coalitions of parent and patient organizations, representing a wide range of birth defects, are better able to lobby successfully to increase availability of and accessibility to appropriate medical services for care and prevention. By educating politicians, healthcare providers and the public about their needs, these alliances play a crucial role. By advocating for the engagement of concerned parents and patients in health care policy decisions, and by lobbying for new research efforts and collaborating with science and industry, lay support groups and the alliances they participate in promote a model of community partnerships around common health interests and goals.

Health professionals and lay support groups share the same goals: to alleviate the toll of birth defects for individuals, families and communities; to accelerate research to prevent, treat, ameliorate and care for birth defects; and to develop high quality genetic services.

Taking into account parent/patient needs can help ensure that services for the care and prevention of birth defects are appropriate, accessible, and user friendly. They can also allow patients and their families to make informed choices and derive maximum benefit from genetic information.

The World Alliance of Organizations for the Prevention and Treatment of Genetic and Congenital Conditions was founded in 1994 at the initiative of the March of Dimes. The goal of the World Alliance is to foster strategic partnerships of patient/parent organizations, NGOs, academic institutions, government and industry with the goals of spurring scientific discovery, implementation of genetic services in underserved populations and ensuring that these services respect the needs of patients.

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APPENDIX A

Background to the Modell Birth Defects Database

In response to the current lack of reliable data on the national and global birth prevalence of birth defects, Professor Bernadette Modell commenced efforts to model a solution for this in the 1990s. This was a continuation of work she began for WHO in the 1980s on carrier frequencies and birth prevalence of the hemoglobin disorders and G6PD deficiency. Results of these efforts were published in several WHO reports and recently in the report of a meeting sponsored by the WHO European Office, *Folic Acid: From Research to Public Health Practice* (Modell et al., 1992; WHO, 1989, 1994; WHO/EURO, 2002). The database presented in Appendix B of this report is based on earlier spreadsheets developed as part of the work of the WHO Collaborating Centre on Community Control of Hereditary Disorders at University College London Centre for Health Informatics and Multiprofessional Education (CHIME). An earlier version was produced in 2003 as a basis for work with Professor Arnold Christianson on genetics in developing countries (Christianson and Modell, 2004).

Demographic data were obtained for this database from the 2003 UNICEF report on *The State of the World's Children* (UNICEF, 2003). The data it contains are taken from the United Nations Demographic Yearbook for 2001 and include valuable additional information on under-five mortality rates.

The starting point for the database was the perception that birth prevalence data obtained from well-established birth defect surveillance systems and registries could be broadly applied to generate baseline estimates of country-specific birth prevalence. The birth defect surveillance systems and registries used to generate the baseline estimates drew from northern European populations for whom preventive interventions, such as food fortification and supplementation with folic acid, medical genetic screening, and fetal ultrasound, had not yet been widely applied. The baseline estimates of national birth prevalence of birth defects, thus, reflected the situation in the absence of national prevention interventions.

The baseline birth prevalence of birth defects of genetic or partially genetic origin in the database—including single gene disorders, chromosomal disorders, congenital malformations (essentially multifactorial birth defects) and genetic cause unknown—is broadly based on the work of Patricia Baird and colleagues in 1988 (Baird et al., 1988). The baseline birth prevalence of congenital malformations utilized data collected by Andrew Czeizel for the Hungarian Congenital Malformation Registry (Czeizel and Sankaranarayanan, 1984). Both of the registries have been functioning for over 40 years and their methods of data collection are rigorous and documented. The registries ascertain birth defects to 25 and 20 years of age, respectively. The fact that their birth prevalence rates for specific disorders have been stable over a long period suggests complete reporting. The rates reported are also broadly consistent with EUROCAT (EUROCAT, 2002) and the International Clearing House for Birth Defects (WHO/ICHBDMS/EUROCAT, 2003). The one exception was rates for congenital dislocation of the hip, which were far higher in the Hungarian registry than elsewhere. The Hungarian rates were, therefore, not used to generate international estimates of congenital dislocation of the hip (Czeizel and Sankaranarayanan, 1984).

The derived baseline estimates were further adjusted to account for circumstances that would substantially alter the birth prevalence of birth defects in particular countries or regions of the world.

These circumstances included variations in carrier rates for common recessive conditions, prevalence of consanguineous marriage, and maternal age distribution (Christianson and Modell, 2004). The additionally adjusted estimates are reflected in the following data categories in Appendix B: annual birth prevalence, annual affected births and total birth defects with no prevention applied.

Specific adjustments were made to the estimates of the following disorders.

Background to The Modell Birth Defects Database >

HEMOGLOBIN DISORDERS

Thalassemia and sickle cell anemia are autosomal recessive disorders that became very common in tropical regions because of heterozygote advantage—carriers are protected against the lethal effects of falciparum malaria. These disorders spread through migration of carriers to other regions. Carriers can be detected by simple hematological tests and global data exist on carrier frequencies (Livingstone, 1985). This enables the calculation of affected birth prevalence using standard formulae. Harmless homozygous and compound heterozygous genotypes were excluded from the calculations. These methods will be published in the very near future by Modell and Darlison and will also be available at www.chime.ucl.ac.uk/apogi/.

Background to The Modell Birth Defects Database >

NEURAL TUBE DEFECTS

It is difficult to set up and run birth defect surveillance systems and registries, and reliable data over the full range of abnormalities are generally only obtained after many years of data collection. Assessing the prevalence of neural tube defects (NTDs) is an exception, however, because NTDs are generally obvious at birth. Reasonably reliable data on the prevalence of NTDs are, therefore, available for a number of middle- and low-income countries. These data have been carefully documented and entered in the database. They were then used to make informed estimates of NTD prevalence for neighboring or similar countries that lack data. This method was felt to yield more accurate estimates of NTD birth prevalence than reliance on registry data (Czeizel and Sankaranarayanan, 1984).

Background to The Modell Birth Defects Database >

COMMON RISK FACTORS

RHESUS HEMOLYTIC DISEASE AND G6PD DEFICIENCY

Rhesus hemolytic disease and G6PD deficiency are inherited risk factors for newborn death or disability from kernicterus (brain damage caused by high levels of neonatal unconjugated bilirubinemia). Rhesus hemolytic disease is also an important cause of intrauterine or neonatal death. G6PD deficiency may also result in favism in children and acute hemolytic reactions to infection and some drugs throughout life.

The effects of Rhesus hemolytic disease of the newborn were estimated from global Rhesus gene frequencies and historical data from Canada and the United Kingdom (Bowman and Pollack, 1965; Clarke and Hussey, 1994; Mollison et al., 1993). Birth prevalence of G6PD deficiency were derived from the work of Livingstone and of Luzzatto and Metha (Livingstone, 1985; Luzzatto and Metha, 1989). Estimates of pathology due to the severe Mediterranean or Southeast Asian mutations were based on work by Wong Hock Boon in Southeast Asia (Wong HB, 1980) and data from Sardinia published by the WHO (WHO, 1989). The pathology related to the milder African type is unknown; therefore, estimates rates are lower.

Background to The Modell Birth Defects Database > Common Risk Factors >

CONSANGUINEOUS MARRIAGE

The incidence of customary consanguineous marriage and its effect on infant mortality in middle- and low-income countries is now well documented (Bittles, 1990; Bittles et al., 1991; Murdock, 1967). The only precise study to date of the effect of parental consanguinity on the birth prevalence of specific categories of disorders was carried out in Birmingham, England (Bundey et al., 1993). Rates from this study were used to derive the effect of parental consanguinity.

In the Birmingham birth study, the ancestry of consanguineous parents was carefully assessed and a coefficient of consanguinity (F) was calculated for each child. Among British Pakistanis, the population coefficient of consanguinity was 0.0431 and this was associated with a 30 to 33 per 1,000 increase in the prevalence of recessive disorders. In other words, there was a 7.0 to 7.7 per 1,000 increase for every 0.01 increase in the coefficient of consanguinity. This relationship is compatible with the results of Bittles' meta-analysis of studies of the relationship between parental consanguinity and infant mortality in middle- and low-income countries and may be cautiously applied to any populations where the coefficient of consanguinity is known.

This procedure was used to calculate the consanguinity-associated increment in autosomal recessive disorders in the database. The increment used was conservative, i.e. a seven per 1,000 increase for every 0.01 increase in population coefficient of consanguinity.

Background to The Modell Birth Defects Database > Common Risk Factors >

MATERNAL AGE DISTRIBUTION

The relationship between advancing maternal age and increasing birth prevalence of chromosomal trisomies, particularly Down syndrome, is well documented. This relationship was defined mathematically using data from European countries accurate for a wide range of maternal age distributions. Using percentages of mothers 35 years and older as obtained from the 2001 *United Nations Demographic Yearbook* (United Nations, 2003), this formula was applied to other countries to estimate the prevalence of Down syndrome.

Background to The Modell Birth Defects Database >

PREVENTION

Modeling of prevalence data for countries in which general or specific prevention programs for birth defects have been implemented required taking into account the effect of these interventions. For those countries in which information relating to prevention strategies was available or their existence known to the authors, a minimum estimated effect of these strategies was calculated. This effect was applied to the total estimated affected and can be found in the row titled "Total birth defects with known prevention" (Appendix B). It should be noted that only limited data were available at this point for this calculation. The authors intend to collect additional data in the near future to refine their estimates of the effect of preventive interventions on the birth prevalence of birth defects

Conclusion

There is a paucity of observational data on the birth prevalence of birth defects in middle- and low-income countries. Constrained diagnostic capability, poor health-related statistics, lack of birth defect surveillance and registries and reliance on hospital-based rather than population-based studies have contributed to this situation, which has led to a systematic underestimation of the toll of birth defects in these regions.

The global estimates of serious birth defects of genetic or partially genetic origin published in this report are, as with most other estimates where absolute figures are not available, a modeled solution. Conservative and minimum estimates were applied wherever possible and necessary to prevent overestimation and consequent exaggeration of birth prevalence rates. Low birth prevalence may, therefore, be a reflection of the absence of available country- or region-specific modifying data, rather than an absence of disease burden. Equally, the absence of an entry in the row labeled "known prevention" may reflect the absence of available prevention data rather than the absence of prevention itself.

The database has two potential uses. First, for many middle- and low-income countries it offers for the first time insight into their burden of birth defects, enabling them to make more informed deci-

sions on developing medical services appropriate to their needs. In deciding the appropriate mix of services, however, all countries should include surveillance to document the baseline birth prevalence of birth defects and to assess the effects of interventions. This will generate robust empirical data on birth defects prevalence that, in time, will replace the estimates in this database. Second, the database offers an important interim resource for those interested in development of policy and programs to improve child health and survival.

As a next step, the authors are contemplating development of the database to generate refined estimates of childhood death and disability resulting from birth defects, as well as estimates of the economic costs of these disorders and the cost-effectiveness of care and prevention. Future reports on these and related topics are envisioned.