MEDICAL GENETICS IN DEVELOPING COUNTRIES

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Abstract  Since Watson & Crick’s 1953 description of the structure of DNA, significant progress has been achieved in the control of congenital disorders, most of which has benefited industrialized countries. Little advantage accrued to developing nations, most of which in the same time frame achieved a significant epidemiological transition, resulting in congenital disorders attaining public health significance. The burden of congenital disorders in these lower-resource countries is high and they need to develop medical genetic services. We present a new pragmatic approach for the care and prevention of congenital disorders in these countries, pioneered initially by the World Health Organization.

INTRODUCTION

Because 2003 was the fiftieth anniversary of the discovery of the structure of DNA, and the draft sequence of the human genome was published in 2001, this is an appropriate time to review the potential impact of developments in human genetics in a global context (97, 114). In 2002, the World Health Organization (WHO) responded to the publication of the sequence with a report on genomics and world health (127). In this report, Bruntland emphasized the need to “harness this knowledge and have it contribute to health equity, especially among developing nations” (127). Her comment acknowledges a general concern that developments in genetics and genomics may add to the already gross disparity between industrialized and so-called developing nations in access to health care, including medical genetics services (5, 14, 127).

In this review we do not attempt to discuss medical genomics, which deals with manipulating DNA sequences. We are concerned with medical genetics, the aspect of medical practice that addresses the congenital contribution to health and disease. We focus on the care and prevention of congenital disorders that start in childhood because (a) their control offers the most extensive experience to date of applying
genetics approaches within health services, (b) their global significance is still not generally recognized, and (c) they are the priority area for developing countries, even though the current emphasis in the literature in industrialized countries is on the genetic contribution to common disorders of adult life (5, 36, 80, 123, 129). However, we aim to elicit useful generalizations that are relevant across the entire field of medical genetics.

We first outline the range and prevalence of congenital disorders in the absence of prevention, and the measures already taken in industrialized countries to reduce their burden for affected individuals, families, and societies. We then assess their current burden in the developing world and discuss approaches for patient care and prevention that are feasible, or are already in place, within health systems in developing countries. The review shows that congenital disorders are more common in the developing than in the industrialized world, that their health burden has been consistently underestimated, and that it can be significantly reduced by a wide range of relatively simple interventions, many of which are well within the range of developing countries. In fact, early implementation of such approaches is necessary for countries currently struggling to improve the health status of their population.

In the course of developing our argument we also examine (a) the biases originating in a high-resource setting that impede objective assessment of the needs and potential of developing countries, (b) the need for care and the priority of prevention in developing countries, (c) the immediate relevance of the new genetic knowledge for prevention, (d) the reliance of all types of care and prevention on primary health care infrastructures, and (e) the potential cost implications of new therapies arising from genomic approaches. We emphasize these points because of the influence scientists in the industrialized world exert on health policy making by international organizations, and the consequent need for them to prioritize approaches that can help lower-resource communities appropriately apply genetic science.

A few definitions are appropriate at the outset. Some international organizations including the United Nations Children’s Fund (UNICEF) divide the industrialized world (Western Europe, North America, Japan, Australia, and New Zealand) from developing countries, including 49 “least developed” countries (100–103). We prefer the World Bank’s more sensitive economic categorization of high-resource, upper medium, lower medium, and low-resource countries, based on per capita gross domestic product (GDP) adjusted for purchasing power parity (PPP) (103, 116). We use “lower-resource countries” as an inclusive term for the last three categories. Annex 1 (follow the Supplemental Material link from the Annual Reviews home page at http://www.annualreviews.org) lists countries by category. Box 1 (follow the Supplemental Material link from the Annual Reviews home page at http://www.annualreviews.org) contains definitions of other key terms.

Figure 1 shows the distribution of the world population by economic level. Tables 1 and 2 show key indicators of health and social development by economic level.
### TABLE 1  Basic demographic data for the world population, by economic level

<table>
<thead>
<tr>
<th>Income level</th>
<th>Number of countries</th>
<th>Population, in millions</th>
<th>Crude birth rate(^a)</th>
<th>Infant mortality rate(^b)</th>
<th>Mortality rate 1–5 years(^c)</th>
<th>Annual births, in thousands</th>
<th>Annual infant deaths, in thousands</th>
<th>Annual deaths 1–5 years, in thousands</th>
<th>% of world population</th>
<th>% of births</th>
<th>% of infant deaths</th>
<th>% of deaths 1–5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>High income</td>
<td>48</td>
<td>931</td>
<td>11.3</td>
<td>5.4</td>
<td>1.2</td>
<td>10,474</td>
<td>56</td>
<td>12</td>
<td>15.1</td>
<td>7.9</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Upper-middle income</td>
<td>52</td>
<td>549</td>
<td>18.8</td>
<td>23.6</td>
<td>4.5</td>
<td>10,304</td>
<td>243</td>
<td>47</td>
<td>8.9</td>
<td>7.8</td>
<td>3.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Lower-middle income</td>
<td>64</td>
<td>2193</td>
<td>17.1</td>
<td>33.4</td>
<td>8.5</td>
<td>37,517</td>
<td>1251</td>
<td>317</td>
<td>35.6</td>
<td>28.5</td>
<td>16.8</td>
<td>9.5</td>
</tr>
<tr>
<td>Low income</td>
<td>67</td>
<td>2482</td>
<td>29.6</td>
<td>80.3</td>
<td>40.4</td>
<td>73,534</td>
<td>5905</td>
<td>2969</td>
<td>40.3</td>
<td>55.8</td>
<td>79.2</td>
<td>88.8</td>
</tr>
<tr>
<td>Total lower income</td>
<td>183</td>
<td>5244</td>
<td>23.2</td>
<td>61.0</td>
<td>27.5</td>
<td>121,355</td>
<td>7400</td>
<td>3332</td>
<td>84.9</td>
<td>92.1</td>
<td>99.2</td>
<td>99.6</td>
</tr>
<tr>
<td>World</td>
<td>231</td>
<td>6155</td>
<td>21.4</td>
<td>56.6</td>
<td>25.4</td>
<td>131,829</td>
<td>7456</td>
<td>3345</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

\(^a\)Annex 1 (follow the Supplemental Material link from the Annual Reviews home page at http://www.annualreviews.org) lists countries by economic category.

\(^b\)Crude birth rate = annual births/1000 population.

\(^c\)Infant mortality rate = deaths before the first birthday/1000 live births. The most widely used basic indicator of the health status of a population.

\(^d\)Mortality rate 1–5 years = deaths between the first and fifth birthday/1000 live births = early childhood mortality.

Under-five mortality rate (the sum of infant and early childhood mortality, not shown here) is adopted by UNICEF as “the single most important indicator of the state of a nation’s children, and of society as a whole” (102).

The table includes all populated countries listed in the United Nations Demographic Yearbook series (99). The total number of countries in column 2 is larger than that shown in UNICEF tables (103) because UNICEF (a) omits very small populations, and (b) combines data for dependencies (e.g., Martinique, Guadeloupe, Reunion, Hong Kong, Macau, Taiwan) with that for the major country (in these cases, France and China). Hence, there are small differences between figures given here (more complete) and those given by UNICEF. Many countries are very small, e.g., the upper middle-income group includes many Caribbean islands and large Latin American countries.
TABLE 2  Selected indicators of development

<table>
<thead>
<tr>
<th>Income level 2001</th>
<th>% of children fully immunized (polio)b</th>
<th>Female literacy rate c</th>
<th>Total fertility rated</th>
<th>% of population urbanizede</th>
<th>Total health expenditure per capita, PPPf</th>
<th>Public health expenditure, % of total health expenditure</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>93</td>
<td>96</td>
<td>1.7</td>
<td>79.2</td>
<td>2435</td>
<td>60.4</td>
</tr>
<tr>
<td>Upper Middle</td>
<td>94</td>
<td>89</td>
<td>2.6</td>
<td>76.7</td>
<td>507</td>
<td>54.8</td>
</tr>
<tr>
<td>Lower Middle</td>
<td>85</td>
<td>79</td>
<td>2.4</td>
<td>45.9</td>
<td>197</td>
<td>52.2</td>
</tr>
<tr>
<td>Low</td>
<td>64</td>
<td>51</td>
<td>4.4</td>
<td>31.4</td>
<td>59</td>
<td>42.0</td>
</tr>
<tr>
<td>World</td>
<td>74</td>
<td>68</td>
<td>3.4</td>
<td>47.7</td>
<td>620</td>
<td>58.3</td>
</tr>
</tbody>
</table>

aData from UNICEF (103) and the World Bank (116).
bPercent of children fully immunized against polio: an indicator of maximum access of the population to any type of health care. Rates are similar for most immunizations provided by governmental health services.
cFemale literacy rate = percent of females 15+ years able to read and write: an indicator of women’s power to protect family health.
dTotal fertility rate = average number of children born per woman of reproductive age.
ePercent of population urbanized: the majority of people living in urban areas are physically within reach of basic health care, whether private or governmental.
fTotal health expenditure per capita. This is expressed in terms of international dollars, adjusted for local purchasing power (PPP = purchasing power parity). One dollar purchases more in lower-resource than in high-resource countries. Average figures for populations conceal wide variations (e.g., by age) and can change rapidly. For example, in some Middle Eastern countries most young women are literate but few older ones are. Obviously, all the above indicators are closely inter-related.

GENETICS AND THE EPIDEMIOLOGICAL TRANSITION

The developing world is frequently perceived as a homogeneous entity characterized by universal poverty, deficient infrastructure, and poor education and health care. However, lower-resource countries differ widely in size, population, and level of service development, and most have achieved steady improvements in socioeconomic level, education, and health care over the last 40 years (80, 103, 129). International organizations including WHO, UNICEF, UNESCO, and the World Bank are important facilitators of such change.

As a result of socio-economic, educational, and infrastructural development, the current high-resource countries completed a demographic transition in the first half of the twentieth century. Improvements in the control of infectious diseases (clean water, sanitation, immunization), nutrition and care of pregnant women and children, and increased access to family planning brought about an associated epidemiological transition entailing a major and continuing fall in infant and child mortality, reduced fertility, and increased longevity. As part of this change, underlying mortality and morbidity due to congenital disorders, previously obscured by the burden of acute environmentally caused disease, were exposed and attained public health significance. Growing recognition of the contribution of these
disorders to infant, childhood, and adult mortality and morbidity then led to gradual incorporation of care and preventive approaches in different medical disciplines, though these were not perceived as parts of a unified strategy (66).

Figure 2 illustrates the global progress of the epidemiological transition in the past 40 years. In the area at the bottom left-hand corner of both charts, under-five mortality is less than 50/1000 and total fertility is less than four births per woman. In 1960, this area included 26 countries (the current industrialized nations), but by the year 2000 it included 91 countries, reflecting the rapid epidemiological transition of much of Latin America, the Caribbean, East Asia, the Middle East, and North Africa (103). Sixty-three percent of countries now have an infant mortality below 50/1000, and many are seeking guidance on developing coherent programs for the equitable care and prevention of congenital disorders (4, 5, 65, 123, 129).

However, the health situation has deteriorated in some parts of the world. The collapse of the former USSR’s economic system has led to poverty comparable in parts to that in sub-Saharan Africa, with increased infant mortality, decreased longevity, and a birth rate far below replacement level (103). The HIV/AIDS pandemic is reversing positive demographic trends in large parts of Africa: For example, in South Africa and neighboring Botswana, 20.1% and 38.8%, respectively, of people aged 15–49 are HIV-positive, and from 1997–1999 infant mortality rose from 49 to 54/1000 in South Africa and from 38 to 46/1000 in Botswana (101–103). In “Environmentally Determined Congenital Disorders,” we describe the relevance of such changes for the development of medical genetics services.

Population age distribution is an important determinant of priorities. Genetic factors most affect health in the early years (congenital disorders), in middle life (premature onset of common chronic diseases), and in old age (determining cause of death). Figure 3 shows that the age distribution in high-resource countries naturally directs interest in genetic medicine toward common chronic disorders of later life (36), whereas in lower-resource countries services oriented to controlling congenital disorders have priority because of the preponderance of infants and children.

HISTORICAL ASPECTS

McKusick (63) identified 1959 as the birth year of clinical genetics, with convergent achievements in molecular, biochemical, and cytogenetics. In the same year a WHO expert group planned the first international study on the epidemiology of birth defects (94). In 1963, opening a meeting on the role of human genetics in public health, Candau, the Director General of WHO, noted that “human genetics is much more than the study of inborn abnormalities; it is the study of endogenous factors in health and disease. It can be hoped that a fuller comprehension of genetics will lead to greater understanding of the complex interactions that have taken place in the past and that exist in the present between man and his changing environment, and also of their implications for the health of future generations” (117). The clustering
Figure 2  (A) The 1960 relationship between under-five mortality and the total fertility rate for 158 countries included in the 2003 UNICEF report on the state of the world’s children (103). Forty years ago, under-five mortality was less than 50/1000 in only 28 countries (18%); total fertility was less than four births per woman in only 26 of these. (B) The 2001 relationship between under-five mortality and the total fertility rate for the same 158 countries (103). Currently, 99 (63%) of these countries have an under-five mortality rate of less than 50/1000; total fertility is less than four births per woman in 91 of these countries.
Figure 3  (A) Age distribution in a typical high-resource country (United Kingdom 1998) (99). Median age is around 40, and the age distribution dictates that disorders of middle and later life will have high medical priority. (B) Age distribution in a typical lower-resource country that is experiencing demographic transition (Iran 1998) (99). Improved primary health care greatly reduced infant and childhood mortality, leading to a growing number of young people. Effective delivery of family planning has now enabled a rapid fall in birth rate. The median age of the population is about 20 years. Because of this age distribution, disorders of infancy and childhood have high medical priority.
of these events was not coincidence. They highlighted the industrialized world’s successful epidemiological transition, and the growing importance of congenital disorders and genetically determined noncommunicable diseases.

The first medical genetic services were initiated by specialists in a range of medical disciplines including pediatrics, obstetrics, hematology, and neurology. The need for more specialized clinical and laboratory diagnostic services and genetic counseling then led to the emergence of today’s tertiary specialist medical genetic services. These focus mainly on the differential diagnosis of rare congenital disorders and genetic counseling for patients and their families, and are usually situated in academic centers because service evolution is highly research-dependent. Consequently, these services have developed with little contact with public health—or community-based services. Ongoing patient care is usually provided by relevant clinical specialists (79, 81), but the extraordinary diversity of the natural history and clinical implications of inherited disorders has favored development of disease-specific services (e.g., for cystic fibrosis, hemophilia, thalassemia, sickle cell disorders, or metabolic diseases) that have little contact with each other and fail to recognize their commonalities.

This extreme fragmentation of services and perceptions makes it difficult to achieve a comprehensive view of the place of genetics in medicine. The reality is that (a) the bulk of care for and prevention of congenital disorders is carried out routinely in primary and secondary care, (b) the most common interventions in medical genetics are diagnosis and information, and (c) the simple basic principles of human inheritance provide the basis for much genetic counseling. However, these facts are often overlooked and perceptions of medical genetics among health workers, health decision makers, and the general public tend to focus on highly specialized, technical, expensive, and controversial aspects of diagnosis, treatment, and prevention.

The situation is gradually changing as scientific advances enhance the role of genetic approaches for common chronic disorders (e.g., familial cancers), and increasing public demand and economic realities are forcing the integration of genetic approaches into medical practice (40a, 81). Nevertheless, the perception that all genetics services are “high tech” and expensive, and lower-resource countries “have higher priorities” persists as a powerful influence in international and national policy making (40, 123, 124, 128).

Some lower-resource countries, including India, South Africa and some Latin American countries, initiated medical genetics centers in the 1960s and 1970s. However, reflecting the pattern in high-resource countries, most were academic-and research-orientated centers that provided limited services for the urban educated population that could access and afford them (47, 79). There are outstanding exceptions. A public health–oriented genetics program was initiated in Hungary in the 1960s (27); Cuba integrated medical genetic services at the primary, secondary, and tertiary levels of health care in 1981 (43); a primary health care clinical genetic service staffed mainly with genetic trained nurses was established in 1990 in the rural Limpopo province of South Africa (23); and Iran is currently integrating
genetic approaches into primary health care (A. Samavat & B. Modell, personal communication).

The relationship between public health and medical genetics was objectively analyzed in 1981 when the WHO recognized that the epidemiological transition was driving the initiation of genetics services in lower-resource nations. It realized that existing models in high-resource countries were inappropriate, and that lower-resource countries needed to develop public health approaches that could be delivered through primary health care (128). The challenge was to apply the general principles gleaned from the basic science-orientated, individual- and family-directed medical genetics practice of the industrialized world to the public and primary health care systems of lower-resource countries (65, 79, 128). The result has been the stepwise formulation of an integrated, holistic approach to the initiation and development of genetics services both for lower-resource nations and for underserved populations in high-resource countries (4, 123, 124, 129).

A 1985 WHO report resolved some important ambiguities and formulated the following basic philosophical and ethical principles (65, 128).

- The aim of medical genetics services is to help people with a genetic disadvantage to live and reproduce as normally as possible. This definition (a) embraces both people with a congenital disorder and people at increased reproductive risk (patients, parents, other relatives, and those identified by genetic screening), and (b) establishes that patient care and prevention are not alternatives, but are complementary and inseparable aspects of a service for individuals and families.

- To address patient care and prevention simultaneously calls for “an integrated strategy combining best possible patient care, with prevention by community education, population screening, genetic counseling, and the availability of prenatal diagnosis.” This was defined as a control program. The word control, “inherited” from earlier WHO programs for infectious diseases, was redefined in the context of medical genetics, but some still find it unacceptable. The concept may be redefined today as “an integrated strategy combining best possible patient care, with risk identification and management through community education, population screening, genetic counseling, and availability of appropriate services.” The definition applies equally to congenital disorders of genetic and environmental origin or both, thus encompassing all birth defects.

- Core ethical principles of genetic counseling include (a) the autonomy of the individual or couple, (b) their right to full information, and (c) strict confidentiality. These principles emphasize the community’s right to information, patients’ and families’ rights to genetic counseling, and professionals’ collective responsibility to provide these interventions.

The report also concluded that the broadest of the real ethical issues is the limited availability of medical genetic services for underserved populations.
In the process of developing and refining these concepts, it soon became clear that strategies initially envisaged as particularly appropriate for lower-resource countries are universally applicable because high-resource countries do not have equitable medical genetic services. Barriers to access include ethnicity, language, culture, religion, poverty, and geographic location (77, 129).

Since 1994, the WHO Office for the Eastern Mediterranean Region (EMRO) has been developing the concept of community genetics services and facilitating thinking on ethical issues particularly relevant to Islamic societies. These include appropriate genetic counseling in relation to customary consanguineous marriage, the acceptability of prenatal diagnosis and selective abortion, and noninvasive perinatal postmortem examination (4). Concluding reports from the WHO Human Genetics Program present detailed guidance for countries on the rational development of medical genetic services (123, 124, 129).

THE BURDEN OF CONGENITAL DISORDERS

In view of the pervading influence of genetic factors and the way that clinical services are organized, it is not realistic to deal with the genetic component in any medical service in isolation. A pediatrician examining a child with mental retardation must take into account all possible prenatal causes, whether environmental, genetic, or a combination of both, and management will not necessarily be related to cause. Thus, we include disorders due to prenatal environmental risks in this assessment of the global burden of congenital disorders.

Outcomes for infants born with a severe congenital disorder depend on the level of development of health services. In low-resource settings most affected infants die undiagnosed, but as services become available an increasing proportion are cured (mainly by pediatric surgery), or maintain good health on continuing treatment (congenital hypothyroidism, phenylketonuria, thalassemia), or survive with chronic disability (Down syndrome, neural tube defect, mental retardation) (32). As survival of those in the last two groups improves, the number requiring care rises annually, and there comes a point when health planners are forced to recognize the true burden of these disorders for individuals and families, their high cost to health systems, and the need for prevention (see Figure 4) (5). This process has been particularly marked where the epidemiological transition has been rapid, as in much of the Middle East.

When considering the epidemiology of congenital disorders it is necessary to distinguish clearly between birth prevalence and population prevalence. Birth prevalence (number of infants who have or will develop a congenital disorder per 1000 live births) is the appropriate prevalence indicator. It enables comparisons between different populations, assessment of changes with time, and projections of health burden. Population prevalence (affected individuals per 1000 of the whole population) is usually far lower than birth prevalence because most congenital disorders shorten life. In low-resource countries this effect is so marked that surveys identify few or no living individuals with a congenital disorder, as occurred with
Figure 4  Thalassemia major: estimated increase in patient numbers with three historical management schemes. Calculations for a situation where there is one birth per year. With no treatment (bottom line) patients survive less than 2 years so the cumulative number of living patients is only twice the annual number born. Regular blood transfusion (initiated in the late 1950s in some centers) improves survival but leads to death from transfusional iron overload at a median age of 16 years: The cumulative number of living patients therefore stabilizes at 16 times the annual number born. Since the mid-1970s, treatment has included nightly subcutaneous infusion of the iron chelating agent desferrioxamine, and bone marrow transplantation (BMT) became available in the mid-1980s for the approximately 25% of patients with a fully compatible related donor. Those remaining on transfusion are expected to live more than 50 years, so the number of patients requiring treatment is expected to stabilize at about 50 times the annual number born. In the same interval, the cost of patient care (1997 prices) rose from nearly nothing to $2400 per patient per year for transfusion alone, to $17,250 per patient per year for current conventional treatment (49). Because about 80% of treatment cost is for iron chelating drugs, which are marketed at the same price worldwide, this data permits reliable projections for increasing costs of patient care for any country.

Down syndrome in South Africa (22). As effective treatment becomes available population prevalence rises gradually toward birth prevalence and will ultimately equal it, in the absence of prevention.

ENVIRONMENTALLY DETERMINED CONGENITAL DISORDERS

Disorders due to environmental teratogens are the most readily preventable group of congenital disorders. A teratogen is a physical or chemical agent or an altered maternal metabolic state that adversely affects the functional or structural...
development of the embryo or fetus. Common teratogens include maternal infections (including, we propose, HIV/AIDS), maternal malnutrition or illness, recreational and therapeutic drugs, and environmental toxins.

Maternal Infections

Teratogenic maternal infections include rubella, toxoplasmosis, cytomegalovirus, syphilis, and HIV/AIDS. In high-resource countries most congenital infections are effectively controlled. Congenital rubella has been virtually eradicated by universal immunization (usually with the triple measles/mumps/rubella vaccine). Toxoplasmosis can be largely prevented by telling pregnant women how to avoid contact with cat excreta or undercooked meat. There is still no way to avoid cytomegalovirus infection. However, major anomalies associated with fetal rubella, toxoplasmosis, and cytomegalovirus can be detected by fetal anomaly scanning (85), permitting the option of selective abortion. Congenital syphilis has been virtually eliminated by screening and penicillin treatment during pregnancy. Vertical transmission of HIV/AIDS prior to delivery is preventable by public information, screening of pregnant women, and drug treatment to reduce transmission to the fetus and improve the mother’s survival.

However, only 40% of all countries have rubella immunization programs: The remainder experience rubella epidemics every four to seven years, and an estimated 263,000 children with congenital rubella are born annually—a global birth prevalence of almost 2/1000 (26). In the absence of prevention, about 0.4/1000 infants have congenital toxoplasmosis and a similar proportion have congenital cytomegalovirus (10, 93). The prevalence of disorders due to sexually transmitted diseases varies more widely. Congenital syphilis is among the world’s major causes of neonatal death. In sub-Saharan Africa 6% to 16% of pregnant women have active syphilis (71, 72), and it is assumed that 4–10/1000 live-born babies suffer from congenital syphilis.

Globally, more than 600,000 infants are infected annually with HIV by vertical transmission from their mother, the majority in Saharan Africa, the epicenter of the pandemic, where adult HIV prevalence reaches 38/1000 in parts of southern Africa (103). The uncontrolled spread of HIV in sub-Saharan Africa can partly be ascribed to the absence of a comprehensive, experienced health infrastructure capable of accessing the whole population with information and the means of prevention. The approaches and services needed to prevent vertical HIV transmission from mother to child, and for care for children with HIV/AIDS, are the same as those needed for the care and prevention of congenital disorders. This raises the question of the relationship between services needed for the control of HIV/AIDS and those needed for the control of other congenital disorders. In lower-resource countries most of the care and prevention of childhood disability, whether acquired or congenital, is undertaken in primary health care (23). However, the serious implications of the AIDS crisis may potentially stimulate the creation of disease-specific “vertical” programs for managing maternal and childhood HIV/AIDS. Implementing a
vertical service would take priority in many countries, ensuring that systems for the management of other problems, and primary health care itself, would stagnate. The ideal approach for controlling childhood HIV/AIDS is to focus on building the overarching framework of primary health care, lack of which allows uncontrolled spread of infection in the first place, and which will still exist once the HIV/AIDS pandemic is controlled.

Maternal Malnutrition

Iodine deficiency is very common in inland, arid, and mountainous regions. It can cause spontaneous abortion and neonatal death, and it affects intellectual development to varying degrees: In 1997, at least 60,000 cretins were born due to iodine deficiency (globally, 0.45/1000) (100). Iodine deficiency was eliminated long ago in high-resource countries by iodinating salt. In 1990, UNICEF initiated a major program for preventing iodine deficiency, and by 2002 iodized salt was used in 70% of households worldwide, protecting 85 million infants annually—but 35 remain unprotected (83, 100). (We discuss dietary folate deficiency and maternal folate metabolism in “Genetic Risk Factors,” below.)

Maternal Illness

Maternal insulin-dependent diabetes affects about 0.5% of pregnancies in high-resource countries. It significantly increases the risk of serious congenital malformation. For example, in a Libyan study, about 14% of diabetic mothers and 3% of nondiabetic mothers had infants with easily recognizable congenital malformations (4, 50). In high-resource societies risk is greatly reduced by good diabetic control, and diabetic mothers are offered fetal anomaly scanning with the option of selective abortion if the fetus is affected. Epilepsy and its drug treatment can also lead to malformation, and risks are managed in the same way. In addition, a growing proportion of people with inherited disorders (e.g., sickle cell disorder, thalassemia, cystic fibrosis, phenylketonuria) are surviving to reproductive age, and health care services need to provide appropriate care before and during pregnancy (4, 123).

Drugs—Recreational and Therapeutic

In the industrialized world, the average prevalence of fetal alcohol syndrome is 0.97/1000, but prevalence is much higher in South Africa. In a study in the wine-growing Western Cape Province, 24% of women attending for antenatal care had an alcohol intake entailing a high risk for the fetus, and over 4% of 6 to 7 year-old children had fetal alcohol syndrome (the highest rate ever reported for a stable community). Comparable studies found that in urban Johannesburg 2.7% of children were affected, but in the rural Limpopo Province there were few affected, indicating a role of urbanization in this growing problem (23, 25, 107). If the findings apply to the rest of sub-Saharan Africa, up to a quarter of a million
affected children may be born annually in Africa alone. Similar studies are needed in all lower-resource countries where alcohol is used by women of reproductive age.

Maternal smoking increases the risk of spontaneous abortion, preterm delivery, and sudden infant death syndrome, with a small increased risk of cleft lip and/or palate (123). Health education discouraging use of alcohol and smoking during pregnancy is relatively effective in high-resource countries. Its potential in lower-resource countries remains to be assessed.

Pregnant women are rarely exposed to teratogenic therapeutic drugs in high-resource countries, but in lower-resource countries over-the-counter sales and self-medication are common and risks are higher. Teratogenic drugs such as phenytoin may be used instead of safer, more expensive alternatives (92); thalidomide (withdrawn from the market in the early 1970s) is prescribed for leprosy, and misoprostol (a teratogenic antiulcer drug) is sometimes used as an abortifacient where abortion is illegal. The Latin American Collaborative Study of Congenital Malformations (ECLAM) reported 33 infants with limb defects due to thalidomide, and in Brazil 34% of mothers of infants with malformations due to vascular disruption had used misoprostol during their pregnancy (20, 75). The true scale of such problems can only be assessed through congenital abnormality monitoring systems.

When the above figures are considered together, we calculate that, in high-resource countries, implementing basic reproductive health approaches avoids early death or disability in 10–15/1000 live births. That is, they add 1% to 1.5% of unaffected children to each birth cohort, equivalent to a gain of more than one year in healthy life expectancy per head of the population. Implementing these approaches is feasible in most lower-resource countries (123), and would significantly improve the long-term health and well being of their populations.

GENETICALLY DETERMINED CONGENITAL DISORDERS

When evident environmental risks are controlled a large and heterogeneous group of congenital disorders remain. They include malformations of single organs or systems (e.g., club foot, congenital heart defects, cleft lip and palate), multiple congenital malformations, genetic syndromes encompassing all forms of disability, and intractable metabolic disorders. Causes include single gene defects, chromosomal abnormalities, and multifactorial disorders resulting from interactions between environmental and genetic factors. Because of their major genetic component, these may be called genetically determined congenital disorders. Table 3 summarizes baseline data on the birth prevalence and outcomes of these disorders in populations of northern European origin (8, 29, 37, 41).

Very limited prevalence data are available from lower-resource countries because of incomplete registration of births and deaths, poor health-related statistics, limited facilities for diagnosis including diagnosis of cause of death, and reliance
TABLE 3  Approximate birth prevalence and outcomes of congenital/genetic disorders in populations of northern European origin (based on Baird, Czeizel, etc.)

<table>
<thead>
<tr>
<th>Group of conditions</th>
<th>Birth prevalence /1000</th>
<th>% of early mortality</th>
<th>% of chronic problems</th>
<th>% cure</th>
<th>Early mortality /1000</th>
<th>Chronic problems /1000</th>
<th>Cure /1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital malformations</td>
<td>36.5</td>
<td>22</td>
<td>24</td>
<td>54</td>
<td>8.0</td>
<td>8.8</td>
<td>19.7</td>
</tr>
<tr>
<td>Chromosomal disorders</td>
<td>3.8</td>
<td>34</td>
<td>64</td>
<td>2</td>
<td>1.3</td>
<td>2.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Genetic risk factor</td>
<td>2.6</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>0.0</td>
<td>0.0</td>
<td>2.6</td>
</tr>
<tr>
<td>Single gene disorders</td>
<td>12.3</td>
<td>58</td>
<td>31</td>
<td>11</td>
<td>7.1</td>
<td>3.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Total</td>
<td>55.2</td>
<td>29.8</td>
<td>27.2</td>
<td>43.0</td>
<td>16.5</td>
<td>15.0</td>
<td>23.7</td>
</tr>
</tbody>
</table>

The broad groups shown overlap considerably. In this review, malformations due to chromosomal abnormalities or single gene defects are classed by cause, rather than with congenital malformations.

Figures apply for situations where environmental risks are largely controlled.

on hospital-based as opposed to population-based studies (4, 72, 123, 128). However, there is growing confidence that the baseline prevalence data obtained in higher-resource countries is broadly applicable. Therefore, it is possible to generate country-specific prevalence estimates by including local data on carrier rates for common recessive conditions, maternal age distribution, and prevalence of consanguineous marriage (11, 12, 99, 119, 120). Figure 5 shows the baseline burden of serious genetically determined disorders calculated by aggregating such country estimates (B. Modell & A. Czeizel, work in progress). The total is considerably higher in lower- than in high-resource countries.

Annex 2 (follow the Supplemental Material link from the Annual Reviews home page at http://www.annualreviews.org) gives more information on factors considered when undertaking the calculations.

Congenital Malformations

Congenital malformations are the largest and most treatable group of genetically determined congenital disorders. Table 4 shows their approximate prevalence by organ system and broad outcomes in a higher-resource situation.

CARE AND PREVENTION OF CONGENITAL MALFORMATIONS In the absence of health services, most severe malformations are lethal in early childhood. However, when primary health care and pediatric surgery are available, over 40% can be corrected (e.g., congenital heart defects, pyloric stenosis, cleft lip and palate, squint, cataracts, clubfoot, undescended testicles). About half the remainder cause early death, and about half cause chronic disability (29, 32, 121).
TABLE 4  Birth prevalence and outcomes of the main groups of major congenital malformation, in the absence of prevention. Groups are listed in order of decreasing prevalence.a

<table>
<thead>
<tr>
<th>Group of congenital malformation</th>
<th>Prevalence /1000 live births</th>
<th>% of total</th>
<th>Early deaths /1000 live births</th>
<th>Cure /1000 live births</th>
<th>Chronic problems /1000 live births</th>
<th>% of early deaths due to malformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular system</td>
<td>7.9</td>
<td>27.0</td>
<td>2.7</td>
<td>3.9</td>
<td>1.4</td>
<td>41.2</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>2.2</td>
<td>7.5</td>
<td>1.7</td>
<td>0.1</td>
<td>0.4</td>
<td>26.5</td>
</tr>
<tr>
<td>Alimentary system</td>
<td>2.8</td>
<td>9.6</td>
<td>0.6</td>
<td>2.0</td>
<td>0.1</td>
<td>9.9</td>
</tr>
<tr>
<td>Skeletal system</td>
<td>2.1</td>
<td>7.2</td>
<td>0.4</td>
<td>1.3</td>
<td>0.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Urinary organs</td>
<td>1.6</td>
<td>5.5</td>
<td>0.3</td>
<td>0.7</td>
<td>0.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>0.3</td>
<td>1.0</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Eye</td>
<td>0.3</td>
<td>1.0</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Cleft palate, +/− cleft lip</td>
<td>1.4</td>
<td>4.8</td>
<td>0.0</td>
<td>1.1</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Ear, face, neck</td>
<td>0.5</td>
<td>1.7</td>
<td>0.0</td>
<td>0.3</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Genital organs</td>
<td>7.5</td>
<td>25.6</td>
<td>0.0</td>
<td>6.5</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Miscellaneous, including multiple</td>
<td>2.7</td>
<td>9.2</td>
<td>0.6</td>
<td>1.6</td>
<td>0.6</td>
<td>9.6</td>
</tr>
<tr>
<td>TOTAL</td>
<td>29.3</td>
<td>100</td>
<td>6.5</td>
<td>17.7</td>
<td>5.1</td>
<td>100</td>
</tr>
<tr>
<td>Percent of malformations</td>
<td>100</td>
<td>22.2</td>
<td>60.4</td>
<td>17.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aPrevalences are based on Reference 29, with the exclusion of (a) musculoskeletal malformations because the high prevalence of congenital dislocation of the hip in Hungary distorts the figures, and (b) congenital malformations associated with chromosomal anomalies because chromosomal disorders are discussed separately. Estimates of outcome are from Czeizel & Sankaranarayanan (29).

Fetal anomaly scanning at 18 to 20 weeks’ gestation is now routine in many high-resource countries. It can detect most severe malformations, permitting (a) planned delivery of affected infants in a facility with expert pediatric surgery, and (b) the option of selective abortion when an intractable abnormality is present. Figure 6 shows the current rate of pregnancy termination for severe congenital disorders in Western Europe, where approximately 50% of pregnancies in which the fetus has an intractable severe congenital disorder are terminated (37).

Fetal anomaly scanning requires high-quality equipment and training and is often considered outside the range of lower-resource countries. However, ultrasound examination is highly valued in general obstetrics, equipment is improving, costs are falling, and personnel are equally receptive of training in lower- and higher-resource settings. Consequently, there is increasing scope for fetal anomaly scanning, especially for high-risk groups of women.
Figure 6  Data from the eighth EUROCAT report (37), showing the rate, per 1000 live births, of terminated pregnancies for severe congenital malformations in participating congenital abnormality registers in Western European countries. If not detected, some affected pregnancies would have ended in a stillbirth, but most would have ended with a live-born child with an intractable, severe congenital malformation. On average in Western Europe at present, an average of 3.5/1000 pregnancies are terminated because of severe fetal abnormality.

Chromosomal Disorders

The most common chromosomal disorders include Down syndrome, which is often associated with congenital heart disease and causes mental retardation, and sex chromosome abnormalities, which have a relatively small effect on survival but seriously affect quality of life (46).

CARE AND PREVENTION OF DOWN SYNDROME  In the absence of specialist care most children with Down syndrome die in infancy or childhood from their congenital heart disease or infections (21, 22). In settings where complications are treated and educational and social support is available, quality of life has greatly improved and average survival has increased to over 50 years—the maximum life span of a condition that often involves premature Alzheimer’s disease (9). In high-resource countries, the population prevalence of Down syndrome is therefore approaching 70% of its birth prevalence though this is falling because of family planning, available information on age-related risk, antenatal screening, prenatal diagnosis, and selective abortion.

Family planning  When couples use family planning there is usually a marked fall in the proportion of older parents, and an even more marked fall in the birth prevalence of infants with Down syndrome and other chromosomal disorders whose prevalence increases with maternal age. Figure 7 illustrates the changing
proportion of older mothers in Western Europe since the 1950s, as family planning has been more widely used. The birth prevalence of Down syndrome consequently fell from about 2.5 to less than 1.5/1000 live births between 1950 and 1970, before prenatal diagnosis was available (66). The proportion of older mothers has since risen, but the birth prevalence of Down syndrome has not, because of prevention. The present situation in some lower-resource countries resembles that in industrialized countries prior to 1950. In these circumstances, promoting family planning to older women might greatly reduce the birth prevalence of Down syndrome.

Population screening and prenatal diagnosis When prenatal diagnosis by fetal karyotyping (with the option of selective abortion) is available and acceptable, its impact depends on how it is offered. The essential first step is to identify women at increased risk to offer them definitive prenatal diagnosis. In high-resource countries the initial approach was originally to offer fetal karyotyping to older women, but in many countries all pregnant women are now offered routine screening, using various combinations of ultrasound scanning and maternal blood tests, in the first or second trimester of pregnancy. This approach detects up to 80% of fetuses with Down syndrome (112), and in Western Europe today an average of 50% of affected pregnancies end in abortion (37).

In many lower-resource countries prenatal diagnosis is available for those who are able to pay, but these are not necessarily those at highest risk. Even when karyotyping is available within a health service, access is often restricted because of limited cytogenetic laboratory services, ignorance that the service is available among mothers and primary health care workers, late booking for pregnancy care, and cost.

When karyotyping is available, the simplest form of screening for risk of Down syndrome, a routine simple inquiry of the pregnant woman’s age, is feasible in primary health care in lower-resource countries. However, experience in South Africa is illuminating. Down syndrome was long, erroneously, considered rare in Africa, but this was because of high mortality rather than low birth prevalence (23). It is also known that about 80% of older South African women offered genetic counseling request amniocentesis, and a similar percentage with a fetus with a serious congenital disorder accept abortion (78, 108). In Johannesburg, medical genetic and prenatal diagnostic services have been available since the 1980s at minimal cost in three academic hospitals. However, less than 4% of the approximately 6000 older women who deliver annually in these hospitals actually have an amniocentesis. This is mainly because they were not asked their age or offered genetic counseling, even though 70% presented in primary health care before 20 weeks’ gestation. (S. Schön & A.L. Christianson, unpublished data). Formal training of primary health care practitioners is essential for even such a simple and obvious screening program to work—a lesson that should have been learned from experience in the industrialized world.
Genetic Risk Factors

Genetic risk factors are common gene variants that cause problems relatively rarely. The category includes many risk factors for later-onset disease such as hemochromatosis, alpha-1 antitrypsin deficiency, and the apolipoprotein E4 polymorphism. Examples considered here, in the context of congenital disorders, are Rhesus negativity, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and genetic factors affecting folate metabolism.

RHESUS NEGATIVITY Antenatal screening for Rhesus blood group was the first genetic population screening program implemented for preventing fetal abnormality. The Rhesus-negative (d) gene frequency ranges from 0.45 to less than 0.01 in different populations (68). An average of 6% of the world population are homozygous Rhesus negative (dd) and at risk for blood group incompatibility between mother and fetus. Immunization of the mother can lead to intrauterine or neonatal death from anemia, or severe neonatal jaundice with risk of physical and mental handicap. This is prevented by administering anti-Rhesus (anti-D) antibody to Rhesus-negative women during pregnancy and after delivery to destroy any Rhesus-positive red cells that have passed from fetus to mother. However, screening and prophylactic anti-D is not available for all groups that need it (24).

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY An estimated 7.5% of the world population carry a gene for this X-linked condition, and 3.4% are glucose-6-phosphate dehydrogenase (G6PD) deficient to varying degrees (119). There are hundreds of variants with differing clinical severity (60, 105). Male hemizygotes, female homozygotes, and some carriers are at varying levels of risk of hemolytic anemia induced by infection, drugs, or eating broad (fava) beans. About 252,000 of the approximately 5 million G6PD-deficient infants born annually (mainly in the eastern Mediterranean, South and East Asia, and Africa) are at risk of neonatal jaundice severe enough to cause death or intellectual disability, cerebral palsy, and deafness. In high-resource settings the diagnosis and care of infants with neonatal jaundice is so effective that G6PD deficiency is barely considered a problem. However, susceptible infants born in lower-resource countries risk significant mortality and morbidity (60, 105, 119).

GENETIC FACTORS AFFECTING FOLATE METABOLISM Tetrahydrofolate (the reduced form of folate) is crucial for cell growth and multiplication, and for morphogenetic movements (such as closure of the neural tube) that depend on focal rapid cell division. Genetic and environmental factors that reduce the availability of tetrahydrofolate predispose to neural tube defects. The enzyme methyl tetrahydrofolate reductase converts dietary folates to tetrahydrofolate. Common genetic polymorphisms of the gene for this enzyme can restrict the availability of tetrahydrofolate (15, 91). They also predispose to common disorders of adult life,
including cardiovascular disease, certain cancers, and possibly dementia, by raising plasma homocysteine levels (55, 62, 109). Thus, most populations include a subgroup at increased genetic risk of having children with neural tube defects. It is neither feasible nor necessary to identify the genetically predisposed group by genetic testing: They can be protected effectively by increasing the dietary folic acid intake of the entire population (35, 45, 69, 84, 111).

Randomized trials have provided conclusive evidence that periconception supplementation with folic acid or multivitamins prevents neural tube defects, and have provided convincing evidence of a similar, though less marked, effect on other congenital malformations (30, 31, 33, 56, 90, 111). The size of the effect depends on both the dose of folic acid and the local prevalence of neural tube defects (67, 110), and available data indicates that the potential effect is greatest in lower-resource communities (Figure 8) (126). If the likely effect on other malformations is included, if all women likely to become pregnant took folic acid supplements at a dose of 4 mg/day, up to 1.5 million unaffected children, who would otherwise have had a serious congenital disorder, might be born annually (Figure 8). However, the maximum effect is precluded by lack of knowledge, cost of vitamin supplements, and the fact that over 50% of pregnancies are unplanned. Folic acid fortification of essential foodstuffs is extremely cheap, has a negligible

Figure 8  Estimated gain per 1000 births in infants free of neural tube defect, with different doses of additional folic acid, in countries at different economic levels. The maximum net effect at the global level would be an increase of about 2 children born free of a congenital malformation per 1000 live births. However, the recommended levels for fortification of basic foodstuffs with folic acid are calculated to deliver between 0.2 and 0.35 mg/day. Calculations based on References 111 and 126.
effect on food price, is feasible in countries at all levels of development, and en-
ables the whole society to benefit (35, 126). Present recommended fortification
levels are suboptimal, and even in the presence of food fortification women who
may become pregnant should still take vitamin supplements.

Single Gene Disorders

More than 6000 early-onset single gene disorders exist (74). Most are rare and
their collective birth prevalence represents a balance between the frequency of
spontaneous mutations (increasing it) and the reproductive disadvantage of the
condition (decreasing it). However, some are common because heterozygotes have
a selective advantage.

Table 5 shows that the estimated global birth prevalence of the main categories of
single gene disorders is higher than that in populations of northern European origin,
owing to the high frequency of hemoglobin disorders and recessive disorders
related to customary consanguineous marriage in many lower-resource countries
(2, 6, 7, 115, 120).

Here we consider the care and prevention of a few common single gene disorders
to illustrate what is feasible in a low-resource environment.

Hemoglobin disorders (thalassemias and sickle cell disorders) are common
because heterozygotes are protected against death from Falciparum malaria. About
5% of the world population carries a clinically significant globin gene variant, and

**TABLE 5** Estimated global birth prevalence of different groups of single gene disorders
among northern Europeans and worldwide

<table>
<thead>
<tr>
<th>Group of disorder</th>
<th>Northern Europeans</th>
<th>World</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Births/1000</td>
<td>% of total</td>
</tr>
<tr>
<td>Dominant</td>
<td>7</td>
<td>58.7</td>
</tr>
<tr>
<td>X-linked</td>
<td>1.3</td>
<td>10.9</td>
</tr>
<tr>
<td>Hemoglobin disorders*</td>
<td>0.5</td>
<td>4.2</td>
</tr>
<tr>
<td>Other recessive disorders</td>
<td>1.7</td>
<td>14.3</td>
</tr>
<tr>
<td>Recessive disorders related to consanguinity</td>
<td>0.22</td>
<td>1.8</td>
</tr>
<tr>
<td>Total recessive</td>
<td>2.42</td>
<td>20.3</td>
</tr>
<tr>
<td>Genetic type unknown</td>
<td>1.2</td>
<td>10.1</td>
</tr>
<tr>
<td>Total</td>
<td>11.92</td>
<td>10.1</td>
</tr>
</tbody>
</table>

*Hemoglobin disorders (B. Modell, unpublished data)

**Birth prevalence/1000** | **% of affected births**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Birth prevalence/1000</th>
<th>% of affected births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell disorders</td>
<td>1.93</td>
<td>82</td>
</tr>
<tr>
<td>Thalassemias</td>
<td>0.43</td>
<td>18</td>
</tr>
<tr>
<td>Total Hb disorders</td>
<td>2.37</td>
<td>100</td>
</tr>
</tbody>
</table>
at least 2.3/1000 of all children born are homozygous and a majority die in the first years of life in the absence of care (57). Hemoglobin disorders are most common in lower-resource countries, but migration is steadily increasing their prevalence in high-resource settings. More than 0.4/1000 pregnancies are affected in North America (76a) and more than 0.56/1000 are affected in the United Kingdom (34; ethnicity data from the 2001 population census at http://www.statistics.gov.uk). Thalassemias and sickle cell disorders have very different clinical and public health implications.

Beta thalassemia major, an intractable anemia, is particularly common in the Mediterranean, the Middle East, and Asia. Treatment by regular monthly blood transfusion, plus iron chelation therapy to remove excess iron introduced in blood, can ensure good survival but is burdensome and expensive (49, 120). Patients with a fully compatible related donor (about 25%) can be cured by bone marrow transplant. In countries where thalassemia is prevalent, it provides a “point of entry” for medical genetics services because the high cost of drug treatment, the feasibility of carrier screening, and the high demand for prenatal diagnosis by at-risk couples make prevention very cost-effective (19, 65). Consequently, prevention programs based on carrier screening and DNA-based prenatal diagnosis are being established in a growing number of lower-resource countries, and provide both a model and a vehicle for further developing genetics services (5).

Sickle cell disorders cause anemia and increased susceptibility to infections, with unpredictable episodes of intravascular sickling that lead to severe pain and tissue damage (2, 88). Neonatal screening for sickle cell disorders is established in the United States and parts of Europe because once risk is recognized, simple interventions, including information for parents and prophylactic antibiotics or antimalarials, greatly improve survival and quality of life. Prenatal diagnosis is also available. In Africa, an average of 7.4/1000 children are born affected (Table 6), with a maximum of more than 20/1000 in some regions (2, 6). In rural settings, most affected children die undiagnosed from malaria or other infections in infancy (2, 38), but in urban areas basic health care is usually available, resulting in improved survival. Sickle cell disorders account for at least 4% of under-five mortality in West and Middle Africa, rising to more than 8% in some countries, and that at least a million urban sub-Saharan African families now include one or more members with sickle cell disorder. Providing these families with basic genetic counseling and support greatly improves affected children’s quality of life, reduces demands on health services, and is highly cost-effective (O.O. Akinyanju, personal communications). In parts of Africa prenatal diagnosis is available and is often requested, but only a minute proportion of those who want it can afford it (3). Even in the face of the AIDS epidemic, this huge and growing health problem should not be ignored.

Oculo-cutaneous albinism is the second most common recessive disorder in sub-Saharan Africa, with a prevalence of 0.2–0.26/1000. Prevalence is higher where consanguineous marriage is customary, the highest recorded being 1/1000 among the Tonga people of Zimbabwe. Affected people have visual problems, are
<table>
<thead>
<tr>
<th>Region</th>
<th>Annual births, in thousands</th>
<th>Potential contribution to Annual births with Hb disorders, in thousands</th>
<th>Infant mortality, %</th>
<th>Under-five mortality, %</th>
<th>Minimum contribution to Infant mortality, %</th>
<th>Under-five mortality, %</th>
<th>Infant mortality, %</th>
<th>Urbanized infant mortality, %</th>
<th>Under-five mortality, %</th>
<th>Urbanized under-five mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Africa</td>
<td>9,350</td>
<td>1,11</td>
<td>148</td>
<td>40</td>
<td>13.3</td>
<td>7.9</td>
<td>40</td>
<td>8.0</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Middle Africa</td>
<td>4,515</td>
<td>125</td>
<td>579</td>
<td>36</td>
<td>10.3</td>
<td>6.4</td>
<td>36</td>
<td>6.6</td>
<td>4.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Eastern Africa</td>
<td>10,792</td>
<td>102</td>
<td>255</td>
<td>25</td>
<td>2.3</td>
<td>1.5</td>
<td>25</td>
<td>1.7</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Northern Africa</td>
<td>4,624</td>
<td>42</td>
<td>57</td>
<td>49</td>
<td>4.1</td>
<td>1.5</td>
<td>49</td>
<td>1.1</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Southern Africa</td>
<td>3,0778</td>
<td>97</td>
<td>77</td>
<td>54</td>
<td>0.0</td>
<td>0.0</td>
<td>54</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Africa</td>
<td>30,778</td>
<td>97</td>
<td>156</td>
<td>38</td>
<td>7.6</td>
<td>4.8</td>
<td>38</td>
<td>4.7</td>
<td>3.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

**TABLE 6** Estimated birth prevalence of sickle cell disorders in Africa, and their potential and minimum contribution to infant and under-five mortality.
prone to sunlight-induced skin disorders including squamous cell carcinoma, and bear a heavy psychosocial burden, being severely stigmatized by their disability. Susceptibility to skin cancer increases with age and proximity to the equator, and in Tanzania and Nigeria only 10% of affected people survive beyond 30 years of age (52–54, 58, 59). A great deal of protection is afforded by using sunscreen and consistently wearing clothes that cover skin (shady hat, long-sleeve shirts, long trousers)—two very simple interventions highly suitable for primary health care. Prenatal diagnosis for albinism was recently requested in South Africa, where it is now available (M. Ramsay, personal communication).

Implications of Customary Consanguineous Marriage

Many large populations have a cultural preference for consanguineous marriage (11, 70). Available data indicate that the birth prevalence of infants with recessively inherited disorders rises by about 7.0/1000 for every 0.01 increase in the coefficient of consanguinity \( F \) (12), enabling a consanguinity-related increment to be calculated when the prevalence of consanguineous marriage is known. A U.K. study shows that the birth prevalence of congenital disorders was twice as high among British Pakistanis (where \( F \approx 0.043 \)) as among the northern European population (\( F \approx 0.003 \)), and the proportion of children surviving with chronic disability was three times higher (Figure 9) (18, 64). There was a particular increase in severe neurological problems, including mental retardation with or without physical disability (Table 7). Prenatal diagnosis is currently feasible for an estimated 40% of genetically determined disorders, but unfortunately

<table>
<thead>
<tr>
<th>Group of conditions</th>
<th>Northern Europeans</th>
<th>British Pakistanis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malformations (including Chromosomal abnormalities)</td>
<td>5.0</td>
<td>7.6</td>
</tr>
<tr>
<td>Mental retardation and neurological problems</td>
<td>0.5</td>
<td>15.2</td>
</tr>
<tr>
<td>Severe mental retardation alone</td>
<td>0.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Mild mental retardation</td>
<td>5.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Idiopathic deafness</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Metabolic and hematological disorders</td>
<td>2.3</td>
<td>9.8</td>
</tr>
<tr>
<td>Other chronic disorders</td>
<td>3.6</td>
<td>4.3</td>
</tr>
<tr>
<td>Total</td>
<td>18.1</td>
<td>43.4</td>
</tr>
<tr>
<td>Prenatal diagnosis possible</td>
<td>7.2</td>
<td>17.4</td>
</tr>
<tr>
<td>Percent prenatal diagnosis possible</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

*Disability due to environmental causes is excluded. Data from the Birmingham birth study (17).
the molecular basis for the recessive single gene disorders influencing the development and functioning of the brain is almost completely unknown.

PREVENTION OF INHERITED DISORDERS

Preventing single gene disorders depends on identifying individuals at risk through their family history or by population screening, and informing them of their risk and options for reducing it. It calls for facilities to have precise genetic diagnosis, and highlights challenging issues such as prenatal diagnosis and selective abortion, preimplantation diagnosis, genetic screening, the need to educate health professionals, availability of full information for affected families, and need for consultation with the community. The question is, to what extent are such developments feasible, acceptable, and cost-effective in lower-resource countries?

A family history often allows identification of potential carriers of an inherited disorder and calculation of a statistical risk. However, it is difficult for people to make life-determining decisions on the basis of such information. They need to be able to progress to a precise genetic diagnosis, to find out definitely whether they are at risk or not, to act to reduce risk. Then, personal risk (e.g., for carriers of a gene for familial hypercholesterolemia) may be reduced by changes in lifestyle and drug treatment, whereas reproductive risk can be reduced by family planning and/or prenatal diagnosis with the option of selective abortion, or even by preimplantation genetic diagnosis. However currently the most common way for a couple to find they are definitely at reproductive risk is through the diagnosis of an affected child, and the diagnosis must often be based on the clinical picture and the family history only. One of the major hopes of the new genetic knowledge is that it will permit precise diagnosis in most cases.

When a precise diagnosis, using DNA or other methods, is feasible in an affected person (as for hemoglobin disorders, cystic fibrosis, and 30% to 40% of rare single gene disorders), precise carrier diagnosis and prenatal diagnosis are also usually possible. The characteristic features of a genetic diagnosis are (a) it is constitutional and, in principle, only needs to be done once, (b) it may be predictive of avoidable risks to the health of the individual or their children, and (c) it has implications for other family members.

Genetic counseling, commonly provided by non-medical counselors, is necessary to help people grasp the implications of a genetic diagnosis, the pattern of inheritance, and options for risk reduction. Basic genetic counseling is both feasible and increasingly necessary in primary health care (23, 82, 129). Prenatal diagnosis is challenging both technically and socially. It entails (a) developing highly specialized obstetric skills in ultrasound examination and fetal tissue sampling, (b) developing specialist cytogenetic and biochemical genetic diagnostic techniques, including DNA-based diagnosis, all performed to the highest possible standard, (c) resolving cultural and religious attitudes, and (d) addressing the practical issues of genetic population screening. Introducing such a service depends on, and is an important agent of, social change.
Figure 10  A family tree illustrating the different perspectives from primary health care and specialist services. The third child of the left-hand couple (A) has cystic fibrosis. The responsible pediatrician or clinical geneticist initiates family studies, starting with the affected person, to identify relatives who carry the same mutation. By contrast, primary care workers start with an unaffected person and work back to find out if there is an affected individual in the family. For example, the young woman (B) intends to marry her first cousin and visits her family doctor (or other responsible primary care worker) to enquire about possible genetic risk. The primary care worker takes a family history, identifies a cousin with a congenital disorder, and refers the couple for genetic counseling and specialist investigations.

The Genetic Family History

One objective in medical genetics is to identify the family at genetic risk, and a pictorial three-generation family tree is a powerful diagnostic tool for this purpose. Figure 10 shows two complementary approaches to risk identification. (a) Specialists usually start from an affected person and draw up a family tree to define inheritance pattern, identify at-risk relatives, calculate the degree of risk, and offer genetic testing when feasible (cascade testing). (b) Primary health care workers usually start with an unaffected person and explore their family history to identify affected relatives. Some risks can be managed in primary care (e.g., risk of cardiovascular disease or diabetes); others require referral to a specialist. Taking and interpreting a basic genetic family history to identify reproductive risk is an important element in preconception and early pregnancy care.

Family planning allows couples who know they are at risk to choose whether to have (further) children. Theoretically, when fertility is high, limiting family size could reduce the birth prevalence of affected children by up to 40% (4, 39, 123), and a fall of this order occurred in practice with phenylketonuria in Iran. However, in most high-resource countries, final family size is small and family planning alone can reduce affected birth prevalence by at most 10%.

The offer of prenatal diagnosis following diagnosis of the first affected child (retrospectively) is very important for families, but even 100% uptake reduces
affected birth prevalence by little more than family planning alone. Only prospective carrier detection and counseling is capable of bringing about a major reduction in the birth prevalence of inherited disorders (4, 121, 128). When reliable tests are available there are two possible approaches for prospective carrier detection—population screening, and extended family studies.

Genetic Population Screening
Population screening is a public health activity that requires commitment by the public health authorities. Screening to support clinical decision making is already routine during pregnancy (e.g., antenatal testing for blood group, rubella immunity, hepatitis B infection, etc.). New elements introduced with genetic screening are (a) the need for large-scale laboratory genetic diagnostic services, and (b) the objective of informed choice by the patient, which requires health workers to adjust attitudes and develop skills in imparting genetic information. Even though screening for hemoglobin disorders is now routine in many lower-resource countries (5), genetic carrier screening is still often perceived as controversial and appropriate only for high-resource countries.

The Practicalities of Genetic Screening
When an infrastructure for screening already exists, it is simplest to use it to deliver genetic screening, in preference to setting up a new system. In practice, people are offered screening at different stages in their lifecycle (Figure 11).

NEONATAL SCREENING

Clinical screening A routine, systematic clinical examination of all newborns by a trained primary health care practitioner is standard in most higher-resource countries. The objective is early diagnosis and management of recognizable congenital disorders. However, it is not standard practice in many low-resource countries. Careful recording and collation of diagnoses made at this point provides the basis for birth defect surveillance. This includes perinatal deaths: Even when full autopsies are not possible, noninvasive external postmortem examination is highly informative (23, 123).

Biochemical screening Biochemical screening is possible when reliable systems exist to collect and transport samples, return reports, and trace patients in the community after discharge from the hospital or clinic. In high-resource countries newborn blood spots are routinely collected for diagnosing congenital hypothyroidism and phenylketonuria; severe mental retardation is then avoided by appropriate life-long treatment. The prevalence of congenital hypothyroidism (usually due to maldevelopment of the thyroid gland) is approximately 0.25/1000 worldwide; that of phenylketonuria is around 0.1/1000 in most European and Middle Eastern populations. Screening for these two disorders has been initiated in countries in Latin America, the Middle East, parts of China, and the Philippines.
Figure 11  Because a genetic diagnosis is constitutional, people only need to be tested once. The chart shows points in a person’s lifecycle where genetic screening is offered in different countries. When a comprehensive health service is available, almost all newborns and pregnant women pass through the medical system, making pregnancy and birth ideal “turnstiles” for genetic screening. Once a screening program is set up at a particular point in cycle, the easiest option is to insert new forms of screening (including genetic screening) at the same point, even when this is not ideal. For example, screening for hemoglobin disorders in the United Kingdom is provided during pregnancy and at birth. New systems are needed for identifying genetic reproductive risk prior to pregnancy to allow at-risk couples access to the full range of choices for risk reduction. Examples include providing information and screening through high schools (e.g., in Montreal), outreach programs target young people (in Sardinia, the Maldives), or premarital screening (in Cyprus, Italy, and Greece). In Iran, premarital screening has been integrated into primary care nationwide (A. Samarvat, personal communication).

(43, 80, 122, 129). Neonatal screening for G6PD deficiency is available in Sardinia, Singapore, and Malaysia, where a severe mutation often causes neonatal jaundice (119). Neonatal screening for sickle cell disorders, which is routine in parts of the United States and Western Europe (73, 76a), would save thousands of lives a year if introduced in select sub-Saharan African countries (6, 7). Neonatal screening for G6PD deficiency should also be considered in certain West African countries, including Nigeria (105, 119).

SCREENING FOR CARRIERS OF RECESSIVE DISORDERS  Carriers of hemoglobin disorders can be detected by relatively simple blood tests. Though carrier screening is offered in numerous ways, people can choose among the full range of available options only if it is offered prior to pregnancy. With thalassemia, population screening backed up with availability of prenatal diagnosis can reduce the affected birth prevalence to less than 10% of expectation, and thus is highly cost-effective
As a result, carrier screening for hemoglobin disorders is now available in at least 12 lower-resource countries, and prenatal diagnosis is available in at least 25 lower-resource countries (5), and these services continue to spread. This experience conclusively demonstrates that DNA-based genetic diagnostic services, genetic screening, and prenatal diagnosis are applicable in a wide range of lower-resource settings. Once established, these approaches may extend to other inherited disorders, stimulating wider applications of DNA technology.

**The Role of Extended Family Studies**

In communities with a cultural preference for consanguineous marriage, gene variants are effectively trapped within extended family groupings. Hence, after the diagnosis of an affected child, extended family studies may identify many carriers and at-risk couples prior to marriage or reproduction. A study in Pakistan using thalassemia as a model shows that an approach targeting the extended family is feasible and cost-effective (1). It produces a high yield of carriers and at-risk couples, counseling is facilitated because family members often have contact with an affected child, and usually only one gene variant is present in a given family, thus simplifying and reducing the cost of DNA-based diagnosis. This approach can overcome the problems of a weak health infrastructure. It applies equally for all inherited disorders, whether common or rare. Hence, screening for a wide range of recessive disorders, with family counseling and family studies, could prove unusually valuable in such communities (4).

**The Power of Prevention**

Table 8 summarizes the potential effects of all the interventions mentioned above on the birth prevalence of genetically determined congenital disorders. Many effective approaches are simple, inexpensive, and noncontroversial. When all available interventions are implemented, as is increasingly the case in high-resource countries, the total burden of congenital disorders may be reduced by more than 70%—a fall in affected births of almost 40/1000, equivalent to a gain of almost three years of healthy life per head of the population (32). Currently, the greatest effect by far is in preventing congenital malformations, the least is in preventing single gene disorders. There is clearly a priority need for new, more effective, and more acceptable approaches for diagnosing and preventing single gene disorders, especially for recessive disorders (51).

**CONGENITAL DISORDERS AND INFANT AND CHILD MORTALITY**

Table 9 shows the estimated annual number of infants born worldwide with a severe genetically determined congenital disorder, derived by applying the prevalence rates shown in Figure 4 to available population data (99). The global figure,
TABLE 8  Summary of estimated potential effects of current interventions for preventing genetically determined congenital disorders

<table>
<thead>
<tr>
<th>Group of disorders</th>
<th>Birth prevalence/1000 live births</th>
<th>Intervention</th>
<th>Maximum fall in affected births or postnatal lives saved/1000 live births</th>
<th>Maximum reduction, %</th>
<th>Estimated average increase in longevity per head of population, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital malformations</td>
<td>36.5</td>
<td>Pediatric surgery</td>
<td>17.7</td>
<td>48.5</td>
<td>1.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Folic acid supplement</td>
<td>11.5</td>
<td>31.5</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prenatal diagnosis</td>
<td>3.5</td>
<td>9.6</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total congenital malfunctions</td>
<td>32.7</td>
<td>89.6</td>
<td>2.29</td>
</tr>
<tr>
<td>Chromosomal disorders</td>
<td>3.8</td>
<td>Family planning</td>
<td>0.75</td>
<td>19.7</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prenatal diagnosis</td>
<td>0.5</td>
<td>13.2</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total down</td>
<td>1.25</td>
<td>32.9</td>
<td>0.09</td>
</tr>
<tr>
<td>Genetic risk factors</td>
<td>2.4</td>
<td>Routine antenatal &amp; neonatal care</td>
<td>2.4</td>
<td>100.0</td>
<td>0.17</td>
</tr>
<tr>
<td>Inherited disorders</td>
<td>11.5</td>
<td>Genetic counseling</td>
<td>1.73</td>
<td>15.0</td>
<td>0.12</td>
</tr>
<tr>
<td>(severe, early onset)</td>
<td></td>
<td>Neonatal screening</td>
<td>0.7</td>
<td>6.1</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prenatal diagnosis</td>
<td>1.15</td>
<td>10.0</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total inherited</td>
<td>3.6</td>
<td>31.1</td>
<td>0.25</td>
</tr>
<tr>
<td>Total</td>
<td>54.2</td>
<td></td>
<td>39.9</td>
<td>73.7</td>
<td>2.8</td>
</tr>
</tbody>
</table>
**TABLE 9**  Estimated numbers (in thousands) of infants born annually with genetically determined congenital disorders, in the absence of prevention, by economic level

<table>
<thead>
<tr>
<th>Economic level</th>
<th>Dominant, X-linked, etc.</th>
<th>Malformations</th>
<th>Chromosomal</th>
<th>Genetic risk factors</th>
<th>Recessives</th>
<th>Total</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>High income</td>
<td>100</td>
<td>329</td>
<td>42</td>
<td>29</td>
<td>25</td>
<td>526</td>
<td>6.7</td>
</tr>
<tr>
<td>Upper-middle income</td>
<td>99</td>
<td>371</td>
<td>40</td>
<td>27</td>
<td>48</td>
<td>585</td>
<td>7.4</td>
</tr>
<tr>
<td>Lower-middle income</td>
<td>358</td>
<td>1257</td>
<td>138</td>
<td>56</td>
<td>170</td>
<td>1978</td>
<td>25.2</td>
</tr>
<tr>
<td>Low income</td>
<td>701</td>
<td>2840</td>
<td>303</td>
<td>201</td>
<td>728</td>
<td>4774</td>
<td>60.7</td>
</tr>
<tr>
<td>Total lower income</td>
<td>1157</td>
<td>4468</td>
<td>482</td>
<td>284</td>
<td>946</td>
<td>7337</td>
<td>93.3</td>
</tr>
<tr>
<td>World</td>
<td>1257</td>
<td>4798</td>
<td>524</td>
<td>313</td>
<td>972</td>
<td>7864</td>
<td>100</td>
</tr>
</tbody>
</table>

7.8 million, is in the same range as the estimated annual 7.5 million infant deaths and 10.8 million under-five deaths (Table 1).

Of the potential 530,000 infants that could be born affected with a serious congenital disorder in high-resource countries, up to 70% of infant defects are avoided or infant lives are saved by the interventions listed in Table 8 (32). In medium-resource countries, at least 30% of the 2.5 million infants born with a serious congenital disorder, and an estimated minimum 50% of the 4.8 million born in low-resource countries, die in infancy and childhood (i.e., a minimum of 3.3 million, but possibly as many as 5.3 million, children with congenital disorders die annually worldwide) (Table 10). However, a series of recent review articles by Black and colleagues (13, 17, 23a, 48, 106) on under-five deaths attribute 42% to neonatal disorders (including birth asphyxia, low birth weight, and perinatal problems) and 37% to infections (respiratory infections 19%, diarrhea 13%, malaria 9%, measles 5%, and AIDS 3%). Only 9% (970,000) were attributed to trauma and noncommunicable disorders, of which congenital disorders are a subset. They recognized that there is often more than one cause (e.g., 53% of the deaths are associated with malnutrition), but a possible role of congenital disorders as either cause or comorbid factor was not considered.

At first glance the fourfold difference between the two sets of estimates appears irreconcilable, but this is not necessarily so. Serious genetically determined congenital disorders predispose to infection and death. In lower-resource countries the deaths of such vulnerable children are absorbed into the general mortality statistics, unrecognized for what they truly represent (127, 129). For example, under-five deaths in West and Central Africa due to sickle cell disorders would be classed as due to malaria or other infection. Black and colleagues document a one-dimensional, infectious disease–orientated appraisal of a far more complex situation. It is now clear that congenital disorders contribute much more than...
### TABLE 10 Calculation of proportion of under-five mortality related to congenital disorders, by income level

<table>
<thead>
<tr>
<th>Region</th>
<th>Annual births, in thousands</th>
<th>Under-five mortality /1000</th>
<th>Annual under-five deaths, in thousands</th>
<th>Births with congenital disorder /1000</th>
<th>Mortality due to congenital disorder /1000</th>
<th>Annual under-five deaths with congenital disorder, in thousands</th>
<th>% of under-five deaths with congenital disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>High income</td>
<td>10,474</td>
<td>6.6</td>
<td>69</td>
<td>50.2</td>
<td>15.2</td>
<td>48</td>
<td>70</td>
</tr>
<tr>
<td>Upper-middle income</td>
<td>10,304</td>
<td>28.1</td>
<td>290</td>
<td>56.8</td>
<td>17.5</td>
<td>180</td>
<td>62</td>
</tr>
<tr>
<td>Lower-middle income</td>
<td>37,517</td>
<td>41.8</td>
<td>1569</td>
<td>52.7</td>
<td>32.0</td>
<td>1201</td>
<td>77</td>
</tr>
<tr>
<td>Low income</td>
<td>73,534</td>
<td>120.7</td>
<td>8874</td>
<td>64.9</td>
<td>52.0</td>
<td>3824</td>
<td>43</td>
</tr>
<tr>
<td>World</td>
<td>131,829</td>
<td>81.9</td>
<td>10,801</td>
<td>59.6</td>
<td>40.1</td>
<td>5284</td>
<td>49</td>
</tr>
</tbody>
</table>

*aAnnual under-five deaths with congenital disorder in high-resource countries were calculated on the basis of 30% of potential deaths, due to prevention.
previously suspected to infant and childhood mortality in lower-resource countries, and it is no more reasonable to exclude them than it is to exclude malnutrition as a factor in the world’s childhood deaths. Seen in this light, the previously obscured burden of congenital disorders should be enough to warrant greater attention, insight, and diligence from public health professionals, health care planners, and government officials in lower-resource nations.

Dilemmas in Treatment and Prevention

It is worth examining the reciprocity of, and tension between, approaches for the care and prevention of congenital disorders. The prime motivator for medical services worldwide is to improve health and reduce suffering, and the first obligation is to best possible patient care. This applies equally in lower- and high-resource countries. There is no mileage in suggesting that severe childhood disorders should be left untreated on grounds of cost: parents’ and health workers’ first concern will always be to achieve best possible care for affected infants and children. On the other hand, the cost of managing chronic disorders and disability is very high—for example, a severely mentally or physically handicapped person requires at least one full-time, life-long care provider.

Because labor costs are proportionate to a country’s resources, simple clinical interventions, information, and social and psychological support can all be managed in lower- as well as high-resource settings. However, things are different when specialist materials produced in high-resource countries are required because prices are usually the same worldwide. For example, the minimum estimated cost for treating hemophilia, phenylketonuria, and thalassemia is approximately 6,000–16,000 U.S. dollars per patient per year (44); most of the cost is for drugs and biological products (see legend to Figure 4). In high-resource countries these costs are usually covered by medical insurance, but in lower-resource countries most affected children must go untreated, and the knowledge that effective treatment exists but is inaccessible only makes matters worse. The dilemmas are identical to those highlighted by the current global struggle over production, patenting, and pricing of anti-AIDS drugs.

Health decision makers in lower-resource countries often face very difficult choices. For example, neonatal screening for congenital hypothyroidism is relatively expensive, but life-long thyroxine replacement is extremely cheap. By contrast, screening for phenylketonuria is cheap but affected infants need low-phenylalanine foods marketed in the West at often unaffordable prices. Consequently, governments in some Latin American and Eastern European countries have approved screening for congenital hypothyroidism but not for phenylketonuria (W. Werteleki, personal communication). In such situations there is increased interest in prevention. For example, in high-resource countries demand for prenatal diagnosis and selective abortion is relatively low for conditions with effective and acceptable treatment (phenylketonuria or hemophilia), and high when treatment is ineffective or perceived as unsatisfactory (Tay Sachs disease, Down
syndrome, thalassemia, cystic fibrosis). In a lower-resource environment, demand for prenatal diagnosis may be equally high for all of these conditions.

Developments in genomics will likely extend and intensify such dilemmas. The problem is foreshadowed by the current situation with Gaucher disease, a rare recessive disorder due to deficiency of the lysosomal enzyme glucosylceramide β-glucosidase. Gaucher disease can now be treated with regular infusions of recombinant enzyme, but the cost per patient is ten times higher than the already expensive treatments mentioned above, and this presents a significant challenge even in high-resource societies (44, 61). Large drug firms are interested in genomic approaches for treatment but have no economic motivation to develop cheap treatments, especially for rare conditions, and have limited commercial interest in prevention. On the contrary, economic considerations prioritize monopolies on expensive drugs. In a global context it is unrealistic to imagine that new expensive genomic treatments will benefit the vast majority of children with inherited disorders. In most cases the only realistic solution is to establish programs combining best possible patient care with prevention based on accurate genetic diagnosis and genetic counseling—and the sooner such programs are established, the more cost-effective they are.

Academic scientists are in a position to address the true needs of lower-resource countries. In our view, the top priorities are (a) acquiring an objective view of global realities, (b) training scientists from lower-resource countries in appropriate molecular technologies and providing ongoing support, (c) developing methods for cheap and reliable diagnosis of the widest possible range of inherited disorders, and (d) developing cheap nonproprietary drugs for treating genetic disorders.

MEDICAL GENETIC SERVICES IN LOWER-RESOURCE COUNTRIES

The Pragmatic Nature of Medical Services

So far, the discussion has been ordered scientifically according to causes. However, it is hard to apply this logic in the pragmatic context of public health and primary health care, where practitioners think in terms of “care packages” for patients encountered under different circumstances or at key points in life.

Primary health care is defined as the first point of contact between patients and the health service: In high-resource countries this may be the family doctor, or a community-based specialist in internal medicine, pediatrics, or obstetrics and gynecology. In lower-resource countries the first point of contact is often a nurse or trained health worker in a local clinic, and the main tasks of primary health care are (a) delivery of public health programs and monitoring environmental health, (b) care of women (family planning, sexual health, safe delivery), (c) care of newborns and young children (immunization, oral rehydration, nutrition), (d) health education, (e) best possible care (detection of disease, basic
treatment, appropriate referral), and (f) returning health statistics to the system (89). The many interventions that have contributed to the control of congenital disorders in high-resource countries need to be repackaged under similar pragmatic headings for public health and primary health care workers.

The following discussion draws particularly on Christianson’s (23) experience of developing community genetics services in the rural Limpopo province of South Africa. The first issue to consider is provision of patient care.

The Concept of “Best Possible Patient Care”

People with congenital disorders, and their families, are entitled to expect the best care available in the prevailing circumstances. The concept of “best possible care” accepts that all modalities for care, including sufficient highly trained specialists and costly drug treatments, are not universally available (4, 23, 129). In general, care comprises diagnosis, therapeutic intervention, and genetic counseling with psychosocial support.

A medical genetic diagnosis depends on a clinical and family history, physical examination, and laboratory testing. The family history is particularly important in genetic diagnosis, and eliciting, documenting, and interpreting a three-generation family tree is within the capability of primary health care practitioners. They can also be taught to recognize the physical signs of common genetic disorders (e.g., Down syndrome, neural tube defect, albinism, sickle cell disorder presenting with hand-foot syndrome), how to confirm the diagnosis, and when and where to refer the family (23).

An early and accurate diagnosis enables a realistic care plan that takes into account the family’s and community’s circumstances and inherent limitations. For example, where people usually travel on foot, a single visit to a distant specialized resource may be feasible, but repeated visits carrying a handicapped child or adult are ruled out. Care should be undertaken in situ as far as possible, and patients should be referred only when a diagnosis cannot be made or further management (e.g., pediatric surgery) will likely improve the prognosis. Thus, responsibility for ongoing management including terminal/palliative care falls to the primary health care practitioner (23). Annex 3 (follow the Supplemental Material link from the Annual Reviews home page at http://www.annualreviews.org) includes many simple and effective therapeutic measures that are within the ambit of primary health care. More complex interventions (e.g., cardiac surgery for children with Down syndrome) may not be available, and even if they are they may not be offered because of competing priorities. In lower-resource settings, community-based rehabilitation encompassing physiotherapy and occupational and speech therapy to help with the social integration of people with disabilities is the most viable option (42). Primary health care practitioners are inherently involved in such strategies.

Primary health care practitioners live, and are greatly respected, in the communities they serve. They speak the language, understand the customs, and are
eminently suited, with appropriate training and support, to offer genetic counseling with psychosocial support. In addition, in many countries patient/parent support groups provide much of the continuing psychological, emotional, and social support needed by families with a chronically sick or dying child (4, 23, 129).

Prevention of Congenital Disorders

Patient care is an absolute, but prevention is the ideal (23). In general, disease prevention depends on risk detection, information, and interventions to reduce risk, and relies heavily on education for health professionals and the public. Box 2 (follow the Supplemental Material link from the Annual Reviews home page at http://www.annualreviews.org) shows the conventional “logical” classification of approaches for prevention. However, from a primary health care perspective, prevention is most conveniently considered in categories matching packages of care (123).

BASIC PUBLIC HEALTH APPROACHES Some relevant public health approaches such as iodination of salt or fortification of basic foodstuffs with iron and folic acid must be implemented at the governmental or even intergovernmental level. Public health planners are also responsible for defining prevention policies, ensuring appropriate education of health workers, and surveillance.

PRECONCEPTION CARE AND FAMILY PLANNING Preconception care is a relatively new concept that aims to ensure the optimal physical and mental well-being of women and their partners at the onset of pregnancy to facilitate a normal pregnancy and delivery of a healthy infant (28, 113). Family planning is concerned with healthy reproduction rather than with reducing fertility. For example, in Hungary 30% of couples use an “optimal family planning service” that aims to reduce genetic and environmental risks before and during early pregnancy. It covers the following information and services, and users have a lower rate of pregnancy loss and congenital abnormality than nonusers (28).

- Information on: the need for a diet adequate in iron, iodine, and folic acid; how to avoid risk of teratogenic infections (e.g., toxoplasmosis); avoiding smoking, alcohol, and most medications; increased risk of miscarriage and chromosomal abnormality with maternal age; and availability of prenatal diagnosis.
- Testing for hemoglobin level, Rhesus blood group, and rubella immunity status.
- Diagnosis and treatment of sexually transmitted diseases.
- A genetic family history and appropriate referral when this suggests a genetic reproductive risk.
Genetics in Developing Countries

- Offer of testing for locally relevant genetic risks (e.g., hemoglobin disorders, G6PD deficiency, cystic fibrosis), arranging tests, and acting on results.

Many of the above steps are part of family planning, primary care, or pregnancy care in many countries. To do this job properly, primary care workers need training in drawing up and interpreting a basic family tree, and in providing information and basic counseling related to genetic screening programs. It is time to teach them as components of an integrated strategy, and to develop standardized instruments to enable the best performance in high- and lower-resource countries alike.

Safe Pregnancy

If the above information and services are not included in family planning or preconception care they must be included in early antenatal care (though this is often too late for the best outcomes). Other services can only be provided during pregnancy, for example, managing maternal infections and identifying women at increased risk of sporadic disorders such as Down syndrome or congenital malformations and referring them for fetal anomaly scanning, genetic counseling, and the offer of prenatal diagnosis.

CARE OF NEWBORNS AND YOUNG CHILDREN

A standardized neonatal examination, taking blood spots for biochemical screening and acting on the results, routine immunizations (including the Measles, Mumps, and Rubella vaccination), and ongoing surveillance of child growth and development are all primary care responsibilities.

Ethics, Equity, and Education

Historically, genetic concepts are often abused by being invoked to support racist attitudes and racist politics. In particular, the consciousness of populations in industrialized societies was scarred by the Nazi racist genocide of the 1930s and 1940s. Consequently, a portion of the funding for the human genome project was allocated to the study of ethical, legal, and social issues (ELSI) in medical genetics. The result is a burgeoning “ELSI industry” intended to demonstrate that genetic advances are implemented ethically to the advantage of individuals, communities, and populations, and a plethora of organizations, including HUGO, UNESCO, NIH, and the WHO, have allocated substantial resources in this area. However, because most developments in medical genetics have occurred in industrialized nations, current ELSI norms are imprinted with the history, traditions, societal values, economic interests, and anxieties of high-resource communities. It is not appropriate to expect Western approaches to be directly exportable to lower-resource countries, nor to burden them with the West’s past mistakes. A WISER (Worldwide Insight in Social and Ethical Reasoning) approach in medical genetics is required to ensure that the interests of lower-resource countries are encompassed, in a
debate in which they are represented proportionately by their own people. The first issue on this agenda is the social injustice of the global inequity in the provision of medical genetic services and its contribution to the health care divide between high- and lower-resource countries.

Though the need for medical genetic services in lower-resource nations is gradually gaining acceptance, in international policy controlling communicable diseases still has priority over controlling noncommunicable diseases, particularly congenital disorders (127, 128). The concept that countries usually perceive the need for medical genetic services when infant mortality drops below 40–50/1000 live births has been helpful in concentrating attention on the need for these services in lower-resource countries (65, 129). However, health services—particularly maternal and child health services—should not practice apartheid on the basis of infectious disease or congenital disorders. All too often both are involved in childhood illness, death, and disability. Social justice and commonsense now demand a realistic reappraisal of when and how to initiate medical genetic services in light of current epidemiological data, and all lower-resource countries need to consider how to integrate medical genetic services (appropriate to their needs and available resources) into existing services.

The United Nations named 2002 the year of the child and held a special General Assembly to consider children’s issues exclusively. WHO followed suit, with Bruntland prioritizing “children and the young” in her address to the World Health Assembly (103, 125). In view of the evidence that a minimum one third of the current 10.8 million annual early-childhood deaths are associated with genetically determined congenital disorders, and a significant number are due to fetal environmental causes, most in lower-resource countries, the question can no longer be when to initiate medical genetic services in lower-resource countries. If the focus is on children and the young, the answer is that all countries should introduce genetic services appropriate to their needs, and guidance from WHO is available (4, 123, 129).

Overcoming Barriers to Service Development in Lower-Resource Countries

The outmoded stereotype of medical genetic services as very expensive, complex, and controversial, and an inappropriate luxury for low-resource countries, presents a major barrier to service development (128). It persists for various reasons.

First, the earlier neglect of teaching genetics in medical schools means that most health workers now in practice perceive this as a difficult area accessible only to specialists and lack confidence in their ability to cope with it, instead of realizing its basic simplicity and logic.

Second, the true burden of genetically determined disorders has been consistently underestimated at the official, medical, and community levels. The five recent Lancet papers on child survival (13, 17, 23a, 48, 106) provide a conspicuous
example of this blindness to the burden, and scope for care and prevention of congenital disorders.

Third, there is an unwritten antipathy to confronting some issues, including selective abortion and assisted reproduction. Because there is still no effective management for many congenital disorders, the principal present application of emergent genetic knowledge is for risk identification and diagnosis, including prenatal diagnosis. This gives disproportionate prominence to selective abortion as a major intervention and links genetics to the abortion controversy. The liberalization of abortion laws in Europe, which started in Sweden in 1963 and the United Kingdom in 1967, proceeded slowly and not without controversy. The gradual acceptance of such services in industrialized countries provides insight into the unofficial distancing of officialdom. Some fundamentalist Christian sects and the Roman Catholic Church are absolutely opposed, and when abortion was legalized in largely Roman Catholic Belgium in 1990 the matter was so sensitive that the king abdicated temporarily to allow the law to be passed (40). The issues still have to be resolved in Eire, Malta, and Poland, and are a recurrent flashpoint of serious contention in the United States. The Western experience led many to assume that genetic services would not gain social, religious, or legal approval in many lower-resource countries. However, in practice, most religions adopt an open-minded attitude to abortion for genetic reasons, especially when it can be done early in pregnancy. Iran provides a classic example of a rational approach to community consultation by providing premarital screening for thalassemia, recording the reactions of intending carrier couples, and responding with a fatwa permitting termination of pregnancy for serious congenital disorders before 16 weeks of pregnancy (5; A. Samarvat, personal communication). There have been similar decisions in other Islamic countries including Pakistan (1), the Maldives (N. Firdous, personal communication), and Palestine. Abortion for genetic reasons is also legal in China, Cuba, Cyprus, India, Sri Lanka, and South Africa. The matter is ultimately one of choice for individuals, communities, and countries.

Fourth, the mistaken identification of medical genetics with tertiary specialist services has promoted a perceived association with high technology and complexity. It is true that in the protein era genetic diagnosis was often complex and disease-specific. However, introducing DNA technology, particularly the polymerase chain reaction (PCR), has created a radical simplification because it is simple, logical, and applicable for a wide range of conditions. As a result, the purchase of even expensive gene sequencing equipment is reasonable in lower-resource countries for large-throughput services at a national level. It is the application of genetic and genomic technology for patient care that is expensive and “high tech.”

There is no foundation for believing that lower-resource countries are presently not capable of obtaining and appropriately applying molecular genetic technology. A large component of medical genetic services for primary care and prevention does not need high technology.

Fifth, economic considerations are usually offered without due consideration as an excuse for the low priority of medical genetic services (123, 129). However, the
real question is whether lower-resource countries can afford not to implement basic genetic services. To be ethical these services must be equitable and accessible and provide simultaneously for the care and prevention of congenital disorders. This causes a catch-22 situation: financing them is potentially expensive, especially the portion for patient care. The cost of care increases with a service’s success and accompanying patient longevity, thereby jeopardizing long-term viability. To ensure cost-efficiency and guarantee long-term sustainability of medical genetic services, simultaneously implementing patient care with prevention strategies is required to counterbalance the burgeoning costs of care by reducing the birth prevalence and birth rate of birth defects. In addition, increasingly expensive therapeutic options are becoming available, and their use is promoted at the expense of preventive options. Public health practitioners, health care planners, and government officials need to be conversant with the cost implications of medical genetic services (5, 123, 129).

The most recent barrier to medical genetic services is the insidious idea that genomics can autonomously improve world health (124). This embraces the potential application of genomic knowledge and biotechnology to chronic common disorders and overlooks the pressing immediate need for medical genetic services for congenital disorders. Knowledge and technology, including that anticipated from genomics, require services and systems through which it can be applied. Those advocating the development of medical genetic services recognize these services as being within the “overarching strategies to improve health, for example through the alleviation of poverty, development of health systems, improved education and classical public health approaches” (127). This tension, which still exists, must be resolved so genomics does not become yet another endeavor that exacerbates global inequities (14, 124, 127).

All these obsolete and discriminatory myths should be confined to history to enable public health practitioners, health care planners, and government officials in lower-resource countries to obtain the political will and financial commitment to confront the issues of medical genetic services.

Professional and Community Education

Overcoming ignorance of congenital disorders also requires educating and training for the medical and paramedical profession, including medical geneticists, scientists, and specialists in secondary care, for their role in supporting initiatives in primary health care, and most importantly, investing in primary health care practitioners. Primary health care practitioners in lower-resource countries undertake a broad range of responsibilities, often in relatively isolated and difficult circumstances, with limited or distant contact with secondary or tertiary services. They daily practice medicine that in an industrialized setting would be the responsibility of trained specialists working in a well co-ordinated system. It is now necessary to add responsibility for the control of congenital disorders. To enable them to perform their duty of best possible patient care and prevention they require
education and training appropriate to their station, ability, and expected responsibility. The system they work in must ensure that they have continuing education and training, adequate facilities and support, and lines of communication from and to secondary and tertiary medical facilities (clinical and laboratory). New technologies are becoming available to assist with this, including telematic medicine and information technology. Extensive online medical genetic resources are now available to assist specialists in their education and everyday practice. Tools for primary health care practitioners are currently in short supply, but will be developed in the not-too-distant future (76, 95).

Community education is critical for the success of medical genetic services. The public must be able to understand and accept the basis of the services, know how to access and use them properly and to their advantage, and have confidence that care, discretion, and confidentiality will be provided. Public education is health promotion. It should be undertaken by government and non-government organizations, including patient/parent support groups and schools. Patient/parent support organizations for specific disorders, grouped into national and international alliances, continue to develop throughout the world. They play a crucial role in supporting and educating their members, health professionals, and the public, and in promoting relevant research (4, 23, 129). In 2003, the International Genetic Alliance (of patient/parent support groups) was initiated in Lyon, France (A. Christianson, personal communication).

The enlightenment of all involved in developing medical genetic services in lower-resource nations is necessary for these services to migrate out of tertiary care, and to ensure that appropriate supporting infrastructure is developed. Only in this manner can the ethical, legal, and social issues that these services involve be faced and resolved, according to local needs and circumstances.

CONCLUSION

The international burden of congenital disorders has been greatly underestimated, and the need and possibilities for care and prevention of congenital disorders, especially in lower-resource nations, have also not been recognized. These impediments can be overcome, and a rational systematic approach to providing medical genetics services is available (4, 123, 129). It is time for outdated, partial, and negativistic views on the care and prevention of congenital disorders to be replaced by positive, forward-looking attitudes, entailing a willingness to examine real problems and work on practical, cost-effective, and rational solutions.

The principle of equity in health care now demands that the gap between medical progress and services for controlling congenital disorders is narrowed in lower-resource nations. What is lacking to achieve this is the critical component: international and national political will and commitment to caring for and preventing congenital disorders.

If children and the young are to be the focus of international and national efforts to improve health care, then the burden of congenital disorders and the
need for medical genetic services in lower-resource nations must be officially recognized and publicly embraced by those in a position to make the difference (125). Organizations currently taking a stand on this issue and providing concrete support for countries in their efforts include the Pan American Health Organization (PAHO), Centers for Disease Control in Atlanta, and the March of Dimes through its Global Programs initiative. Nationally, however, responsible lower-resource countries can make the difference. Even if all they can afford is to recognize the reality and offer the most basic services for care and prevention, this is the first step toward resolving the situation. There is no point in waiting for tomorrow and improved circumstances: Beginning now is the first step toward improved circumstances for tomorrow.

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Figure 1  Population of different regions of the world, by income level [World Bank criteria (116)].

Figure 5  Minimum global estimates of the birth prevalence of genetically determined congenital disorders according to economic level. The total burden is at least 20% higher in low-resource than in high-resource countries.
Figure 7  Proportion of mothers 35+ years old in some Western European countries. In the 1950s, on average, 20% of births were to women 35 or older, the birth prevalence of Down syndrome was more than 2/1000 live births, and the majority of affected infants were born to older mothers. With increasing use of family planning, the proportion of older mothers fell to almost 5% in most of these countries by 1980. There was a corresponding fall in birth prevalence of Down syndrome to about 1.2/1000 live births, and most affected infants were born to younger mothers (66). The proportion of older mothers has been rising steadily since the mid-1980s, and currently in Western Europe 12% to 20% of mothers are now 35 or older. Knowledge among informed women that most chromosomal disorders can now be avoided may have contributed to this change.
Figure 9  Comparison of birth prevalence and outcomes of genetically determined congenital disorders among U.K. northern Europeans and British Pakistanis (17). More than 75% of British Pakistanis are married to a relative, and 55% are married to a first cousin. (Among British Pakistanis the current F is about 0.0431, compared to about 0.003 for most northern European populations).