SERVICES FOR THE PREVENTION AND MANAGEMENT OF GENETIC DISORDERS AND BIRTH DEFECTS IN DEVELOPING COUNTRIES

Report of a joint WHO/WAOPBD meeting
The Hague, 5-7 January 1999

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1. EXECUTIVE SUMMARY

Introduction

The benefits of the enormous progress in medical genetics during the past two decades in the industrialized nations, have had little or no impact in the developing countries, where more than 80% of the world's population lives. In order to assess the status of genetic services in developing countries, the World Health Organization (WHO) and the World Alliance of Organizations for the Prevention of Birth Defects (WAOPD) convened a group of experts in medical genetics who either work in, or are familiar with the social, economic and health problems of developing countries. A joint WHO /WAOPBD meeting on Prevention and Care of Genetic Diseases and Birth Defects in Developing Countries was held in The Hague from 5 to 7 January 1999. Its purpose was to review the current status of genetic services in the developing world, and make recommendations to further the implementation of programs for the management and prevention of genetic disorders and birth defects at the primary health care and community levels in those countries.

Goals of genetic services

Genetic services deal with all the medical aspects of genetic disorders, as well as of all birth defects and congenital malformations, regardless of their causes. Genetic services care for the management and prevention of those conditions. When they are targeted to individuals and families their goal is to enable people with a genetic disadvantage, and their families, to live and reproduce as normally as possible. The people need access to relevant medical services (diagnostic, therapeutic, counselling, rehabilitative and preventive) and social support systems, to help them acquire the appropriate knowledge and information to enable them to adapt to their unique situation and to make educated and voluntary choices on health and reproductive matters.

When targeted to populations, genetic services have public health goals of reducing the burden imposed by genetic disorders and birth defects on the population.

Demographic and health characteristics of developing countries

Generalizations based on averages do not capture the wide range
of existing realities, pertaining in most developing nations. They are characterized by low gross national products (10-40 times lower than average for developed countries), large inequalities in income distribution, economic dependency, low levels of urbanization, deficient water sanitation, and poor transportation, communications and technological development. Education levels are low, particularly for women, and fertility is high.

The average life expectancy is lower than in developed nations and the major portion of childhood mortality being attributable to acute respiratory infections, diarrhea, perinatal causes, measles and malaria, with malnutrition a common associated cause. However, many developing countries are experiencing an epidemiological transition, with a relative increased role of genetic factors in health and disease. Numerous indicators are available pointing to the presence of a higher prevalence of genetic disorders in developing countries than in industrialized nations. Health services are chronically underfunded and characterized by deficient planning and implementation, overlapping functions, poor coordination, with the emphasis on individual curative medical services, rather than community-based preventive approaches.

Prevalence of genetic disorders and birth defects

Because of underreporting, genetic disorders and birth defects are systematically underestimated in developing countries and recorded frequencies must be considered minimum estimates. Although the prevalence of genetic disorders and birth defects is probably higher than that in the industrialized nations, the burden that these conditions impose on populations of the developing world is greater, because of their limited resources.

The haemoglobin disorders are a major public health problem in the developing world, where 90% of affected individuals live. Cardiovascular diseases, malignancies, mental illness, obesity and diabetes are increasingly affecting people in the developing countries, particularly in urban populations.

Current status of genetic services

A number of deficiencies characterise genetic services in developing countries, in part because of:
- The load of unmet needs in other aspects of health care;
- Genetic conditions not considered priorities by the medical profession and public health officials;
- Genetic services are misperceived as expensive and concerned only with rare diseases;
- Genetic services are more diagnostic than therapeutic, and means of their prevention are usually perceived as interruption of affected pregnancies; and
- The public is largely unaware about genetic risks and the possibilities of prevention.

In spite of these difficulties, a number of genetic services have been implemented in developing countries, particularly patient/family genetic services in major urban centres at tertiary care university hospitals. The approach has largely been individual, with emphasis in clinical genetics, dysmorphology, cytogenetics and prenatal diagnosis of chromosome anomalies. Biochemical genetics laboratories, on the other hand, are scarce. DNA-based diagnosis is only incipient. In a few countries there are, however, population-based programs for the control of genetic disorders and birth defects.

Main conclusions and recommendations

1. Need to recognize the burden imposed by genetic disorders and birth defects

Notwithstanding significant variations among countries in the relative role of genetic and congenital factors in disease and disability, the consensus of the Group was that most nations in the developing world were already at a stage that required some attention to genetic disorders and birth defects, even though infectious diseases and malnutrition were not yet completely under control. Although scarce health resources should not be diverted from the attention of the latter, the Advisory Group’s contention is that governments in the developing countries should start devoting attention and resources to the control of genetic disorders and birth defects. Public health authorities must acknowledge the reality that these conditions are indeed major causes of disease, disability, suffering and death in their countries, and recognize that there are approaches for their management and prevention that can significantly reduce their burden in a cost efficient manner.
2. Need for political will and commitment

Governments must demonstrate beyond rhetoric, a political will to improve health and wellbeing of the people by making all types of health services, including genetic services, available, equitable and accessible. The commitment must originate and be driven from the highest levels of government, and be translated into appropriate resource allocation. Health authorities should recognize that:

- Priorities can be established so that there is no need to “start with everything at the same time”;
- A number of genetic services can be implemented without excessive financial investments;
- Many genetic services are cost effective; and
- The societal costs of inaction in genetics, measured in terms of avoidable human suffering and burden to public health, are very high.

The Advisory Group specifically recommends that Ministries of Health of developing countries allocate resources for genetic programs and set up a distinct Office of Genetic Services within their administrative structure to determine the existing burden of genetic disorders and birth defects in the population, the status of existing programs for their control. The Office of Genetic Services should organize at the level of the Ministry of Health a permanent advisory council on genetic services with participation of interested parties to recommend and oversee the appropriate steps and priorities for genetic services in the country.

3. Improve epidemiological knowledge about genetic disorders and birth defects.

Research should be stimulated to provide better data on the prevalence and types of birth defects, genetic diseases and genetic predispositions to common diseases at the national level. In addition, information on what impact specific genetic disorders and birth defects have on individuals, families, and communities should be developed. These studies would typically include data on the natural history of conditions, mortality, morbidity, quality of life and reproduction,
utilization of the health care system, hospitalisations, manpower requirements for their management, costs of services, etc.

4. Define goals of genetic services in terms of individual/family wellbeing and of public health.

The basis for defining goals of genetic services in a particular country or community are:

- The existing burden of specific genetic disorders and birth defects and their impact upon society in human and economic terms;
- The burden of other health problems;
- The resources available and the potential of raising funds from external sources;
- The state of the art of established screening, diagnostic, preventive and therapeutic methodologies for particular conditions (for example, preconceptional folic acid supplementation for the prevention of neural tube defects, screening and prenatal diagnosis of thalassaemias, genetic predisposition to cancer, etc); and
- The expectations of the community.

5. Improve pre- and perinatal services.

The prevention of a number of genetic disorders and birth defects will follow an improvement in the quality and accessibility of preconception, prenatal and perinatal services. The improvement of preconception care should include:

- Encouragement of procreating in the optimal age period (20-35 years of age);
- Public education about methods that allow couples to have children when they want them, and provision of services to make those methods accessible;
- Rubella immunization before pregnancy;
- Education on the avoidance of teratogens during gestation, particularly alcohol;
- Education on the need for, how and when to access prenatal care services.

Prenatal services including facilities for prenatal diagnosis require to be developed and to the greatest extent possible. Each mother should have the opportunity of being delivered by a trained birth attendant, in a hospital or clinic if possible. Newborn services should allow for each neonate to undergo a complete physical examination
prior to discharge to detect the major and common genetic disorders and birth defects.

6. **Organize genetic services in a comprehensive and integrated manner, with roots in the primary health care level.**

Genetic services should always be comprehensive and combine the best possible patient care available in the country, with population-based prevention strategies.

Furthermore, genetic services must be integrated with related services, such as reproductive health, prenatal care, newborn care, child growth and development monitoring, nutrition, cancer prevention, etc. In some cases, genetic services will be part of specific categorical programs, such as newborn metabolic screening, the control of haemoglobin disorders, haemophilia or mental retardation.

Genetic services must be extended into primary health care settings, where genetic risks should be identified. In order to avoid duplication of services and ensure cost efficiency, genetic services should be regionalized, with tertiary centres responsible for specific geographic and administrative areas. Insertion of genetic services into the community is key to the success of any genetic program. Services should have an emphasis on the family and should rely on modern cost/efficient information technology. Continuity of care, long-term management and quality assurance of clinical and laboratory services are essential components.

7. **Select programs and targets according to prevalence, severity and predicted outcomes**

Prevention of congenital rubella by immunization of susceptible children should be a priority. Educational and social programs to prevent alcohol consumption during pregnancy will help prevent fetal alcohol syndrome, which has high prevalence in some population groups. Neural tube defects can be partially prevented through preconceptional folic acid supplementation, maternal serum screening programs and fetal ultrasonography. Prevention of Down syndrome could be accomplished to a considerable degree through community education and family planning to encourage procreation before 35 years of age, and, depending on availability of resources, implementation of
maternal serum antenatal screening followed by prenatal diagnosis. Women of advanced maternal age who become pregnant could be offered prenatal diagnosis (amniocentesis, chorionic villus sampling), according to availability of resources. These programs require the development of efficient educational programs, genetic counselling and adequate fetal medicine and laboratory facilities.

Some of the most common severe inherited conditions, such as haemoglobin disorders, cystic fibrosis, fragile-X syndrome, haemophilia and muscular dystrophies, contribute considerably to chronic morbidity in childhood in many developing countries. Programs for the prevention and care of affected children with these conditions may significantly reduce the overall burden due to chronic disease at the community level.

Newborn metabolic screening should only be considered in countries with the infrastructure and resources necessary to guarantee efficiency and desired outcomes. Newborn metabolic screening should always be a policy decision by the government, which should allocate the necessary resources for its implementation.

8. Respect ethical principles and cultural diversity

The health beliefs, traditions, religious observances and social expectations of individuals and communities should be assessed properly before setting program goals, and respected thereafter. These goals should never be set in ways to impose certain genetic tests or reproductive decisions on individuals. Governments should recognize that within any country there exists diversity of cultures and opinions about a number of issues relevant to genetics. These include human reproduction issues and community and individual approaches to the significance of disabilities.

This diversity should be respected. Ethical principles of justice, autonomy, beneficence and respect for the dignity and basic intelligence of persons should be adhered to.

9. Train health professionals in genetics

Serious efforts need to be undertaken in genetic education to health professionals. Undergraduate curricula of the health professions (primarily physicians, nurses, psychologists and social workers) should be modernized and the practical aspects of medical genetics included in
clinical teaching. The relationships between genetics and public health should be addressed in the schools of public health. For those health professionals already in practice, continuing education programs to familiarize them with the modern concepts of clinical genetics are essential. Officials in charge of public health programs should be targeted specifically for continuing education in genetics.

Although clinical geneticists and specialized laboratory personnel are scarce, efforts need to be directed towards training in genetics of different health professionals including physicians, nurses, genetic counsellors psychologists, and social workers. At the same time, existing clinical geneticists should be educated in public and community health.

10. Educate the public in genetics

Public education about genetic disorders and birth defects should be attuned to the prevailing cultures, beliefs and values of the populations in any given community. Particular attention should be paid to the vulnerable groups in society (the poor, ethnic and linguistic minorities, etc). Proper use of the media (particularly radio and TV) is invaluable. Community meetings should be encouraged to discuss important issues, such as the use of alcohol in pregnancy, rubella immunizations, self-medications, the value of learning about one's own family medical history, where to go for genetic counselling, etc. Education on these topics should begin in high school. Educational messages require to be simple, explicit but understandable and couched in a manner that does not cause offence.

11. Encourage the formation of parent/patient organizations

Throughout the industrialized and developing worlds, affected individuals and their families have acquired the awareness and creativity to advocate for their own needs. Hundreds of parent/patient organizations have been instrumental in drawing attention to the need for clinical services and preventive programs for genetic disorders and birth defects, as well as asserting their right to be treated with dignity and without discrimination. A number of legislative initiatives in several countries have been the result of the actions of parent/patient organizations. The medical profession and governments should support the development of these independent lay organizations. It is important
that they be truly independent and able to respond to the legitimate needs of their constituencies, and not be controlled by the medical establishment or government.

2. INTRODUCTION

A W.H.O. scientific group in 1993 reviewed the current and potential applications of genetic knowledge for improving human health (WHO, 1996). The group confined most of its analysis and recommendations to the conditions of the industrialized countries, although it acknowledged that genetic disorders and birth defects in developing countries occur at a particularly high frequency.

In order to address this problem in the context of the distinct socio-economic, cultural and health circumstances of the developing countries, WHO joined WAOPD to convene a group of experts in medical genetics who either work in, or are familiar with the problems of developing countries, in order to analyse the situation with respect to genetic disorders and birth defects in those countries. The joint WHO /WAOPBD meeting on Prevention and Care of Genetic Diseases and Birth Defects in Developing Countries was held in The Hague from 5 to 7 January 1999 to review the current status of genetic services in the developing world, and make recommendations to further the implementation of programs for the management and prevention of genetic disorders and birth defects at the primary health care and community levels in those countries.

The rationale for this meeting was that the benefits of the enormous progress in medical genetics during the past two decades in the industrialized countries, where less than 20% of the world’s population lives, have had little or no impact in the Third World. The purposes of the meeting were to assess the status and characteristics of whatever programs existed in the developing world, examine the possible reasons for their deficiencies, and propose guidelines for the implementation of programs for the management and prevention of genetic disorders and birth defects that take into account the social, cultural, religious and economic realities of developing countries.
3. GENETIC DISORDERS AND BIRTH DEFECTS

The terminology used in medical genetics is sometimes confusing and/or overlapping. A birth defect is any type of functional or structural abnormality determined largely by factors operating before birth, in utero, or in the immediate postnatal period. Structural abnormalities are usually called malformations. Functional abnormalities are exemplified by inborn errors of metabolism, haemoglobin disorders, or mental retardation. The term congenital implies present at birth. It is important to note that any of these birth defects may not be apparent immediately and some can become clinically evident only days, months or even years after birth. The causes of birth defects may be genetic, environmental, or mixed.

Genetic disorders are conditions in which a defect lies in the DNA of the genes and plays a major role in causation of a pathological condition. Genetic disorders can be inherited (hereditary), that is transmitted from parents to offspring, or sporadic, a result of a new mutation.

The three categories of genetic disorders are chromosomal abnormalities, single-gene disorders and multifactorial conditions of gene-environment interaction.

Chromosomal abnormalities are characterized by an excess or deficiency of genetic material. The majority of these conditions are caused by random errors of cell division in the formation of gametes, and are usually sporadic, not hereditary. The most common is trisomy 21 or Down syndrome; the risk of its occurrence increases with maternal age. Chromosome abnormalities affect at least 10% of conceptions, 90% of which end in spontaneous abortions. About 6 per 1000 liveborns have a chromosomal abnormality leading to congenital malformations, mental retardation and/or disorders of sexual differentiation.

Single-gene disorders are caused by mutations in a single major gene. Their clinical manifestations are quite variable, depending on the function of the normal gene. About 4,000 of the approximately 10,000 gene loci known thus far are associated with single-gene disorders (MIM). Typical examples are inborn errors of metabolism, the haemoglobin disorders, cystic fibrosis, and haemophilia. Individual
single gene disorders range in frequency from 1 per 2500 to 1 per 25000 births. The global prevalence at birth of all single gene disorders is about 10 per 1000.

These conditions are inherited following the patterns of dominant, recessive, autosomal or X-linked inheritance.

**Multifactorial conditions** are due to the interaction of several genes and/or environmental factors. The genetic factors confer an inborn predisposition to the development of a particular condition in interaction with environmental factors. Examples of conditions in this category are some common congenital malformations including cleft lip and palate, neural tube defects and congenital heart defects. Other examples include insulin dependent diabetes mellitus, coronary heart disease, epilepsy, asthma and some cancers. The global prevalence at birth of multifactorial conditions ranges between 50 and 250 per 1000, depending on the inclusion criteria.

**Environmental causes** of birth defects are those that interfere with the normal embryonic or fetal development and include physical agents (e.g. radiation, hyperthermia), chemicals (e.g. some medications, alcohol, tobacco and drugs, both legal and illicit), and infections (e.g. rubella, toxoplasmosis and cytomegalovirus).

Collectively, all genetic disorders and birth defects have a minimum prevalence at birth of 50 per 1000. The prevalence at later ages is affected by the natural history of those conditions, because some are lethal early in life, whereas others only become manifest in adulthood. Given that genetic factors are being unveiled in an increasing number of common chronic conditions (cancers, coronary heart disease, mental illness, etc), it is likely that at least 25% of the people will develop eventually a condition determined totally or partially by genetic factors.

4. GOALS OF GENETIC SERVICES

Genetic services deal with genetic disorders, as well as all birth defects and congenital malformations (regardless of cause). These conditions are caused largely by genetic and/or environmental factors, operating before the birth of the individual, pre-conception, during gestation, or during the perinatal period.
Genetic services can be conceived with two major goals, depending on their type. Services targeted to individuals and families try to enable people with a genetic disadvantage, and their families to live and reproduce as normally as possible, assuring access to relevant medical services (diagnostic, therapeutic, counselling, rehabilitative and preventive) and social support systems, helping them to adapt to their unique situation and providing information to enable educated and voluntary choices in health and reproductive matters.

Genetic services also have public health goals of reducing the burden that genetic disorders and birth defects impose on the population. Public health genetic services target entire populations or population subgroups with specific genetic risks with measures for the primary, secondary and tertiary prevention of genetic disorders and birth defects. (see Section 10). The public health goal of genetic services should not be confused with those of eugenics. Eugenics is a discredited pseudo-scientific concept that improperly claims an ability to “improve” the human gene pool by enforcing social policies that limit the reproduction of individuals with “undesirable” traits, and encourages reproduction of individuals with “desirable” traits (Kevles, 1995). There is no scientific basis for “improvement” of the gene pool and the concept of “desirable” and “undesirable” traits is both arbitrary and political, usually defined by prejudice. Eugenic methods applied in the past (i.e. forced sterilization and/or social and economic sanctions) to reach these stated goals have not only been ineffective, but also violated fundamental human rights (Kevles, 1995). In the first half of the 20th century social prejudices and rudimentary knowledge of genetics fuelled racist “eugenic” policies of several governments with abhorrent consequences for mankind.

It is currently recognized that preventive goals of medical genetics must always respect the reproductive rights of individuals and the social and health rights of people with disabilities.

Thus, while reducing the frequency of a particular genetic disorder is a legitimate public health goal, it should always be tempered by respect for the autonomous reproductive decisions of couples and implemented through measures that provide people with options to make voluntary decisions regarding genetic risks. Thus, public health genetic goals should be interpreted within the context of personal, cultural and societal values regarding reproduction, health, and respect
for people with disabilities.

5. ECONOMIC, DEMOGRAPHIC AND HEALTH CHARACTERISTICS OF DEVELOPING COUNTRIES

Approximately 80% of the world's population lives in countries with low gross national products (GNP) and have not reached the levels of economic development of industrialized nations. The term usually applied to these countries is that of "developing", but a number of recent indicators suggest that the economic situation in the majority of those countries is stagnant, or even deteriorating (UNDP, 1998). No single indicator captures the economic, cultural, social and political complexities of underdevelopment. In addition to low income, developing nations are characterized by economic dependency, lesser urbanization, poor levels of technology, deficiency in qualified human resources and a number of other social, demographic and health correlates of poverty.

It should be noted, however, that generalizations about the developing world based on averages fail to capture the wide range of realities that characterize poverty. There are wide differences in economic and social development among developing countries and even diverse population groups within each country. Concurrently, the stereotypic image of the industrialized world can also be deceptive, as exemplified by significant pockets of poverty even in the economically most advanced nations.

The role of genetic factors in health and disease moved to the forefront in the industrialized countries during the past 40 years, as a consequence of the control of infectious and nutritional diseases and the advances in genetic technology. In contrast, for the populations living in the developing world, main causes of morbidity and mortality are still linked to environmental factors correlated with poverty, infections and malnutrition. An epidemiological transition, however, is taking place in many of these countries wherein the problems of acute diseases are gradually being controlled and chronic disorders are assuming an ever-increasing role in health, mandating that their management and prevention be recognized as a need rather than a luxury.
5.1. High fertility and reduced life expectancy

Ninety percent of the 140 million births in the world in 1995 occurred in developing countries (UNICEF, 1998). Although their total fertility rate declined from 6.0 in 1960 to 3.2 in 1996, it is still almost twice the 1.7 recorded in industrialized nations. The combination of high fertility and low life expectancy leads to a population age structure with a high proportion of young people (40% under 18 years of age, as compared with 23% in industrialized nations) (UNICEF, 1998).

5.2. Low level of urbanization

Only 37% of the population is urbanized in developing countries, as compared with 77% in industrialized nations (UNICEF, 1998). This, however, is rapidly changing because of the movement of people from impoverished rural areas to cities.

Presently some of the world’s largest megacities are in developing nations, e.g. Mexico City, Sao Paulo, and Beijing.

5.3. Deficient infrastructure

The percentages of population with access to safe water (70%) and adequate sanitation (42%) are significantly lower than in the industrialized nations, where they approach 100%. Transportation, communication and technology are also deficient.

5.4. Poverty

Per capita gross national product (GNP) of developing nations is 10-40 times lower than that of industrialized countries. Moreover, the gap between the rich and poor countries has been widening. Over the past 30 years, the industrialized countries’ share of the world’s global GNP increased from 70.2% to 82.7%, whereas that of the countries with the poorest 20% of the world’s population declined from 2.3% to 1.4%. (World Bank, 1993). By 1989 the income of the richest 20% of the world’s population (living largely in the industrialized countries) was 60-fold higher than that of the poorest 20% (living largely in developing countries) (UNDP, 1998). In addition, developing countries are characterized by a greater inequality in the distribution of incomes between rich and poor, than that which pertains in the industrialized
nations.

5.5. Poor educational levels

Educational levels in developing countries tend to be low, as measured by literacy rate (average: 71%; range: 57-87%, depending on the region; compared to 98% in industrialized countries) and the proportion of children reaching grade 5 of primary school (average: 75%; range 59-91%, depending on the region; compared to 99% in industrialized countries) (UNICEF, 1998). All educational indices are significantly lower for women.

5.6. Health conditions

In general, health standards are lower in developing countries than in the industrialized world. The average life expectancy is 62 years in the former, compared to 77 in the latter. Infant mortality varies widely among developing countries, ranging from the lowest of 9/1000 live births in Cuba to the highest of 191 in Niger. It is under 10/1000 live births in the industrialized nations (UNICEF, 1998). Although the mortality of children under 5 years of age declined significantly in the last 25 years, its rate in developing countries is still 12 times that of the industrialized countries.

In the mid-1990s, the World Health Organization estimated that approximately 70% of the 11.6 million deaths of children under 5 years of age that occur annually in the developing countries were attributable to five illnesses: acute respiratory infections (19%), diarrhoea (19%), perinatal causes (18%), measles (7%) and malaria (5%), with malnutrition an associated cause in 54% of all the deaths (Murray & Lopez, 1996). Forty-two percent of deaths at all ages in developing countries were potentially avoidable (communicable diseases, maternal and perinatal conditions, and nutritional deficiencies). In contrast in the industrialized nations this was the case in only 6% of deaths. Adding to this toll, the AIDS pandemic is currently ravaging some developing countries, particularly in Sub-Saharan Africa and South-East Asia. An estimated 30 million people have contracted the HIV and 90% of new infections occur in developing countries, where the disease has already reduced life expectancy in some countries by more than a decade. Moreover AIDS is diverting scarce resources from treatment and prevention of other diseases (World Bank, 1997).
Prevalence of contraceptive usage from 1990-97 was only 54% in developing countries, compared to 72% in the industrialized world (UNFPA, 1998).

Lack of access to safe therapeutic abortion continues to be a serious health issue in developing countries, independent of the legalities of interruption of pregnancies. It is notable that contrary to commonly held assumptions a sizable proportion of the population of the developing world lives in countries that permit induced abortion under a variety of circumstances (i.e. China, India, South Africa, Cuba and a few other Latin American countries) (UNFPA, 1998). Furthermore, legal restrictions to induced abortion in some developing countries do not deter its practice, but instead make abortions unsafe, forcing them to be performed in an environment lacking minimal medical standards and by persons without the necessary skills. Of the 45 million abortions annually taking place worldwide, 20 million are unsafe, and 90% of the latter take place in developing countries, accounting for 13% of maternal deaths (UNFPA, 1998). Maternal mortality as a whole is alarmingly high in developing countries, reaching catastrophic figures in Africa, with an average of 477 per 100,000 as compared with 13 per 100,000 in the industrialized world (UNFPA, 1998). Obstructed labour, haemorrhage and postpartum infection account for almost one half of maternal mortality.

5.7. Access to health services

The structural and functional deficiencies of health services in the developing world have complex historic, political, cultural and economic roots (World Bank, 1993). Deficient comprehensive health planning and implementation, overlapping functions and poor co-ordination compound underfunding. Scarce health resources are allocated with a bias that favours tertiary centres in large cities at the expense of more cost-effective primary health care units. Specialized and high technology services are primarily accessible to the small wealthier segment of the population, who have expectations and enjoy services somewhat equivalent to those of the industrialized countries (Penchaszadeh, 1999).

Training of health professionals tends to emphasize individual curative medicine rather than community-based preventive approaches (World Bank, 1993).
The public health sector in the developing world is chronically underfunded. In 1990 the average expenditure for health in developing countries was only 4% of their meagre GNP, compared to 9.2% in industrialized nations (World Bank, 1993). Total (public and private) average annual per capita health expenditure in developing countries in 1990 was US$ 41 compared with US$1861 in the industrialized countries. These averages, obviously, mask significant spending inequalities between the well to do who pay high fees in the private for profit sector, and the majority who rely on the underfunded public sector (Penchaszadeh, 1999).

5.8. Influence of tradition and religion

In the developing world, the role of tradition in shaping health beliefs and patterns of health care is very strong. The structure of the family assigns an important authority role to the elders, and members of the extended family are active in decision-making regarding health. The various cultural meanings of disease and causal explanations affect decisions regarding prevention and treatment. Although religion plays an important guiding role everywhere in the world, its directives tend to be more rigid, authoritarian and conservative in the developing countries than in the industrialized ones.

Consanguinity has been practiced for centuries in many populations and it is deeply rooted in a web of social, economic and cultural factors. Although the practice has declined in industrialized nations, it continues to be prevalent in numerous areas of the developing world, particularly in parts of Africa, the Middle-East and the Indian subcontinent, where it ranges from 25% to 61% (Khat & Khoury, 1991; Bittles et al, 1991; Khlat, 1997).

To a lesser extent, consanguineous marriages are also common in Brazil, 0.6-9%, (Freie-Maia, 1989) and Japan, 1.6-3.9% (Imaizumi, 1986). Marriage between relatives increases the likelihood of homozygosity among the offspring and is associated with higher frequency of autosomal recessive conditions, congenital malformations, stillbirth, neonatal or childhood death, and mental retardation (Bittles et al, 1991; Jaber at al, 1998; WHO, 1996). Thus, consanguinity may contribute to a limited extent to the burden of genetic diseases in some communities in the developing world, particularly in those that are experiencing a significant reduction in infant mortality. However, consanguinity has important social, economic and cultural roles relating
to inheritance of property and land rights and the maintenance of social fabric, in some traditional societies. The beneficial effects of consanguinity perceived by these communities thus outweigh the potential negative health effects. Therefore efforts to discourage it would be ill advised and probably futile.

5.9. Epidemiological transition

Despite the general assessment of the developing world's health problems described above, living conditions are improving for many individuals in a sizable proportion of developing countries. Between 1960 and 1997, the average infant mortality rate in developing countries fell from 138 to 65/1000. This reduction was particularly manifest in Latin America and the Caribbean (103 to 33/1000), East Asia and the Pacific (133 to 40/1000) and the Middle East and North Africa (154 to 48/1000). Simultaneously, in these nations there has been a significant decrease in the under-5 years mortality rate (216 to 96/1000), a 48% decline in fertility rates and, between 1970 and 1997, a nine-year increase in life expectancy. By comparison, there has been less progress in the least developed countries, many of which are in sub-Saharan Africa and South Asia (UNICEF, 1999).

The improving health indices in some developing countries are indicative of social and economic progress associated with improved health care services and control of infectious diseases and malnutrition. Consequently, genetically determined disorders and birth defects have begun to constitute an increasing proportion of infant and general mortality and morbidity, and thus gained public health significance (Rimoin et al., 1996; WHO/EMRO, 1997; PAHO, 1998a, 1998b). As an expression of this epidemiological transition, the percentage contribution of genetic disorders and birth defects to the infant mortality rate is greater in countries where the latter are lowest, reaching 25% or more in some Middle Eastern and Latin American Countries (WHO/EMRO, 1997; PAHO, 1998a, 1998b).

Improving socio-economic indicators and health indices in such developing countries are also associated with urbanisation and modernisation in some sectors of the population. These processes result in the breakdown of traditional ways of living and changes in lifestyle, which in turn, when combined with increased longevity, result in a concomitant change in the pattern of mortality and morbidity in adult life. Thus
common chronic multifactorial conditions with a genetic predisposition, including cancer, diabetes, hypertension, coronary artery disease and mental illness, begin to become pre-eminent in the health statistics of the middle and upper years of the lifespan (Penchaszadeh, 1999). As the situation further improves, late onset genetic diseases are expected to become increasingly evident. Thus in the 1990s, deaths from malignancies in Latin American countries ranged from 8 to 25% of the total as compared to 23% in the USA. Similarly the percentage of deaths due to cardiovascular diseases in this region ranged from 8 to 46%, which is approaching the 54%, recorded in the USA (PAHO, 1998a).

In each country, efforts to manage genetically determined disorders and birth defects would depend on local frequencies of the individual conditions, the health burden that they represent, and the resources available for their care and prevention, and the health care infrastructure (WHO, 1996). Although in developing countries infectious diseases and malnutrition still present a considerable burden, the changes described above have brought many developing nations to the stage where health services must give due consideration to the care and prevention of birth defects, genetically determined disorders and late onset complex disorders.

The importance of genetic disorders and birth defects tends to be recognised in countries when their infant mortality rate falls below 40/1000 live births (Modell & Kuliev, 1998). In order to anticipate this, health care planners should initiate appropriate strategies of care and prevention when an infant mortality rate of 50/1000 has been reached. In 1997 fully 67(47%) of the world's 142 developing nations had an infant mortality rate < 40/1000, and a further 8 (5.6%) countries a rate between 41 and 50/1000 live births. The population of those 75 countries (with an IMR < 50/1000 live births) was 2.8 billion, or 60.5% of the developing worlds' peoples. In all the countries, except one, the life expectancy at birth was 65 years or greater (UNICEF, 1999).

The prevalence of genetic disorders and birth defects, which are recognisable in 2-3% of all newborns, varies according to geographic, ethnic, socio-cultural and socio-economic characteristics of a population (WHO/EMRO, 1997; ICBDMS, 1998). Factors that predispose to higher prevalences of these disorders in developing countries include:

- Traditional consanguineous marriages resulting in a higher frequency of autosomal recessive conditions including congenital malformations, stillbirths, neonatal and childhood deaths and mental retardation;
- Advanced parental age. Continued child bearing into the upper
end of the reproductive lifespan is associated with high frequencies of chromosomal abnormalities in women of advanced maternal age (>35 years) and conditions due to new autosomal dominant mutations in men of advance paternal age (>55 years);

- Socio-economic factors. The increased risk of birth defects in families of low socio economic status has long been recognised. At least in part this is due to inadequate pre and post conception nutrition, including deficient intakes of micronutrients (folic acid and other vitamins, iodine);

- Adequate health care prior to and during pregnancy. This can predispose to an increased frequency of congenital infections in particular syphilis and rubella, or birth defects consequent on inadequate control of diabetes, and the unsupervised intake of drugs and traditional medicines;

- Selective reproductive advantage of carriers of genes for haemoglobin disorders and G6PD deficiency which contribute to the high prevalence of these conditions in some areas of the world.

The observed birth prevalence of genetic disorders and birth defects is only the tip of the iceberg of the overall prevalence of these conditions (Christianson et al, 1981; WHO/EMRO,1997; Venter et al, 1995). Extrapolating from these studies it has been suggested that the actual prevalence of severe genetic disorders and birth defects by age five years in developing countries could reach 78.6/1000 live births (Figure 1). This unrecognised high prevalence of genetic disorders and birth defects has recently become apparent in a number of developing countries that are undergoing epidemiological transition. In six of ten Latin American countries with infant mortality under <50/1000, genetic disorders and birth defects are now placed among the three leading causes of infant mortality (WHO, 1998). Similarly, of ten Middle Eastern nations, eight had infant mortality less than 50/1000 and in four of these the proportion of infant mortality due to congenital anomalies was equal to or higher than the 25% recorded for the United Kingdom, a typical industrialised nation (Table 1).

The significance of genetic disorders and birth defects has also found expression in emerging morbidity statistics from this region where the percentage of inpatient paediatric admissions for such problems has been recorded as ranging from 8 to 19 percent (WHO/EMRO, 1997). Similarly, in most Latin American countries congenital anomalies have risen to the 3rd or 4th place as a cause of infant mortality (PAHO,
Moreover, birth defects and genetic conditions account for 10-25% of pediatric admissions in some urban centres, imposing their burden of more extensive and costly hospital stays (Barreiro et al, 1976; Penchasazedeh, 1979; Carnevale et al, 1985).

In other developing countries, including some that have entered the phase of epidemiological transition described above, the burden of genetic disorders and birth defects has yet to be recognised. Their significance is veiled by the continuing prevalence of infectious diseases and malnutrition. This, associated with limited diagnostic capability in clinical genetics, unreliable health records and statistics and infant and early childhood mortality of affected individuals, result in failure of documentation of the majority of those deaths, which are absorbed into the general mortality statistics and thus are not acknowledged for what they truly represent (WHO, 1996).

6. FREQUENCIES AND IMPACT OF GENETIC DISORDERS AND BIRTH DEFECTS IN DEVELOPING COUNTRIES

Deficiency in diagnostic capacity and unreliability of health records and statistics due to underreporting prevent an accurate assessment of the prevalence of genetic disorders and birth defects in the developing world. Recorded diagnoses typically reflect acute intervening illnesses rather than the basic constitutional conditions that predispose to morbidity and mortality and make affected children more vulnerable to infections and malnutrition (Penchaszadeh, 1999).

Thus, congenital conditions are systematically underestimated (WHO, 1996) and recorded frequencies must be considered minimum estimates. There are a number of indications that the global prevalence of birth defects and genetic diseases in developing countries is probably higher than that in the industrialized nations (Penchaszadeh, 1999). Moreover, the burden that these conditions impose on populations of the developing world is greater, because their limited resources are used for the most basic services.

6.1. Congenital malformations

The average prevalence at birth of recognizable congenital malformations in developing countries is about 2-3%, which is similar to that in the industrialized world (Mutchinik et al, 1988; Ciao et al, 1988; Castilla & Lopez-Camelo, 1990; ICBDMS, 1991; Saborio, 1992;
Heredero, 1992; Delport et al, 1995; Venter et al, 1995; WHO/EMRO, 1997). Some malformations show wide geographical variations. Thus, neural tube defects have high prevalence at birth in Egypt (Hashem, 1978), China (Xiao et al, 1989), Mexico (Mutchinik, 1988) and Central America (Saborio, 1992), whereas cleft lip and palate are frequent among Amerindian and Asian populations (Xiao, 1988; ICBDMS, 1991) and microtia in Ecuador (Castilla & Orioli, 1986). Interactions between environmental and constitutional factors underlie most observed variations in frequency among populations. In some cases, however, environmental factors play the major role, such as with fetal alcohol in South Africa (Baleta, 1998).

6.2. Chromosome abnormalities

Studies on Down syndrome show that maternal age-specific rates are similar worldwide. However, because of social and cultural traditions and reduced access to family planning, many women in developing countries continue to reproduce until advanced age (Penchasazadeh, 1999).

The proportion of births to women over 35 years averages 11-15% in different regions of the developing world, compared to 9% in industrialized countries (UNFPA, 1998). Advanced maternal age and the reduced availability of prenatal diagnosis and selective abortion lead to a relatively higher birth prevalence of chromosome anomalies (6 per 1000) (WHO, 1996) and particularly of Down syndrome (2-3 per 1000) (WHO, 1985, Modell & Boulyjenkov, 1988; Castilla & Lopez-Camelo, 1990; Zhang et al, 1991; Christianson, 1996). The same phenomenon is behind the high proportion of babies with Down syndrome born to mothers of advanced age in some eastern Mediterranean countries where 50% of Down syndrome babies are born to mothers over 40 years of age (WHO/EMRO, 1997).

The death rate of children with Down syndrome by one year of age in South America is 34% for those with a congenital heart defect and 21% for those without one. The latter figure is about twice that for the United Kingdom (Castilla at al, 1998). In South Africa, two-thirds of babies with Down syndrome die by age 2 years of age (Christianson, 1996).

Sex chromosome abnormalities are also frequent (Temptamy et
al, 1992), although their morbidity and mortality are much less than the autosomal aneuploidies.

6.3. Single-gene disorders

Major single-gene disorders in the developing world have a global incidence similar to that of industrialized countries, approximately 3.5 per 1000 (WHO, 1985). The frequency of individual conditions varies in different regions according to ethnicity, founder effects, inbreeding, genetic drift and/or carrier selection (Penchaszadeh, 1999).

The haemoglobin disorders (sickle-cell disorder and thalassaemias) constitute a major public health problem among genetic conditions internationally, but particularly in the developing world which has the least resources for coping with the problem. Abnormal haemoglobin genes, originated in Africa, Asia and the Mediterranean basin, and were maintained at high frequencies in those populations because of selective advantage of carriers in resistance to malaria (Serjeant, 1989; Weatherall, 1995). The slave trade and later migrations disseminated genes for abnormal haemoglobins worldwide. Approximately 250 million people (4.5% of the world population) carry a potentially pathological haemoglobinopathy gene and annually 300000 infants are born with a major hemoglobin disorders (Angastiniotis et al, 1995).

The average carrier rate of abnormal haemoglobins in Africa, mostly sickle cell disease, is 13.3% and the estimated prevalence at birth for homozygotes is 7.26 / 1000, which extrapolates to 216000 affected births annually, or about 75% of the world’s affected children. Studies in Nigeria suggest an 80% mortality of people with sickle cell disease before 15 years of age (Angastiniotis et al, 1995).

In Latin America, sickle haemoglobins predominate in the countries with the higher proportions of people of African origin (Caribbean islands, Panama, Brazil and Guyana) (Penchaszadeh, 1993). In Cuba, where African ancestors account for 30-40% of the population, the carrier frequency of sickle haemoglobins is 3.7% (Granda et al, 1991). In Brazil sickle haemoglobins have a carrier frequency of 1% in whites, 4% in those of mixed origin, and 7% in those of African origin (Salzano, 1985). The average thalassaemia carrier frequency in Brazil is about 1%, occurring primarily among descendants of Italian immigrants (Naoum et al, 1984; Martins et al,
In Arab countries the most common abnormal haemoglobin is S, with carrier frequencies that range from <1% to almost 20% in some areas, although both alpha- and beta-thalassaemias are also very frequent (El-Hazmi & Warsy, 1997a). In the Mediterranean basin betathalassemia predominates (WHO, 1993).

In South East Asia the average carrier frequency of betathalassaemia is 11.6% (Modell & Boulyjenkov, 1988). In Thailand, up to 40% of the population carry a potential significant haemoglobin mutation, and all the major thalassaemias are common (Winichagoon et al, 1990). In China, alpha and beta thalassaemias are prevalent in the south and south-western provinces (Zeng Ninety five & Huang, 1987).

Deficiency of glucose-6-phosphate dehydrogenase is another single gene condition frequent in areas of the world where malaria was and is prevalent, including the Mediterranean basin, Africa and the Middle East (El-Hazmi & Warsy, 1996).

Most of the several hundred known single-gene conditions have been described in the developing world. A number of populations in the New World originated from a small number of migrants who later experienced restricted mobility for many generations, leading to pockets of increased endogamy. The combination of founder effects, genetic drift and geographic and cultural isolation has led to clusters of single gene conditions, both recessive and dominant (Castilla & Sod, 1990; Freie-Maia, 1981; Arias 1981, Teebi, 1994). Some of these clusters may represent significant public health challenges, as the needs of hundreds of patients with severe disabling conditions in a small geographical area may impinge upon an already strained health services, as is the case with Huntington disease in Venezuela (Avila-Giron, 1973) and spino-cerebellar atrophy type 2 in Cuba (Auburger et al, 1990).

In addition, many populations of the developing world are characterized by unusually high frequencies of particular single-gene conditions, such as spondylocostral dysplasia in Puerto Ricans (Perez-Comas & Garcia-Castro, 1974), oculo-cutaneous albinism in South Africa (Kromberg &Jenkins, 1982), and spinal muscular atrophy in Arabs (Al-Rajeh et al, 1993).
6.4. Conditions of genetic predisposition

Multifactorial conditions with genetic predisposition include most birth defects and chronic diseases affecting all age groups. Prevalence of the latter becomes more apparent as childhood mortality due to infections and malnutrition declines and life expectancy rises. Indeed, although the burden of infectious diseases is still large, cardiovascular diseases, malignancies, mental illness, obesity and diabetes are increasingly affecting the developing world, particularly its urban populations (Penchaszadeh, 1999). In Saudi Arabia, for example, the prevalence of diabetes mellitus type 2 ranges from 1.9 to 7.2% in the overall adult population, but reaches 22% and 17% in males and females, respectively, over 45 years of age (El-Hazmi et al, 1996,1998). A similar situation is observed with obesity (El-Hazmi & Warsy, 1997b).

7. CURRENT SITUATION OF MEDICAL GENETIC SERVICES IN DEVELOPING COUNTRIES

7.1. Delivery of genetic services

In most countries genetic services are at an early stage of development and in many have yet to be established (WHO, 1996). However even in the industrialized nations, where the organization and funding of health services are better, there are still numerous technical, social, ethical, and legal challenges that act as barriers to the ultimate achievement of control of genetic disorders and birth defects (WHO, 1996). In the developing world these barriers also exist and are compounded by several other factors that result in serious challenges for the delivery of genetic services (Penchaszadeh, 1999). These include:

- The absence of comprehensive registers and reliable statistics;
- Lack of clinical expertise and awareness in health professionals;
- A considerable burden of unmet needs in other aspects of health care;
- Genetic disorders and birth defects are not considered a priority by the medical profession and public health officials;
- Genetic services are incorrectly perceived as expensive,
inextricably linked to high-tech laboratory tests and concerned only with rare and esoteric diseases;
- Genetic services are considered as mainly diagnostic rather than therapeutic.
- The means for the prevention of genetic disorders and birth defects is considered only in terms of selected interruption of affected pregnancies;
- Genetic disorders and birth defects are seen as complex and the sole responsibility of medical geneticists;
- The public is largely unaware about genetic risks and the possibilities of prevention, and is developing fears towards genetics due to lack of knowledge and the sensationalist reaction of the media to certain topics of genetic research.

In spite of the above-mentioned difficulties, a number of patient/family genetic services have been implemented in developing countries during the past two decades. These are typically set in major urban centres at tertiary care university hospitals by medical geneticists trained abroad. The approach has largely been individual, without much coordination with other health services. The emphasis has typically been in clinical genetics, dysmorphology, cytogenetics and prenatal diagnosis of chromosome anomalies. Biochemical genetics laboratories, on the other hand, are scarce. DNA-based diagnosis is only incipient in few centres and for a limited number of conditions (Penchasazdeh & Beiguelman, 1997; Penchasazdeh, 1999). The practice of prenatal diagnosis shows significant variations among developing countries. In countries such as China, India, South Africa, Cuba and Cyprus, prenatal diagnosis is publicly funded for accepted indications and is part of comprehensive policies of prevention of genetic disorders. In many other developing countries, however, there is a lack of public funds for prenatal diagnosis, and its practice is restricted for the most part to the private sector, in response to the growing demand for this service by the middle and upper classes. Unfortunately, prenatal diagnosis in the private sector is characterized by little or no quality control and only perfunctory genetic counselling, making this a fragmented service of unpredictable quality and accessible only to those who can afford it (Penchasazdeh, 1999). Legal restrictions to induced abortions, where they exist, do not seem to affect the practice of prenatal diagnosis in the private sector.
Newborn screening programs for phenylketonuria and congenital hypothyroidism have been introduced in urban centres in some developing countries. Common pitfalls of these programs are lack of public allocation of resources, lack of laboratory quality control and deficient provisions for the follow-up of abnormal initial screening results and the long-term treatment of affected infants (Penchasazdeh, 1999).

In some countries with high prevalence of hemoglobinopathies, there are population-based prevention programs for the detection of carriers. These programs offer prenatal diagnosis to the couples at risk and have been very successful in Cuba and Cyprus (WHO, 1993). Sickle cell disease is a common problem in Cuba, as 3.7% of the population is heterozygous for the gene (Granda et al, 1991).

The sickle cell prevention program in Cuba is based on routine haemoglobin electrophoresis of pregnant women at 16 weeks of gestation, identification of carrier couples, genetic counselling and offering of amniocentesis with the option of voluntary termination of affected fetuses. A single laboratory in Havana performs all the fetal DNA tests for HbS. The coverage of this program is close to 90% of the pregnancies in Cuba and the population acceptance is high (Granda et al, 1991; Granda et al, 1994; Dorticos-Balea et al, 1997).

In Cyprus, 16% of the population carry the beta-thalassaemia trait and thalassaemia major was a main public health problem. A substantial proportion of financial resources for health services were consumed by the chronic treatment of affected patients. A plan for prevention was laid out in 1972, based in health education of the public, community involvement, carrier detection in the general population and genetic counselling (Angastiniotis & Hadjiminas, 1981). The program, however, did not influence people’s behaviour in choosing spouses or in reproduction, until prenatal diagnosis became available in the early 1980s. Later, a premarital certificate attesting that the marrying couple was tested for thalassaemia carrier status in a government laboratory and counselled appropriately became a requirement for marrying in church (no results were disclosed to third parties). A comprehensive prenatal diagnosis program followed. Over the ensuing years the annual birth incidence of thalassaemia homozygotes dropped 97% as a result of campaigns of public education, community participation, genetic counselling and voluntary prenatal diagnosis followed by the option of pregnancy termination of affected fetuses (Angastiniotis et al, 1986).
Prenatal screening of neural tube defects and other fetal malformations by measurement of maternal serum biochemical markers has been common practice in most industrialized countries for a long time (Milunsky, 1998a). Latterly this has been augmented by fetal ultrasonography (Ville et al, 1998). Among developing countries, Cuba has implemented population-based program for the detection of fetal anomalies based on the combination of the above tests in the second trimester of pregnancy. The program covers 95% of the pregnancies and when severe fetal malformations are detected, couples are counselled and given the option of pregnancy termination. As a result, prevalence of neural tube defects fell 90% (Rodriguez et al, 1997; Heredero, 1998).

In summary, genetic services in developing countries are typically patient/family oriented and based in tertiary centres, without much coordination and regionalization and with wide variations in the quality and accessibility of services rendered. On the other hand, and except for the few examples cited above, population-based programs rarely exist, as departments of public health do not have explicit policies and resource allocations for the management and prevention of genetic disorders and birth defects (Penchaszadeh, 1999).

7.2. Genetic education of health professionals

Few medical schools in the developing world teach courses in clinical genetics, and most practicing physicians have a poor grasp of the modern applications of genetics in medical practice. Similar situations prevail in the training of allied health personnel, such as nurses and midwives. The expertise in clinical genetics remains largely confined to a very small number of medical geneticists concentrated in academic institutions and/or in private practice (Penchaszadeh, 1999). However, during the last decade, teaching of genetics to medical students has become a part of the medical curriculum in an increasing number of medical schools in several developing countries. Additionally, courses and workshops are being organized to train clinicians and other health personnel in medical genetics.

7.3. Genetic education of the public and role of parent/patient organizations

Very little attention has been paid to-date to the need to educate
society at large in developing countries about developments in human genetics and their application in health and wellbeing. Information about genetics usually reaches the public through the sensationalism and distortion of the mass media. However, in a some developing countries parent/patient groups have been organizing with the purpose of increasing awareness of the public and their governments about the plight of people with birth defects, genetic disorders and disabilities. Through their assertiveness and knowledge of the needs of affected people and their families, these organizations are bringing a humane approach to available genetic services and prevention programs. Concomitantly, they are raising the public’s and governments’ awareness that genetic disorders and birth defects are not rare, they affect a sizable proportion of the population and, most importantly, affected individuals and families can benefit from a number of measures such as improvement of the quality and accessibility of services and the adoption of a compassionate and non-discriminatory approach to the needs of the affected and their families. In many countries alliances are being formed between these lay groups and the medical profession. Such cooperative efforts tend to humanize and improve patient/family services as well as population/based prevention programs (Poortman, 1999).

7.4. Recent developments

For the many reasons reviewed above, health care in general is inadequate for the majority of people in the developing world. This inadequacy has been most pronounced with respect to medical genetic services, which do not yet have a place among established health priorities. However, the decline in morbidity and mortality due to infectious diseases and malnutrition is determining an epidemiological transition to a growing relevance of genetic factors in disease causation. Furthermore, improvements in health care delivery are reducing the load of diseases that had been caused by inadequate prenatal and delivery care in significant segments of the population. Thus, infant mortality rates have fallen under 40 per 1000 in a substantial number of countries. This is, in turn, has led to a growing, albeit uneven, demand of services for the management and prevention of genetic disorders and birth defects. The challenge is to address the growing health issues posed by congenital and genetic disorders, with the scarce resources available in limited health care delivery systems, at the same time as there is still a high proportion of preventable, environmentally caused morbidity and mortality (Penchaszadeh, 1999).
In spite of these obstacles and difficulties, in many regions of the developing world there is an increasing awareness among health professionals, public health officials and the public at large of the importance of genetic factors in health and disease, resulting in some progress in the delivery of genetic services. The region that probably leads this process is Latin America, where the specialty of medical genetics has been recognized in Mexico, Cuba, Brazil and Argentina. With a population of about 500 million, Latin America has an average distribution of about one physician with training in medical genetics per million, compared to 2.7 per million in Europe (Harris, 1997). It is also fortunate to have numerous centres of excellence in clinical genetics, cytogenetics and prenatal diagnosis, as well as for the management of hemoglobin disorders. A well-established congenital malformations registry, which covers 200,000 births annually in South America, provides reliable data on the prevalence of these anomalies in the region (Castilla & Lopez-Camelo, 1990). Currently, a proposal to create a Latin American network of biochemical genetics laboratories to improve the diagnosis of inborn errors of metabolism is being considered (Giugliani & Coelho, 1998). Molecular diagnosis is slowly developing for a limited number of conditions (Penchasazdeh & Beiguelman, 1998a). Under the auspices of the Pan American Health Organization (PAHO/WHO), four meetings of experts in medical genetics from the region were held over the past 15 years to review and recommend the implementation of population based prevention programs and the delivery of patient/family genetic services (PAHO, 1984,1987, 1998b; Penchasazdeh & Beiguelman, 1998b).

The WHO Regional Office for the Eastern Mediterranean Region (EMR) held three meetings between 1993 and 1996 to discuss the situation of genetic services in member states, to develop strategies that are appropriate to the Region, and to standardize epidemiological research for genetic and congenital disorders (WHO/EMRO, 1997). Several countries of the EMR have recognized the importance of genetic services and the Arab League Technical Committee sponsors annual meetings of their members. In South Africa, Department of Health officials are integrating genetic/disability services into primary health care and developing clinical guidelines for the management of common birth defects (Department of Health of South Africa, 1998; Penchasazdeh, 1998).
8. DEFINITION AND GOALS OF GENETIC SERVICES

Genetic services are health measures implemented to help people with genetic disadvantages to live and reproduce as normally as possible (WHO, 1985, 1996). They combine the best available medical care with prevention strategies. According to their nature and goals, genetic services can be targeted to individuals and their families (clinical genetic services) or to the population at large (public health genetic programs). The goals of individual/family based clinical genetic services are as follows (see also Section 9):

- To address the medical and psychosocial needs of affected individuals and their families. The main strategies are early and accurate clinical and laboratory diagnosis, coordination of the multidisciplinary and long-term management of patients, anticipatory guidance of predicted problems based on the natural history of the condition, genetic counselling and psychosocial support to the patient and family.

- To maximize the probability of offspring free of genetic disease among individuals and/or families with increased genetic risk. The strategies to implement this goal are the detection of genetic risk factors as early as possible in the reproductive cycle (ideally preconception, although most commonly early in gestation), genetic counselling, genetic testing, prenatal diagnosis and offering reproductive options.

- To manage the risk that some healthy individuals have of developing a late-onset single-gene disorder or multifactorial condition due to gene-environment interaction. The strategies and instruments to achieve this goal are the detection of high genetic risk by family history, genetic education and counselling, and the use of pre-symptomatic or predisposition genetic testing followed by prevention and therapeutic interventions.

The population-based (public health) genetic programs are targeted to the population at large and/or to population subgroups identified by their genetic risk category (e.g. specific ethnic groups). The goals of public health genetic programs are the primary, secondary and tertiary prevention of genetic disorders and birth defects at the population level. The strategies of public health genetic programs include prenatal screening for birth defects and chromosome abnormalities, newborn metabolic screening, population screening for carrier status for common recessive conditions and public education campaigns for the avoidance of exposure to teratogenic agents. (see also Section 10).
9. GOALS AND COMPONENTS OF PATIENT/FAMILY-BASED GENETIC SERVICES

9.1. Addressing the medical and psychosocial needs of patients and families

The application of genetic principles to the practice of medicine is a development that has gained impetus and acceptance in developed nations since the 1960s, consequent on technological advances and an epidemiological transition characterized by an increased public health significance of genetic disorders and birth defects. Associated with this has been the evolution of clinical genetic services for the application of the advances in medical genetics in diagnosis, management and prevention of human diseases (McKusick, 1996). The likely future change of emphasis in the field of medical genetics from rare conditions to common complex diseases will require further development of medical genetic services.

The objective of medical genetic services is to help people with a genetic disadvantage to live and reproduce as normally as possible (WHO, 1985). This definition encompasses with genetic disorders or birth defects and those with a genetic reproductive risk. Simultaneously it avoids any misperceived contradiction between treatment and prevention. This apparent contradiction is possibly engendered in texts by the used of the word "control" in relationship to hereditary diseases or genetic disorders and birth defects. (WHO, 1985, 1996; WHO/EMRO, 1997). This may suggest to some that prevention takes precedence in the management of these conditions. However a "control" programme for a hereditary disorder has been defined as "an integrated strategy combining the best possible patient care with prevention by community education, population screening, genetic counselling and the availability of prenatal diagnosis." (WHO, 1985; WHO/EMRO, 1997). Management of any medical condition should integrate treatment and prevention, and the above definition ensures the primacy of attention to patient's needs, in medical genetic programmes.

Both in developed and developing countries, economic constraints, lack of appropriately educated and trained manpower, the isolation of medical genetic services in academic centres, and the burgeoning public demand for medical genetic care have resulted in inequities in genetic
service delivery. From the patient’s perspective, barriers to care include lack of information, poverty, ethnicity, religion, culture, language and geographic location. To help overcome these barriers, and given the increasing inclusion of medical genetic knowledge and technology in all fields of medicine, the increasing demands of the public for clinical genetic services and information will have to be answered at the community level and be undertaken by primary health care practitioners. (WHO, 1985, 1996, 1998; Paul & Kavanagh, 1990; Jenkins, 1992; Bernholdt & Pyeritz, 1992; Penchasazadeh, 1992; Qurestin & Raeburn, 1993).

Perhaps one lesson that can be learnt from the industrialised countries' experience, that will most benefit the nascent medical genetic services in developing countries, is that from the outset these services should have a strong base in the community at the primary health care level. (Christianson AL et al, 1995; Penchasazadeh, 1999) Therein, primary health care practitioners should receive appropriate education and training to ensure that they are capable of rendering the best possible patient care within the framework of their country's health care system.

Patient care, in this context, includes diagnosis, therapeutic intervention if possible and available, genetic counselling and psychosocial support, with all of these implemented within the context of each country's cultural, religious and legal milieu.

Care of patients with genetic disorders and birth defects is challenging for all providers and the outcomes for patients are limited even in the best of circumstances (Table 1). In the developing countries, where facilities are limited, the prognosis for many such patients is poor and often includes infant or early childhood mortality. Nevertheless, all these patients are still entitled to the best possible care available for them. A large part of the responsibility for care will continue to fall on the shoulders of primary practitioners, especially for the common genetic disorders and birth defects prevalent in each country. To facilitate this, management guidelines for specific conditions should be available, examples of which are those produced by WHO (WHO, 1996b, 1996c, 1996d, 1996e) and others available in developed countries (Bernhardt and Pyeritz 1992; Carey, 1992). It should be recognised that many patients and families with genetic problems have particular need for continuing and coordinated care from different specialities and sectors.

9.2. Genetic diagnosis

An accurate clinical diagnosis is important in the management of a
patient with a genetic disorder or birth defect. Specific and definitive diagnoses help establish the aetiology, natural history, treatment and recurrence risks of conditions. However, even when a definitive diagnosis is not derived, patients can and should get the best possible care available.

The process of making a genetic diagnosis should proceed in a logical sequence of history taking, physical examination and laboratory investigation. Common indications for genetic evaluation are listed in Table 2. A family history, summarised in the form of a pedigree diagram using accepted conventional symbols, is necessary to establish a possible genetic cause and pattern of inheritance of the problem and to document possible intra-familial variability. Information regarding the pregnancy including possible exposure to teratogens, the length and course of the gestation and the results of antenatal tests (e.g. sonograms) are important to assess fetal well being and risks. Birth and neonatal information, including circumstances of delivery, anthropometric measurements (weight, length and head circumference), physical examination and state of wellbeing are necessary for the assessment of possible genetic disorders and birth defects.

Finally, subsequent history should be obtained with respect to general health, growth, neurological development, and the details of any previous investigations.

Physical examination should include physical measurements and recording of significant physical features (e.g. ear length, hand/palm length) and major and minor anomalies (dysmorphic features). The number and complexity of genetic syndromes may require special expertise on the part of the clinician to make the correct diagnosis. However, general physicians and other health professionals can be trained to suspect and diagnose genetic conditions that are particularly prevalent in their communities. Diagnostic guidelines and the possibility of consultations with specialists will enhance this capacity.

Special tests (radiology, pathology, biochemical, cytogenetic, molecular and others) may be required to confirm some diagnoses. These tests can also be utilised as a guide to therapy (Table 3). As genetic disorders and birth defects occur in families, in some instances it may be necessary to conduct investigations on family members, after counselling and with informed consent. The costs of genetic tests, however, may render this process prohibitively expensive. In order to minimise costs, genetic diagnostic tests must be selectively applied to patients following accepted indications and guidelines developed in accordance of each
country’s context. Cost efficiency of genetic laboratories increase with proper regionalisation and avoidance of duplication of services.

9.3. Genetic Counselling

At the conclusion of the diagnostic procedure the available medical facts are discussed with the patient and/or the family, in the process of genetic counselling. Obviously this is greatly enhanced when a definitive diagnosis has been reached, but is not absolutely dependent thereon. Genetic counselling has been defined (American Society of Human Genetics,1975) as:

"A communication process, which involves an attempt of one or more appropriately trained persons to help the individual or the family to:

- Comprehend the medical facts including diagnosis, the probable course of the disorder and the available management;
- Appreciate the way heredity contributes to the disorder and the risk of recurrence;
- Understand the alternatives for dealing with the risk of recurrence;
- Choose the course of action which seems appropriate to them in view of their risk, their family goals, and their ethical and religious standards, and act in accordance with their decision;
- Make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.

In the 25 years after this definition was formulated in the United States, the concept and practice of genetic counselling has expanded in developed and developing countries to address not only retrospective counselling after the birth of an affected child, but also prospective counselling on genetic risks at different stages of the life cycle, including the preconception and prenatal periods. Furthermore, in addition to dealing with reproductive genetic risks, genetic counselling is increasingly sought by healthy individuals with a genetic predisposition to late-onset disorders to discuss options regarding genetic susceptibility testing and preventive interventions.

Central to the process of genetic counselling are its educational, voluntary and non-prescriptive nature. The main goal is to empower individuals and couples to make their own informed decisions when facing genetic risks, according to their own values, and then support these choices. It should be recognised, however, that genetic counselling takes place within the context of individual countries, and is shaped by the
capabilities of their health care system and social, cultural, religious and legal environments (WHO, 1998).

9.4. Therapeutic Interventions

Treatment of genetic disorders and birth defects is often burdensome for the patient and the family and this burden tends to be heaviest in the developing countries. In addition it has economic implications for health care resources (WHO, 1985; WHO, 1996). Due consideration is therefore required to ensure that specific interventions are evidence based. Table 3 lists the possible options for best care therapy for a number of common conditions, and indicates which of these can be undertaken at primary health care level. One of the therapeutic options available in the primary health care setting, that is often overlooked, is neurodevelopmental therapy (NDT) for patients with disabilities (intellectual, physical, auditory, or visual). NDT includes physical therapy, occupational therapy and speech therapy. In developing countries this can be administered by community based rehabilitation workers using programmes specifically designed for the circumstances in which they live and work.

9.5. Psychosocial Support

The diagnosis of a genetic disorder or birth defect has lifelong implications for the patient and family that will result in the need for psychological, emotional and social support for these individuals. In a continuum of care, the primary health care practitioner is ideally placed to be a key provider. These professionals live and are a part of the same community as the patient and are therefore cognisant of the social, cultural, religious and economic factors that may influence the course of their patient’s lives. Invaluable collaboration in this process can be obtained from patient support groups or the arrangement of a meeting with another patient or parent of a child with a similar problem. Thus the concerns and uncertainties of patients and families can be addressed where possible, and the validity of their feelings acknowledged (Poortman, 1999).

10. GOALS AND COMPONENTS OF POPULATION-BASED GENETIC SERVICES

One of the goals of genetic services at the population level is the
reduction of the burden of genetic disorders and birth defects. A number of strategies have been developed over the past two decades to reach this goal (WHO, 1996), focusing on primary prevention, prevention by reproductive options and secondary prevention.

10.1. Primary prevention

Primary prevention aims at reducing the incidence of specific genetic disorders and birth defects. Conditions most amenable to primary prevention are birth defects caused by environmental factors that can be removed or neutralized, and non-hereditary genetic disorders such as chromosomal abnormalities, in which the association with advanced maternal age offers a basis for prevention. General strategies for primary prevention include:

- Public efforts to improve health, nutrition, education and self reliance, particularly of women;
- Avoidance of unintended pregnancies and proper birth spacing through access to contraception and other methods of family planning;
- Improved access to and quality of prenatal care;
- Improved quality of birth care;
- Control of possible occupational risks.

More specific primary prevention strategies are:

- Voluntary premarital genetic screening and counselling may dissuade couples at risk to marry and thus could play a preventive role particularly in countries where abortion is not allowed. This strategy would only be ethical if it is strictly voluntary, implemented through non-directive genetic counselling, and not coerced through direct or indirect social pressures;
- Pre- and periconceptional supplementation of vitamins, including folic acid, for women in the reproductive age group to reduce the risk of neural tube defects and possibly other birth defects;
- Encouraging women to procreate at the ideal reproductive ages (20-35 years) to reduce the risk of non-dysjunction chromosomal abnormalities;
- Avoidance of exposures to mutagens and teratogens (radiation, rubella, alcohol, tobacco, self-medications) during pregnancy.
All primary prevention is usually centrally planned and population based, and requires the involvement of primary health care providers as well as community awareness and education.

10.2. Secondary prevention

Secondary prevention aims at avoiding the birth of affected fetus, minimizing clinical manifestations of a condition after the birth of an affected infant or detecting the genetic predisposition for a condition that presents later in life. Strategies at the population level include:

- Early detection of congenital malformations by systematic physical examination of newborns, followed by appropriate treatment;
- Newborn metabolic screening for serious diseases amenable to early and cost efficient treatment (e.g. congenital hypothyroidism, phenylketonuria);
- Monitoring of child growth and development for the early detection and treatment of genetic conditions;
- Presymptomatic genetic testing for late onset conditions followed by surveillance and medical intervention (e.g. genetic testing of children with a parent affected with familial adenomatous polyposis, followed by serial colonoscopies and eventual colectomy if the individual has the causative gene).

Newborn metabolic screening programs for certain specific conditions deserve special mention because they are being implemented in many countries. For this strategy to be cost/efficient, the disorders included in newborn screening should be relatively prevalent, clinically severe and screened by automated laboratory methods for which there are confirmatory tests. It is essential that there be a demonstrated benefit of their early detection and treatment measured by long term outcomes. Examples of such conditions are congenital hypothyroidism, phenylketonuria and sickle cell disorders. Newborn screening should always be a high-level health policy decision and should include all births in a population. Follow-up of abnormal results by confirmatory testing, counselling and long-term follow-up and treatment of detected cases are prerequisites as is public education. All steps of the program should be publicly financed. The laboratory infrastructure and procedures for newborn screening should be highly centralized and
subjected to stringent quality control. The decision whether to develop a newborn screening program and for which conditions, should be guided by the criteria outlined above and may vary from country to country according to the prevalence of different conditions, the public health resources and the general health priorities. A medical genetic centre (see Section 11.3) may be an appropriate site to set the laboratory infrastructure for newborn screening, and particularly for the confirmation of diagnosis, treatment and follow-up of suspected cases, although other alternatives may be considered.

More recently, as environmental and genetic factors predisposing to common multifactorial disorders are being recognized, attempts are being made to identify such factors in the population. Preventive measures and treatment of conditions such as diabetes, obesity, coronary disease and some cancers can be implemented now and are likely to be even more effective in the future (WHO, 1996). For example, recent studies suggest that bilateral mastectomy and/or tamoxifen may be of value in preventing breast cancer in women with BRCA1 or BRCA2 mutations (Hartmann et al, 1999).

10.3. Prevention based on reproduction options.

The technological developments in medical genetics of the last two decades have enabled the implementation of a novel form of prevention, which is based on reproductive options. The goal of the latter is to maximize the chances that individuals at increased risk of affected offspring will have children free of the disorder in question. This strategy is concerned with early detection of individuals or couples at increased genetic risk for having a child with a serious disorder, followed by genetic counselling and the offer of prenatal diagnosis. The facts that these services are always voluntary, that prior informed consent is required and those individuals can freely make their own reproductive decisions clearly distinguish this strategy from imposed eugenic policies.

Prevention based on reproductive options is best accomplished at the primary health care level, starting with the detection of genetic risk factors in the population. These include a positive family history for a birth defect or a genetic disorder, carrier detection of a recessive trait frequent in the community, maternal age, exposure to teratogens, and prenatal screening for neural tube defects and Down syndrome by measurement of maternal serum biochemical markers and/or fetal ultrasonography.
Couples found to be at increased genetic risk are offered genetic counselling on available voluntary reproductive options to manage the risk. Reproductive options vary according to the condition in question, the personal and cultural factors involved, and what is available and permissible in a particular country. These may include:

- Abstention from further reproduction;
- Adoption, sperm or egg donation, in vitro fertilization and preimplantation diagnosis;
- Initiation of a pregnancy and carrying to term without prenatal diagnosis;
- Initiation of a pregnancy and prenatal diagnosis for reassurance that the future child will be free of the disorder in question, or for preparing for the birth of an affected child, or for termination of an affected pregnancy;

All these services are voluntary and the international experience is that most couples at increased genetic risk of a serious genetic disorder or birth defect favour prenatal diagnosis to avoid the birth of an affected infant. This strategy has been successfully applied to the prevention of chromosome anomalies and several recessive conditions (thalassaemia, Tay-Sachs disease and others), both in industrialized and developing countries.

Among prevention programs based on reproductive options, the prenatal screening of pregnancies to detect fetuses with trisomy 21 has become a standard of prenatal care in many developed countries. The technologies used are measurement of fetal substances in maternal serum and ultrasonography, either alone or in combination, towards the end of the first trimester and early in the second trimester (Milunsky, 1998b, Ville, 1998). The detection rate varies between 50 and 80%. The caveat of these programs is that, because of the high sensitivity and low specificity of existing tests, they place a large number of pregnancies (about 5%) in a high risk category, all of which must then be offered amniocentesis to confirm or rule out the diagnosis. Approximately 200 amniocenteses are needed to confirm one case of Down syndrome. This may impose an excessive burden on health finances in a developing country where competing priorities exist. Thus such programs should only be implemented in a country that is willing to invest in the necessary resources to offer and perform amniocenteses in about 5% of all pregnancies. As with other population screening
programs elsewhere, the decision to implement prenatal screening for
trisomy 21 in a developing country will have to originate from a high
health policymaking level and take into consideration technical,
financial, cultural, legal and religious factors.

10.4. Tertiary prevention

Tertiary prevention of birth defects and genetic diseases aims at
averting deterioration, complications, disability and dependency of the
patient and the family. The strategies are anticipatory guidance (e.g.
prevention of obesity in Down syndrome), proper interventions to avert
complications (e.g. laminectomy to alleviate spinal cord compression in
achondroplasia), and rehabilitation of disabilities (e.g. speech therapy,
hearing aids in hypoacusia, physical therapy in neuromuscular
diseases). _Psychosocial support_ of affected individuals and their
families is an essential, albeit commonly neglected, component of the
care of genetic disorders and birth defects.

In summary, the combination of patient/family services for
diagnosis, counselling, management and prevention and population-
based preventive programs constitute the pillars of genetic services.
Patient/family services follow the structure of health care in steps of
increasing complexity, at the primary, secondary and tertiary care
levels, with intervention of allied health personnel, family practitioners,
medical specialists, and clinical geneticists. Collaboration with other
sectors including education and social welfare are also necessary.

Population-based programs undertaken in collaboration with
public health departments require appropriate planning, appropriate
resource allocation, and training of personnel at the different levels of
care, with emphasis on the primary health care level.

11. ORGANIZATION OF THE DELIVERY OF GENETIC SERVICES

Among the key characteristics of genetic services anywhere is
their multidisciplinary nature. Indeed, since most genetic disorders and
birth defects are multisystem and lifelong, medical actions for their
management and prevention must involve several types of health
professionals in a coordinated fashion. The exact training needed by
professionals to provide those services will depend on a number of
factors: level of care, structure of the health professions in the country,
rural versus urban settings, etc. Where clinical geneticists are available, they work in coordination with primary health care physicians, different medical specialists (pediatricians, obstetricians, neurologists, oncologists, haematologists, etc) and other health personnel (nurses, social workers, genetic counsellors, etc). Genetic services cannot exist as stand alone vertical structures but should be integrated with related medical services, such as preconception and prenatal care, family planning, child growth and development monitoring, special clinics, and rehabilitation of disabilities, to name a few. The clinical geneticist deals primarily with the genetic aspects of the management, including clinical diagnosis, genetic testing and interpretation, and genetic counselling. Prenatal genetic services require coordination between clinical geneticists, obstetricians and ultrasonographers. Because the number of clinical geneticists is limited in most developing countries, they should primarily be involved in training and supervision of other health personnel.

The delivery of genetic services should be organized at all levels of care in a way that takes full advantage of the existing resources, maximizes efficiency and avoids duplication of services.

11.1. Primary health care level

The primary level of care should be the backbone of all health actions in genetics, with emphasis in programs that employ low-level technology and reach a large proportion of the community. Examples of actions at the primary health care level are:

- Public education in genetics;
- Detection of genetic risks in the community by due attention and recording of family history in all patient encounters with the health system;
- Rubella immunization;
- Prevention of fetal alcohol effects;
- Encouragement of reproduction at optimal maternal ages;
- Carrier detection of recessive traits for disorders of high prevalence in the community (e.g., sickle-cell disease or others);
- Prenatal screening for maternal biochemical markers for Down syndrome risk;
- Genetic counselling for simple problems.
The sites for primary health care actions in medical genetics are community health centres, clinics and hospitals, physicians' offices, schools and community organizations. The personnel involved in medical genetic services at the primary level will most likely be primary care practitioners with task-oriented basic training in applied genetics (including physicians, nurses, and/or midwives, depending on the country or community). In order to accomplish the goals stated above, there should be adequate links with secondary and tertiary levels of genetic care for consultation by the primary provider, as well as appropriate referral channels. Actions at the primary health care level should follow established guidelines and be supervised by the secondary and tertiary levels.

11.2. Secondary care level

The secondary care level, based in medium-size hospitals, is staffed with medical specialists and allied health personnel and has available general clinical laboratory, radiology and ultrasound facilities.

In addition to all the functions typically performed at the primary health care level and described above, the secondary level deals with genetic problems of intermediate complexity, which cannot be solved at the primary health care level. Problems referred from the primary health care level comprise confirmation of suspected diagnoses, follow-ups of initial screening tests, management of specific conditions and genetic counselling of intermediate complexity. In some cases, fetal ultrasonography and prenatal diagnosis procedures can be done in this level. These services are performed by personnel with special training in applied genetics and genetic counselling, which can take several forms in different countries. For example, secondary-level genetic services in Cuba were initially implemented by pediatricians and obstetricians with special genetic training (Heredero, 1992, 1998), and later formally trained clinical geneticists replaced them. South Africa, on the other hand, resorted to specially trained nurses (Jenkins, 1990). Periodic outreach visits by clinical geneticists from tertiary care centres are helpful to deal with special problems, for education of personnel and for supervision purposes. When ultrasound and prenatal diagnosis procedures are offered dedicated personnel with appropriate training should undertake them.
11.3. Tertiary care level: medical genetics centres

The tertiary level of genetic services represents the best care available for genetic disorders and birth defects in a country. It is typically a medical genetic center, usually located in a university hospital or tertiary health center in a major city. Such facilities are a referral center for the secondary levels of genetic services. Thus, adequate referral channels for patients and feedback mechanisms to the referring level, with information and guidance required for the continuing follow-up of the patient and his/her family, are essential. Ideally the medical genetic center should have a designated area of coverage, with a number of secondary and primary health care level units under its responsibility. It is assumed that this tertiary level will concentrate mostly on diagnostic services, provide complex counseling and care to patients and families with severe genetic disorders, as well as develop research and implement training programs in the field.

The number and complexity of tertiary genetic centers depend on the size of the country, the relative importance of genetic disorders and birth defects in the health of its population and the human and material resources available. They should cooperate to ensure a broad national base of medical genetic services without unnecessarily duplication. Smaller and/or poorer countries may be able to sustain only a single such center or none at all; in the latter scenario, the more complex cases and/or laboratory tests can be referred out of the country. The following enumeration of functions performed by medical genetic centers describes best-case scenarios arrived at in a long process of service development. They should be considered ultimate goals rather than starting requirements. Moreover, it should be understood that a center will rarely have all the resources indicated.

11.3.1. Clinical genetics evaluation and genetic counselling

Patients referred from the lower levels of care are evaluated to make a specific diagnosis, to provide appropriate genetic counselling and to design suitable therapeutic measures, when available. These services are provided by physicians trained in clinical genetics and other specialties, in conjunction with non-medical personnel trained in genetics, including nurses, social workers, psychologists and genetic counsellors. Access to Internet and computerized systems of syndrome
identification are important diagnostic tools. Additional diagnostic services including pathology, radiology and ultrasonography must be readily available. There should also be access to consultation with other medical specialties, like haematology, oncology, neurology, ophthalmology. The medical genetics team should also be trained to provide treatments for selected conditions, like inherited metabolic diseases.

Genetic counselling is provided as an integral component of genetic services, including prenatal counselling about genetic risks in the offspring of people who are planning a pregnancy or who are already pregnant.

Prenatal genetic diagnosis is another important service offered in medical genetic centres. Components of this service include genetic counselling, obstetrical procedures (ultrasound and sampling fetal tissue) performed in the centre or at obstetrical sites, and laboratory testing (see Section 11.3.2). The goal of this service is to provide prospective parents at risk for a particular genetic condition in their offspring, with information on the status of the fetus with regard to a specific condition and the alternative reproductive options available in the country. Prenatal diagnosis should be strictly voluntary and preceded by non-directive genetic counselling (WHO, 1998).

Counselling about teratogens can be a tool of primary prevention of birth defects when it prevents exposures that can lead to malformations. Exposures to potential teratogens are very common in developing countries, because of the widespread use of pesticides and other environmental pollutants and the pervasive use of unprescribed medications and home remedies. It is not uncommon that after exposure to a potential teratogen, prospective parents resort to termination of pregnancy without sound reasons for it, out of fear of fetal damage. In this context, counselling provides objective evidence that may prevent unfounded pregnancy terminations. Access to teratogen databases is advisable, as well as easy consultation by health professionals via telephone or electronic mail (Clavijo et al, 1992; Schuler et al, 1993). A teratogen information service can function in a genetics centre, although other organizational schemes are also effective.

Finally, the clinical genetics unit should develop appropriate registers of genetic disorders and birth defects for their region and store data on the cases seen, for future follow-up of patients as needed as well as for research. Confidentiality and respect for the privacy of
genetic information, however, should be strictly enforced.

11.3.2. Laboratory diagnosis

Most genetic diagnoses require specialized laboratory techniques. Although a number of such laboratories exist in many developing countries, appropriate regionalization and streamlining of their services is required to improve their utilization and cost/efficiency. Because of technical and economic reasons, these laboratories should be centralized to insure an appropriate minimum workload, quality monitoring and cost-efficiency. Systems for the transportation or shipment of specimens from primary and secondary levels of care should be implemented.

Cytogenetic analysis for chromosome abnormalities in blood cells, amniotic fluid and/or chorionic villi is an essential component of a medical genetics centre. The most common indications for chromosome analysis after birth are confirmation of the diagnosis of aneuploidies especially Down syndrome, multiple congenital anomalies of unknown origin, unexplained mental retardation, disorders of sexual development and infertility. During pregnancy, chromosome analysis is indicated when there is an increased risk for a fetal chromosome abnormality, such as advanced maternal age, abnormal maternal serum biochemical screening or fetal malformations detected by ultrasonography. Precise risk figures that constitute an indication for offering prenatal chromosome analysis are variable. In most industrialized countries the standard of practice is to offer prenatal chromosome diagnosis when the risk of a chromosome abnormality at birth is 0.5% (for example: maternal over 35 years) or higher. Individual developing countries will have to set the cut-up point for the indication of prenatal chromosome analysis depending on factors such as availability of the prenatal diagnostic services, the skill of the obstetricians, fetal risk of the procedure, the availability of cytogenetic laboratories and their own economic and policy considerations.

A biochemical genetics laboratory is a valuable addition to the center. Simple techniques such as chemical screening tests in urine and chromatography/electrophoresis of amino acids, sugars, oligosaccharides and glycosaminoglycans are helpful in ruling out a number of suspected metabolic conditions. More complex techniques, such as the quantitative assay of amino acids, organic acids, very long
chain fatty acids and assays for selected enzymes, depend on high-cost equipment and highly-trained personnel. Moreover, the conditions studied are individually very rare and the yield of positive diagnoses is low. For these reasons, very few such laboratories can be justified in developing countries. A cost-efficient strategy may be the regional development of networks of laboratories that complement each other and cover very large populations of one or more countries (over 20 million).

Increasingly, the diagnosis of genetic disorders is relying on molecular, or DNA testing. Although the standard laboratory of molecular genetics does not require high-cost equipment, it is dependent on a continuous supply of expensive consumables and the techniques are usually labour intensive. The decision of setting up molecular genetics testing for clinical purposes requires a thoughtful process and depends on considerations of cost/efficiency and priorities, where factors such as the existence of a genetic disease of high prevalence (i.e. sickle-cell disorder) or the implementation of a prevention program based on prenatal diagnosis of a specific genetic condition that is only diagnosable by DNA testing. In any case, if a DNA testing facility is set up, it should be highly centralized and regionalized to maximize its cost/efficiency and minimize duplication of resources. If two or more such facilities are present in a country they should cooperate to ensure the tests they offer do not overlap. At a minimum, the genetics centre should be able to extract DNA from blood samples and ship them for testing to specialized laboratories in other countries. The ability to bank genetic material (plasma, urine, leukocytes, fibroblasts, DNA, etc.) would be important to support future studies in undiagnosed cases, to allow research projects on rare diseases, and to enhance cooperation projects with other centres. Ethical guidelines to insure confidentiality and privacy of genetic information should be adhered to (WHO, 1998). (See Section 16).

Finally, in some countries the medical genetics centre may be the site for the administrative and laboratory components of some population screening programs, such as newborn metabolic screening or prenatal screening for Down syndrome (see Sections 10.2 and 10.3), although different organizational schemes are viable. Any program to incorporate genetics into health care should follow a step-wise approach, with short, medium and long term goals.

Close attention should be paid to cost/benefit ratios when deciding on establishing different types of genetic laboratories. Key
principles are centralization, regionalization and complementation among laboratories, to avoid duplication of services. The proposal of a network of biochemical genetic laboratories in Latin America (Giugliani & Coelho, 1998) illustrates that complementation can also occur at the regional, supranational level. However, while it may be logical to concentrate most of the clinical and laboratory components of tertiary level genetic services in one or few sites, public health officials of developing countries should consider the whole context of the country or region before making policy decisions, as some of those components may already be operating in different settings.

11.3.3. Research

As the improvement of knowledge on genetic diseases depends largely on the investigation of affected patients, genetic centres are the natural sites to conduct research to contribute new and valuable information, especially on disorders of high prevalence in their population. In addition, some research projects can bring further financial support to the centres and contribute to the better training of human resources. The genetic centre also contributes to establish guidelines for the transition of research findings into the practice of genetic services.

11.3.4. Teaching and training

Genetic centres are usually established in university hospitals, facilitating the teaching of medical genetics to undergraduate students, which contributes significantly to the expansion of the awareness about genetic disorders and birth defects among health professionals. The training of young medical doctors through residence programs is also highly desirable to further enable qualified personnel to work in this field. The centre should also be involved, whenever possible, in postgraduate courses, providing training to health professionals in syndrome identification, laboratory investigation, prenatal diagnosis and genetic counselling, among other issues. The organization of courses to update health professionals on the rapidly evolving field of medical genetics and the diffusion of information to the general public should also be addressed.
11.3.5. General organizational principles and funding strategies

The installation of medical genetic centres in developing countries should only be conceived as a part of a comprehensive program designed to improve the care of these disorders. This is because of the large number of birth defects and genetic diseases, the rarity of any one condition, the complexity of the diagnostic process involved, the multidisciplinary nature of the care programs, and the costs involved. Ideally, these centres should be located in (or have easy access to) general hospitals that provide tertiary medical care. An association with university hospitals would enhance research and training, which could multiply the results of the work.

Depending on the size of the country, its stage of economic development and the relative impact of genetic disorders in health, there may be one or more tertiary level medical genetics centres. A single well staffed genetic centre could provide services to a population of 5-10 million people, particularly in a regionalized health care system that ensures absence of duplication of services and is linked with secondary and primary health care levels. To overcome the usual barriers of access to tertiary care level units, the genetic centre should be related to the community, through a referral network of secondary and primary health care medical units and clinics. In turn, the genetic centre should provide supervision and direction to the lower levels of care. However, a genetic centre should not be construed as absolutely hegemonic towards the rest of genetic services or the health professionals working at secondary and primary levels of care. The principles to follow are those of collaboration in a network with mutual responsibilities rather than authority.

To maintain a stable operation in the usually unstable economic environment of developing countries, the genetic centre should maintain a broad menu of funding options, including not only the health services but also research agencies, education funds, parents’ organizations, other lay support groups and industry. There is no general rule to organize the funding of the genetic centre, as this issue will depend on the specific characteristics of each country. However, the general rule of providing patient care, education and research usually enlarges the range of agencies that could be asked to support the centre. Besides the funds that could be raised from patient services provided, some alternatives for fund raising can be considered:
The association with non-governmental organizations, such as parents' groups, which could raise funds for several activities of the centre, including research projects;

- The development of research projects that could allow the centre to apply for support to national and international funding agencies;

- The development of training programs that could allow the centre to apply for support to educational authorities and to international educational funds;

- The development of special projects such as teratogen information services (which could obtain support from the pharmaceutical industry) or neonatal screening (which could be maintained by governmental special budgets or by parents associations).

12. TRAINING AND EDUCATION OF HEALTH PROFESSIONALS IN GENETICS

The latter half of the 20th century has witnessed rapid and remarkable advances in human and medical genetics and biomedical technology. This progress has resulted in an increasing understanding of the genetic contribution to health and disease. This is bound to continue and accelerate, with a likely shift of emphasis from rare genetic disorders to the more common multifactorial diseases, and towards new approaches of prevention and therapy. By the beginning of the next century all fields of medicine, including primary health care, will be utilising these advances in their practice (Harper et al, 1996; Harris & Williamson, 1996)

Associated with these developments, in industrialised countries, has been the evolution of clinical and laboratory medical genetic services, to meet the needs of the public for genetic care and information. The ability of these health care systems to cope with the current and expected increased demands for such services, particularly in the field of clinical genetics is limited by lack of appropriately educated and trained manpower (Holtzman, 1989; Harper et al 1996).

Thus to ensure the future development of genetic services at all levels, including primary health care, medical genetics must be included in the core curriculum of under- and post-graduate physicians and nurses, and other allied professionals, (genetic counsellors, social workers, psychologists, community health care workers) who are involved in the
provision of counselling and support.

Education and training in medical genetics in developing countries is currently limited, although it has been initiated in several countries (WHO, 1998; WHO/EMRO 1997; Jenkins T, 1990). Given the increasing role that medical genetics is already playing in medicine, the delineation of objectives of medical genetics education for the health professions in developing countries cannot be ignored.

A core medical genetics curriculum in the training of health professionals should have the following objectives (Baird, 1988; WHO/EMRO, 1997; Graham et al 1989; Johnston, 1990):

- The acquisition of a sound basic knowledge of genetic mechanisms in health and disease, and the role of genetic technology in medicine for diagnosis, treatment and prevention;
- The engendering in the student of appropriate attitudes towards the patient and family;
- The installation of a culture of lifelong learning in the student.

These goals can be obtained through a core curriculum that addresses the knowledge needed to be conversant with current developments in the field, the skills needed to apply this knowledge in practice and the attitudes necessary for optimal care and support of the patient and families.

Each country has its own characteristic pattern of common genetic disorders and birth defects that require to be managed within that country's social, cultural and legal milieu and health care framework. Until medical genetic services are well and equitably established in developing nations, a greater burden than usual for medical genetics care will be placed upon primary health care providers, including general physicians, nurses and non-medical personnel. As a basic principle these professionals should be educated and trained to manage common problems to the greatest extent possible, with the facilities available, at the primary health care level, and refer only those patients who require special care in terms of diagnosis, investigation and treatment.

The development of a medical genetics core curriculum for each country will require that these influences be accommodated and that the curriculum then be appropriately adapted to the needs of the different health care professionals. Having provided initial education and training for medical, nursing and paramedical personnel, it is necessary to develop a system of continuing professional development. Thereby individuals will
have the opportunity to keep abreast of the rapid advances in the field and their appropriate application to daily work within the health care system.

**COMPOSITION OF A CORE MEDICAL GENETIC CURRICULUM**

**Basic topics**

- Basic Cytogenetics - Chromosome structure, function, terminology and common abnormalities.
- Basic Molecular genetics - DNA, gene structure, function and mutation. DNA techniques and application.
- Mendelian patterns of inheritance.
- Non-Mendelian patterns of inheritance - multifactorial, mitochondrial, uniparental disomy, genetic imprinting.
- Congenital malformations and teratology.
- Cancer genetics.
- Genetic counselling.
- Prenatal diagnosis and genetic screening.
- Ethical issues

**Skills**

- Take an adequate history. Includes constructing a family tree and identifying patterns of inheritance.
- Undertake a physical examination including being capable of eliciting common dysmorphic features (professionals involved in clinical diagnosis).
- Be capable of utilising the above to derive common genetic diagnoses (professionals involved in clinical diagnosis).
- Undertake a rational plan of investigation and/or care with appropriate referral when necessary. Management includes non-directive genetic counselling and psychosocial support.

**Attitudes**

The rights of patients and families and the responsibility for upholding these, need to be imparted to students who will qualify to become medical genetic caregivers.
The patient’s rights include:

- Respect and empathy for patients and family;
- Full non-directive disclosure of information and counselling with respect to:
  - What is the diagnosis.
  - The aetiology of the condition.
  - The prognosis/consequences of the condition.
  - Management of the condition, and possible prevention in future pregnancies.
- Full autonomy with respect to their own informed choices and support for these.
- The confidence that the caregiver has the knowledge and ability to supply refer appropriately when indicated.

13. GENETIC EDUCATION OF THE PUBLIC

As it was already stated in this Report, that it is essential that the public be educated with the appropriate knowledge necessary to take advantage of the prevention programs and the genetic services. As many of the outcomes of these programs depend on personal decisions of patients and persons at risk, the aim of public education in genetics is to empower people to make their own decisions in ways that maximize their wellbeing and health.

Educational activities in schools, community organizations and health care institutions are among the many possible alternatives. The mass media should be enlisted as allies of this endeavour. Messages should be simple, in language that is easily understood and free of derogatory, guilt-provoking or discriminatory overtones. A South-American experience of disseminating a “Decalogue for Primary Prevention of Birth Defects” (Castilla, 1999) constitutes a good example of public education that could be extended to other regions and other topics. The decalogue is worded as follows:

- Any woman of fertile age can be pregnant even if she is not aware of it;
- It is better to complete your family while you are young;
- Prenatal controls are the best guarantee for the health of a pregnancy;
- Get rubella vaccine before you become pregnant;
- In pregnancy, avoid all medications except the essential ones;
- In pregnancy, avoid alcoholic beverages in any quantity;
- In pregnancy, avoid smoking and smoking places;
• Eat well and consume varied foods, including vegetables and fruits;
• Ask if your regular job entails any risk to your pregnancy;
• In doubt, consult your physician or a specialized service.

14. PARENTS/PATIENTS ORGANIZATIONS

Patients and their families concerned in genetic disorders and birth defects often face severe emotional, psychosocial, physical and economic lifelong burdens. Standard health care services are currently not equipped to meet the needs of these people. Wherever they live, they need to have answers to many questions such as:
- where to find proper care
- where to obtain comprehensive, understandable and relevant information
- why did this happen to them
- could they have prevented it
- what does it mean to their families
- how to cope with the consequences of the disease
- what to tell other people about their problem
- how to get in contact with people involved with the same problems.

A rough estimate by the Dutch National Health council indicates that some 10 to 35% of hereditary diseases can be prevented if the available information reaches the people involved in time (Poortman, 1999). Although genetic counselling services in academic genetic centres (see Section 11.3) usually satisfy the above mentioned concerns, most people in need are not aware of these services, and neither are general physicians, so referrals tend to be late or are never made.

14.1. Medical support and self help

Most disorders caused by mutations in a single gene are rare. In developed countries families often experience prolonged delays before getting a diagnosis and advice from the professionals about the management of the condition. Even when a timely diagnosis is made, lay patient support groups play an important role as a resource and a reservoir of practical knowledge for advice and support of its management on a day-to-day basis. In many parts of the developing world access to medical help for genetic disorders and birth defects is even more difficult because the health care systems devote their
attention to more acute problems. The latter affect larger numbers of people and their management usually offers immediate gains through effective treatment and prevention. In developing countries, thus, support groups and mutual help are not just helpful, but essential.

Most people, wherever they live, have little or no exposure to or knowledge about genetic disorders and birth defects. As a consequence, there is no reservoir of understanding or appreciation of what impact any such disorder has on the affected person and his or her family. An affected person therefore can feel isolated and even rejected and stigmatized, because of failure to appreciate the genetic cause of the condition which leads to feelings of guilt and self-blame for the condition. Meeting others in the same situation is a source of great relief, because of acceptance and understanding, and also generates knowledge about practical management of the condition.

Patient support groups of developing countries have better access than single individuals to external sources of help (such as similar organisations in the industrialized world), which may be able to share their own resources or provide tangible support for their sister groups in developing countries. Informed, mutual self help will often lead to the development of patient groups in more formal ways, which in turn can result in political pressure for change, improved services and support and better health care for those affected.

14.2. Objectives of parents/patients organisations

Parents and patients have become united on a national, continental, and global level. Through disease-oriented organisations and national “genetic alliances”, they address specific concerns such as genetic causes of disability, means of prevention, management, public awareness, biomedical research, patenting of genetic material, and ethical and psychosocial aspects. Genetic coalitions have been founded in an ever-increasing number of developed and developing countries. In North America, Australia, and Western Europe, continental alliances of genetic support groups are well established. Hundreds of such groups exist in Latin America. More recently such alliances were founded in the Ukraine, in South Africa, and in India.

The European Alliance of Genetic Support groups (EAGS) serves about 350 national support groups through nine European disease-oriented alliances and eight national genetic umbrella organisations. About six million families are affiliated with the member
associations of EAGS.

The objectives of these organisations are:
- Stimulate research into the causes, prevention, and treatment of relevant diseases;
- Improve the wellbeing of patients with genetic impairments and their families;
- Improve the health status by providing qualified, accredited, accessible and affordable genetic services as an integral part if all health services;
- Voice the opinions of its members.

At the meeting of the European Alliance of Genetic Support groups (EAGS) in London in 1995 the following consensus statements were developed:
- Primary and secondary healthcare providers are currently not capable of dealing with genetic diagnosis and genetic counselling;
- Level of awareness of health care officials about genetics is minimal or entirely lacking;
- Production of reliable, up to date educational materials is urgently needed for the professionals, the people concerned, and the population at large;
- Appropriate and timely decisions concerning reproduction is often thwarted by late and inaccurate diagnosis, inefficient referral systems and unbalanced and unreliable information;
- Research into the causes of congenital disorders has been relatively limited and its importance underestimated;
- Impact of genetics and congenital disorders on the people concerned has been underestimated; adequate guidance is hard to find;
- The voice of the people concerned should be clear and heard and must be transmitted through the official channels.

The Advisory Group recognised that the above statements (which have been endorsed worldwide by hundreds of parents’ and patients’ organisations concerned with genetic disorders and birth defects) is also applicable to developing countries. While much of the following text is based on the experience of patients’ parents’ organisations of developed countries, particularly in Europe, the Advisory Group felt that the principles stated apply equally to developing countries.
14.3. *The role of parents/patients organisations.*

These organisations strive to make government officials and political leaders aware of new genetic knowledge and its applications.

Parents' and patients' organisations tend to work closely with academic clinical genetic centres. With their support, they are able to produce comprehensive educational materials for the general public, which include audio-visual presentations, audiotapes and lesson packets of teaching materials for schools. They also produce television series in the context of Open University programmes; they establish public awareness campaigns that spread information about the availability of genetic services. Recent campaigns addressed the importance of folic acid as a primary preventive in the preconception period and described the available services making use of free publicity, advertisements etc. These organisations also take stands on topics such as about patenting of genetic material, the various international declarations pertaining to the human genome in the context of human rights and the need for genetic services throughout the world.

The media and the political leaders have shown an increasing interest in the opinions of parents and adult patients who have become experts themselves, because of their personal experiences. Another potential is their contribution to research efforts by encouraging their members to participate in biomedical research.

In most countries the alliances are recognised by governmental bodies. They have increasing political influence because of the large numbers of individuals whom they represent. The Advisory Group considers that parents' and patients' organisations play already an important role in developed and developing countries in the wellbeing of individuals affected with genetic disorders and birth defects. Governments and genetic professionals should encourage their formation and support their work.

15. RESEARCH IN MEDICAL GENETICS

As stated previously in this Report, the Group feels that research is an important component of medical genetics in developing countries, especially as insufficient data are available on the epidemiology of genetic disorders and birth defects, the expectations of the population and the outcomes of genetic services.
Genetic research in developing countries should be applied in nature, and concentrate on generating knowledge regarding conditions that are particularly prevalent in the developing world. Emphasis should be given to epidemiological research on the prevalence and risk factors for genetic disorders and birth defects. Setting up registers of genetic disorders and birth defects will provide data for research as well as support and guide the implementation of care and prevention of these conditions. Research should take advantage of characteristics only or primarily found in each developing country, including particular ethnicities, exposure to specific environmental agents, large families, inbred populations, genetic disorders especially frequent in some areas.

Health services research with the purpose of finding new approaches to prevention and treatment of genetic disorders also deserves support. Psychosocial, cultural and ethical aspects of genetic services have largely been neglected in developing countries, where prevailing stereotypes most likely do not reflect the variety of opinions within a single culture.

Technological research should be directed at developing diagnostic and therapeutic technologies appropriate to the economic and social conditions and the needs of populations of developing countries.

16. ETHICAL ASPECTS OF GENETIC SERVICES

Ethical considerations have been part of the practice of medicine since its inception. The traditional sources of ethical guidelines in medicine (respect for the dignity and autonomy of persons, beneficence, non-maleficence and justice) apply equally to medical genetic services worldwide. Moreover, the ethical concerns of medical genetics extend beyond those that medicine has held traditionally, as genetic information may affect an entire family rather than only an individual, it may predict future adverse events and presents choices that may affect future generations. In addition, the approach of medical genetics to patients and their families in genetic counselling tends to non-directive, in contrast with the directiveness of traditional medicine. The opportunities for prevention of genetic disorders and birth defects afforded by the technological advances in prediction and diagnosis, trigger novel ethical dilemmas, particularly in the public health
applications of genetics.

Specific ethical dilemmas may be particularly poignant in developing countries, because of the circumstances described in Sections 5 and 6 of this document. Poverty, unequal distribution of wealth and scarcity of resources for health care pose serious ethical dilemmas in policy decisions regarding the place of genetic programs among competing priorities. Low levels of education of the public, and particularly of women, combined with traditional medical paternalism challenge the practice of non-directiveness and respect for individual autonomy. In many cultures prevailing in developing countries, the weight of traditions may conflict with modern views associated with the application of genetic technologies. A recent WHO panel of experts in medical genetics and ethics representing developed and developing countries proposed international guidelines to be followed in the implementation and practice of medical genetic services (WHO, 1998). It is apparent from these guidelines that, while the particular social, cultural, economic, legal and religious realities of individual countries must be acknowledged, most ethical principles in genetics are fairly universal and applicable to both developed and developing countries.

16.1. Ethical principles applied to genetic services

The following basic ethical principles should be followed in the implementation and practice of genetic services:

- Fair allocation of public resources for the management and prevention of genetic disorders and birth defects on the basis of need, defined by the magnitude and severity of problems to address and the benefits anticipated from actions;
- Respect for human genetic and cultural diversity;
- Respect for people's basic intelligence and for those whose views are in the minority;
- Education of the public, health professionals, teachers, clergy, etc in genetics;
- Participation of the public in the setting of goals of genetic services and their implementation;
- Voluntary approach of genetic testing, prevention and treatment. Avoidance of coercion by government, society or the medical profession;
- Timely provision of indicated services or follow-up and treatment. Refraining from providing tests or procedures not medically indicated. Ongoing provision of quality control of services;
- Freedom of choice in all matters relevant to genetics. Women
should be important decision-makers in reproductive matters;

- Prevention of unfair discrimination and/or stigmatization on the basis of genetic constitution;

- All genetic testing should be voluntary, preceded by adequate information and based on informed consent. Special caution should be exerted when testing healthy individuals for susceptibility to genetic and multifactorial conditions of adult onset that have no proven beneficial medical interventions. Testing of asymptomatic children should only be performed if there are potential medical or psychological benefits;

- Prenatal diagnosis should be done only to give parents and physicians information about the health of the fetus. Its use to enforce social policies of any kind or for non-medical medical indications, like paternity testing or gender selection, apart from sex-linked disorders, is ethically unacceptable.

- Medically indicated prenatal genetic diagnosis should be voluntary and available, within the context of each country, regardless of the couple's stated views on abortion. The prospective parents should decide whether a genetic disorder warrants prenatal diagnosis and/or termination of an affected pregnancy, as prenatal diagnosis may be used occasionally to prepare for the birth of a child with a disorder.

- The woman's and/or the couple's choices in a pregnancy with an affected fetus should be respected and protected, within the framework of the family and of the laws, culture and social structure of the country. The couple, not the health professional, should make the choice.

16.2. Ethical principles applied to genetic counselling

The goal of genetic counselling is to empower individuals to make their own informed decisions pertaining to their genetic risks and/or the genetic risks of their offspring. This is accomplished by providing the individuals with accurate, full and unbiased information in a manner that is clear and understandable. It should take place in a manner that is empathetic and non-coercive. Thereafter the individuals are allowed to make their decisions, in their own time, in accordance with their own beliefs and customs, and the re-assurance that their choices will be fully supported by their medical attendents. These elements are the hallmark of what has been termed "non-directiveness" in genetic counselling. This approach has largely derived from the fact that todate medical
genetics offers mainly diagnosis and prediction rather than treatment. It is likely that, as medical genetics advances and more treatments become available, the approach to genetic counseling may become similar to current approaches in general medicine, where the health professional may recommend beneficial treatments and/or lifestyles changes.

In summary, therefore, ethical principles applied to genetic counseling include:

- Respect for the personal values and culture of individuals and families.
- Full disclosure of all information relevant to health with accurate and unbiased information.
- Non-coercion towards a particular decision.
- Protection of the privacy of genetic information from unjustified intrusions from third parties.
- Informing individuals about the wisdom of disclosing genetic information to spouse or partner if children are intended, as well as the possibility of harmful effects on the marriage from disclosure.
- Informing individuals of their moral duty to disclose a genetic status that may affect public safety.
- Non-directive approach whenever possible. When treatment is available a more directive stance may be advisable.

Policymakers of all countries should take these principles into consideration in formulating policies for the management and prevention of genetic conditions and birth defects. Concurrently, close dialog between the health professions and the public should be fostered to allay fears of misuse or abuse of genetic information.

17. GENERAL CONCLUSIONS AND RECOMMENDATIONS

17.1. Need to recognize the burden imposed by genetic disorders and birth defects

The key and obvious first step to address a problem is to recognize its existence. As this report has documented extensively, genetic disorders and birth defects constitute a significant public health problem in most of the developing world. A number of factors (biological, medical, cultural, social) contribute to their occurrence and to their impact on health and wellbeing. The burden of these conditions
in the developing world is dynamic, with an ongoing epidemiological transition from infections and malnutrition, on the one hand, to genetic disorders and birth defects as the principle causes of disease and disability. It is recognised that there is a significant variation among developing countries in the relative role of genetic disorders and birth defects in disease and disability. The consensus of the Group was however that most nations in the developing world have reached the stage in which some attention needs to be paid to genetic disorders and birth defects, even if infectious diseases and malnutrition are not yet completely controlled. Although scarce health resources should not be diverted from the prevention and care of infections and malnutrition, the Group’s contention is that governments in the developing countries should also devote attention and resources to the management and prevention of genetic disorders and birth defects. For this to happen, public health authorities must acknowledge the reality that these conditions indeed are major causes of disease, disability, suffering and death in their countries, and recognize that there are approaches for their management and prevention that can significantly reduce their burden in a cost efficient manner.

17.2. Need for political will and commitment

For genetic services to be implemented in a meaningful way and to benefit a sizable proportion of populations in need, governments must demonstrate beyond rhetoric, a political will to improve health and wellbeing of the people by making all types of health services, including genetic services, available and accessible.

The commitment must come from the highest levels of government, and be translated into appropriate resource allocation. Moreover, by the nature and factors involved in genetic disorders and birth defects, the approach to their management and prevention are necessarily multidisciplinary and multisectorial, with involvement of health, social welfare, education, nutrition and other agencies. Generating political will and commitment from government authorities will require lobbying and educational efforts on the part of the medical community and non-governmental organizations such as parents/patients groups.

Cost/benefits analyses will help authorities to realize that:
- Priorities can be established so that there is no need to “start with everything at the same time”;
- A number of genetic services can be implemented without large financial investments;
- Many genetic services are cost/effective;
- Costs of inaction in genetics to society, measured in terms of avoidable human suffering and burden to public health, are much higher.

The Advisory Group specifically recommends that Ministries of Health of developing countries allocate resources for genetic programs and set up a distinct Office of Genetic Services within their administrative structure. This office should be directed by an individual with appropriate expertise in genetic services and would have the following tasks:

(a) Determine the existing burden of genetic disorders and birth defects in the population
(b) Determine the status of existing programs for the prevention and care of genetic disorders and birth defects, their human and material resources, their distribution, their financial needs and outcomes.
(c) Organize at the level of the Ministry of Health a permanent advisory council on genetic services with participation of interested parties, including clinical geneticists, other relevant medical specialties, public health specialists, paramedical personnel and parents/patients organizations. This advisory council would be instrumental in recommending the appropriate steps and priorities for genetic services in the country.

17.3. Improve epidemiological knowledge about genetic disorders and birth defects.

In order to improve the knowledge of the impact of genetic disorders in developing countries, epidemiological research should be stimulated to provide better data on the prevalence and types of birth defects, genetic diseases and genetic predispositions to common diseases at the country level. Population and/or hospital based registries of congenital malformations are good sources of epidemiological data on genetic disorders and birth defects detectable at birth. Special registries of specific conditions, such as haemophilia, thalassaemia, skeletal dysplasias, inborn errors of metabolism and others, can provide data on which to base policies for the management and prevention of
these conditions. Epidemiological studies should be standardized to enable international comparisons and include the demographic and social characteristics of countries and their influence on the prevalence of genetic disorders and birth defects and on the delivery of services. Consanguinity, founder effects, cultural and geographic isolation must be studied to assess their influence on the prevalence of specific conditions and, particularly on geographical clusters of genetic diseases.

In addition to standard epidemiological data, it is useful to develop information on what impact specific genetic disorders and birth defects have on individuals, families, and communities. These studies would typically include data on the natural history of conditions, mortality, morbidity and survival, quality of life and reproduction, utilization of the health care system, hospitalizations, manpower requires for their management, costs of services, etc.

The above recommendations should be implemented by Ministries of Health and academic institutions, in the form of established data gathering programs or specific research projects.

17.4. Define goals of genetic services in terms of both individual/family wellbeing and public health.

Genetic programs and services have two complementary objectives. They alleviate suffering and help individuals and families touched by or at risk for a genetic disorder or birth defect, to benefit from medical interventions. Additionally, through public health genetic programs, they aim to reduce the burden of these conditions in the population. In establishing genetic services there has to be a balance between individual and public health goals. The latter should never override autonomous reproductive decisions by individuals. In other words, public health goals should not be confused with the concept of eugenics, wherein population genetic goals, however defined, are imposed by coercion and discrimination (see section on ethical principles). Reliance on education, non-directive counselling and respect for peoples' reproductive decisions should not interfere with success in genetic programs in industrialized as well as developing countries. Public health authorities have to be aware and accept the fact that occasionally an individual's decision may be a direction apparently

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contrary to an implicit or explicit public health goal (i.e. when a couple decides to continue a pregnancy with an affected fetus).

The basis for defining goals of genetic services in a particular country or community are:

a) the existing burden of specific genetic disorders and birth defects and their impact upon society in human and economic terms;
b) the burden of other health problems;
c) the resources available and the potential of raising funds from external sources;
d) the state of the art of established screening, diagnostic, preventive and therapeutic methodologies for particular conditions (for example, preconceptional folic acid supplementation for the prevention of neural tube defects, screening and prenatal diagnosis of thalassaemias, genetic predisposition to cancer, etc);
e) the expectations of the community.

Whenever setting goals for genetic services it is important to bear in mind that by their very nature, these services accomplish primary, secondary and tertiary prevention objectives at the same time. For example, the diagnosis of fragile-X syndrome in a child with mental retardation enables secondary and tertiary prevention strategies to minimize the impact of that condition on the child and his family; at the same time, it may set in motion primary prevention measures, such as genetic counselling for the family to give options to avoid recurrences in the same couple or other relatives at risk.

17.5. Improve pre- and perinatal services.

The prevention of a number of birth defects will follow an improvement in the quality and accessibility of preconception, prenatal and perinatal services. The improvement of preconception care should include:

a) improvement of preconception and prenatal nutrition
b) encouragement to procreate in the optimal age period (20-35 years of age);
c) public education about methods that allow couples to have children when they want them, and provision of services to make those methods accessible;
d) rubella immunization before pregnancy;
e) avoidance of teratogen exposures during
f) gestation, particularly alcohol;
g) accessible prenatal care;
h) proper delivery care;
i) enhancement of newborn services by increasing the proportion of babies born in institutions, and by insuring that they have a complete physical examination to detect congenital malformations such as congenital hip dysplasia, cleft palate, congenital heart defects and others whose outcome can be improved by early intervention;
j) newborn metabolic screening of relevant conditions.

17.6. Organize genetic services in a comprehensive and integrated manner, with roots in the primary health care level.

The key to the implementation of genetic services is the application to genetics of the strategy advocated by WHO for health care in general, that is of extending primary health care to all segments of the population, while linking the primary health care level with secondary and tertiary levels in a regionalized manner that makes the best possible use of existing resources. Genetic services should always be comprehensive, that is, they should combine the best possible patient care available in the country, with population-based prevention strategies such as public education, screening and control of genetic risks and genetic counselling (WHO, 1996; WHO/EMRO, 1997). Furthermore, genetic services cannot exist in a vacuum. They must be integrated with related services, such as reproductive health, prenatal care, newborn care and child growth and development monitoring, nutrition, cancer prevention, etc. In some cases, genetic services will be part of specific categorical programs, such as newborn metabolic screening, the control of haemoglobin disorders, haemophilia or mental retardation.

A key ingredient for success of genetic programs in the developing countries is the extension of genetic services coverage into primary health care settings, where genetic risks should be identified. In order to avoid duplication of services and to be as cost efficient as possible, genetic services must be regionalized, with tertiary centres responsible for specific geographic and administrative areas. Programs at secondary and primary health care levels should be supervised by tertiary centres in a collaborative rather than authority mode.
What is practically needed is the organization of different programs according to the needs and resources of individual countries. Organization of such programs is facilitated by their integration within existing primary health programs. Such integration is more feasible and cost-effective than establishing a new vertical genetic program. Insertion of genetic services into the community is key to the success of any genetic program. This approach of community genetics was outlined by the World Health Organization and has led to the formulation of strategies appropriate for the developing world (WHO, 1996). The idea is that the health personnel in charge of primary health care be trained to address also the genetic components of prevention and care.

Genetic services should have an emphasis in the family and should rely on modern cost/efficient information technology, such as internet. Care should be coordinated among different specialties and disciplines, and provide for continuity of care and long-term management. Quality assurance of clinical and laboratory services should not be considered a luxury but rather an essential component of genetic services.

17.7. Select programs and targets according to prevalence, severity and predicted outcomes

Preventive actions should focus on specific conditions that have a significant impact on health because of their prevalence and severity, and the feasibility of their prevention. In this regard, prevention of congenital rubella by immunization of susceptible children should be a priority. Educational and social programs to prevent alcohol consumption during pregnancy will help prevent fetal alcohol syndrome, which has high prevalence in some population groups. Neural tube defects can be partially prevented through preconceptional folic acid supplementation, maternal serum screening programs and fetal ultrasonography.

Primary prevention of Down syndrome could be accomplished to a considerable degree through community education and family planning to encourage procreation before 35 years of age. Prevention by reproductive options would require, depending on availability of resources, a program of prenatal screening based on maternal serum biochemical markers and/or ultrasound followed by prenatal diagnosis. Similarly, women of advanced maternal age who become pregnant could be offered prenatal diagnosis, according to availability of
resources. These programs are strictly voluntary and require the development of efficient educational programs, genetic counselling and adequate fetal medicine and laboratory facilities. All programs should have standardized protocols for evaluating their effectiveness.

Some of the most common severe inherited conditions, such as haemoglobin disorders, cystic fibrosis, fragile-X syndrome, haemophilia and muscular dystrophies, contribute considerably to chronic morbidity in childhood in many developing countries. Programs for the prevention and care of affected children with these conditions may significantly reduce the overall burden due to chronic disease at the community level.

Newborn metabolic screening should only be considered in countries with appropriate infrastructure and resources that guarantee efficiency and desired outcomes. Conditions to include in a newborn screening program should be clinically severe, relatively prevalent, capable of being screened and diagnosed with simple and low cost methods, and subject to treatment that will clearly be more beneficial if started immediately after birth. The condition that most clearly fits all these criteria is congenital hypothyroidism. Newborn metabolic screening should always be a policy decision by the government, which should allocate the necessary resources to its implementation, including a funded centralized laboratory, follow-up and confirmation of initial abnormal initial screen results, and long term treatment of affected children.

17.8. Respect ethical principles and cultural diversity

The health beliefs, traditions, religious observances and social expectations of individuals and communities should be assessed properly before setting program goals, and respected thereafter. These goals should never be set in ways to impose certain genetic tests or reproductive decisions on individuals. Governments should recognize that within any country there exists diversity of cultures and opinions about a number of issues relevant to genetics, such as human reproduction issues as well as about the significance of disabilities. This diversity should be respected. Ethical principles of justice, autonomy, beneficence and respect for the dignity and basic intelligence of persons should be adhered to.
It should be stressed that the major ethical issues in present medical genetic practice are inadequate services, deficient genetic knowledge of medical and para-medical practitioners and inequitable access to existing services. Accepted ethical guidelines of public health programs in genetics stipulate that genetic testing should always be voluntary, respecting the autonomous decisions of the patients, and should be preceded by proper information in the form of non-directive genetic counselling (WHO, 1998). Public health goals cannot override the cultural and personal values and beliefs of individuals and their reproductive rights, and oppose stigmatization and discrimination of affected persons (WHO, 1998).

17.9. Training health professionals in medical genetics

Serious efforts should be undertaken in genetic education for health professionals. Undergraduate curricula of the health professions (primarily physicians, nurses, psychologists and social workers) requires to be continually updated and the practical aspects of medical genetics included in clinical teachings. The relationships between genetics and public health, largely neglected in most health professional circles, should be addressed in the schools of public health of developing countries. For those health professionals already in practice, continuing education programs are essential to familiarize them with the modern concepts of clinical genetics. Officials in charge of public health programs should be targeted specifically for continuing education in genetics.

Training of health professionals in genetics can be implemented by the already existing medical geneticists in developing countries, usually concentrated in tertiary care institutions, affiliated with academic institutions and research centres. When the human resources in any particular country are insufficient for this task, manpower should be pooled at a regional level, so that teaching materials are developed and shared in countries with similar backgrounds and health problems. Training partnerships should be developed not only among developing countries, but also between developing and developed countries. An initiative worth undertaking is the joint development of medical genetics curricula that address the needs of developing countries, and that target separately primary health care physicians, pediatricians, obstetricians, nurses and public health officials. The Internet is ideally suited for this type of endeavour. One of the objectives of this training should be that, with proper supervision, genetic counselling becomes a tool that most health professionals are able to apply in practice.
Another aspect to consider is the training of clinical geneticists and specialized laboratory personnel, whose number is clearly insufficient to provide all the genetic services needed in the developing countries. However, few developing countries have the manpower to engage in, and the resources to devote to, this highly specialized training. Therefore, rather than training additional such personnel, efforts should be directed towards training in genetics of different health professionals such as physicians, nurses, psychologists, and social workers. Nonetheless, it is important that existing academic clinical geneticists be educated in public and community health, so that they recognize the social and population impact of the services they provide.

17.10. Educate the public in genetics

It is well recognized that, both in the industrialized as well as developing countries, there are serious misconceptions about birth defects, genetic disorders and the role of medical genetics in their management and prevention. As individuals and families increase their active participation in health and reproductive decisions, it is essential that the public at large be educated in the clinical and social aspects of genetic services. Education empowers people to take control of their health and their lives. This is particularly true for women, whose educational standards are much lower than those of men in the developing world. It is well known that the mother’s educational level is the single most important predictive factor in the health and survival of children in the developing world.

Public education about genetic disorders and birth defects should be attuned to the prevailing cultures, beliefs and values of the populations in any given community. Particular attention should be paid to the vulnerable groups in society (the poor, ethnic and linguistic minorities, etc).

Proper use of the media (particularly radio and TV) is invaluable. Community meetings should be encouraged to discuss important issues, such as the use of alcohol in pregnancy, rubella immunizations, self-medications, the value of learning about one’s own family medical history, where to go for genetic counselling, etc. Education on these topics should include high schools. Educational
messages should be simple and in a language that is not derogatory or discriminatory.

Education in genetics should also target other relevant professionals such as lawyers, judges and legislators, and political authorities who very frequently make decisions regarding genetic problems.

Journalists, as key players in the dissemination of medical genetics knowledge to the general public, should be enlisted as allies in this endeavour and be offered training in relevant genetic topics.

17.11. Encourage the formation of parent/patient organizations

Throughout the industrialized and developing worlds, affected individuals and their families are acquiring awareness and creativity to advocate for their own needs. Hundreds of parent/patient organizations have been instrumental in bringing attention to the need for clinical services and preventive programs for genetic disorders and birth defects, as well as asserting their right to be treated with dignity and without discrimination. A number of legislative initiatives in several countries have been the result of the actions of parent/patient organizations. The medical profession and the governments should support the development of these independent organizations. It is important that these organizations be truly independent and able to respond to the legitimate needs of their constituencies, and not be controlled by the medical establishment or the government.

18. SPECIFIC RECOMMENDATIONS AT DIFFERENT STAGES OF THE REPRODUCTIVE CYCLE

A number of recommendations for the management and prevention of genetic disorders and birth defects in the developing world have been proposed over the past 15 years. Some of these recommendations have emphasized comprehensive and non-categorical programs (PAHO, 1984; WHO, 1985; Penchasazdeh, 1992; WHO, 1996; WHO/EMRO, 1997; Penchasazdeh and Beiguelman, 1998; PAHO, 1998; Penchasazdeh, 1999), while others have focused on primary prevention of birth defects of environmental origin (Castilla, 1999).
The Group recommended that the following programs be given priority in the field of genetic disorders and birth defects in the developing world. It was recognized that actual priorities are to be determined by each country according to needs and resources. It was also noted that any program should have identifiable targets and expected outcomes. The measures recommended are conceived along the different stages of the life cycle, as follows:

18.1. Recommendations for the preconception period

a. Improve access and quality of reproductive health services, including family planning and encouragement for women to complete their reproduction by 35 years of age.

b. Insure adequate nutrition and vitamin supplementation (especially folic acid) to women in reproductive age.

c. Expand rubella immunization to eliminate rubella infection in pregnancy.

d. Standardize family history taking at the primary health care level for the detection of genetic risk factors and referral of high-risk patients for genetic counselling.

18.2. Recommendations during pregnancy

a. Adequate prenatal care, nutrition and delivery services

b. Raise awareness of the need to avoid exposure to teratogens, specially alcohol, tobacco, radiation and unnecessary and unsupervised medications

c. Manage maternal conditions that can affect the health of the fetus, such as diabetes and hypertension

d. Implement programs for the detection of increased risk of neural tube defects, other congenital malformations and chromosome anomalies by maternal serum screening and fetal ultrasonography, followed by the offer of prenatal diagnosis.

e. Implement programs for the detection of increased risk of selected
single-gene disorders that are specially prevalent in the population (i.e., sickle cell disease, thalassaemia), followed by the offer of genetic counselling and prenatal diagnosis.

18.3. Recommendations for newborns, infants and children

a. Implement systematic physical examination of newborns to detect congenital malformations, particularly of those whose outcome can be improved by early intervention (such as congenital hip dysplasia, cleft lip and palate).

b. Metabolic screening of newborns for conditions that are clinically severe, prevalent, easy detectable at birth and derive clear benefit when treatment begins in the newborn period. The clearest example of such condition is congenital hypothyroidism.

c. Monitoring of child growth and development for the early detection of genetic disorders and intervention for secondary and tertiary prevention.

d. Psychosocial support and genetic counselling for families of children affected with congenital malformations, Down syndrome and single-gene disorders of high prevalence and severity in the community.

18.4. Recommendations for adults

a. Promote healthy lifestyles to prevent chronic diseases, such as cancer and coronary occlusion.

b. Detect individuals at risk of developing late-onset genetic diseases and offer genetic counselling and presymptomatic testing if medical intervention is feasible and beneficial.

19. SPECIFIC RECOMMENDATIONS FOR CATEGORICAL (VERTICAL) PROGRAMS

The following categorical programs were selected by the Group as examples of high priority in most developing countries, recognizing that each country should set its own priorities after careful analysis of their reality.
19.1. Prevention of congenital malformations

a) Expand rubella immunization programs with the aim of covering all children.

b) Implement programs to raise awareness of the need to avoid exposure of pregnant women to known teratogens, such as alcohol, tobacco, radiation and unnecessary or unsupervised medications.

c) Evaluate the feasibility of folic acid fortification of foods for the prevention of neural tube defects.

d) Expand the accessibility of ultrasonography for the detection of severe fetal malformations.

19.2. Prevention of Down syndrome

a) Encourage women, through public education and family planning programs, to complete reproduction by age 35.

b) Increase accessibility to genetic counselling and voluntary prenatal diagnosis to pregnant women of advanced maternal age.

c) Study the feasibility of implementing prenatal screening programs for Down syndrome risk, by maternal serum markers and fetal ultrasonography, followed by prenatal diagnosis.

19.3. Prevention and management of selected single-gene disorders of high prevalence and impact.

a) Conduct studies to determine the most prevalent severe single gene disorders in the population and their impact on morbidity and mortality (e.g. haemoglobin disorders, cystic fibrosis, fragile X syndrome, etc).

b) Implement carrier detection programs for these conditions, coupled with genetic counselling and voluntary prenatal diagnosis. At the same time, implement services for the care of affected individuals and provide psychosocial support to patients and their families.
19.4. Genetic education of the health professionals

a) Develop and implement educational curricula with emphasis on clinical and public health aspects of genetics at undergraduate levels for students of medicine, nursing, psychology, social work and public health.

b) Develop and implement genetic education for practicing family physicians and allied health personnel.

c) Encourage multidisciplinary educational workshops among clinical geneticists, public health professionals and patient/parents organizations.

19.5. Public education in health aspects of genetics

a) Develop and implement educational and awareness programs addressed to the general public about prevention and care of genetic diseases.

b) Encourage the formation of patient/parents organizations related to birth defects and genetic diseases.

20. FINAL STATEMENT

The WHO Expert Group convened in The Hague under the auspices of WHO and WAPBD should consider the above recommendations as a starting point to define the proposals that will emerge from this meeting, adding the proposed strategy to carry out each recommendation.

The fate of genetic services in the developing world ultimately rests upon the wisdom and political will of statesmen, public health officials, and medical educators. For the right to health care to be meaningful, it should include prevention and care of genetically determined conditions. Genetic health professionals in developing countries must act in conjunction with public health officials, other health professionals, patient-oriented organizations and other community organizations to achieve an adequate allocation of resources for health care in general and genetic services in particular, making equity the highest priority.
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22. REFERENCES


Castilla EE (1999). How to apply epidemiological information from malformations registries to the practice of primary prevention of birth


Department of Health of South Africa (1997). White Paper for the


Kromberg JGR, Jenkins T (1982). Common birth defects in South


Cumulative incidence / 1000 live births of severe congenital

* = derived from Christiansen RE et al., 1981

† = derived and extrapolated from Khrouf N et al., 1986

Figure 1: Congenital Anomalies Iceberg
<table>
<thead>
<tr>
<th>Country</th>
<th>Socio-Economic Indicators</th>
<th>Health Indices</th>
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<tr>
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<td>GNP per Capita (US$) 1995</td>
<td>Adult female Literacy (%) 1980-1995</td>
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<tr>
<td>Egypt</td>
<td>1080</td>
<td>26</td>
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<tr>
<td>Iran</td>
<td>1033</td>
<td>37</td>
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<td>-</td>
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<td>Industrialised Countries</td>
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</table>

Table 1: Epidemiological Transition in the Eastern Mediterranean region
TABLE 2: Reasons for Presentation of Patients for Medical Genetic Care

The presence of birth defect(s)/dysmorphic features

Mental retardation

Neuro-developmental regression

Neonatal lethargy/coma, anorexia, vomiting, acidosis, ketosis, or a combination thereof.

Abnormal patterns of growth

Abnormal sexual development, amenorrhoea, aspermia

Unexplained partial or complete hearing and/or visual loss

Unexplained neurodegeneration

Unexplained abnormalities of skin, hair and bones

Unexplained anaemias or bleeding disorder

Abnormal newborn screening test for an inborn error of metabolism

Family history of a specific condition

Indications for prenatal diagnosis (e.g. advanced maternal age)

Fetal abnormality indicated by prenatal diagnosis

Ethnic background indicates a risk of a specific disorder (e.g. Tay-Sachs disease)

Consanguinity

Exposure of a pregnant woman to a teratogen
**Table 3: Options for Best Possible Care in Common Genetic Disorders and Birth Defects**

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>SPECIFIC COMPLICATIONS</th>
<th>INVESTIGATIONS</th>
<th>THERAPEUTIC INTERVENTION</th>
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<tr>
<td><em>Spina bifida</em></td>
<td>Spinal lesion</td>
<td>Brain scan</td>
<td>Surgery/ Palliative care*</td>
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<td>Hydrocephalus</td>
<td>Developmental*/* psychometric assessment</td>
<td>Surgery</td>
</tr>
<tr>
<td></td>
<td>Developmental delay</td>
<td></td>
<td>NDT*</td>
</tr>
<tr>
<td></td>
<td>Paraplegia</td>
<td></td>
<td>Prevention UTI*</td>
</tr>
<tr>
<td></td>
<td>Incontinence</td>
<td></td>
<td>Self catheterisation*</td>
</tr>
<tr>
<td><em>Cleft lip/ Palate</em></td>
<td>Feeding problems</td>
<td>Audiological/ Speech evaluation</td>
<td>Surgery /Buccal plate</td>
</tr>
<tr>
<td></td>
<td>Speech problems</td>
<td></td>
<td>NDT*</td>
</tr>
<tr>
<td><em>Tallipes Equinovarus</em></td>
<td>Abnormal foot position</td>
<td>X-rays*</td>
<td>Manipulation* / Plaster of paris*</td>
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<td><em>Undescended testes</em></td>
<td></td>
<td></td>
<td>Surgery</td>
</tr>
<tr>
<td><em>Achondroplasia</em></td>
<td>Short stature</td>
<td>DNA</td>
<td>Counselling on spinal posture*</td>
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<tr>
<td></td>
<td>Spinal gibbus</td>
<td>X-rays*</td>
<td>Surgery</td>
</tr>
<tr>
<td></td>
<td>Spinal cord compression</td>
<td>X-rays*</td>
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<td>Brain scan</td>
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<td>Tumors</td>
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<tr>
<td>Condition</td>
<td>Symptoms</td>
<td>Investigations</td>
<td>Treatments</td>
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<td>-------------------</td>
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<tr>
<td>Seizures</td>
<td>Learning disability / Mental retardation</td>
<td>EEG Developmental* / Psychometric assessment</td>
<td>Anticonvulsant therapy*</td>
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<td></td>
<td>Long bone bowing</td>
<td>X-rays*</td>
<td>NDT*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgery</td>
</tr>
</tbody>
</table>
| Thalassaemia      | Chronic anemia                               | Hemoglobin electrophoresis / DNA             | Blood transfusion*/
<p>|                   | Splenomegaly                                  | Full blood count*                           | Haematinics*                      |
|                   | Hepatomegaly                                  |                                               | Splenectomy                       |
|                   | Iron overload                                 | Iron studies                                  | Desferoxamine*                    |
| Haemochromatosis  | Iron overload                                 | DNA                                           | Venesection                       |
|                   | Cirrhosis                                     | Iron studies                                  | Diet* / Insulin* / Diabetic        |
|                   | Diabetes                                      | Liver function tests                          | medications*                      |
|                   | Cardiac failure                               | Glucose tolerance test                        | Cadiac failure therapy*           |
|                   | Arthritis                                     | ECG* / X-rays* / Ultrasound                   | Anti-inflammatories*              |
|                   |                                               | Angiogram                                      |                                  |
|                   |                                               | X-rays*                                        |                                  |
| FragileX-syndrome | Mental retardation                            | DNA                                           | NDT*                             |
|                   | Behavioural problems                          | Developmental* / Psychometric assessment      | Behavioural management*           |
| Haemophilia A     | Bleeding                                      | DNA                                           | Factor VIII replacement*          |
|                   | Diathesis                                     | PI / PTT                                       | Physiotherapy* / Surgery          |
|                   | Joint Arthrioses                              | Factor VIII assay                             |                                  |
|                   |                                               | X-rays*                                        |                                  |</p>
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Symptoms</th>
<th>Investigations</th>
<th>Therapies</th>
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<td>Mental retardation</td>
<td>Chromosomes Developmental* / Psychometric assessment</td>
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<td>ECG* / X-rays* / Ultrasound</td>
<td>Cardiac failure therapy* / Surgery</td>
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<tr>
<td></td>
<td>Ocular abnormalities</td>
<td>Angiogram</td>
<td>Surgery</td>
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<td>Recurrent infection</td>
<td>Ophthalmological evaluation</td>
<td>Surgery (cataracts) / Glasses</td>
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<td>Serous otitis media / Hearing loss</td>
<td>Auditory / Speech evaluation</td>
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<td><strong>Turner syndrome</strong></td>
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Report of a joint WHO/WAOPBD meeting
The Hague, 5-7 January 1999
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* Can be undertaken at primary health care level
For the above conditions clinical diagnosis, genetic counselling and psycho-social support are possible at primary health care level.