

Spectrum of genetic disorders and the impact on health care delivery: an introduction

M.A.F. El-Hazmi¹

SUMMARY Until recently, infectious diseases and malnutrition-related disorders constituted the major cause of ill health and mortality in the world population. However, advances in treatment of such disorders and increased understanding of the molecular basis of heredity have led to genetically transmitted conditions becoming a major cause of morbidity and mortality. Several disorders, including chromosomal (Down syndrome, Turner syndrome), single-gene (sickle-cell disease, thalassaemia, glucose-6-phosphate dehydrogenase deficiency, haemophilia, inborn errors of metabolism) and multifactorial disorders (coronary artery disease, arteriosclerosis, diabetes mellitus, hypertension, obesity) are common and becoming increasingly important. As there is no agreed-upon definitive cure with acceptable risk, these disorders are a significant burden on the health care delivery system. This is because the chronic nature of genetic diseases requires lifelong medical attention, expensive supportive and symptomatic therapy and specialist care. This review outlines the genetic disorders, their impact on health care delivery systems and the general framework required to prevent and control these disorders.

Introduction

The spectrum of diseases affecting humankind is wide, ranging from those which are purely acquired (environmental) to those which are purely genetic (Figure 1). Purely acquired disorders are those resulting from infections caused by a wide variety of microorganisms, and those due to nutritional deficiencies. For centuries these disorders have been a major cause of morbidity and mortality. However, over the past few decades, significant advances in immunization, the discovery of antibiotics, improvement in general hygiene and nutritional habits and an overall improvement of

health status have led to a significant shift, where the overall prevalence of acquired diseases has decreased considerably in most populations of the world. This has led to the surfacing of genetic disorders as a major cause of morbidity and mortality [1-4]. These diseases include the purely genetic diseases, which may be either single-gene disorders or chromosomal disorders, and multifactorial disorders, which result from an interaction between both genetic and environmental factors.

This paper describes the overall spectrum of the genetic diseases known to affect humans and discusses the impact these disorders have on the health care delivery sys-

¹Medical Biochemistry Department and WHO Collaborating Centre for Haemoglobinopathies, Thalassaemias and Enzymopathies, College of Medicine and King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia.

Received: 26/11/98; accepted: 31/10/99

tem, particularly in developing countries, including Arab populations.

Genetic diseases

Genetic diseases are a large group of disorders resulting from major or minor alterations (mutations) in the genetic component of cells, i.e. DNA located in the nucleus or the mitochondria. These diseases can be grouped into:

- chromosomal disorders
- single-gene disorders
- multifactorial disorders
- mitochondrial disorders.

Chromosomal disorders

Down syndrome was first recognized to be caused by an additional chromosome 21 in 1959. Advances in techniques of chromo-

somal analysis, including banding techniques, led to the identification of a large number of other chromosomal disorders, which involve either an increase or decrease in the total number of a chromosomes or abnormalities in the structure of a chromosome (i.e. additions, deletions, translocation, inversions, ring chromosomes) [1-6]. Hence chromosomal disorders may be numerical or structural. The advanced techniques have also confirmed that loss or gain of a very tiny fraction of the chromosome may have a devastating effect [7]. In fact, several rare conditions with serious consequences such as mental retardation result from such minute deletions, which cannot be detected even by the most powerful microscope. They are referred to as submicroscopic deletion syndromes. Some of the common chromosomal disorders with approximate frequencies are presented in Figure 2a.

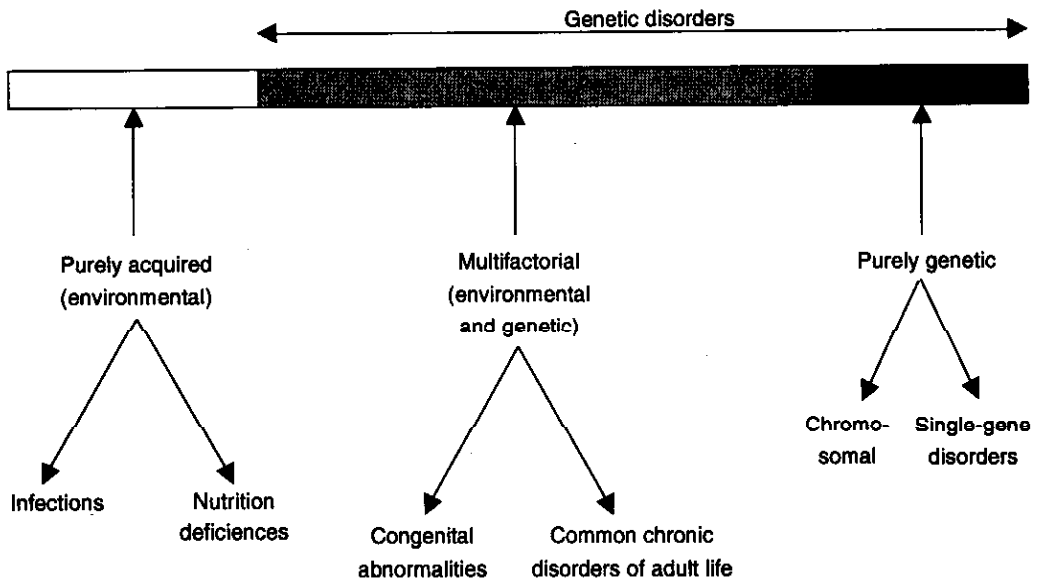


Figure 1 Spectrum of diseases affecting humans

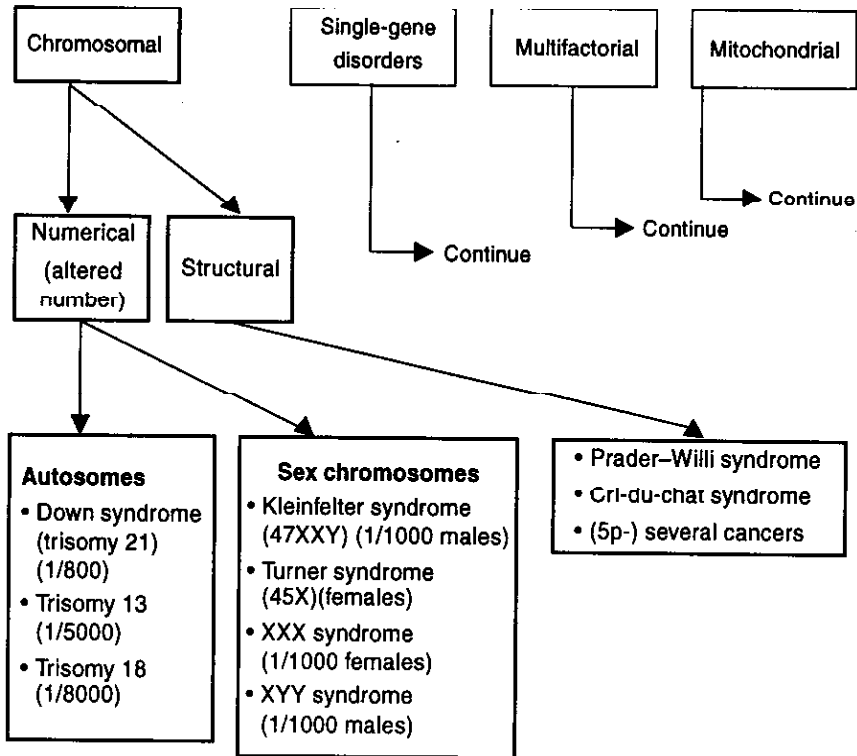


Figure 2a Chromosomal genetic disorders [1-4]

Single-gene disorders

The recognition by Garrod of alkaptonuria as a genetic defect led to the discovery of a very large number of such conditions, which result from a mutation in or around a single gene [1, 4, 6, 8, 9]. Over 6000 such disorders have been identified and many more are expected to be unveiled since it is recognized that the total human genetic component carries between 50 000 and 100 000 structural genes. These disorders may be autosomal or sex-linked (i.e. Y- or X-linked), which may be either dominant or recessive [8]. They follow a very clear pedigree pattern of inheritance and examples of a few of these disorders with the approx-

imate frequency are presented in Figures 2b and 2c.

Multifactorial disorders

Most of the common congenital malformations (e.g. cleft lip, cleft palate, neural tube defects) and most of the common diseases of adult life (e.g. diabetes mellitus, hypertension, obesity, coronary heart disease, schizophrenia) have a significant genetic component in the etiology, in addition to environmental factors which are required for their development [1-4, 10, 11]. Such disorders are referred to as multifactorial as they result from the interplay of multiple environmental factors and genes. The con-

tribution of genetic factors has been well documented by family studies and studies on twins. The genetic predisposition to disease reflects the cumulative effect of multiple genes at different loci, each with a small effect on the phenotype. Such diseases are said to be polygenic [12]. Several of the normal human traits such as height and skin colour are multifactorial in nature. Multifactorial disorders are now believed to contribute greatly to human morbidity and mortality. Figure 2d gives examples of some of the congenital and adult-onset multifactorial disorders.

These disorders do not follow a clear-cut pattern of inheritance, although they concentrate in families. It must also be emphasized that it is not the disease which is genetically determined, but it is the susceptibility to the disease and there is signifi-

cant genetic heterogeneity in the disease development.

Mitochondrial disorders

The rate of mutation of mitochondrial DNA (mtDNA) is reported to be almost 10 times that of nuclear DNA, and several diseases are known that are caused by an alteration in mtDNA [1,4,13]. A few examples of these are listed in Figure 2e. The mitochondria are ova derived in all offspring and hence mitochondrial inheritance is referred to as ‘maternal inheritance’, where a trait is transmitted from the mother to all her children but never from the father. Since mitochondria replicate autonomously from nuclear DNA and they segregate in daughter cells independently of nuclear DNA, this plays an important role in the variable and tissue-specific phenotype of mitochondrial

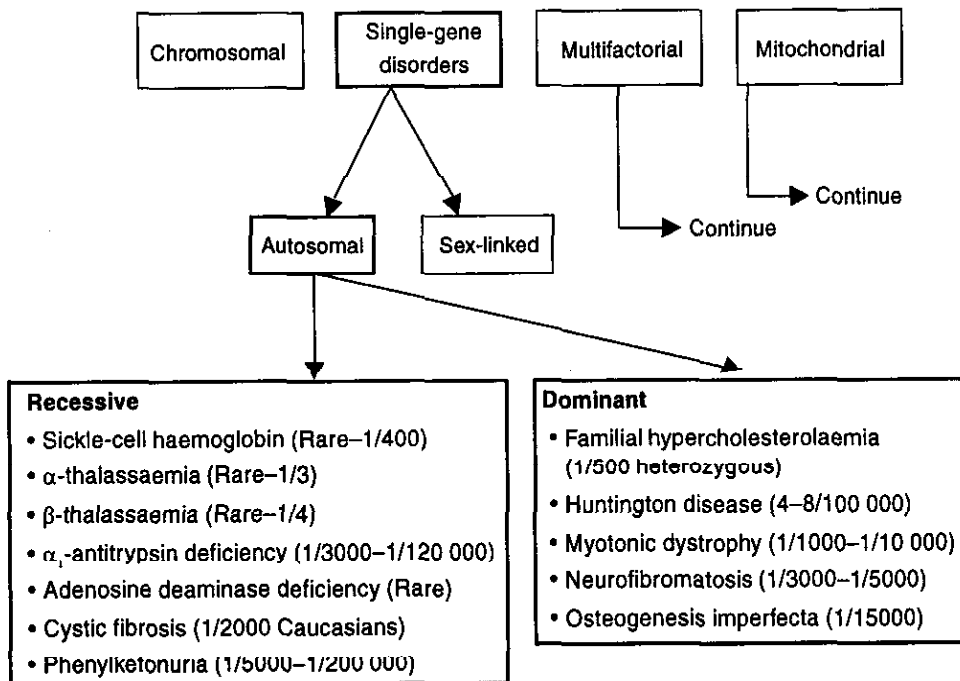


Figure 2b Autosomal, single-gene genetic disorders [1-4]

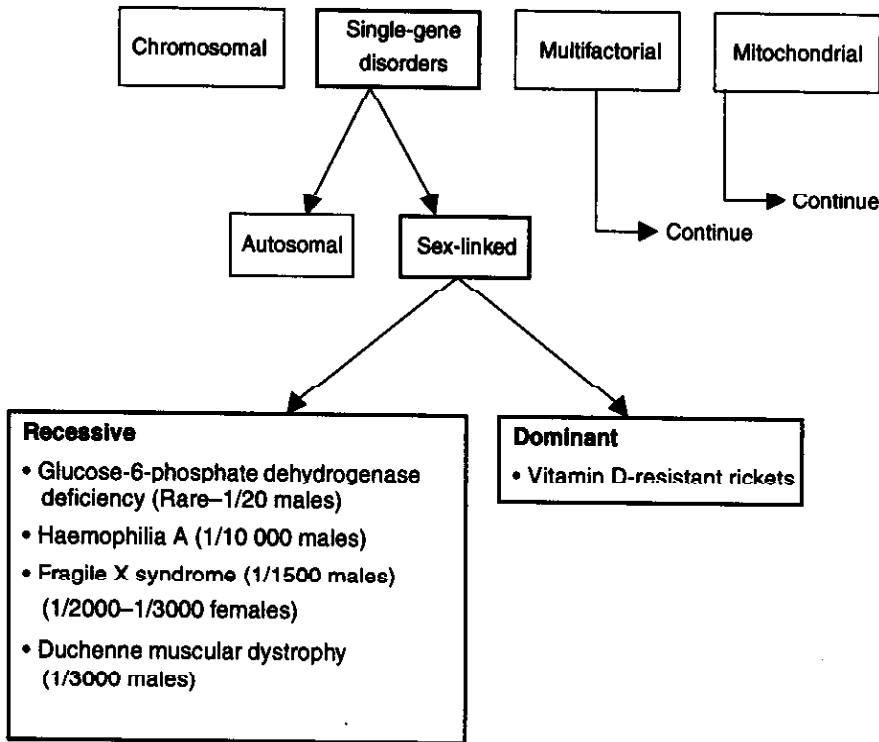


Figure 2c Sex-linked, single-gene genetic disorders [1-4]

diseases [13]. In addition, since mitochondria play an important role in cellular metabolism and energy production, these disorders affect the central nervous system, skeletal muscles and heart more than other tissues.

Emergence of genetic disorders

The nature and frequency of genetic disorders differ in different populations. Several extensive population surveys have been carried out and have provided an insight into the frequency of these disorders in some populations. However, such informa-

tion is not generally available in developing countries.

According to the World Development Report 1993, congenital malformations constitute 6.5% of the total disease burden for children under 5 years of age in developing countries and 4% of all deaths during 0-4 years of age [14]. Surveys carried out in different countries show the incidence of major congenital malformation to range from 1.06% to 4.7% (Table 1).

In a major screening study conducted by Baird et al. in Canada, where 1 million consecutive live births were screened and a population-based register was evaluated, it was found that 53 or more per 1000 live-born individuals could be expected to de-

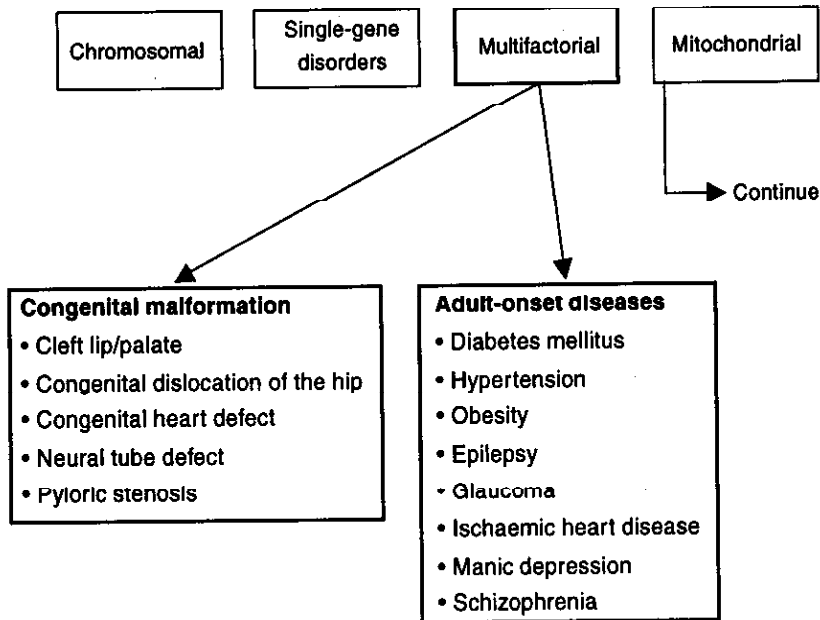


Figure 2d Multifactorial genetic disorders [1-4]

velop genetic disorders under 25 years of age, while the estimate would be 79 per 1000 live-born individuals if all congenital anomalies were considered as part of the genetic load [6]. Of the genetic disorders, single-gene disorders occurred in 3.6 per 1000 (autosomal recessive = 1.7 per 1000; autosomal dominant = 1.4 per 1000 and X-linked recessive = 0.5 per 1000), chromosomal anomalies affected 1.8 per 1000 and multifactorial disorders 46.4 per 1000 [6].

In a study of major birth defects in Saudi Arabs at King Faisal Hospital, Al-Hafouf, carried out by retrospective analysis of medical records of 30 159 infants, it was found that 2.2% had one or more defect, and a higher incidence was found in infants of diabetic mothers, mothers with higher mean age (> 33 years) and mothers with higher parity (> 8) [15]. The

systems affected were mainly the cardiac system (20.8%), the musculoskeletal system (18.7%) and the central nervous system (18.3%).

In another survey of 33 332 live-born infants in the Libyan Arab Jamahiriya, congenital anomalies were reported in 2.8% (of which 79% were major malformations and 21% were minor) [16]. The systems mainly affected were: musculoskeletal (8.9 per 1000), cardiovascular (3.5 per 1000), chromosomal (2.72 per 1000) and gastrointestinal (2.66 per 1000).

Finally, several surveys have clearly shown that at least 1 in 50 neonates has a major congenital abnormality, about 1 in 100 has a unifactorial disorder, 1 in 200 has a major chromosomal abnormality and over 60% of early spontaneous abortions are due to chromosomal abnormalities. Among the

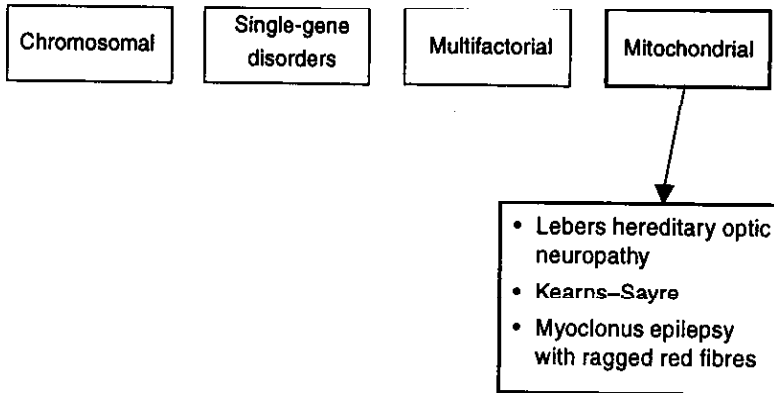


Figure 2e Mitochondrial genetic disorders [1-4]

single-gene disorders, 7 in 1000 are autosomal dominant, 2.5 in 1000 are autosomal recessive and 0.5 in 1000 are X-linked. Chromosomal abnormalities are the cause of 6%–7% of still births and neonatal deaths (> 1% sex chromosome anomalies, 3% autosomal trisomies and the rest are structural and other abnormalities) [1].

Table 1 Incidence of major congenital malformation in various countries

Country	No. screened	Incidence (%)
Benghazi, Libyan Arab Jamahiriya	32 332	2.38
British Columbia, Canada	5 176 815	4.70
Brussels, Belgium	10 000	1.70
Southern Islamic Republic of Iran	9 623	1.54
Zaira, Nigeria	22 774	1.40
Kabul, Afghanistan	5 276	2.40
Sweden	159 500	1.06

Source: reference [16]

Impact of genetic disorders on health care delivery

Genetic diseases are chronic in nature with no cure and they often require lifelong care and management strategies [17]. The impact of a given disease may vary with the severity of the disease itself and also varies with individuals and families. In general, these conditions are a leading cause of spontaneous abortion, neonatal death, increased morbidity in children and adults and an increase in childhood mortality. They are a significant health care and psychosocial burden for the patient, the family, the health care system and the community as a whole [18,19]. Hence, the best approach is to prevent the occurrence of genetic diseases which have serious consequences.

General framework for the prevention and control of genetic diseases

In an attempt to avoid or decrease the serious consequences of genetic diseases, an

essential approach is to prevent the occurrence of these disorders. Various strategies have been put forward for the prevention of chromosomal, multifactorial and single-gene disorders. WHO defines a control programme as "an integrated strategy combining optimal patient care with prevention based on community education, prospective carrier diagnosis, genetic counselling and the offer of prenatal diagnosis". In other words, both treatment and prevention are included in the control programme.

A general framework for the prevention and control of genetic diseases is described below. It indicates that control and prevention can be directed at three levels, i.e. primary, secondary and tertiary; of these three, primary prevention is the most desirable.

Primary prevention

This level of prevention aims at preventing the birth of a child with a genetic disease. Various strategies can be used [17,19].

Avoidance of environmental factors implicated in producing genetic disorders
These environmental factors include maternal nutrition, infections and other illness, or exposure to toxic or mutagenic agents. This strategy has been most useful in primary prevention of several congenital anomalies. Maternal and paternal age seem to play a significant role in increasing the overall incidence of chromosomal disorders, e.g. Down syndrome.

Screening and carrier detection

Screening at the population level and pre-marital level, followed by genetic counselling to prevent the conception of a child with a genetic abnormality in a high-risk group is one of the most effective strategies in primary prevention. The best example of the application of this strategy is the control of thalassaemia by carrier screening [20]. In

Cyprus, Sardinia and the Ferrara district of north-east Italy, almost no thalassaemia major births have been reported since 1982, although the incidence was very high during the 1970s. Counselling to reduce consanguineous marriages in high-risk families is also beneficial, to prevent the birth of a child with recessively inherited disorders. Recently, preimplantation diagnosis has been introduced [21], where the *in vitro* fertilized ovum at the blastomere stage is tested for the suspected disease. If found to be free of the disease, then it is implanted, while if abnormal, it is discarded. This approach is now applied to several diseases for which diagnosis at the gene level is standardized. Prenatal diagnosis has been carried out by fetoscopy, amniocentesis and chorionic villus sampling to detect abnormality in the fetus [2]. If found to be abnormal, the pregnancy is terminated to prevent the birth of the child with a genetic disease. This strategy is used in several countries, but among Muslims, the termination of pregnancy is prohibited and hence such as strategy raises several ethical issues.

Secondary prevention

Secondary prevention is a strategy involving early recognition of a genetic disease and early treatment intervention to reduce the detrimental effects of a disease [17,19]. Neonatal screening plays an essential role, as a child with an abnormality can be detected early and given the proper nutrition, treatment or surgical correction. It is clearly of value where the condition diagnosed is common, easily detectable, severe and treatable. The best examples of early detection and proper treatment which have led to the prevention of serious clinical consequences are congenital heart disease, cleft lip and cleft palate, and congenital dislocation of the hips, where surgical correction is used for correction of the defect.

Tertiary prevention

The last strategy in prevention involves the patient diagnosed as suffering from a genetic disease. The consequences of genetic diseases can be ameliorated and further deterioration prevented by proper management and treatment programmes and rehabilitation programmes. Some examples of tertiary prevention are the prevention of mental retardation in patients with phenylketonuria by the reduction of phenylalanine in their diet, and the treatment of congenital hypothyroidism by the early administration of thyroid hormone.

Conclusion

Well designed preventive genetic services are becoming an intrinsic part of the genetic services available in a country. Most industrialized countries have specialist genetic centres with a key role in the development and organization of community genetic services, with an input from all health services. In developing countries, such planning has been initiated in some countries but not in others. However, considering the serious consequences of genetic disorders, such genetic services should be introduced in the health care plan as soon as possible.

References

1. Emery AEH, Rimoin DL. *Principles and practice in medical genetics*, 2nd ed. London, Churchill Livingstone, 1999:3-6.
2. Weatherall DJ. *The new genetics and clinical practice*, 3rd ed. Oxford, Oxford University Press, 1991.
3. Connor JM, Ferguson-Smith AM. *Essential medical genetics*, 3rd ed. Oxford, Blackwell Scientific Publications, 1991.
4. Gelehrter TD, Collins FS, Ginsburg D. *Principles of medical genetics*. London, Williams and Williams, 1998.
5. Epstein CJ. Down's syndrome (trisomy 21). In: Scriver CR et al., eds. *The metabolic and molecular basis of inherited diseases*, 7th ed. New York, McGraw-Hill, 1995:749-94.
6. Baird PA et al. Genetic disorders in children and young adults — a population study. *American journal of human genetics*, 1988, 42:677-93.
7. Emannel BS. The use of fluorescence in situ hybridization to identify human chromosomal anomalies. *Growth genetics and hormones*, 1993, 9:6-12.
8. McKusick VA. *Mendelian inheritance in man*, 11th ed. Baltimore, Johns Hopkins University Press, 1994.
9. Scriver CR et al., eds. *The metabolic basis of inherited diseases*, 7th ed. New York, McGraw-Hill, 1995.
10. King RA, Rotter JI, Motulsky AG, eds. *The genetic basis of common diseases*. Oxford, Oxford University Press, 1992.
11. Mueller RF, Young ID. *Emery's elements of medical genetics*, 9th ed. London, Churchill Livingstone, 1995.
12. Bell JI. Polygenic disease. *Current opinions in genetic development*, 1993, 3:466-9.
13. Johns DR. Review: mitochondrial DNA and disease. *New England journal of medicine*, 1995, 333:638-44.
14. *Guidelines for the study of genetic effects in human populations*. Geneva, World

- Health Organization, 1985 (Environmental Health Criteria, No. 46).
15. Refat MY et al. Major birth defects at King Fahd Hospital: prevalence, risk factors and outcome. *Annals of Saudi medicine*, 1995, 15:339-43.
 16. Mir N et al. Easily identifiable congenital malformation in children: survey of incidence of patterns in 32 332 live-born neonates. *Annals of Saudi medicine*, 1992, 12:366-71.
 17. *Community control of genetic and congenital disorders*. Alexandria, Egypt, WHO Regional Office for the Eastern Mediterranean, 1995 (EMRO Technical Publication Series, No. 24).
 18. Czeizal A, Sankaranarayanan K. The load of genetic and partly genetic disorders in man. I. Congenital anomalies estimates of detriment in terms of years of life lost and years of impaired life. *Mutation research*, 1984, 128:73-103.
 19. *Community approach to the control of hereditary disease*. Geneva, World Health Organization, 1985.
 20. Angastiniotis MA, Hadjiminis MG. Prevalence of thalassaemia in Cyprus. *Lancet*, 1981, 1:1369-80.
 21. Verlinsky Y, Kuliev A, eds. *Preimplantation diagnosis of genetic diseases*. New York, Wiley-Liss, 1993.

**Status of papers submitted to
the EMHJ as at 31 December 1999**

Category	1995	1996	1997	1998	1999	Total (%)
Received ¹	128	119	157	293	282	979 (100.00)
Accepted ²	76	89	91	154	107	517 (52.81)
Published ²	75	88	86	111	68	428 (43.72)
Withdrawn ²	5	2	2	1	2	12 (1.23)
Rejected and closed files ²	47	28	64	133	101	373 (38.10)
In process ²	0	0	0	5	72	77 (7.86)

¹During the year = accepted + withdrawn + rejected and closed + in process.

²From the above papers, until the end of 1999.