Community Control of Genetic and Congenital Disorders
Community control of genetic and congenital disorders

Ala‘din Alwan
Regional Adviser
Noncommunicable Diseases
World Health Organization
Eastern Mediterranean Regional Office
Alexandria

Deirdre Modell
Professor of Community Genetics and Director, WHO Collaborating Centre for Community Control of Hereditary Disease
Department of Primary Care and Population Sciences
University College
London

With contributions from

Alan Bittles
Professor of Human Biology
Faculty of Science and Technology
Edith Cowan University
Perth

Andrew Czeizel
Professor of Human Genetics
Department of Human Genetics and Teratology
National Institute of Public Health
Director, WHO Collaborating Centre for the Community Control of Hereditary Diseases
Budapest

Hanan Hamamy
Professor of Medical Genetics
Mustansiriya College of Medicine
Bagdad

WORLD HEALTH ORGANIZATION
Regional Office for the Eastern Mediterranean
Alexandria, Egypt
1997
# Contents

Foreword ................................................................................................................................. 7
Preface ..................................................................................................................................... 8
Acknowledgements .................................................................................................................. 9

## Part 1. Introduction

Chapter 1. The increasing importance of genetic disorders ................................................. 13
  1.1 Introduction ....................................................................................................................... 13
  1.2 Frequency of congenital and genetically-determined disorders .................................. 13
  1.3 Possibilities for treatment and the need for prevention ................................................ 17
  1.4 Genetic diagnosis ............................................................................................................ 18
  1.5 Importance of the molecular revolution ...................................................................... 19
  1.6 Conclusion ....................................................................................................................... 20

## Part 2. Regional situation

  2.1 Introduction ....................................................................................................................... 25
  2.2 Congenital malformations in the Eastern Mediterranean Region ................................ 25
  2.3 Some preventable causes of congenital malformations .............................................. 31
  2.4 Chromosomal aberrations .............................................................................................. 33
  2.5 Conclusion ....................................................................................................................... 38

  3.1 Introduction ....................................................................................................................... 39
  3.2 Common inherited disorders .......................................................................................... 42
  3.3 Relevance of demographic factors for the pattern of inherited disorders in the Eastern Mediterranean Region .............................................................. 50
  3.4 Data on inherited disorders obtained from newborn screening studies .................. 54
  3.5 Conclusion ....................................................................................................................... 56
Chapter 4. Hereditary disorders in the Eastern Mediterranean Region:
common diseases ................................................................. 57
4.1 Introduction ........................................................................ 57
4.2 Environmental factors in common diseases .......................... 59
4.3 Genetic factors in common diseases ..................................... 60
4.4 Prevention of common diseases .......................................... 62
4.5 Challenges for the future .................................................... 62

Chapter 5. Hereditary disorders in the Eastern Mediterranean Region:
role of customary consanguineous marriage ............................ 63
5.1 Introduction ........................................................................ 63
5.2 Frequency and types of consanguineous marriage ............... 63
5.3 Changes with time in the frequency of consanguineous marriage 67
5.4 Reasons for choosing to marry a cousin .............................. 67
5.5 Genetic implications ........................................................... 70
5.6 Effects of consanguineous marriage at the population level .... 73
5.7 Consanguineous marriage and fertility ............................... 75
5.8 Parental consanguinity and infant and childhood mortality ... 76
5.9 Parental consanguinity and morbidity ............................... 78
5.10 Conclusion ...................................................................... 79

Part 3. Available approaches for prevention

Chapter 6. Approaches in primary health care ............................ 83
6.1 Introduction ........................................................................ 83
6.2 Basic public health approaches .......................................... 83
6.3 Pre-conception information and counselling ........................ 89
6.4 Identification in primary health care of patients and families requiring referral for specialist genetic counselling .......................... 91
6.5 Health education for the public .......................................... 92
6.6 Conclusion ...................................................................... 92

Chapter 7. Identification of genetic risk: family history and population screening ......................................................... 94
7.1 Introduction ........................................................................ 94
7.2 The family history or family-oriented approach .................... 94
7.3 Genetic population screening ............................................ 98
7.4 What is the best point in life for genetic screening? .............. 100
7.5 Genetic screening tests in antenatal care ............................. 101
7.6 Conclusion ...................................................................... 104
### Contents

Chapter 8. Genetic counselling ................................................. 105  
8.1 Introduction .......................................................................... 105  
8.2 Dilemmas in genetic counselling ........................................... 105  
8.3 Ethics in genetic counselling .................................................. 108  
8.4 Genetic counselling in the Eastern Mediterranean Region .......... 109  
8.5 Premarital screening and choice of marriage partner ................. 110  
8.6 Choices for couples at risk detected by premarital screening ........ 113  
8.7 Choices for couples at risk who are already married ............... 114  
8.8 Genetic counselling and customary consanguineous marriage ...... 116  
8.9 The clinical approach for consanguineous marriage ................. 118  
8.10 Conclusion ........................................................................... 121  

Chapter 9. Prenatal diagnosis .................................................... 123  
9.1 Introduction ........................................................................... 123  
9.2 Fetal tissue sampling techniques ............................................. 124  
9.3 Ultrasound scanning for diagnosis of congenital malformations .... 129  
9.4 Ethical issues in obstetric ultrasound scanning ......................... 131  
9.5 Fetal treatment ....................................................................... 131  
9.6 Research areas in prenatal diagnosis ....................................... 132  
9.7 Potential drawbacks in the use of prenatal diagnosis ................. 134  
9.8 Conclusion ............................................................................. 134  

Chapter 10. Neonatal screening .................................................. 136  
10.1 Introduction .......................................................................... 136  
10.2 Clinical screening ................................................................... 136  
10.3 Biochemical neonatal screening ............................................. 137  
10.4 Neonatal screening for research ............................................. 138  
10.5 Conclusion ............................................................................ 138  

Part 4. Prevention in practice

Chapter 11. Estimating costs and benefits of prevention: experience  
with thalassaemia ...................................................................... 141  
11.1 Introduction .......................................................................... 141  
11.2 Policies for managing and preventing an inherited disease ........ 143  
11.3 Effects of the six policies on the number of new affected births ... 148  
11.4 Costs of the six policies .......................................................... 148  
11.5 Conclusion ............................................................................ 151
Chapter 12. Organization of community genetics services ...................... 152
12.1 Introduction ........................................................................ 152
12.2 Prerequisites ...................................................................... 153
12.3 Initiating a national programme ........................................... 154
12.4 Preparing a national plan ..................................................... 155
12.5 Addressing major needs ...................................................... 156
12.6 Strategies and approaches .................................................... 158
12.7 Evaluation of national programmes ...................................... 159

Chapter 13. Role of education in the control of genetic disorders ........ 160
13.1 Introduction .......................................................................... 160
13.2 A modern medical genetics curriculum ............................... 161
13.3 Genetics teaching in medical schools of the Eastern Mediterranean Region ......................................................... 164
13.4 Continuing education for existing health professionals .......... 167
13.5 Genetics education in schools .............................................. 168
13.6 Information for families with affected members .................... 170
13.7 Information for the public ................................................. 170
13.8 Conclusion ............................................................................ 172

Chapter 14. Conclusions and recommendations ............................ 173
14.1 Epidemiology ....................................................................... 173
14.2 Consanguineous marriage .................................................... 174
14.3 Prevention of genetic disorders .......................................... 175
14.4 Education .......................................................................... 177
14.5 Organization of genetics services ....................................... 178

Annexes

Annex 1. Details of the calculation of the annual number of infants born with Down Syndrome in some Eastern Mediterranean Region countries 183
Annex 2. Registers of congenital abnormalities .............................. 184
Annex 3. Calculation of costs of treatment and prevention of thalassaemia ................................................................. 194

References .................................................................................. 200
Foreword

Available data indicate that the health burden of genetic disorders is as significant in some Member States of the Eastern Mediterranean Region as in the industrialized world. Some of these disorders, particularly haemoglobinopathies, are extremely common in this Region. Many countries are entering the stage when health services must pay greater attention to the prevention and control, throughout the lifespan, of chronic and handicapping disorders to which genetic factors have a major contribution.

Recognizing the increasing importance of congenital and genetically determined disorders in the Region, the WHO Regional Office for the Eastern Mediterranean undertook a number of initiatives to assist Member States in establishing programmes and implementing activities to prevent and control these disorders, and to improve health care services to the individuals and families affected. The epidemiological situation of hereditary disorders was initially reviewed and a regional task force, set up by WHO in 1993, identified specific priorities for prevention, based on the needs of countries of the Region. Subsequently, a Regional Consultation on Community Genetics Services was held in the Regional Office in 1994 at which preventive strategies were discussed.

Guided by the conclusions reached and recommendations made during the Regional Consultation, this publication reviews the epidemiological situation in the Eastern Mediterranean Region, discusses preventive strategies and provides technical and managerial guidelines for promoting and strengthening initiatives for the prevention and control of genetic and congenital disorders in Member States.

The control of genetic and congenital disorders is a rapidly expanding field. With the considerable achievements made in the control of infectious diseases of childhood, national health authorities will be expected to respond to the increasing importance of congenital and genetically-determined diseases. There is a clear need for public health professionals and clinicians with knowledge and expertise in the prevention and control of these diseases. I hope that this book will serve as a useful resource for health professionals in their attempt to meet this challenge.

Hussein A. Gezairy, MD, FRCS
Regional Director for the Eastern Mediterranean
Preface

The need for public health action to control genetic and congenital disorders is reflected in the significant magnitude and considerable burden that these problems represent in populations of the Eastern Mediterranean Region. Furthermore, the remarkable scientific developments and advances in understanding the genetic component in disease, the increasing power of diagnostic techniques and the expanding possibilities for identifying genetic diseases and predispositions emphasize this need and call for the development of effective genetics services and prevention programmes throughout the Region.

This publication summarizes the available data on the situation of congenital malformations and genetic disorders in the Region, identifies priorities and approaches for their prevention that are feasible and appropriate to the Region, and outlines public health interventions that can be integrated into existing health care systems. It also provides technical and managerial guidelines for the establishment of prevention and control programmes at the national and local levels. Throughout the publication, special emphasis has been placed on strengthening the role of primary health care, integrating interventions into reproductive health programmes and ensuring feasibility of strategies, as well as on the increasingly important issues related to cost-effectiveness of proposed interventions.

The conclusions and recommendations of the WHO Regional Consultation on Community Genetics Services, held in Alexandria, Egypt, from 17 to 21 April 1994 have been included in Chapter 14.

We sincerely hope that this publication will have a positive contribution in motivating action to control congenital and genetic disorders among Eastern Mediterranean populations. If health authorities are committed, the agenda for action is clear and should include collecting reliable data, identifying national or local priorities, selecting appropriate strategies and interventions, promoting the training of health care professionals, increasing the efficiency of existing services and fostering greater involvement of the community in prevention and care through education.

A. Alwan, MD, FRCP, FFPHM
B. Modell, MD, PhD, FRCP, FRCOG
Acknowledgements

The valuable contributions made by the participants of the Regional Consultation on Community Genetics Services held in the WHO Regional Office for the Eastern Mediterranean in Alexandria in April 1994 are gratefully acknowledged. The conclusions and recommendations of the Consultation appear in Chapter 14.

Professor E. Abdel Salam, Egypt
Professor N. Hashem, Egypt
Dr M. Angastiniotis, Cyprus
Dr S. Al-Arrayed, Bahrain
Dr S. Al-Awadi, Kuwait
Professor A. Bittles, Australia
Professor A. Czeizel, Hungary
Professor D. Farhud, Islamic Republic of Iran
Professor H. Hamamy, Iraq
Professor M.A.F. Al-Hazmi, Saudi Arabia
Dr H. Chaabouni, Tunisia
Dr A. Kuliev, USA
Professor B. Modell, UK
Dr A. Alwan, WHO
Dr H.A. Gezairy, WHO
Dr M.A. Khalil, WHO
Dr M.H. Khayat, WHO

We are also grateful to Professor J.V. Leonard, Institute of Child Health, London, UK for his contribution on metabolic disorders.

The contributions of the following participants to sections of this book are gratefully acknowledged:

Professor A. Bittles (consanguinity)
Professor A. Czeizel (registers of congenital abnormalities)
Professor H. Hamamy (epidemiology of hereditary disorders in the Eastern Mediterranean Region; and Chapter 13. Role of education in the control of genetic disorders).
Part 1
Introduction
Chapter 1
The increasing importance of genetic disorders

1.1 Introduction

When social and economic conditions improve and the incidence of primarily environmental diseases declines, genetically-determined disorders come to account for an increasing proportion of death, morbidity, chronic handicap and disability. This pattern, already observed over the last two generations in more industrialized countries [1], has recently become apparent in a number of countries in the Eastern Mediterranean Region, where favourable socioeconomic development has been translated into superior diagnostic and health care services. Further widespread changes of this nature, envisaged throughout the Region during the next few decades, will have a significant impact on requirements for, and costs of, health services.

Therefore, it is now necessary to evaluate the present and likely future magnitude of congenital and genetically-determined disorders within the Region, and to develop appropriate structures for their prevention and control within the health care systems of Member States.

1.2 Frequency of congenital and genetically-determined disorders

Contrary to the generally-held belief, the limited epidemiological data currently available from the Region (summarized in Part 2) indicates that congenital and genetically-determined disorders are at least as important in this Region as in more industrialized regions of the world. For example, almost 19% of paediatric inpatients in a Saudi Arabian hospital (1985–1989) had congenital or genetically-determined disorders [2]. In Beirut, Lebanon (1961, 1966, and 1971), 17% of admissions to the paediatric service of the American University Hospital were due to a genetically caused or predisposed disease [3]. In Tunisia (1993), congenital anomalies and genetic disorders constituted between 8% and 15% of paediatric
hospital admissions [4]. In Bahrain (1991) congenital anomalies and hereditary anaemias constituted 7.3% of all hospital discharges, and hereditary anaemias rank second among hospital diagnoses [5]. In a Kuwaiti hospital (1985), 37.5% of paediatric deaths were attributed to congenital heart disease, and 12.5% to single gene disorders [6].

Reliable prevalence figures are, however, not yet available for the Region. The data can be difficult to collect because the conditions involved are highly diverse, only some are detectable at birth, and those that lead to early death often remain undiagnosed in the absence of specialist services. Therefore, at present, estimates must start from figures obtained from industrialized countries.

Table 1.1 shows that in industrialized countries about 8% of children are born with a potential chronic handicap [7] and that about 50% of these disorders are genetically determined, or have a major genetic component. About 2.5 per 1000 children die from such a disorder within the first year of life. This figure may seem relatively unimportant when infant mortality is high, but becomes a major concern when it approaches 10 per 1000 (Table 1.2).

Congenital and genetic disorders are even more important as determinants of chronic childhood disease and handicap, and account for over 30% of paediatric hospital admissions in industrialized countries [1,7]. The general birth prevalence of infants with these disorders (including many that are routinely and relatively easily corrected) is between 25 and 60 per 1000 in industrialized societies [8,9,10].

<table>
<thead>
<tr>
<th>Type of disorder</th>
<th>Prevalence per 1000 births</th>
<th>Genetic component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital malformations and genetic disorders**</td>
<td>&gt;50</td>
<td>About 50%</td>
</tr>
<tr>
<td>Mental subnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild/moderate</td>
<td>25.0</td>
<td>Up to 30%</td>
</tr>
<tr>
<td>severe</td>
<td>3.5</td>
<td>Most</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>2.6</td>
<td>Very small</td>
</tr>
<tr>
<td>Deafness (severe)</td>
<td>1.0</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Blindness</td>
<td>0.6</td>
<td>50%</td>
</tr>
</tbody>
</table>

* Based on reference [7] and other sources.
** Congenital malformations and genetic disorders overlap with other categories of congenital handicap. For the purpose of this table the genetic component of mental handicap, blindness, and deafness has been subtracted from "congenital malformations and genetic disorders" and inserted under the relevant heading.
TABLE 1.2 Contribution of genetic and congenital disorders to infant and childhood mortality in a typical industrialized country (United Kingdom, 1989)*

<table>
<thead>
<tr>
<th>Main causes of death below 1 year (9.6 per 1000)</th>
<th>%</th>
<th>Main causes of death of children aged 1–14 years (0.9 per 1000)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal factors</td>
<td>38</td>
<td>Accidents</td>
<td>31</td>
</tr>
<tr>
<td>Congenital and genetic disorders</td>
<td>25</td>
<td>Congenital and genetic disorders</td>
<td>23</td>
</tr>
<tr>
<td>Sudden infant death syndrome (SIDS)</td>
<td>22</td>
<td>Neoplasms</td>
<td>16</td>
</tr>
<tr>
<td>Infections</td>
<td>9</td>
<td>Infections</td>
<td>11</td>
</tr>
<tr>
<td>Others</td>
<td>6</td>
<td>Others</td>
<td>9</td>
</tr>
</tbody>
</table>

* Based on reference [7] and other sources.

With follow-up to 12 years of age, the prevalence rises to almost 80 per 1000 [11] (Table 1.3). The estimated incidence of disorders with a genetic component over the whole life span of the population may exceed 60% if later onset disorders with a genetic component, such as thyroid disease, diabetes mellitus, psychoses, hypertension, myocardial infarction, and familial cancers are included [11].

Table 1.3 lists different groups of congenital and genetic disorders according to underlying cause. Congenital malformations1 are by far the most frequent. However, the severest and most intractable problems are often due to chromosomal aberrations and single gene disorders. Recessively-inherited diseases are likely to be more important in the Region because their frequency increases when consanguineous marriage is customary.

Available evidence from the Region (see Part 2) suggests a relatively high birth prevalence of infants with congenital and genetic disorders (perhaps 50% higher than in industrialized countries), due to a long reproductive span, a high frequency of haemoglobin disorders and glucose-6-phosphate dehydrogenase (G6PD) deficiency, and a customary preference for consanguineous marriage. The frequency of common disorders with a genetic component, such as coronary heart disease, hypertension, and diabetes mellitus, is also rising in many Eastern

---

1 Since this book is written for a wide readership, some terms are used in a popular sense that differs from the usage of specialist dysmorphologists. Here the term "congenital anomaly" includes all congenital abnormalities and genetic disorders present at the time of birth, whether detected at that time or not. The term "congenital malformation" includes all abnormalities of form present at birth, whatever their origin. Dysmorphologists use the term "congenital abnormalities" in the latter sense, within which they distinguish sub-categories such as malformations that are due to disturbances of embryonic development, and deformations such as talipes that arise as secondary alterations of normally-developed organs.
<table>
<thead>
<tr>
<th>Major category</th>
<th>Sub-category</th>
<th>Estimated births per 1000</th>
<th>Commonest diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single gene disorders</td>
<td>Dominant</td>
<td>7.0</td>
<td>Familial hypercholesterolaemia, Adult polycystic kidney disease, Neurofibromatosis, Huntington disease, Achondroplasia</td>
</tr>
<tr>
<td></td>
<td>X-linked</td>
<td>1.33</td>
<td>X-linked mental retardation, Muscular dystrophy: Duchenne type, Haemophilia and Christmas disease</td>
</tr>
<tr>
<td></td>
<td>Recessive</td>
<td>1.66</td>
<td>Glutathione deficiency, Cystic fibrosis, Phenylketonuria, Amino acid disorders, Werdnig-Hoffman disease, Thalassaemias</td>
</tr>
<tr>
<td>Sub-total</td>
<td></td>
<td>Approx. 10</td>
<td></td>
</tr>
<tr>
<td>Chromosomal disorders</td>
<td>Autosomes</td>
<td>1.69</td>
<td>&gt;70% Down syndrome, Klinefelter and Turner syndrome</td>
</tr>
<tr>
<td></td>
<td>Sex chromosomes</td>
<td>1.80</td>
<td></td>
</tr>
<tr>
<td>Sub-total</td>
<td></td>
<td>Approx. 3.5</td>
<td></td>
</tr>
<tr>
<td>Congenital malformations</td>
<td>Genetically determined</td>
<td>0.6</td>
<td>Split hand and foot, Polydactyly</td>
</tr>
<tr>
<td></td>
<td>With a genetic component (multifactorial)</td>
<td>30</td>
<td>Neural tube defect, Congenital cardiovascular malfunctions, Talipes equinovarus, Congenital dislocation of hip, pyloric stenosis, cleft lip palate</td>
</tr>
<tr>
<td></td>
<td>No genetic component</td>
<td>Varies</td>
<td>Terminal transverse limb deficiency, Fetal rubella syndrome, Fetal alcohol syndrome</td>
</tr>
<tr>
<td>Sub-total</td>
<td></td>
<td>Approx. 31</td>
<td></td>
</tr>
<tr>
<td>Multifactorial disorders</td>
<td></td>
<td>10.1</td>
<td>Epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetes mellitus, Obesity</td>
</tr>
<tr>
<td>Genetic, unknown type</td>
<td></td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Total genetic</td>
<td></td>
<td>Approx. 56</td>
<td></td>
</tr>
<tr>
<td>Total genetic + non-genetic</td>
<td></td>
<td>Over 75</td>
<td></td>
</tr>
</tbody>
</table>

* Based on reference [11].
Mediterranean countries as a more modern lifestyle replaces traditional practices (Chapter 4).

1.3 Possibilities for treatment and the need for prevention

Table 1.4 [9,10] shows that over 40% of children born with a congenital or genetic disorder may be successfully treated, mostly by paediatric surgery. Many abnormalities such as club foot, congenital dislocation of the hip, inguinal hernia, and undescended testicles are corrected as a matter of routine. However, many serious abnormalities such as multiple malformations or malformations of the heart or central nervous system cannot be corrected, and lead to early death and/or handicap.

About 30% of children born with a congenital or genetic disorder may be expected to die in infancy, and about 30%, mostly with genetic diseases, will suffer from chronic severe disability. A limited number of inherited disorders can be treated well enough for schooling, work, marriage, and sometimes even for reproduction to be possible. However, this often involves lifelong, burdensome and expensive management, as for haemoglobin disorders, phenylketonuria, or cystic fibrosis.2

<table>
<thead>
<tr>
<th>Category of abnormality</th>
<th>Births per 1000 (approx.)</th>
<th>Main therapeutic needs</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Early mortality %</td>
</tr>
<tr>
<td>Major congenital malformation</td>
<td>30.0</td>
<td>Paediatric surgery, social support</td>
<td>22</td>
</tr>
<tr>
<td>Chromosomal disorders</td>
<td>3.2</td>
<td>Social support</td>
<td>34</td>
</tr>
<tr>
<td>Single gene disorder</td>
<td>7.0</td>
<td>Medical management, social support</td>
<td>58</td>
</tr>
<tr>
<td>Total</td>
<td>40.2</td>
<td></td>
<td>29</td>
</tr>
</tbody>
</table>

*Based on references [8,9] and [10].

---

2 Radical cure by tissue transplantation (e.g. bone marrow transplantation for haemoglobin disorders and some metabolic diseases; heart-lung transplantation for cystic fibrosis) is sometimes possible for some patients in some countries.
In the absence of prevention, successful management can have unforeseen cost implications. Instead of dying in childhood, affected people survive into adult life. As new patients continue to be born, the number of cases requiring treatment, and the costs of treatment, rise cumulatively. The number of people in Europe with cystic fibrosis, phenylketonuria and haemoglobin disorders has been projected as increasing up to fivefold over the next 50 years, if there is no prevention [9]. It is estimated however that over 75% of severe congenital disorders can be treated or prevented, though a wide range of approaches and an appropriate health infrastructure are required [12]. Some disorders can be prevented from arising in the first place by correcting their cause (primary prevention). Others can be avoided by early detection and appropriate management, or by identifying individuals and couples at risk and providing genetic counselling. Prevention helps to contain the number of affected people, and so may permit communities to provide a standard of care for existing patients that would not otherwise be possible. Increased understanding of the role of genetic predisposition in common diseases is also opening the door for prevention based on identifying susceptible individuals or groups. These may then be advised to modify their lifestyle so as to avoid exacerbating environmental factors, or may be offered regular surveillance. The role of genetic diagnosis in general medical practice is developing rapidly.

1.4 Genetic diagnosis

Genetic diagnosis usually starts with the family history. Clustering of a disorder within families suggests a genetic cause, though infectious diseases, for example, may also cluster within families for environmental reasons. Disorders that are due to mutation in a single specific gene (e.g. family cancer syndromes, haemophilia, or haemoglobin disorders) often follow classical (Mendelian) inheritance patterns, and this permits a diagnosis of inherited disease, even when no appropriate laboratory tests are available.

When a genetic disorder is diagnosed in a family member, the question of how many relatives carry the same gene, and if they could develop the same disorder or pass it on to their children immediately arises. Access to modern genetic diagnostic services, including deoxyribonucleic acid (DNA), and biochemical and cytogenetic facilities is needed in order to answer such questions, but these resources are very limited in the Eastern Mediterranean Region.
1.5 Importance of the molecular revolution

The last two decades have seen an exponential increase in human understanding of and ability to manipulate the DNA and proteins that control the fundamental processes of life [13,14,15]. Some techniques that have emerged from the molecular revolution are exceptionally powerful, simple and relatively inexpensive. Clinical molecular geneticists are quietly taking over whole areas of traditional pathological diagnosis. Detection of characteristic bacterial or viral DNA sequences, e.g. in tuberculosis, hepatitis B or C and human immunodeficiency virus (HIV), is now used routinely to diagnose infection and for tracing sources. DNA-based genetic fingerprinting is proving far more powerful than traditional fingerprinting for establishing, or excluding, responsibility for a crime.

A basis for developing and applying molecular techniques such as the following already exists in some countries of the Region.

- Synthesis of short DNA probes complementary to known DNA sequences, that bind to them when present. Specific probes provide the basis for most genetic diagnosis.

- The polymerase chain reaction (PCR). DNA probes are used, together with specific DNA polymerases and restriction enzymes extracted from bacteria, to amplify selected DNA sequences rapidly from very small samples. The amplified sequence can then be studied by more conventional methods. Polymerase chain reaction is simple, and is largely responsible for the rapid penetration of DNA methods into routine pathological diagnosis.

- Simple DNA sequencing methods that allow rapid analysis of unknown DNA, including identification of specific disease mutations.

- Combination of the new DNA methods with traditional cytogenetic techniques allowing fluorescence-enhanced in situ hybridization, so that the presence, number, etc. of specific DNA sequences can be directly observed under the microscope, in non-dividing as well as in dividing cells.

- DNA sequences have been defined, spaced randomly along all chromosomes of the human genome. If a hitherto undefined genetic disorder is diagnosed within a family, the chromosomal position of the gene involved can often be established relatively rapidly using these markers. Random DNA sequences may prove particularly useful in unravelling the genetic component in common (multifactorial) disorders.
More complex and sophisticated techniques are also being rapidly developed. They include pharmacological production of protein therapeutic agents such as erythropoietin, insulin, and factor VIII; production of transgenic animals (with one or more copies of specific human genes) as animal models of human disease, or to produce useful human proteins; and approaches for gene therapy.

A particularly important future application of genetic technology will be in diagnosis and treatment of cancer, which is now understood to be due to mutations in growth-controlling genes in somatic cells. Preliminary clinical trials of genetic methods for targeting chemotherapeutic effects specifically on cancer cells, and for increasing the activity of tumour-suppressor genes, are under way. There are also early clinical trials of gene therapy for serious inherited diseases such as adenosine deaminase deficiency (a usually lethal immune deficiency disorder), cystic fibrosis, and familial hypercholesterolaemia. The future for gene therapy may include treatment (or prevention) of disorders such as diabetes mellitus, coronary heart disease and autoimmune disorders.

The Human Genome Project is an important feature of the molecular revolution. It represents an international effort to systematize existing human genetic research, to create an ordered map of the human genome, and to make the data available worldwide for research purposes. Though the Human Genome Project is a pure research enterprise, aimed to increase understanding of the way genes generate normal structure and function, it is intimately related to medicine. In the first place, understanding of the normal usually depends on identification and analysis of the abnormal; in the second, knowledge of normal mechanisms is required for diagnosis and treatment of abnormalities.

1.6 Conclusion

Many countries of the Eastern Mediterranean Region are entering the stage when health services must pay greater attention to the prevention and control of chronic and handicapping disorders in both early and later life. A major contribution of genetic factors to such disorders is becoming increasingly apparent and many conditions can now be prevented by feasible public health interventions. At the same time, a molecular revolution is increasing the power of medical diagnostic techniques, and expanding the possibilities for identifying genetic disease and predispositions. This molecular revolution is likely to transform the diagnosis and treatment of many disorders within the foreseeable future.
It is important for the countries of the Region to take account of these developments. Appropriate first steps include reviewing the genetic resources already available in each country, strengthening such resources, considering the case for early introduction of a range of DNA diagnostic technologies, collecting epidemiological information on congenital and genetic disorders and common diseases with a genetic component, and collaborating to develop approaches for prevention and treatment that are appropriate for populations of the Region.
Part 2
Regional situation
Chapter 2

Hereditary disorders in the Eastern Mediterranean Region: congenital malformations and chromosomal disorders

2.1 Introduction

This section reviews current knowledge of the frequency of congenital malformations and chromosomal disorders in the Eastern Mediterranean Region. It is based on studies carried out in different countries of the Region, and on local social and demographic characteristics relevant for the frequency of congenital disorders. These include parental age distribution, customary consanguineous marriage, limited public health approaches for the prevention of maternal infection and malnutrition, and the general lack of services for diagnosis, treatment, and prevention of congenital and genetic diseases. Because of their relevance for the epidemiology of congenital and genetic disorders, available demographic data on the countries of the Region is summarized in Table 2.1 [16].

2.2 Congenital malformations in the Eastern Mediterranean Region

Congenital malformations affect about 5% of all infants. They arise during intrauterine life and are thus present at birth, whether they are recognized at that time or not. Causative factors include chromosomal anomalies, multifactorial etiology, single gene disorders and environmental factors, but no cause can be found for many cases. There are considerable ethnic and geographical variations in the birth prevalence of specific congenital malformations.

Recent studies in the Region (Table 2.2) show that congenital malformations are as important a cause of perinatal mortality as in industrialized countries [17,18,19]. With improved perinatal care, the proportion of infant deaths due to
### TABLE 2.1 Basic demographic data for countries of the Eastern Mediterranean Region

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>18 879</td>
<td>52.0</td>
<td>981.7</td>
<td>165.0</td>
</tr>
<tr>
<td>Bahrain</td>
<td>549</td>
<td>26.4</td>
<td>14.5</td>
<td>19.9</td>
</tr>
<tr>
<td>Cyprus</td>
<td>735</td>
<td>16.8</td>
<td>12.3</td>
<td>9.0</td>
</tr>
<tr>
<td>Djibouti</td>
<td>558</td>
<td>46.0</td>
<td>27.4</td>
<td>114.0</td>
</tr>
<tr>
<td>Egypt</td>
<td>60 873</td>
<td>29.5</td>
<td>1 795.8</td>
<td>33.6</td>
</tr>
<tr>
<td>Iran, Islamic Republic of</td>
<td>59 885</td>
<td>22.0</td>
<td>1 317.5</td>
<td>34.0</td>
</tr>
<tr>
<td>Iraq</td>
<td>10 064</td>
<td>30.0</td>
<td>776.6</td>
<td>02.0</td>
</tr>
<tr>
<td>Jordan</td>
<td>4 226</td>
<td>32.4</td>
<td>136.9</td>
<td>34.6</td>
</tr>
<tr>
<td>Kuwait</td>
<td>1 620</td>
<td>26.3</td>
<td>42.6</td>
<td>12.1</td>
</tr>
<tr>
<td>Lebanon</td>
<td>3 082</td>
<td>27.0</td>
<td>83.2</td>
<td>34.6</td>
</tr>
<tr>
<td>Libyan Arab Jamahiriya</td>
<td>4 748</td>
<td>46.0</td>
<td>218.4</td>
<td>29.0</td>
</tr>
<tr>
<td>Morocco</td>
<td>26 590</td>
<td>27.4</td>
<td>728.6</td>
<td>57.4</td>
</tr>
<tr>
<td>Oman</td>
<td>2 096</td>
<td>39.0</td>
<td>81.7</td>
<td>23.0</td>
</tr>
<tr>
<td>Pakistan</td>
<td>130 564</td>
<td>41.0</td>
<td>5 353.1</td>
<td>80.0</td>
</tr>
<tr>
<td>Palestine</td>
<td>3 092</td>
<td>35.0</td>
<td>108.2</td>
<td>40.0</td>
</tr>
<tr>
<td>Qatar</td>
<td>603</td>
<td>19.2</td>
<td>11.6</td>
<td>12.8</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>17 600</td>
<td>32.5</td>
<td>569.9</td>
<td>30.0</td>
</tr>
<tr>
<td>Somalia</td>
<td>6 000</td>
<td>50.0</td>
<td>300.0</td>
<td>129.0</td>
</tr>
<tr>
<td>Sudan</td>
<td>25 596</td>
<td>38.1</td>
<td>975.2</td>
<td>70.0</td>
</tr>
<tr>
<td>Syrian Arab Republic</td>
<td>13 812</td>
<td>42.0</td>
<td>600.1</td>
<td>34.6</td>
</tr>
<tr>
<td>Tunisia</td>
<td>8 785</td>
<td>25.3</td>
<td>222.3</td>
<td>41.0</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>2 230</td>
<td>23.5</td>
<td>52.4</td>
<td>9.5</td>
</tr>
<tr>
<td>Yemen, Republic of</td>
<td>15 804</td>
<td>52.6</td>
<td>831.3</td>
<td>77.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>427 921</td>
<td>35.6</td>
<td>15 241.0</td>
<td>69.0</td>
</tr>
</tbody>
</table>

% of world 8.2 10.7

Source: WHO/EMRO [16].

### TABLE 2.2 Data on the contribution of congenital malformations to perinatal mortality in some countries of the Eastern Mediterranean Region

<table>
<thead>
<tr>
<th>Place</th>
<th>Years of study</th>
<th>Perinatal mortality per 1000 births</th>
<th>Perinatal deaths due to congenital malformations Deaths per 1000 % of deaths</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riyadh, King Khaled University Hospital</td>
<td>1982–1986</td>
<td>14.5</td>
<td>3.3</td>
<td>23</td>
</tr>
<tr>
<td>Riyadh Armed Forces Hospital</td>
<td>1983–1987</td>
<td>13.2</td>
<td>4.7</td>
<td>35.6</td>
</tr>
<tr>
<td>Abu Dhabi</td>
<td>1986–1987</td>
<td>11.8</td>
<td>3.7</td>
<td>31.5</td>
</tr>
</tbody>
</table>

[17] [18] [19]
### TABLE 2.3 Contribution of congenital malformations and perinatal factors to infant mortality rates in some Eastern Mediterranean Region countries (comparison with figures from the United Kingdom)

<table>
<thead>
<tr>
<th>Country</th>
<th>Year [reference]</th>
<th>IMR per 1000</th>
<th>Lethal CA per 1000</th>
<th>CA/IMR %</th>
<th>CA/all deaths %</th>
<th>PF per 1000</th>
<th>PF/IM %</th>
<th>PF/all deaths %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egypt</td>
<td>1990 [21]</td>
<td>33.8</td>
<td>1.5</td>
<td>4.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iran, Islamic Republic of</td>
<td>1990 [21]</td>
<td>45*</td>
<td>3.3</td>
<td>10.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iraq</td>
<td>1985 [21]</td>
<td>51</td>
<td>3.8</td>
<td>7.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuwait</td>
<td>1990 [21]</td>
<td>10.7</td>
<td>0.0</td>
<td>01.0</td>
<td></td>
<td>4.1</td>
<td>66.7</td>
<td></td>
</tr>
<tr>
<td>Morocco</td>
<td>1991 [21]</td>
<td>54**</td>
<td>1.7</td>
<td>3.2</td>
<td></td>
<td>28.7</td>
<td>53.1</td>
<td></td>
</tr>
<tr>
<td>Oman</td>
<td>1993 [21]</td>
<td>25</td>
<td>4.0</td>
<td>21.6</td>
<td></td>
<td>11.0</td>
<td>50.6</td>
<td></td>
</tr>
<tr>
<td>Qatar</td>
<td>1992 [22]</td>
<td>11.8</td>
<td>3.7</td>
<td>31.7</td>
<td></td>
<td>4.7</td>
<td>5.7</td>
<td>48</td>
</tr>
<tr>
<td>Syrian Arab Republic</td>
<td>1992 [21]</td>
<td>34**</td>
<td>4.0</td>
<td>11.8</td>
<td></td>
<td>2.8</td>
<td>25.8</td>
<td>5.5</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>1992 [20]</td>
<td>10.9</td>
<td>2.9</td>
<td>26.8</td>
<td></td>
<td>3.6</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1987 [7]</td>
<td>9.6</td>
<td>2.4</td>
<td>25</td>
<td></td>
<td>3.6</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

* 1988
** 1990

IMR: Infant mortality rate
CA/IMR: contribution of congenital abnormalities (malformations) to infant mortality rate
CA/all deaths: contribution of congenital abnormalities (malformations) to all deaths
PF/IM: contribution of perinatal factors to infant mortality rate
PF/all deaths: contribution of perinatal factors to all deaths

Perinatal factors (ICD code 760–779) will decline, leaving congenital malformations as an increasingly important residual cause of infant and total mortality.

Table 2.3 presents figures on the contribution of congenital malformations to infant mortality in some countries of the Region. Congenital malformations are now recognized as the leading cause of infant mortality in the United Arab Emirates, and the second leading cause in Bahrain, Kuwait, Oman, and Qatar [20,5,21,22].

The studies summarized in Table 2.2 give a figure for lethal congenital malformations (3 to 5 per 1000) that is considerably higher than the 2.5 per 1000 typical for industrialized countries. This may be partly because some perinatal deaths due to congenital malformations in the Region might have been avoided with improved neonatal and paediatric services. However, in view of the high level of expertise at the reporting centres, a more likely explanation is an unusually high frequency of congenital malformations. This might be related to several factors, including those in the following outline.
• A higher frequency of congenital malformations due to autosomal recessive inheritance, related to traditional consanguineous marriage in the Region (see below).

• A relatively high birth rate of infants with chromosomal disorders related to advanced maternal age: a proportion of these have severe malformations that lead to perinatal or infant death.

• A relatively high birth rate of infants with malformations due to new dominant mutations, related to advanced paternal age.

• Inadequate health care prior to and during pregnancy leading to increased frequency of:
  - congenital infections including rubella and toxoplasmosis
  - poorly controlled maternal diabetes mellitus
  - unsupervised intake of drugs or folk remedies during pregnancy
  - inadequate dietary intake of folate, other vitamins, iron, and iodine before and during pregnancy.

Recent reports from countries of the Region on the birth incidence of infants with congenital malformations are summarized in Table 2.4.

Anomalies of the musculoskeletal system were the commonest in most studies where types of malformation were reported. However, the frequency of congenital cardiovascular malformations, the commonest type of serious congenital malformation (prevalence 6 to 8 per 1000), has certainly been underestimated in most studies, as diagnosis can be difficult and many cases present later in childhood. Etiological factors identified in 320 Saudi Arabian children with congenital heart disease included Down syndrome (10%), rubella syndrome (2%), maternal diabetes mellitus (2%), prematurity (patent ductus arteriosus) (1.5%), familial (1%), and other syndromes (3.5%). Etiology was uncertain in the remaining 80% [34].

A study of the birth prevalence of congenital malformations initiated in Bahrain (1978) illustrates a typical phenomenon: the observed birth incidence rose from 7.24 per 1000 in 1978 to 18.5 per 1000 in 1985 [23]. The change reflects improved diagnosis, once attention is focused on the issue, and shows that reliable figures can be obtained only by building up a congenital abnormality registry over many years.
TABLE 2.4 Observed congenital malformation rates in some countries of the Eastern Mediterranean Region

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
<th>Sample size</th>
<th>Year</th>
<th>All CA %</th>
<th>MCSR per 1000</th>
<th>CNS per 1000</th>
<th>UG per 1000</th>
<th>CCM per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahrain</td>
<td>[23]</td>
<td>9,398 delivery</td>
<td>1978</td>
<td>0.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12,394 delivery</td>
<td>1985</td>
<td>1.85</td>
<td>2.82</td>
<td>1.5</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Egypt</td>
<td>[24]</td>
<td>1,800 children</td>
<td>–</td>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3,000 newborn</td>
<td>–</td>
<td>0.77</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Giza area)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3,000 births</td>
<td>–</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Boulak area)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[22]</td>
<td>14,000 births</td>
<td>1978</td>
<td>2.4</td>
<td>4.0</td>
<td>0.0</td>
<td>1.6</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>[26]</td>
<td>9,487 births</td>
<td>1966</td>
<td>1.17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[27]</td>
<td>2,529 newborn</td>
<td>–</td>
<td>1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iran, Islamic</td>
<td>Republic of</td>
<td>1,800 newborn</td>
<td>–</td>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lebanon</td>
<td>[29]</td>
<td>37,500 newborn</td>
<td>1975–85</td>
<td>6.32</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Libyan Arab</td>
<td>Jamahiriya</td>
<td>33,332 liveborn</td>
<td>1982–84</td>
<td>3.00</td>
<td>8.9</td>
<td>1.36</td>
<td>2.47</td>
<td>3.15</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>[31]</td>
<td>66,209 liveborn</td>
<td>1983–87</td>
<td>0.85</td>
<td>2</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[32]</td>
<td>30,159 liveborn</td>
<td>1990–92</td>
<td>2.27</td>
<td>4.8</td>
<td>4.7</td>
<td>1.9</td>
<td>5.3</td>
</tr>
<tr>
<td>United Arab</td>
<td>Emirates (Al–Ain)</td>
<td>16,419 births</td>
<td>1992–94</td>
<td>1.05</td>
<td>0.3</td>
<td>1.07</td>
<td>0.42</td>
<td>0.6</td>
</tr>
</tbody>
</table>

CA: congenital malformations  
MCSR: musculoskeletal malformations  
UG: urogenital malformations  
CCM: congenital cardiovascular malformations  
CNS: central nervous system malformations including neural tube defects

The wide variation in the rates of congenital malformations reported in the Region may be ascribed to a multitude of factors including:

- local variations in experience and expertise
- local variations in the demographic factors
- the age at which diagnoses were made and registered
- design of the study (e.g. prospective or retrospective)
- inclusion or exclusion of stillbirths and neonatal deaths
- the extent of physical examination and investigations performed
- differentiation between major and minor anomalies, how the latter are defined, and the extent of exclusion
- lack of postmortem examination.

The birth prevalence of infants with neural tube defects is considered a relatively reliable figure, since these malformations are rarely missed. Reports of their frequency give varying rates: figures from Bahrain, Libyan Arab Jamahiriya, and Tunisia are 1.5, 1.36, and 2.6 per 1000 respectively [23,30,35]. In Saudi
Arabia, one study of 74,923 births gave an incidence of 0.82 per 1000 while a previous study reported 1.6 per 1000 [36,37]. There may in reality be a change with time, as the prevalence of neural tube defects seems to be decreasing throughout the world. In Kuwait, the observed birth prevalence of anencephaly was 3.2 per 1000 in 1968, but 1.33 per 1000 in 1983 [38]. Similarly in Egypt, the observed birth prevalence of anencephaly was 3 per 1000 in Alexandria in 1966 [26], but 1.1 per 1000 in Cairo in a more recent report [25]. Thus there may be a real trend, possibly related to improved food quality and changes in diet.

Few studies refer to the outcome of congenital malformations in countries of the Region. Of 448 newborns with major congenital malformations detected in the Eastern Province of Saudi Arabia from 1983 to 1987, 32% required neonatal surgery. The cases included 102 babies with gastrointestinal anomalies, 24 with spina bifida, 9 with haematocele, and 9 with choanal atresia [31]. In Benghazi, Libyan Arab Jamahiriya (1982–1984) 58 of 770 malformed infants died in the early neonatal period (75 per 1000), compared with 11.8 per 1000 of all live births [30].

The contribution of genetic and congenital disorders to paediatric disability also reveals wide variations between countries and disabilities (Table 2.5).

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Severe mental handicap</th>
<th>Deaf-mutism</th>
<th>Blindness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahrain</td>
<td>1981</td>
<td>0.25</td>
<td>0.34</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–14 yrs</td>
<td>1.77</td>
<td>0.92</td>
</tr>
<tr>
<td>Egypt</td>
<td>1976</td>
<td>0.01</td>
<td>0.06</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–14 yrs</td>
<td>0.2</td>
<td>0.31</td>
</tr>
<tr>
<td>Kuwait</td>
<td>1980</td>
<td>0.21</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–14 yrs</td>
<td>2.21</td>
<td>0.48</td>
</tr>
<tr>
<td>Pakistan</td>
<td>1981</td>
<td>0.05</td>
<td>0.2</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–14 yrs</td>
<td>0.37</td>
<td>0.7</td>
</tr>
<tr>
<td>Tunisia</td>
<td>1984</td>
<td>0.09</td>
<td>0.27</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–14 yrs</td>
<td>1.14</td>
<td>1.11</td>
</tr>
<tr>
<td>Typical industrialized</td>
<td>3.5</td>
<td>1</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>countries to 12 years [11]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Compiled from reference [39].
TABLE 2.6 Importance of genetic and congenital factors in chronically handicapping disorders in some countries of the Eastern Mediterranean Region

<table>
<thead>
<tr>
<th>Type of disorder</th>
<th>Country</th>
<th>Reference</th>
<th>Population surveyed</th>
<th>Genetic/congenital</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Number</td>
<td>Source</td>
</tr>
<tr>
<td>Mental handicap</td>
<td>Egypt [40]</td>
<td></td>
<td>474</td>
<td>Genetic unit</td>
</tr>
<tr>
<td></td>
<td>Iraq [41]</td>
<td></td>
<td>185</td>
<td>Paediatric unit</td>
</tr>
<tr>
<td>Hearing impairment (sensorineural)</td>
<td>Saudi Arabia [42]</td>
<td></td>
<td>6421</td>
<td>Random sample</td>
</tr>
<tr>
<td>Blindness</td>
<td>Iraq [43]</td>
<td></td>
<td>150</td>
<td>Special school</td>
</tr>
<tr>
<td>All disability</td>
<td>United Arab Emirates [44]</td>
<td></td>
<td>Cholei &lt;2 yrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2–4 yrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5–9 yrs</td>
<td></td>
</tr>
</tbody>
</table>

The sharp increase in observed prevalence of childhood disability between 0–4 years and 5–14 years, particularly for mental subnormality and deaf-mutism, may be explained by better detection of these handicaps among children of school age. The figures quoted for between 5 and 14 years probably give the best approximation to the true rates, although they include both congenital and acquired cases resulting from environmental factors operating during infancy and childhood, and exclude early death.

The scarce data available on the contribution of genetic and congenital factors to the etiology of disabilities in countries of the Eastern Mediterranean Region (see Table 2.6) suggests that they are very important, and that there may be an unusually large genetic component in blindness and deafness in the Region.

2.3 Some preventable causes of congenital malformations

2.3.1 Nutritional deficiencies

Iodine deficiency is well established as the commonest single cause of preventable mental subnormality of all degrees in the Region, particularly in mountainous areas and where there is a subsistence economy. A concerted effort to eliminate the problem through iodization of salt and provision of iodized oil is under way in the Region [45].

Folate deficiency has been implicated in the origin of neural tube defects and probably some other serious congenital malformations [46,47]. There is no available data on its frequency in the Region. There is also inadequate data on the
frequency and distribution of births of infants with neural tube defects that might indicate areas of relative folate deficiency.

Iron deficiency is known to be common in the Region among women and children. Though there is no evidence that iron deficiency contributes to congenital malformation, it affects physical and intellectual performance, and should be diagnosed and corrected at the population level. However, it can be hard to assess the true extent of iron deficiency in populations where mild a-thalassaemia is also common (as in many countries of the Region). a-thalassaemia slightly reduces the haemoglobin level, so accepted standards for anaemia based on haemoglobin level may not apply in such populations [48,49]. It is important to develop simple methods for diagnosing iron deficiency anaemia and standards that are appropriate for Eastern Mediterranean populations. The introduction of population screening for carriers of haemoglobin disorders provides opportunities and an infrastructure for measuring the true frequency of iron deficiency, and monitoring the results of approaches for correcting it.

2.3.2 Maternal infections

There are very few reports from the Region on the birth prevalence of infants with fetal infections, but there have been several useful studies of the prevalence of antibodies to teratogenic organisms among women of childbearing age.

Rubella antibody prevalence among 6308 women of childbearing age in Saudi Arabia was 88%, rubella specific IgM was found in only 15 out of 10 504 (0.14%) cord blood samples, and only one neonate showed clinical stigmata of fetal rubella syndrome [50]. However, this does not necessarily mean the problem is unimportant. There may be a high risk to the non-immune 12% of women, and the frequency of congenital rubella syndrome varies greatly with the occurrence or otherwise of epidemics. In another study, 78% of 1186 pregnant women in Riyadh, Saudi Arabia, were positive for rubella antibodies, and two of the babies of the 261 seronegative mothers had congenital rubella syndrome. In the same study, 2 out of 10 women with syphilis had congenitally abnormal infants. Thus almost 4 per 1000 of the study women had children with avoidable congenital anomalies. Immunity to Herpes simplex 1 and 2 was also detected in 92% and 6.3% of the pregnant women respectively [51].

Toxoplasmosis. In Shiraz, Islamic Republic of Iran, 77% of 320 pregnant women tested for Toxoplasma antibodies were positive, the highest prevalence being
among women from poorer, more crowded areas. The proportion of seropositive women rose from 15% in the age range of 21–30 years to over 92% in the age range of 31–40 years [52], and the older women also had the highest antibody titre. The data suggest a high infection rate during the childbearing period. Consideration may be given to monitoring seronegative pregnant women, as fetal abnormality may be avoided if infection is diagnosed and treated [53].

Figures on Toxoplasma infection rates are also available from other countries. In the Libyan Arab Jamahiriya, a study of 53 women of childbearing age showed an antibody prevalence of 43.4% (by indirect haemagglutination) and 82.3% (by the immunofluorescence antibody test [IFAT]) [54]. In Saudi Arabia, 37% of 3679 women had Toxoplasma IgM. Although only one neonate was severely affected, with low birth weight and splenomegaly [55], all positive infants are at risk of developing serious problems later in life. In an Egyptian study, 3 out of 500 cord blood samples (0.6%) contained specific anti-Toxoplasma IgM [56].

Cytomegalovirus antibodies were detected in 97% of 798 Jordanian blood donors in Amman [57]. In Riyadh, Saudi Arabia, 830 apparently healthy subjects from various age groups were tested. Eighty per cent (80%) of children under five years of age tested positive, indicating that infection is widespread and is acquired early in life. The prevalence of positive tests increased with age, to plateau in the 26–35 age group [58]. The same study notes that 85% of children aged between 1 and 5 years in Egypt and 91% aged between 2 and 10 years in Kuwait were antibody positive for cytomegalovirus, as well as 98% of 100 Moroccan blood donors. Early exposure to cytomegalovirus infection in the Eastern Mediterranean Region countries should lead to a low incidence of intrauterine infection: only one case of cytomegalovirus infection was detected (0.08%) among 1186 pregnant women in Riyadh [51].

2.3.3 Maternal diabetes

In a study of 32 332 live births in the Libyan Arab Jamahiriya, 13.8% of the infants of mothers with insulin-dependent diabetes mellitus had easily identifiable congenital malformations, compared with 3% in the non-diabetic population [30].

2.4 Chromosomal aberrations

Chromosomal aberrations are relatively uncommon, but because of their intractability they are among the most important causes of congenital malformation
Community control of genetic and congenital disorders

and mental handicap. They also contribute to many other problems including infertility, abnormal sexual development, and spontaneous abortion. Accepted basic figures for the frequency and types of chromosomal abnormalities in live births in European and Japanese populations [59] are shown in Figure 2.1. Laboratory facilities for karyotyping are useful for diagnosing these conditions, for diagnosis and prognosis in some malignancies, and in monitoring environmental mutagens and teratogens.

Down syndrome is a recognized important cause of severe mental retardation in the Region. In Baghdad, Iraq, 26% of 781 children aged between 6 and 14 years registered in institutions for the mentally handicapped had Down syndrome [60], and similar figures were reported among 422 mentally retarded children referred to a genetic unit in Egypt [61].

Chromosomal abnormalities are also known to be the cause of at least 50% of spontaneous abortions, a fact that partly explains the increased frequency of spontaneous abortion with rising maternal age (see Chapter 6). Spontaneous abortion may thus be viewed as a common genetic problem at the community level.

On average, one partner carries a balanced chromosome abnormality in 5% to 15% of couples with recurrent spontaneous abortion. Cytogenetic studies of couples with repeated spontaneous abortion in Qatar and Iraq revealed a

![Figure 2.1 Relationship between maternal age at delivery and risk of a liveborn child with a chromosomal abnormality (data from reference [59])]
chromosome aberration in one of the parents in 5.3% and 8% of families respectively [62,63].

Sex chromosome aneuploidy may also cause infertility. Klinefelter syndrome accounted for 22% of azoospermic males referred to one cytogenetic laboratory in the Region [64]. Turner syndrome was diagnosed in 8.5% and autosomal recessive disorders in 8% of females with primary amenorrhoea referred to a genetic unit in Iraq [65,66]. In Tunisia, 26% of patients referred with puberty problems had chromosomal anomalies, and an 8% anomaly rate was found among subfertile couples [67]. Such knowledge is of paramount importance for prognosis and genetic counselling, and cytogenetic studies should be included among the investigations performed for infertility or recurrent miscarriage.

Because of inadequate cytogenetic diagnostic services, there is limited observational data on the frequency of chromosomal disorders in most countries of the Region. An alternative approach is to use accepted maternal age-related rates to estimate the birth prevalence of infants with chromosomal aneuploidies. As there is (as yet) no evidence that these figures vary with ethnic group or geographical location, they can legitimately be related to maternal age distribution (when known) to predict the birth prevalence of infants with Down syndrome. Table 2.7 shows the results of this calculation for 10 Eastern Mediterranean Region countries with figures on maternal age distribution from the 1991 UN Demographic Yearbook [68]. Details of the calculation are given in Annex 1.

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Annual births (thousands)</th>
<th>Total Down births per year</th>
<th>Down births per 1000 births</th>
<th>% of births to mothers 35+</th>
<th>% of births to mothers 40+</th>
<th>% Down births to mothers 35+</th>
<th>% Down births to mothers 40+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahrain</td>
<td>1990</td>
<td>13.4</td>
<td>32</td>
<td>2.38</td>
<td>16.3</td>
<td>4.6</td>
<td>70</td>
<td>48</td>
</tr>
<tr>
<td>Cyprus</td>
<td>1989</td>
<td>10.4</td>
<td>12</td>
<td>1.15</td>
<td>7.6</td>
<td>1.1</td>
<td>39</td>
<td>14</td>
</tr>
<tr>
<td>Egypt</td>
<td>1988</td>
<td>1913</td>
<td>4452</td>
<td>2.33</td>
<td>18.1</td>
<td>5.4</td>
<td>74</td>
<td>50</td>
</tr>
<tr>
<td>Kuwait</td>
<td>1987</td>
<td>52.4</td>
<td>98</td>
<td>1.88</td>
<td>15.8</td>
<td>3.7</td>
<td>66</td>
<td>38</td>
</tr>
<tr>
<td>Libyan Arab Jamahiriya</td>
<td>1981</td>
<td>118.2</td>
<td>295</td>
<td>2.49</td>
<td>18.0</td>
<td>6.3</td>
<td>77</td>
<td>56</td>
</tr>
<tr>
<td>Pakistan</td>
<td>1988</td>
<td>3195</td>
<td>8811</td>
<td>2.76</td>
<td>19.4</td>
<td>7.2</td>
<td>78</td>
<td>58</td>
</tr>
<tr>
<td>Qatar</td>
<td>1990</td>
<td>11.0</td>
<td>22</td>
<td>1.97</td>
<td>15.1</td>
<td>3.6</td>
<td>65</td>
<td>40</td>
</tr>
<tr>
<td>Tunisia</td>
<td>1989</td>
<td>199.5</td>
<td>346</td>
<td>1.73</td>
<td>14.3</td>
<td>3.5</td>
<td>66</td>
<td>38</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>1982</td>
<td>42.0</td>
<td>62</td>
<td>1.47</td>
<td>9.0</td>
<td>2.3</td>
<td>56</td>
<td>36</td>
</tr>
</tbody>
</table>

Note. Full details of the calculations on which these figures are based are given in Annex 1.
For most countries of the Region, the estimated birth rate of children with Down syndrome considerably exceeds the figure of 1.2 to 1.7 per 1000 typical for industrialized countries [59]. This is mainly because of the relatively high proportion of births to older mothers in the Region: up to 50% of children with Down syndrome in the Region are estimated to be born to mothers aged 40 or over (Figure 2.2).

Similar estimates can be made for the birth prevalence of Klinefelter syndrome. In industrialized countries it is about half as common as Down syndrome, but is likely to be about a third as common in the Eastern Mediterranean Region, since its maternal age relationship is less strong (Figure 2.1).

Experience in the European Region shows that the proportion of older mothers can change very rapidly with increased utilization of family planning,
leading to a major reduction in the birth prevalence of children with Down syndrome and some other important chromosomal aberrations [9].

In some local studies (Table 2.8) the observed prevalence of all chromosomal aberrations at birth was lower than expected, though not lower than the world’s figures. It is possible that these abnormalities occur less commonly in Eastern Mediterranean Region populations. However, a more likely explanation is underestimation, because karyotyping was performed on clinical indication rather than as a screening method. The observed prevalence of Down syndrome among live births in the Eastern Mediterranean Region varied from 1.15 per 1000 in the United Arab Emirates [33] to 2.5 per 1000 in Egypt [25], the latter figure corresponding well with expectation.

The proportional distribution of the types of chromosomal abnormality detected in Down syndrome cases varied in different studies. The Egyptian study of 36 cases detected among 14,543 newborns reported a proportional distribution of 34:1:1 for trisomy, mosaicism, and translocation respectively [25], comparable to documented figures. In other studies there was an excess of mosaicism: 13.5% in Egypt and 18.1% in Baghdad, Iraq [61,69]. Such unexpected results may be explained by selective referral of non-typical cases to expert units.

Observations in the Region raise the question of whether figures for the frequency of chromosomal disorders, obtained primarily in European and

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
<th>Population surveyed</th>
<th>Year</th>
<th>Incidence per 1000 chromosomal anomalies</th>
<th>Down syndrome</th>
<th>Edwards syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahrain</td>
<td>[23]</td>
<td>12,394 deliveries</td>
<td>1985</td>
<td>1.13</td>
<td>–</td>
<td>(2.83)</td>
</tr>
<tr>
<td>Egypt</td>
<td>[25]</td>
<td>14,543 LB</td>
<td>1985–1986</td>
<td>3.0</td>
<td>2.46</td>
<td>(2.30)</td>
</tr>
<tr>
<td></td>
<td>[61]</td>
<td>17,762 LB</td>
<td>1978–1983</td>
<td>1.8</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[27]</td>
<td>2,529 NB</td>
<td>–</td>
<td>1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Libyan Arab</td>
<td>Jamahiriya</td>
<td>33,332 LB</td>
<td>1982–1984</td>
<td>2.72</td>
<td>1.7</td>
<td>(2.49)</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>[32]</td>
<td>30,159 LB</td>
<td>1990–1992</td>
<td>2.1</td>
<td>1.8</td>
<td>–</td>
</tr>
<tr>
<td>United Arab</td>
<td>Emirates</td>
<td>16,419 births</td>
<td>1992–1994</td>
<td>1.7</td>
<td>1.15</td>
<td>(1.47)</td>
</tr>
</tbody>
</table>

LB: Live births  
NB: Newborns  
* Expected rates for Down syndrome calculated as in Table 2.7.
Japanese populations, are universally applicable. Factors predisposing to chromosomal aneuploidy are poorly understood. Extrinsic causes such as biological, physical, or chemical mutagens have been implicated. The effect of parental consanguinity, if any, has not been clearly defined [69,70,71]. The maternal age-related increase in frequency appears to be a constant entity, but other possibly genetic factors may affect the birth rate of aneuploid infants to younger mothers (less than 35 years old). The question will be settled only by epidemiological studies.\(^3\)

### 2.5 Conclusion

Despite the scarcity of data, and although available prevalence figures vary from one country to another, there is enough evidence to show that congenital and genetic disorders are responsible for a major proportion of infant mortality, morbidity, and handicap in the Region.

Some countries in the Region already have plans to establish registers of congenital malformations and specific genetic disorders. The main purpose of the registers is to provide information for planning services, prevention of congenital and genetic disorders, and improvement of patient care. Details of the organization and requirements for a register of congenital abnormalities are given in Annex 2.

Population-based studies of the frequency of chromosomal disorders in the Region are also needed. This will require the availability of appropriate cytogenetic diagnostic services.

Standardized and comparable epidemiological studies of congenital and genetic disorders in the countries of the Region, with special emphasis on avoidable causes, are a priority.

---

\(^3\)Two separate pieces of evidence point in this direction. First, the risk of having a second affected child is increased above the age-related risk for women who were less than 30 when their first affected child was born, but not for older women. Second, there may be an excess of Alzheimer disease in the families of women who had a Down syndrome child before the age of 30 [72]. The suggestion is that both the birth of a Down syndrome child and Alzheimer disease are manifestations of a genetic predisposition to premature aging. Since predisposition to Alzheimer disease is often linked to inheritance of the apolipoprotein E4 polymorphism [73] whose frequency differs in different populations, there may be a genetic basis for population differences in the birth prevalence of Down syndrome. However, such differences are likely to be seen among younger, rather than older women.
Chapter 3

Hereditary disorders in the Eastern Mediterranean Region: single gene disorders

3.1 Introduction

Conditions with a characteristic clinical picture due to mutation in a specific gene usually follow relatively clear-cut (Mendelian) inheritance patterns that directly reflect the transmission of the variant gene (Figure 3.1).

There appears to be a considerable divergence between the figures given in Table 1.3 for the frequency of dominant, X-linked and recessively-inherited disorders in industrialized societies and the pattern in the Eastern Mediterranean Region. In order to clarify these differences, it is useful to review briefly the origin and fate of mutations.

Mutation (a spontaneous change in DNA sequence) is an intrinsic property of DNA. Mutations that occur during the development of germ cells may be passed on to offspring and lead to individual variation, and sometimes to genetic disease. Since all genes are liable to mutate, the possibility exists for thousands of inherited diseases. The human mutation rate is not constant but varies with the demographic characteristics of a population [74]. Some types of spontaneous mutation arise more often in the male than the female germ line, their frequency increasing with paternal age [75].

When it first arises, a mutation affects only one of a gene pair, i.e. the person is heterozygous. If the single altered gene causes a disease, this is a dominant disorder that manifests itself in the first generation. If the presence of the remaining normal gene is adequate to prevent disease, the condition is recessive and may not become apparent for many generations, if at all.

A new mutation may not be passed on to descendants if it is lethal in infancy, or if the first carrier has no children, or they do not inherit the mutated gene, or because of other chance events. Alternatively, it may be transmitted in the family
a) Dominant inheritance. Everyone who inherits one gene for the disorder is liable to develop the disorder (although this risk varies). Affected individuals have a 50% chance of passing the gene on to offspring, independently of the genetic make-up of their partner. There is often a strong family history: cases that occur without a family history may be due to a new mutation. Examples: tuberous sclerosis, neurofibromatosis, adult polycystic kidney disease, Huntington disease, familial cancers, familial hypercholesterolaemia.

b) X-linked inheritance. Female carriers of one such gene are not usually affected themselves. However, they have a 25% chance of an affected son in each pregnancy, independently of the genetic make-up of their partner. There is often a family history, but up to one third of cases may be due to a new mutation. Examples: haemophilia, Duchenne muscular dystrophy, fragile-X syndrome, G6PD deficiency.

c) Recessive inheritance. Carriers are extremely common (most people carry one of two such genes), but affected individuals are relatively uncommon (from 1 to 40 for every thousand carriers). Carriers have a reproductive risk only if their partner also carries the same recessive disorder — then there is a 25% risk of an affected child in each pregnancy. Consanguineous marriage increases the chance that the partner will also be a carrier: this effect is more important for rare than for common recessively-inherited disorders. Examples: haemoglobin disorders, cystic fibrosis, Tay-Sachs disease, Werdnig-Hoffman disease.

FIGURE 3.1 Typical Mendelian inheritance patterns
as a rare inherited disorder. Occasionally, with the passage of time, an inherited disorder may become relatively common in a population. This can happen in one of two ways. In small, relatively isolated populations descended from a few founding members, random effects may lead to clusters of affected individuals. Such founder effects are not uncommon in the Region. Genetic disorders can become common in large populations only if the mutation concerned confers some selective advantage on those who carry it which allows them to leave, on average, more children who survive to reproductive age than non-carriers do.

Thus, for practical purposes, single gene disorders fall into two broad groups. There is a relatively small number of common conditions where carriers have some sort of advantage (Table 3.1). These include haemoglobin disorders [76,77] and G6PD deficiency [78] (which are common throughout the Region because carriers are protected against *Plasmodium falciparum* malaria) and cystic fibrosis [79], all of which are discussed below (sections 3.2, 3.4). Such common disorders account for up to half of all cases of inherited disease, and are natural targets for population screening.

The second group consists of several thousand rare conditions whose collective birth prevalence reflects a balance between the frequency of spontaneous mutations (tending to increase it), and the reproductive disadvantage conferred by the mutant genes (tending to decrease it). The mutation rate is likely to be higher in those Eastern Mediterranean populations where men father children late in their life, than in populations where childbearing is usually completed before the father is forty. Such a difference might be reflected in a higher prevalence of rare inherited disorders.

**Table 3.1 Some common single gene disorders and the selective advantage they are thought to confer on carriers**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Carrier frequency (relevant populations)</th>
<th>Advantage to carriers</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recessive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle cell</td>
<td>up to 40%</td>
<td>Protection against malaria</td>
<td>[77]</td>
</tr>
<tr>
<td>Thalassaemias</td>
<td>up to 17%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>3% to 5%</td>
<td>Protection against infantile diarrhoea</td>
<td>[79]</td>
</tr>
<tr>
<td><strong>X linked</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>up to 30%</td>
<td>Protection (? females only) against malaria</td>
<td>[78]</td>
</tr>
<tr>
<td><strong>Dominant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huntington disease</td>
<td></td>
<td>Increased fertility</td>
<td>[80]</td>
</tr>
</tbody>
</table>
The mutation rate in a population can be investigated by registering births of children with sentinel mutations. These are a handful of clear-cut and readily-diagnosed conditions, such as achondroplasia and Apert syndrome, that are nearly always due to a new mutation [75]. If information on paternal age at birth is included in the data collection, the contribution of paternal age-related mutation to the burden of genetic disease in a population can be evaluated. Though no such study has been reported from the Region, the data might be collected in some countries without great difficulty.

### 3.2 Common inherited disorders

#### 3.2.1 General

The haemoglobin disorders and G6PD deficiency are the commonest single gene disorders encountered in the Region. They represent major health problems, as the associated chronic ill health and complications place a considerable burden on health services. Results of detailed surveys are available for some countries of the Region, but at the other end of the spectrum are countries where the disorders are commonly encountered in clinical practice, but no reliable prevalence figures are available. Table 3.2 provides estimates on the frequency of haemoglobin disorders in the countries of the Region [81]. For simplicity, a single prevalence estimate is given for each country, though this is clearly unsatisfactory. In Saudi Arabia and Tunisia micro-mapping has shown wide geographical variations. For example, in Tunisia overall carrier frequency of haemoglobin disorders is 4.5%, being highest in the north-west (10.9%) [82].

The epidemiological picture is complicated by the marked molecular and clinical heterogeneity of the thalassaemias and sickle cell disease. Since β- and α-thalassaemias and haemoglobin S coexist in most countries of the Region, and other abnormal haemoglobins such as HbC and HbO Arab also occur, there may be complex interactions in some families.

#### 3.2.2 Sickle cell disorders

Table 3.2 indicates that sickle cell disorders are very unevenly distributed in the Region. Results of recent studies on the incidence of sickle cell disorders in some countries are shown in Table 3.3.
<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>% of population carrying:</th>
<th>Carriers (thousands)</th>
<th>Affected</th>
<th>Annual number born with:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HbS</td>
<td>HbC</td>
<td>$\beta$ thal</td>
<td>HbE</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Bahrain</td>
<td>10</td>
<td>3</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Cyprus</td>
<td>1</td>
<td>15</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Egypt</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Iran, Islamic Republic</td>
<td>1</td>
<td>1 to 12</td>
<td>4</td>
<td>2230</td>
</tr>
<tr>
<td>Iraq 0 to 20</td>
<td>3</td>
<td>6</td>
<td>1175</td>
<td>50</td>
</tr>
<tr>
<td>Jordan</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Kuwait</td>
<td>+</td>
<td>+</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Lebanon</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>110</td>
</tr>
<tr>
<td>Libyan Arab Jamahiriya</td>
<td>2</td>
<td>1 to 2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Morocco</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>1671</td>
</tr>
<tr>
<td>Oman</td>
<td>5</td>
<td>1</td>
<td>6</td>
<td>94</td>
</tr>
<tr>
<td>Pakistan</td>
<td>+</td>
<td>+</td>
<td>2 to 6.5</td>
<td>5</td>
</tr>
<tr>
<td>Palestine</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>93</td>
</tr>
<tr>
<td>Qatar</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>1 to 25</td>
<td>+</td>
<td>2 to 10</td>
<td>1410</td>
</tr>
<tr>
<td>Sudan</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>1621</td>
</tr>
<tr>
<td>Syrian Arab Republic</td>
<td>1</td>
<td>5</td>
<td>6</td>
<td>779</td>
</tr>
<tr>
<td>Tunisia</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>460</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>82</td>
</tr>
<tr>
<td>Yemen, Republic of</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>739</td>
</tr>
</tbody>
</table>

HbS: Haemoglobin S  
HbC: Haemoglobin C  
$\beta$ thal: $\beta$ thalassaemia  
CC: Heterozygous HbC  
C/β thal: HbC/β thalassaemia  
S/C: HbS/C disease  
SS: Sickle cell anaemia  
HbS/β thal: HbS/β thalassaemia  
HbE/β thal: HbE/β thalassaemia  

* Based on reference [81].  
Note: Values given in italics are estimates.  
+ Present (low frequency)
TABLE 3.3  Studies on prevalence of sickle cell disease in the Eastern Mediterranean Region

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
<th>Population studied</th>
<th>% with SCD</th>
<th>% carrier of AS</th>
<th>S gene frequency</th>
<th>% SCD births predicted*</th>
<th>Increase over expectation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahrain</td>
<td>[83]</td>
<td>10327 neonates</td>
<td>2.1</td>
<td>11.2</td>
<td>0.077</td>
<td>0.59</td>
<td>× 3.6</td>
</tr>
<tr>
<td>Iraq (southern)</td>
<td>[84]</td>
<td>610 women</td>
<td>1.7</td>
<td>16</td>
<td>0.097</td>
<td>0.94</td>
<td>× 1.8</td>
</tr>
<tr>
<td>Lebanon</td>
<td>[3]</td>
<td>3000</td>
<td>–</td>
<td>0.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Oman</td>
<td>[85]</td>
<td>952</td>
<td>0.37</td>
<td>6.1</td>
<td>0.034</td>
<td>0.12</td>
<td>× 3.1</td>
</tr>
<tr>
<td>Sauudi Arabia</td>
<td></td>
<td></td>
<td>247 cord blood</td>
<td>–</td>
<td>6.0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>All country</td>
<td>[86]</td>
<td>9979 neonates</td>
<td>1.37</td>
<td>13.1</td>
<td>0.079</td>
<td>0.63</td>
<td>× 2.2</td>
</tr>
<tr>
<td>Khaiber</td>
<td>[87]</td>
<td>580 children and adults</td>
<td>1</td>
<td>23.9</td>
<td>0.129</td>
<td>1.68</td>
<td>× 0.6</td>
</tr>
<tr>
<td>Tehamat</td>
<td>[88]</td>
<td>1582 children and adults</td>
<td>0.63</td>
<td>12.3</td>
<td>0.073</td>
<td>0.53</td>
<td>× 1.2</td>
</tr>
<tr>
<td>Badr</td>
<td>[87]</td>
<td>377 children and adults</td>
<td>–</td>
<td>6.8</td>
<td>0.034</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Al-Qassim</td>
<td>[89]</td>
<td>1015 adults</td>
<td>–</td>
<td>0.197</td>
<td>0.01</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

SCD: Sickle cell disease
AS: Sickle cell trait
*– none found
*On the basis of the S gene frequency, with random mating.

Note. In many studies the observed number of affected individuals exceeds the number that would be predicted from the carrier frequency on the assumption of random mating. The level of consanguineous marriage reported in the Region would be expected to about double the birth incidence of affected children (see Chapter 5). The contribution of the following factors should also be considered: technical error in homozygote diagnosis—particularly difficult with neonatal screening; and coexistence of β-thalassaemia trait (newborns with HbS/β-thalassaemia are easily misdiagnosed as having sickle cell anaemia).

Studies in Saudi Arabia give an incidence of 2% to 27% for the carrier state and up to 1.4% for the major sickle cell disorders in some areas. The rates are highest in the eastern region [86,87,88,89] and the lowest in the central region [90,91]. Sickling disorders in general run a relatively mild course in the eastern region. This appears to be due to a modification in the DNA adjacent to the sickle gene that permits patients to produce an unusually high level of fetal haemoglobin (HbF), which inhibits red cell sickling. In provinces where this modifying mutation is uncommon, sickle cell disease can be as severe as in people of African extraction [91]. In southern Iraq, it is also reported that sickle cell disease generally tends to run a mild course [84].

Sickle cell disorders are often underdiagnosed. One of the main risks is sudden death in infancy, and when this occurs the true cause is often overlooked. Many patients may be asymptomatic for long periods, and the multiple and varied
manifestations in those who are not may be mistakenly attributed to a variety of other medical causes.

Correct diagnosis, information and education for the parents and genetic counselling reduce the mortality due to sickle cell disease and improve quality of life [92]. International guidelines on the management of sickle cell disease exist [93]. However, early diagnosis is essential for these basically simple approaches to be useful. Therefore, neonatal screening for sickle cell disorders is recommended and is being increasingly widely adopted [94].

In many areas of the Region there is a need for good epidemiological studies, starting with neonatal screening to assess the carrier frequency, birth incidence, and early and later mortality attributable to sickle cell disease. Relevant information could be obtained rapidly by comparing the results of neonatal screening with those of screening different age cohorts such as pregnant women, and the elderly

### 3.2.3 β-thalassaemia

Table 3.2 shows wide variation in the frequency of β-thalassaemia between the countries of the Region. There is similar variation in different geographical areas within the same country. Thalassaemia is increasingly important because, as paediatric services improve, an increasing proportion of affected children, who would previously have died of infection or heart failure in the first years of life, are diagnosed and require treatment. At present this involves monthly blood transfusion to maintain a mean haemoglobin level of 12 g/dl, and injection or infusion of the iron chelating agent desferrioxamine between 5 and 7 days per week [95]. With this basic management and attention to other details, the prognosis for affected individuals can now be very good, including education, work, marriage and having a family.

The cost of management is substantial and, as treated children survive into adult life, the annual cost of treatment rises in direct proportion to the number of new thalassaemic infants diagnosed. When the annual number of affected births is known, reliable projections can be made of future requirements of blood and drugs for the management of both thalassaemia and sickling disorders (see Chapter 11).

The blood requirement should not pose a major problem, as countries with an adequate voluntary blood donation system can usually meet the need:
difficulties here may indicate that the blood transfusion service needs up-grading. Greater difficulty arises with meeting the growing need for iron-chelation treatment. Although there is promising research on oral iron chelators, controlling iron overload is always likely to be an expensive affair. Bone marrow transplantation, which can offer a definitive cure to a proportion of patients, and in the long run is less expensive than lifelong conventional treatment, is as yet available in only a few centres in the Region. The increasing burden of inherited disorders such as thalassaemia on health systems and on families promotes a strong interest in prevention programmes.

Most inherited disorders, including β-thalassaemia, can be caused by many different mutations. Knowledge of the spectrum of specific DNA defects in a population is scientifically valuable, helps in understanding the clinical picture, and is essential for planning preventive measures. Molecular studies have been initiated in a small number of the Eastern Mediterranean countries and they need to be developed further. Basic equipment is not expensive. The main expenses are for training and the reagents needed for DNA diagnosis [81]. Costs and benefits of control programmes for inherited diseases are discussed in Chapter 11, taking thalassaemia as an example.

3.2.4 α-thalassaemia

Each human chromosome 16 has two α-globin genes in tandem, so the normal human complement is four α-globin genes. There are consequently two main types of α-thalassaemia, mild and severe.

Mild α-thalassaemia mutations due to deletion or inactivation of one of the two α-globin genes on a chromosome, are extremely common. They are rarely implicated in disease and may be viewed as normal human polymorphisms. Their only effect, in carriers and homozygotes, is to reduce red cell size, and lower the mean haemoglobin by 0.5 – 1 g/dl [96]. This may help to protect against malaria. Mild α-thalassaemia is common in many populations of the Region, and particularly in the Arabian peninsula. For instance, 45% of the population of Oman is homozygous for mild α-thalassaemia [85] and at least 24% of Bahraini newborns carry mild α-thalassaemia [83]. The prevalence in Saudi Arabia differs according to geographical area, ranging from 2% to 50%, the highest levels being in the eastern province [87,88,97]. There is little clear information on the prevalence of α-thalassaemia in other countries of the Region. The information
can be important, as a significant frequency of α-thalassaemia in a population can lead to over-diagnosis of iron deficiency anaemia [48,49].

Severe α-thalassaemia mutations are uncommon. They are of two kinds. First, deletion of both α-globin genes on the same chromosome is found in south-east Asia, and less frequently in Cyprus and Turkey. It leads to Hb Bart’s hydrops fetalis in the homozygous state. Hb Bart’s hydrops fetalis has not yet been reported from other countries of the Eastern Mediterranean Region, leading to the conclusion that this form of α-thalassaemia is very rare in the Region. Secondly, some non-deletion mutations in the α-globin gene complex greatly reduce the activity of both α-globin genes on the affected chromosome. One non-deletional form of α-thalassaemia found in Saudi Arabia and Bahrain [86,87] causes severe anaemia (haemoglobin H disease) in the homozygous state. This mutation may also occur in some other countries of the Region. This question needs to be investigated in molecular epidemiological studies.

3.2.5 Glucose-6-phosphate dehydrogenase deficiency

The global distribution and health burden of G6PD deficiency has been reviewed by WHO [98,99]. About 7.5% of the world’s population carry a gene for G6PD deficiency, the proportion ranging from a maximum of 35% in parts of Africa to 0.1% in Japan and parts of Europe. Although the condition is inherited as an X-linked recessive, females may account for up to 10% of G6PD deficiency in the Region, owing to the high gene frequency and frequent parental consanguinity. In addition, 10% of carrier females are G6PD deficient because of unequal inactivation of their X chromosomes.

G6PD deficiency may cause neonatal jaundice, haemolytic anaemia (favism) following consumption of broad (fava) beans, especially by children, and occasionally haemolytic anaemia following treatment with specific drugs. All these problems occur predominantly in males, while the protective effects (against malaria) may benefit mainly females. Thus the frequency of the manifestations of G6PD deficiency may be influenced by other environmental factors in addition to malaria, such as the extent to which broad beans are a basic element of the diet.

Table 3.4 presents the frequency of G6PD deficiency observed in different countries of the Region. Several extensive epidemiological studies have been performed in some countries while only limited and non-standardized methodologies have been used in others.
### TABLE 3.4 Prevalence of G6PD deficiency in some countries of the Eastern Mediterranean Region

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
<th>Number</th>
<th>Age</th>
<th>Sex</th>
<th>Locality</th>
<th>% G6PD deficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahrain</td>
<td>[83]</td>
<td>10 327</td>
<td>Newborn</td>
<td>Both</td>
<td></td>
<td>20.9</td>
</tr>
<tr>
<td></td>
<td>[100]</td>
<td></td>
<td>Adult</td>
<td>Male</td>
<td></td>
<td>26.4</td>
</tr>
<tr>
<td>Egypt</td>
<td>[101]</td>
<td>500</td>
<td>Adult</td>
<td>Male</td>
<td></td>
<td>26.4</td>
</tr>
<tr>
<td></td>
<td>[102]</td>
<td>200</td>
<td>1-15 yr</td>
<td>Both</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>[103]</td>
<td>650</td>
<td>Male</td>
<td></td>
<td></td>
<td>4.9</td>
</tr>
<tr>
<td>Iran, Islamic Republic of</td>
<td>[104]</td>
<td>722</td>
<td>Male</td>
<td>South</td>
<td></td>
<td>17.9–22.8</td>
</tr>
<tr>
<td>Iraq</td>
<td>[105]</td>
<td>563</td>
<td>Adult</td>
<td>Baghdad (central)</td>
<td></td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td>[106]</td>
<td>305</td>
<td>Adult</td>
<td>Baghdad</td>
<td></td>
<td>12.4</td>
</tr>
<tr>
<td></td>
<td>[107]</td>
<td>177</td>
<td>Adult</td>
<td>Baghdad (north)</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Jordan</td>
<td>[108]</td>
<td>270</td>
<td>Children</td>
<td>North valley</td>
<td></td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>[109]</td>
<td>395</td>
<td>Newborn</td>
<td>Amman (central)</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Kuwait</td>
<td>[110]</td>
<td>255</td>
<td>Adult</td>
<td></td>
<td>20.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>206</td>
<td>Newborn</td>
<td></td>
<td>22.3</td>
<td></td>
</tr>
<tr>
<td>Lebanon</td>
<td>[3]</td>
<td>549</td>
<td>Adult</td>
<td>Male</td>
<td></td>
<td>3.09</td>
</tr>
<tr>
<td>Libyan Arab Jamarinny</td>
<td>[111]</td>
<td>400</td>
<td>Male</td>
<td>Benghazi (north-east)</td>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td>Oman</td>
<td>[85]</td>
<td>435</td>
<td>Male</td>
<td></td>
<td>27.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>517</td>
<td>Female</td>
<td></td>
<td>12.4</td>
<td></td>
</tr>
<tr>
<td>Pakistan</td>
<td>[112]</td>
<td></td>
<td></td>
<td></td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>[113]</td>
<td>190</td>
<td>Male</td>
<td>Al-Hafouf (east)</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>Female</td>
<td>Al-Hafouf (east)</td>
<td></td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>457</td>
<td>Male</td>
<td>Khaibar (north-west)</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>206</td>
<td>Female</td>
<td>Khaibar (north-west)</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>119</td>
<td>Male</td>
<td>Jizan (south-west)</td>
<td></td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>267</td>
<td>Male</td>
<td>Najran (south-west)</td>
<td></td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>786</td>
<td>Male</td>
<td>Riyadh (central)</td>
<td></td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>678</td>
<td>Female</td>
<td>Riyadh central</td>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td>Tunisia</td>
<td>[82]</td>
<td></td>
<td></td>
<td>Northern</td>
<td></td>
<td>1.84–2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Southern</td>
<td></td>
<td>4.5–6.7</td>
</tr>
</tbody>
</table>

* Reviewer did not have access to all original documents, therefore data is incomplete.

Note. The G6PD deficiency gene is always expressed in males, but in females effects range from no measurable change to marked G6PD deficiency. Though figures for observed G6PD deficiency in females are clinically relevant, only the observed figures for males should be used for calculating gene frequency.

High frequencies of G6PD deficiency have been reported in most countries of the Region, with the highest figures in the Arabian Peninsula and the southern part of the Islamic Republic of Iran. In Saudi Arabia, G6PD deficiency exists at variable frequency in the different regions of the country [86,88,113,114,115]. A correlation exists between the frequency of G6PD deficiency and malaria endemicity in some regions but not in others, suggesting that factors other than
protection against *Plasmodium falciparum* malaria may influence the frequency of G6PD deficiency [113]. In the Islamic Republic of Iran, the highest enzyme deficiency rate (22.8%) was found in Chorob village in the south, where the highest seropositive titres for both *Plasmodium vivax* and *Plasmodium falciparum* antigens were detected [104]. A study in Peshawar, Pakistan, revealed that G6PD deficiency was the cause of neonatal hyperbilirubinaemia in 11.6% of 267 jaundiced newborns [116].

In the Islamic Republic of Iran, the main perceived problem associated with G6PD deficiency is seasonal waves of favism leading to peaks of acute hospital paediatric admission with life-threatening haemolytic crises. G6PD deficiency can be detected in newborns by cheap and simple screening methods [98], and neonatal screening and counselling for parents might also be considered in areas where complications associated with G6PD deficiency are common.

As with sickle cell disease, an epidemiological study comparing the frequency of G6PD deficiency in the newborn, adults of reproductive age and the elderly could cast an interesting light on the present and historical lethality of the condition in males.

### 3.2.6 Neonatal jaundice

Neonatal jaundice may be caused by other genetic factors in addition to G6PD deficiency, including ABO and rhesus incompatibility.

Neonatal jaundice was the commonest perinatal problem encountered in a Saudi Arabian study [2]. Bilirubin levels were in the phototherapy range in most cases and exchange transfusion was required only rarely. A cause was found in 45% of cases and the majority were genetic: ABO incompatibility (14.5%), rhesus incompatibility (12.4%), prematurity (11.2%), neonatal sepsis (5.6%) and G6PD deficiency (0.8%).

In a mixed Arab population in Abu Dhabi in 1981, 33 out of 2755 (1.2%) newborns (excluding low birth weight infants) developed clinically significant jaundice due to ABO incompatibility [60]. In 1983, in the same population, 21 out of 5733 (0.37%) required exchange transfusion; of these 21, 12 transfusions were for ABO incompatibility, 3 for G6PD deficiency, and 2 for rhesus incompatibility [117]. In a Benghazi hospital in the Libyan Arab Jamahiriya, rhesus incompatibility was observed in 11 of 1500 newborns delivered in 1980 (0.7%) [118], and in 36 of 1538 (2.3%) newborns delivered to rhesus negative
women in 1981. Fourteen of these 36 needed exchange transfusion and 5 died. Thus perinatal mortality due to rhesus incompatibility was 0.32% among rhesus negative women [119]. The frequency of handicap among the survivors was not reported.

3.3 Relevance of demographic factors for the pattern of inherited disorders in the Eastern Mediterranean Region

Common genetic conditions like those already discussed are often considered at the population level, without reference to family history. However, family history and family structure are extremely important, both for these common disorders and for the rarer genetic conditions discussed in section 3.4.

Most medical genetics research has been conducted within populations of European origin, where family size is characteristically small and partners are unrelated. Exactly the opposite is the case in the Eastern Mediterranean Region, and these demographic differences have important effects on the patterns of genetic disease within a society.

As an example we may consider the transmission of a new dominant mutation (such as a familial cancer mutation), that is likely to be inherited by 50% of offspring, in a typical industrialized and a typical Eastern Mediterranean society. The total proportion of the population carrying the mutation after, for example, five generations is identical in the two societies, but the distribution of the mutation carriers is markedly different. In an industrialized society, mutation carriers are scattered through the general population after a few generations and, as their relationship to each other is usually unrecognized by this time, the family history suggesting a genetic basis for their cancer predisposition is easily missed. By contrast, in an Eastern Mediterranean society the mutation carriers tend to remain concentrated within the extended family, and the genetic nature of their cancer predisposition may be obvious. Similar considerations apply for other conditions with dominant inheritance, such as adult polycystic disease of the kidney or familial hypercholesterolaemia, and for X-linked disorders.

The genetic disadvantages associated with consanguineous marriage are often overestimated. For example, it is easy to misinterpret the pronounced familial aggregation of dominantly-influenced genetic disorders (as already mentioned), or to fall back on consanguineous marriage as an explanation for disorders, such
as cerebral palsy, whose origin is unknown. Misattribution is particularly likely if facilities for genetic diagnosis are not available.

Recessively-inherited disorders are the only group of disorders whose incidence is increased because of the typical Eastern Mediterranean family structure. At present between 20% and 50% of marriages in many countries of the Eastern Mediterranean Region are between blood relatives, compared with less than 1% in most European and North American populations [120]. A marriage between first cousins is usually considered to about double the (approximately 2.5%) risk of having a child with a severe congenital or genetic disorder, and frequent consanguineous marriage increases the incidence of recessively-inherited disorders at the population level. In industrialized countries recessively-inherited disorders (1.66 per 1000 births) account for less than 20% of single gene disorders and less than 5% of congenital and genetic disease (see Table 1.3). First cousin marriage is considered to multiply the risk of recessively-inherited disorders by 15–30 times, making the risk 25 to 50 per 1000 and so doubling the total frequency of congenital and genetic disorders. Nevertheless, the risk remains relatively small and most consanguineous marriages have no adverse genetic effect.

The rarer a recessive gene, the greater the effect of consanguineous marriage (see Chapter 5). Table 3.5, which gives United Kingdom estimates of the frequency of 22 recessively-inherited metabolic disorders, illustrates their diversity, the wide range of clinical and laboratory techniques required for definitive diagnosis, the difficulty and cost of treatment, and the limited success of treatment. The carrier frequencies listed (mostly between 0.5% and 1%) are typical. However, the frequency of individual conditions varies markedly between populations and will be different in Middle Eastern populations. An average of 30% first cousin marriage would increase the birth prevalence of the listed conditions by from 5 to 15 times, and their collective frequency by 5.5 times, from 0.42 to 2.3 per 1000. It would increase the birth prevalence of all recessively-inherited disorders by between 5 and 10 times (from 1.66 per 1000 to between 8.3 and 16.6 per 1000). That is, in most Middle Eastern populations the birth prevalence of severe recessively-inherited disorders may approach that of congenital malformations.4

4Among first cousins, the risk of recessively-inherited disorder in the offspring would be between 25 and 50 per 1000. This fits well with estimates in industrialized populations, and with the results of the meta-analysis described in Chapter 5.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Estimated % carriers</th>
<th>Births, 1 in:</th>
<th>Diagnostic method</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maple syrup urine disease</td>
<td>0.40</td>
<td>250 000</td>
<td>Plasma amino acid, enzyme</td>
<td>Very complex</td>
<td>Poor-good</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>0.40</td>
<td>250 000</td>
<td>Plasma and urine amino acid</td>
<td>Fairly easy</td>
<td>Poor-good</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>0.40</td>
<td>250 000</td>
<td>Enzyme</td>
<td>None</td>
<td>Very poor</td>
</tr>
<tr>
<td>Carbamylphosphate synthetase deficiency</td>
<td>0.45</td>
<td>200 000</td>
<td>Liver enzyme</td>
<td>Difficult</td>
<td>Poor</td>
</tr>
<tr>
<td>Glycogen storage disease 1a</td>
<td>0.60</td>
<td>100 000</td>
<td>Liver enzyme</td>
<td>Complex</td>
<td>Fair-good</td>
</tr>
<tr>
<td>McArdle disease</td>
<td>0.60</td>
<td>100 000</td>
<td>Muscle enzyme</td>
<td>Difficult</td>
<td>Moderate</td>
</tr>
<tr>
<td>Non-ketotic hyperglycaemia</td>
<td>0.60</td>
<td>100 000</td>
<td>Plasma and CSF amino acid, liver enzyme</td>
<td>None</td>
<td>Very poor</td>
</tr>
<tr>
<td>Isovaleric acidemia</td>
<td>0.60</td>
<td>100 000</td>
<td>Urine organic acid</td>
<td>Fair</td>
<td>Fair-good</td>
</tr>
<tr>
<td>Very long chain acyl CoA diagnosis</td>
<td>0.60</td>
<td>100 000</td>
<td>Urine organic acid</td>
<td>Difficult</td>
<td>Good with early</td>
</tr>
<tr>
<td>dehydrogenase deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acid maltase deficiency (Pompe disease)</td>
<td>0.60</td>
<td>100 000</td>
<td>Special investigations</td>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td>MFS I (Hurler)</td>
<td>0.60</td>
<td>100 000</td>
<td>Urine glycosamiroglycans, enzyme</td>
<td>Experimental</td>
<td>Very poor</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>0.67</td>
<td>90 000</td>
<td>Special investigations</td>
<td>Experimental</td>
<td>Poor</td>
</tr>
<tr>
<td>Propionic acidemia</td>
<td>0.70</td>
<td>80 000</td>
<td>Urine organic acid</td>
<td>Easy-difficult</td>
<td>Fair-very poor</td>
</tr>
<tr>
<td>Trifunctional enzyme deficiency diagnosis</td>
<td>0.70</td>
<td>80 000</td>
<td>Urine organic acids, blood acylcarnitines, DNA</td>
<td>Difficult</td>
<td>Good with early</td>
</tr>
<tr>
<td>Citrullinaemia</td>
<td>0.76</td>
<td>70 000</td>
<td>Plasma amino acids, enzyme</td>
<td>Difficult</td>
<td>Poor-good</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>0.82</td>
<td>60 000</td>
<td>Special investigations</td>
<td>Very expensive</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Tyrosinaemia type 1</td>
<td>0.89</td>
<td>50 000</td>
<td>Urine organic acids: enzyme</td>
<td>Complex and costly</td>
<td>Poor-good</td>
</tr>
<tr>
<td>Methyhamaloric acidemia</td>
<td>0.89</td>
<td>50 000</td>
<td>Urine organic acid</td>
<td>Easy-difficult</td>
<td>Good-very poor</td>
</tr>
<tr>
<td>MFS III (Sanfilippo A,B,C,D)</td>
<td>0.89</td>
<td>50 000</td>
<td>Urine glycosamiroglycans, enzyme</td>
<td>None</td>
<td>Very poor</td>
</tr>
<tr>
<td>Galactosaemia</td>
<td>0.90</td>
<td>44 000</td>
<td>Enzyme</td>
<td>Fairly easy</td>
<td>Fair</td>
</tr>
<tr>
<td>Phynylketonuria</td>
<td>1.70</td>
<td>14 000</td>
<td>Plasma amino acids</td>
<td>Difficult</td>
<td>Fair</td>
</tr>
<tr>
<td>Medium chain acyl CoA diagnosis</td>
<td>2.0</td>
<td>10 000</td>
<td>Urine organic acids, blood acylcarnitines, DNA</td>
<td>Straightforward</td>
<td>Good with early</td>
</tr>
<tr>
<td>dehydrogenase deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>16.77</strong></td>
<td><strong>2 400</strong></td>
<td><strong>Total</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Data provided by Professor Iwan Leonard, Institute of Child Health, London. The estimate of these disorders is based on the best available data in 1995 and in some cases must be regarded only as an approximation.
Single gene disorders

Despite strong evidence that recessively-inherited disorders are very important in paediatric and genetic services in the Region, reliable epidemiological data is lacking because appropriate biochemical diagnostic facilities are very scarce. In addition, many biochemical disorders do not present until the first one or two years of life (e.g. haemoglobin disorders, cystic fibrosis, lysosomal storage disorders), so studies that include follow-up from birth are needed to assess their true prevalence. These are difficult to perform and none have yet been conducted in countries of the Region. However, several reliable studies show that recessively-inherited disorders account for a substantial proportion of physical and mental handicap in the Region [40,60,121]. In Al-Ain, the United Arab Emirates for example, autosomal recessive disorders accounted for 80% of single gene disorders and 22% of congenital malformations among 16419 births, with a higher rate of first cousin marriages among parents of congenitally malformed infants than among the general population [33]. A study of metabolic disorders in the district of Riyadh, Saudi Arabia, where suitable diagnostic facilities exist, clearly demonstrates a high prevalence of many metabolic disorders, including those listed in Table 3.5 (122). The results of a follow-up study in the United Kingdom that included families of British Pakistani extraction produced similar results [123].

The only reliable way to assess the quantitative effect of customary consanguineous marriage on the birth prevalence of infants with recessively-inherited disorders is through careful, population-based comparison of the relative frequency of these disorders among offspring of related and unrelated parents, including a follow-up component. Chapter 5 shows that so far most studies have been vitiated by confounding factors such as social class differences, and by limited possibilities for genetic diagnosis or follow-up.

The epidemiology of genetic disorders is especially complicated in the Eastern Mediterranean Region because many whole villages or tribal groups are descended from a limited number of main ancestors, and the disease genes present reflect the sample carried by the founding members. It is to be anticipated that some conditions are confined to specific villages or tribal groups, and that some groups have an unusual burden of genetic disease, while others may be unusually free of genetic disease. It is therefore no surprise that reports from countries in

---

5The study giving this result was performed among British Pakistanis in the United Kingdom. Consanguineous marriage is considerably commoner in this group than in most countries of the Eastern Mediterranean Region.
the Region point to foci of certain, usually rare, autosomal recessive conditions such as the Bardet Biedl and multiple pterygium syndromes (prevalence rates of 1 per 36 000 each in Kuwait [124]), and spinal muscular atrophies (prevalence of 1 per 8300 in Oman [125]). An adequate epidemiological study of genetic disease in such populations must include samples of all local sub-populations. It must be concluded that the true situation in the Eastern Mediterranean Region remains unknown.

Newborn screening studies in the Region have yielded reliable data on a few of the commoner recessively-inherited disorders.

3.4 Data on inherited disorders obtained from newborn screening studies

The aims of newborn screening include research on the incidence of detectable genetic and infectious disease, early diagnosis in order to initiate early management and genetic counselling to allow prevention of new affected births in high risk families (see Chapter 10). Biochemical neonatal screening programmes have been in effect for several decades in some countries.

In the Eastern Mediterranean Region, newborn screening programmes have been carried out for research purposes in Bahrain, Egypt, Islamic Republic of Iran, Jordan, and Saudi Arabia [84,126,127,128,87]. They have provided valuable information on the incidence of haemoglobin disorders, G6PD deficiency, congenital hypothyroidism, phenylketonuria and cystic fibrosis.

Neonatal screening for congenital hypothyroidism is routine in most industrialized countries, where it affects about 1 in 3600 to 5000 newborns [129]. The aim is to detect affected infants as early as possible, and provide replacement thyroxine, which completely prevents severe physical and mental handicap. This disorder is usually due to a congenital malformation (absence or hypoplasia of the thyroid gland), but in about 5% of cases it is a recessively-inherited metabolic disease. The total frequency of congenital hypothyroidism might be expected to be higher in most countries of the Region, due to an increased proportion of recessively-inherited cases. Neonatal screening has shown an incidence of 1 per 3000 in Egypt, 1 per 2666 in Saudi Arabia, and 1 per 1433 in the Islamic Republic of Iran [126,130,127]. It thus seems likely that congenital hypothyroidism is at least as common throughout the Eastern Mediterranean Region as in industrialized countries, and neonatal screening might be appropriate. Analysis
of costs and benefits should take account of the fact that, though screening is expensive (since it involves radioimmunoassay), the disorder is very severe and treatment is very cheap, very effective and lifelong.

The average birth prevalence of phenylketonuria in Caucasians is 1 per 10 000 (range 1 per 6000 to 1 per 16 000). In one study in Turkey (parental consanguinity about 20%), phenylketonuria was diagnosed in 1 per 4370 newborns [131], but in Teheran, Islamic Republic of Iran, the reported incidence is 1 per 8633 neonates [132]—rather similar to that in western Europe. The disorder can also be investigated by studying its prevalence among mentally retarded children. In Iraq 3.8% and in Egypt 1.4% of such children had phenylketonuria [40,41].

Cystic fibrosis is the commonest fatal genetic disease in Caucasian populations, where between 3.5% and 5% of the population are carriers and the birth prevalence is about 1 per 2000. The birth prevalence is much lower in American blacks (1 per 17 000) and very low indeed (1 per 93 000) in American

<table>
<thead>
<tr>
<th>Condition and country</th>
<th>Reference</th>
<th>Affected births per 1000</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital hypothyroidism</td>
<td>[129] 0.2–0.28</td>
<td></td>
<td>Excess over European level could represent an increased contribution of recessively-inherited forms</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>[126] 0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egypt</td>
<td>[127] 0.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iran, Islamic Republic of Saudi Arabia</td>
<td>[130] 0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>[9] 0.1</td>
<td>2</td>
<td>Deduced carrier frequency (%)*</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>[132] 0.116</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Iran, Islamic Republic of</td>
<td>[131] 0.228</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td></td>
<td></td>
<td>Deduced carrier frequency (%)*</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>[1] 0.50</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>American blacks</td>
<td>[1] 0.06</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Egyptian newborns</td>
<td>[134] 0.38</td>
<td>2–3</td>
<td></td>
</tr>
<tr>
<td>Jordanian newborns</td>
<td>[128] 0.39</td>
<td>2–3</td>
<td></td>
</tr>
<tr>
<td>Saudi children</td>
<td>[133] 0.236</td>
<td>(7.15)</td>
<td></td>
</tr>
</tbody>
</table>

*Calculated for the Eastern Mediterranean Region countries using assumption of 30% consanguineous marriage (see Chapter 5)
Orientals. Recent studies suggest that the disease is almost as common in the Eastern Mediterranean Region as in Europe. In Saudi Arabia, cystic fibrosis was found in 1 per 4243 children under 14 years old [133]. The newborn incidence in Jordan is 1 per 2560 [128], and in Egypt 1 per 2608 [134]. Cases have also been reported from the Islamic Republic of Iran, Iraq, Kuwait, Lebanon, Pakistan and Palestine.

All these studies have been small, and may not be representative. Assuming that they are, however, Table 3.6 spells out the implications in terms of carrier frequencies of these disorders (taking account of the national figures for consanguineous marriage given in Chapter 5).

3.5 Conclusion

Probably no aspect of medicine is as influenced by family and population structure as medical genetics. The family structure that is common in the Eastern Mediterranean Region tends to display the genetic elements in disease in a particularly clear fashion. It may offer exceptional opportunities for applying genetic knowledge in clinical practice, and for research on the genetic contribution to human disease. The development of genetic science in the Region is still at an early stage, and this is an appropriate time to take stock of the need for genetics services in the context of regional demographic characteristics. A synthesis of social, demographic, and genetic science will be needed to ensure that genetics services develop appropriately for the populations of the Region.

Haemoglobin disorders and G6PD deficiency are common in most countries of the Region: there is a clear need for organized development of services for these disorders. Though some good studies exist, information on the frequency of other single gene disorders in the Region is still very variable. There is a need for more emphasis on data collection, using standardized methodologies.
Chapter 4

Hereditary disorders in the Eastern Mediterranean Region: common diseases

4.1 Introduction

Current evidence shows that many common diseases have both genetic and environmental components, although in most cases no major single gene is responsible. This large group of multifactorial disorders is becoming increasingly important for health services in the Eastern Mediterranean Region.

The prevalence of hypertension, diabetes and coronary heart disease is growing significantly in the Region. Cardiovascular diseases are now the leading cause of death in many countries of the Region [135]. Data reported from Bahrain, Egypt, Iraq, Jordan, Kuwait and Qatar over the last five years provide valuable indicators of mortality trends. In these countries, the proportions of deaths attributable to diseases of the circulatory system range from 25% to 40% of all deaths [135].

Data from Kuwait indicate an increasing death rate from coronary heart disease and hypertension [136]. Deaths from cardiovascular disease, accidents and malignant neoplasms accounted for almost half the general mortality rate in 1984. Figure 4.1 shows the rapid increase in mortality from cardiovascular diseases in Jordan over the past 30 years. There have been concomitant reductions in mortality caused by communicable diseases. In 1991, cardiovascular disease was the leading cause of death in Jordan [137], accounting for 44.4% of male and 34.5% of female mortality. There have been concomitant reductions in mortality caused by communicable diseases.

The frequency of morbidity caused by cardiovascular diseases in the general populations of countries is not known. However, some prevalence studies have been carried out and other descriptive epidemiological data are available for certain countries. As countries realize the increasing significance of these diseases and the
need for action at the national level, greater importance is being attached to reliable epidemiological data.

Coronary heart disease seems to be the predominant type of cardiovascular disease encountered in most countries. Hospital data indicate rising trends which are associated with a decline in the number of cases of rheumatic heart disease [135, 138]. Data also indicate a considerable proportion of cases of premature coronary heart disease.

A high prevalence of hypertension has been reported in the Region [139]. A recent epidemiological survey conducted in Egypt, using the diagnostic cut-off points for blood pressure of 140/90, revealed that it affects up to 26% of adults aged 20 years and over in urban communities [140]. The prevalence of hypertension is higher in urban than in rural populations.

Data on the epidemiology of the two types of diabetes, non-insulin dependent diabetes mellitus and insulin dependent diabetes mellitus, obtained in the last decade from Egypt, Iraq, Oman, Saudi Arabia, Sudan and Tunisia [141], and more recently from Jordan, Lebanon and Pakistan, suggest a high susceptibility of many Eastern Mediterranean populations. A recent national survey conducted in Oman according to WHO recommendations revealed a prevalence rate of 9.8% in adults.
aged 20 years and above. An additional 10.9% were in the intermediate category of impaired glucose tolerance, raising the prevalence of glucose tolerance abnormalities to the alarmingly high figure of 20.7%. Recent reports from Egypt, Lebanon and Pakistan describe a similar trend [142]. There is also evidence that a considerable proportion of cases are undiagnosed. Only 50% of known cases presented with the classical symptoms of diabetes according to one report [141]. More than 85% of cases are non-insulin dependent. Although reliable data are scarce, reports suggest that maturity-onset diabetes of the young, a dominantly-inherited condition, is not unusually frequent in the Region. Apart from one report from Pakistan, malnutrition-related diabetes mellitus has not been reported in the Region.

Despite the paucity of morbidity and mortality data in most Eastern Mediterranean Region countries, there is good evidence that cancer is also becoming a major public health concern. Mortality statistics now show cancer as one of the leading causes of death: it is estimated that approximately 450 000 new cases of cancer occurred in the Eastern Mediterranean Region in 1995 [143] and they accounted for about 5% of the total cancers in the world. Generally, the cancers common among males include lung, lymphoma/leukaemia, bladder, stomach and mouth/pharynx. Cancers common among females include breast, urinary bladder, lymphoma/leukaemia and cervix. Regional variations exist; for example, nasal pharyngeal carcinoma in males and uterine cervical cancers in females are particularly common in Morocco and Sudan.

Data on the epidemiology of other common diseases are extremely scarce. However, available evidence suggests that asthma and schizophrenia are both major problems, with significant dimensions and impact on public health in the Eastern Mediterranean Region.

4.2 Environmental factors in common diseases

Observations point to a role of environmental factors in the rising trend of cardiovascular diseases, diabetes and cancer in the Eastern Mediterranean Region. Demographic and socioeconomic changes have been dramatic in the last two decades. The decline in infant and under-5 mortality and increased adult survival have led to a progressive rise in life expectancy, which now exceeds 75 years in some countries. Urbanization is progressive, and in some countries up to 95% of the population live in urban areas [142]. Available data generally indicate high rates of smoking, especially among men, and tobacco consumption rates have risen.
considerably over the last two decades. Imports and production of cigarettes are progressively increasing. The significant transition to economic affluence has also been associated with changes in eating habits and nutritional status that promote the development of chronic multifactorial disorders. In many countries, consumption of fat and refined carbohydrates has increased considerably and the availability of calories has risen beyond requirement. High rates of obesity are reported from many Member States [144].

There is also evidence that an adverse environment before birth and in early infancy affects the prevalence of many common diseases including coronary heart diseases, hypertension and non-insulin-dependent diabetes mellitus [145]. It seems that early undernutrition or infection can bring about permanent physiological changes (e.g., increased blood pressure) predisposing to later disease. Such considerations could be particularly important in populations that progress from underdevelopment to affluence in a single generation, as in some parts of the Region.

4.3 Genetic factors in common diseases

The common diseases already mentioned show some familial aggregation, but without a typical (Mendelian) inheritance pattern. Many appear to be caused by an interaction of several genetic and environmental factors and are said to show a multifactorial inheritance pattern.

The existence of a multifactorial disorder in an individual or a population does not necessarily imply the presence of abnormal genes. Many multifactorial disorders seem to be due to interactions between a genetic constitution within the normal range of human variation and environment. Over one-third of human proteins exist in a number of variant (polymorphic) forms which accounts for much human individual variation but can also be implicated in susceptibility to common diseases. For example, some human leukocyte antigen types that are highly protective against specific infections also predispose to autoimmune disorders (insulin-dependent diabetes mellitus, ankylosing spondylitis, haemochromatosis). A change of environment may convert advantage into disadvantage, and vice versa. This may, for example, partly explain the rapidly increasing prevalence of non-insulin-dependent diabetes mellitus in many Eastern Mediterranean populations that have progressed from nutritional scarcity to dietary abundance within a single generation. The Human Genome Project is making it possible to identify such predisposing variants, and the appropriate use of this information is starting to present a major new medical challenge.
Diseases that are thought to have an important genetic component include coronary heart disease, hypertension, diabetes, cancers, psoriasis, rheumatic disease, thyroid disease and schizophrenia. Most of these groups of disorder include some cases caused by genetic factors alone, some caused by environmental factors alone and some related to an interaction. When genetic studies, particularly DNA analysis, succeed in unravelling the genetic element in such disorders, it often emerges as more important than had been anticipated. For example, genetic factors are now known to be particularly important in non-insulin-dependent diabetes mellitus [146].

A small minority of cancers (family cancer syndromes) are clearly inherited, e.g. familial polyposis coli, familial non-polyposis colon cancer, some cancers of the breast and some thyroid cancers. Familial cancers are usually due to inherited mutations in a single growth-controlling gene and show a dominant, late-onset inheritance pattern. The inherited single mutation does not cause disease in itself, but when a new spontaneous mutation inactivates the remaining normal gene in a relevant tissue cell, cancer can arise. Investigation of the mutations underlying familial cancers often leads to identification of genes that are implicated in the commoner forms of cancer.

Most common cancers are due to sporadic mutations affecting growth-controlling genes. Some cancer-causing mutations would happen anyway; others may be related to environmental factors such as smoking, dietary components, carcinogens or sunlight. Increased understanding could lead to recognition of and reductions in environmental carcinogenic stimuli. There is now also known to be a significant genetic component in cancers of the colon and the breast.

In common conditions such as coronary heart disease or cancer of the colon or breast, it can be difficult to distinguish familial from sporadic cases. Features that should arouse suspicion of an inherited predisposition include:

- early onset
- severity (when there is a range of severity)
- similarly affected parents and/or siblings
- occurrence in the less commonly affected sex (when there is a difference in frequency between the sexes, e.g. women with coronary heart disease).

These criteria show that genetic predisposition is particularly relevant in premature onset of common diseases. The increasing proportion of people who escape death from infectious disease, accident or war and survive past their sixties,
are highly likely to die of a common disease, at an appropriate time. Medical concern is thus primarily with premature onset of these disorders. It is exactly here that genetic factors appear to be most important, and there appears to be an excessive number of cases in the countries of the Region.

4.4 Prevention of common diseases

Prevention and control programmes for common disorders can be based on modifying lifestyle characteristics to prevent environmental risk factors from developing. Strategies for the primary prevention of coronary heart disease, hypertension, diabetes and some forms of cancer are based on reducing the risk factor profile of the population, e.g. focusing primarily on smoking prevention, promoting healthy nutritional trends and dietary habits, reducing obesity and promoting physical activity. In non-insulin-dependent diabetes mellitus, such an approach aims to decrease insulin resistance and improve insulin sensitivity. Experience in industrialized countries confirms the feasibility and effectiveness of intervention programmes in bringing about reduction of cardiovascular risk factors and mortality. While such programmes can be directed at the community as a whole, particularly in high prevalence areas, special emphasis should also be given to a high risk strategy including identification and counselling of persons with increased risk due to a genetic predisposition to these disorders. Epidemiological data suggest that the genetic component may be particularly important in the Region and that this should be an important form of research in the Region.

4.5 Challenges for the future

The Human Genome Project will have a considerable impact on the prevention of common disorders. Identification of the numerous genes affecting susceptibility to various types of cancer, or responsible for genetic predisposition to coronary heart disease and diabetes, will lead to exciting prospects for prevention. Additionally, identification and deeper understanding of the genes involved may lead to general improvement of diagnosis and treatment of cancer, for example a DNA screening test for susceptibility for breast cancer could soon become available. Careful assessment of the psychological as well as clinical costs and benefits of such testing will be needed [147].
Chapter 5

Hereditary disorders in the Eastern Mediterranean Region: role of customary consanguineous marriage

5.1 Introduction

Consanguineous marriage is traditionally common throughout the Eastern Mediterranean Region. Many families consider it has significant social benefits, but it is also true that this kinship pattern increases the risk of having children with a recessively-inherited disorder. Health workers may thus experience some tension between their wish to help couples to minimize their genetic risks, and their society’s social and cultural values.

Although the topic is clearly important to health decision-makers, the existing literature contains only very limited guidance. This chapter therefore presents a comprehensive review of present knowledge of the social and genetic implications of customary consanguineous marriage.

5.2 Frequency and types of consanguineous marriage

The term consanguineous literally means related by blood, so consanguineous marriages are defined as marriages between blood relatives. For practical purposes, geneticists usually classify unions between second cousins or closer as consanguineous, because the genetic risk for less closely related couples differs only marginally from that in non-consanguineous unions.

Consanguineous marriage is strongly favoured in many large human populations. Figure 5.1 is based on 98 local, regional, and national studies conducted during the last two generations, sample size varying from 252 to 893 941 [121,148]. In the mainly Muslim countries of the Eastern Mediterranean Region, and in most parts of south Asia, consanguineous marriage accounts for from 20% to over 50% of the total in the present generation. No account has been taken of major populations (e.g. of China and Indonesia) for which there is little
current information on prevalence of consanguineous marriage, although anthropological sources indicate that first cousin marriage used to be traditional in at least a part of the population [149]. The numerically significant communities of Asian or African origin now resident in Western Europe, North America and Oceania are also omitted.

In 1994, the combined population of countries where consanguineous marriage is known to be customary was 732 million, and a further 1468 million live in countries where 1% to 10% of marriages are consanguineous.

The specific types of consanguineous marriage favoured can vary quite widely between and within countries, and religious and cultural factors play a major part in determining social attitudes and legal frameworks at local and national levels. For example, in Lebanon consanguineous marriages are reported to be more prevalent within the Druze community than among Shi’ a Muslims, and less again among Sunni Muslims [150].

First cousins inherit one quarter of their genes from each of their common grandparents, and one eighth of their genes are identical by inheritance. The children of first cousin parents inherit identical gene copies from each parent at one sixteenth (6.25%) of all gene loci, over and above the baseline level of
homozygosity in the general population.\textsuperscript{6} This degree of homozygosity by descent (or, more correctly, autozygosity) is expressed as a coefficient of inbreeding ($F$) of 0.0625.

Double first cousin marriages, where the spouses have both sets of grandparents in common, also occur. Here 12.5\% of children's gene pairs are identical by descent, i.e. $F = 0.125$.

In the countries of the Eastern Mediterranean Region the preference for consanguineous marriage is by no means restricted to Islamic communities; first cousin marriage is also common in some Christian and Jewish communities and among Zoroastrians and Parsis. Uncle–niece and very occasionally aunt–nephew unions have been reported among Sephardi Jewish migrant communities in Israel [151,152]. Double first cousin and uncle–niece marriage involve the same coefficient of inbreeding in the children ($F = 0.125$), but as uncle–niece marriage is prohibited in the Koran, it is unknown in the predominantly Muslim countries of the Region.

Data on the prevalence and types of consanguineous unions reported for the Eastern Mediterranean Region are presented in Table 5.1. The categories reported are:

- D1C, double first cousin ($F = 0.125$)
- 1C, first cousin ($F = 0.0625$)
- 1½C, first cousin once removed ($F = 0.0313$)
- 2C, second cousin ($F = 0.0156$)
- non-consanguineous ($F = 0$)

The figures in Table 5.1 refer to the present generation only. Since the parents or more distant ancestors of many consanguineous couples were also consanguineous, the average coefficient of inbreeding calculated for each locality ($F$ or $\alpha = \sum p_i F_i$) is a minimal estimate.\textsuperscript{7}

There is good agreement between estimates for prevalence of consanguineous marriage in some countries of the Region, e.g. Pakistan, but in others significantly different frequencies have been reported. This may be partly explained by regional

\textsuperscript{6} In certain types of first cousin union, such as mother's brother's daughter (MBD), the coefficient of inbreeding at X chromosome loci ($F_x$) may exceed the equivalent autosomal value. For MBD progeny $F_x = 0.125$.

\textsuperscript{7} $\Sigma$ is the sum of the proportion of couples ($p_i$) in each specific consanguinity class ($F_i$).
or ethnic variations in marriage patterns, or by variations in the survey method, e.g. household survey or survey among obstetric inpatients. In some earlier studies, the small numbers interviewed and data collection only on first cousin unions could have given less reliable results. In general, since most of the data were collected in urban settings and consanguineous marriage is most prevalent in rural areas, the figures in Table 5.1 can best be regarded as minimal estimates of the current levels of close kin marriage in the Eastern Mediterranean Region.
Since in this Region consanguineous marriage usually involves marrying a cousin of some kind, the popular term “cousin marriage” is also used in this report when it seems appropriate.

5.3 Changes with time in the frequency of consanguineous marriage

Some three decades ago it was predicted that with industrialization, greater population mobility, a decline in family size, and higher literacy rates, there would be a rapid reduction in the prevalence of consanguineous marriage [164]. However, such predictions omitted consideration of the fact that in many parts of the world cousin marriage is a cultural tradition, with significant social and economic benefits. In reality, there has been some decline through time in the prevalence of marriages between second cousins or more distant relatives in urban Lebanon [165,166]. However, no such change has been observed at first cousin level in Lebanon [166,161], Jordan [159] or Saudi Arabia [167].

On a long-term view, for most countries of the Region it seems likely that a decrease in completed family size will lead to increased difficulty in contracting a cousin marriage, and that the biologically closest forms, such as double first cousin marriage will be most affected. In Japan, where the prevalence of consanguineous marriage has declined greatly during the last forty years, preliminary studies suggest a parallel reduction in prevalence of deleterious recessive disorders [168].

Among communities in the Eastern Mediterranean Region in which cousin marriage is preferred, the highest rates are consistently reported in the more traditional rural areas, as demonstrated in Table 5.1 for Egypt [156] and in all other countries in the Region [159,169,170,171]. Cousin marriage is also most prevalent among the poorer and less educated sections of society [166,159,167,170,171,172] and among couples marrying for the first time [168]. Paradoxically, a high rate of consanguineous marriage may also occur in families in the highest socioeconomic strata [172].

5.4 Reasons for choosing to marry a cousin

Strengthening of family ties and the maintenance of family property are often cited as major considerations in choosing a cousin marriage [166,173,174]. Marriage with a relative is also preferred because of the comparative ease with
which premarital negotiations can be conducted [148], and because it is considered
to be favourable for the woman’s status, with better relationships between the
bride and her in-laws [174]. In turn, this may explain the observed greater stability
of consanguineous unions, with lower divorce rates than in unions between
unrelated individuals [173,175,176]. Of particular importance is the belief that, by
marrying within the family, hidden uncertainties regarding the suitability of the
union will be minimized.

In many communities where cousin marriage is common, the family name and
property are inherited through the male line (families are patrilineal), the men and
their descendants tending to stay together, especially when the family owns land.
At marriage, a woman leaves her own family to enter her husband’s family. Cousin
marriage often softens the implications of this transition.

By contrast with the situation of a woman who enters a family to which she is
not related (Figure 5.2a), a woman who marries a cousin (Figure 5.2b) has blood
ties in her own right with her mother-in-law or father-in-law or both, e.g. they are
her aunt and uncle, and she is likely to have known them, and her husband, since
childhood. Because the woman has married a relative she often stays in the same
locality and is not separated from her parents, and can discuss problems with both
her in-laws and her parents. These considerations are especially important for
poorer people, whose children are often their unique source of happiness, and who
may find it difficult to keep in touch if they move any distance away.

For the vast majority of people living in the Eastern Mediterranean Region,
the family remains the main source of social security. The multiplicity of ties
confers reciprocal obligations on family members to assist each other when in need,
and the right to expect support when they need it themselves. This applies equally
in childhood, handicap, and old age, and in widowhood, unemployment, and
imprisonment. It is true that such responsibilities can seriously restrict individual
freedom of action, but when times are hard this may seem a small price to pay for
the security they offer. No kinship pattern is perfect and cousin marriage can have
disadvantages. The numerous family ties can place disproportionate obligations
on a few individuals, and disputes within a family gain bitterness when both
disputants are relatives because family members who side with one necessarily
betray the other.

Prosperity and social stability reduce the need for such strong family ties, and
offer increased possibilities for satisfaction through individual and professional
self-development. They may, therefore, be expected to lead to a decrease in the
a) Genetic and social bonds for the woman at the start of a non-consanguineous marriage

b) Genetic and social bonds for the woman at the start of a consanguineous marriage

FIGURE 5.2 Comparison of social and genetic bonds for a woman in a non-consanguineous and a consanguineous marriage

Note. A corresponding set of relationships exist for the man.

a) Unrelated partners. The social impact of this transition depends strongly on cultural norms. In some societies (e.g., some Indian groups) the woman is considered to leave her own family when she joins her husband’s family; her bonds to her own family are weakened, and she must make new relationships with her husband’s relatives. In other societies (e.g., in Cyprus), the families of the spouses are considered to become one by virtue of the marriage. In yet others (most industrial societies) both partners are seen as separating from their family to set up a new unit.

b) First cousin marriage. At the time of the marriage the bride enters her husband’s family without disruption of existing bonds within the family. She usually has pre-existing bonds with her mother-in-law or father-in-law or both. The same applies for her partner, underlining the strength of the extended family structure.
BOX 5.1 Examples of major congenital disorders that are unlikely to be more common when the parents are related

- Many congenital malformations (e.g. spina bifida, congenital heart disease, congenital dislocation of the hip).
- The commonest forms of severe mental handicap (Down syndrome and fragile X syndrome).
- The commonest form of congenital physical handicap (cerebral palsy).
- Common multifactorial conditions (e.g. diabetes, asthma, eczema).
- Dominant and X-linked disorders (e.g. tuberous sclerosis, neurofibromatosis, Huntington disease, most familial cancer syndromes, fragile X syndrome, haemophilia, Duchenne muscular dystrophy).

frequency of cousin marriage. However, this change should take place in its own time and any effort to hasten it for genetic reasons may be harmful, especially for the less advantaged members of society. Indeed, the loosening of family ties is one of the major social problems of more developed societies.

5.5 Genetic implications

Most major categories of congenital disorder are not more common when the parents are related, than when they are unrelated (see Boxes 5.1 and 5.2), and the deleterious genetic effects of consanguineous marriage at the population level are less than is often expected.

Consanguineous marriage does not significantly affect the frequency of characteristics with dominant inheritance, since these are transmitted

BOX 5.2 Examples of congenital disorders that are more common when the parents are related

- Recessively-inherited congenital malformations (including some severe lethal forms).
- Recessively-inherited forms of mental retardation.
- Recessively-inherited forms of blindness and deafness.
- Many metabolic diseases and other very rare disorders.
- Common recessively-inherited disorders (e.g. thalassaemia major, sickle cell disease, cystic fibrosis).
Role of customary consanguineous marriage

independently of the genetic make-up of the partner. It is generally considered to play a minor role in multifactorial inheritance, although the extent of any effect remains to be clarified. It definitely increases the likelihood that recessively-inherited characteristics will be expressed in the offspring because related partners inherit a significant number of identical genes from their common ancestor(s), which may then be passed on to their children in the homozygous state.

Since most recessively-inherited traits are not pathological, in a sense the custom brings out the latent genetic diversity in a population. For example, there may be more blue-eyed people for a given frequency of the relevant recessively-inherited genes than in randomly-mating populations. The same holds for pathological recessive genes. The importance of the effect is inversely related to the frequency of the gene in the population. When a recessive gene is common (like β-thalassaemia in Cyprus or sickle cell trait in eastern Saudi Arabia), a carrier has a relatively high chance of marrying another carrier whatever their biological relationship, and the risk is approximately doubled in a first cousin marriage. This order of effect can be seen in the data on frequency of sickle cell disorders summarized in Table 3.3. However, genes for most types of recessively-inherited disorder are very rare, and a carrier is unlikely to choose another carrier as a partner unless they are related. Thus, consanguineous marriage particularly favours the manifestation of rare recessively-inherited disorders (carrier frequency 1% or less), such as most metabolic diseases, genetic forms of deafness, some types of congenital malformation, and mild to moderate mental retardation [177]. The effect of first cousin marriage on the relationship between carrier frequency and genetic risk is summarized in Figures 5.3 and 5.4 and Table 5.2.

The combined statistical data on the observed relationship between customary consanguineous marriage and early mortality given below (see 5.8) suggests the presence in human populations of genes for about 400 different very rare recessive disorders, with a birth rate of about 1 in 10 000 and a carrier frequency of 1% or less. Table 5.2 shows that even when consanguineous marriage is very common, each of this group of inherited disorders remains individually rare (birth rate less than 0.3 per 1000). It is the large number of different rare conditions that leads to a significant genetic effect of consanguineous marriage. Therefore, where consanguineous marriage is customary, an increased birth prevalence of some types of congenital malformation, deafness and mental handicap is to be anticipated. However, the expected effect is quite modest and the evidence shows that it can be difficult to measure. A more marked effect is to be expected on the birth prevalence of infants with rare metabolic and other recessively-inherited
FIGURE 5.3 Carrier frequency and affected birth rate for lethal recessive disorders

The lower line represents the relationship between carrier frequency and homozygote birth rate in populations with predominantly random mating. The upper line represents the relationship in a hypothetical situation of 100% first cousin marriage. The curve shows clearly that the effect of parental consanguinity is relatively small at high gene frequencies, and has greatest importance at low gene frequencies.

FIGURE 5.4 Carrier frequency and affected birth rate for less common recessive disorders

The relationship between carrier frequency and homozygote birth rate at lower gene frequencies. These curves can be used to estimate the relative increase in frequency to be expected when, for example, 30% of marriages are between first cousins. The expected homozygote birth rate for a given carrier frequency would then be 30% of the distance between the two curves.
TABLE 5.2 Effect of different proportions of consanguineous marriage on the relationship between carrier frequency and homozygote birth rate

<table>
<thead>
<tr>
<th>Carrier frequency (% of population)</th>
<th>Homozygote births per 1000 with Random mating</th>
<th>30% first cousin marriage</th>
<th>Multiplication factor 30% 1C/random</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.0025</td>
<td>0.0093</td>
<td>×37</td>
</tr>
<tr>
<td>0.2</td>
<td>0.001</td>
<td>0.019</td>
<td>×19</td>
</tr>
<tr>
<td>0.5</td>
<td>0.00625</td>
<td>0.053</td>
<td>×8.5</td>
</tr>
<tr>
<td>1.0</td>
<td>0.025</td>
<td>0.119</td>
<td>×4.8</td>
</tr>
<tr>
<td>1.5</td>
<td>0.056</td>
<td>0.195</td>
<td>×3.5</td>
</tr>
<tr>
<td>2.0</td>
<td>0.10</td>
<td>0.288</td>
<td>×2.9</td>
</tr>
<tr>
<td>3.5</td>
<td>0.31</td>
<td>0.646</td>
<td>×2.1</td>
</tr>
<tr>
<td>5.0</td>
<td>0.63</td>
<td>1.10</td>
<td>×1.7</td>
</tr>
<tr>
<td>10.0</td>
<td>2.50</td>
<td>3.44</td>
<td>×1.4</td>
</tr>
<tr>
<td>16.0</td>
<td>6.40</td>
<td>7.91</td>
<td>×1.23</td>
</tr>
<tr>
<td>20.00</td>
<td>10.0</td>
<td>11.89</td>
<td>×1.2</td>
</tr>
</tbody>
</table>

disorders which, in the absence of facilities for biochemical genetic diagnosis, would manifest itself through increased perinatal, infant and early childhood mortality. There is little direct information on the collective frequency of rare recessive disorders in countries of the Region, because of limited availability of facilities for genetic diagnosis. Recent studies from Kuwait and Saudi Arabia have confirmed a high frequency of rare recessively-inherited metabolic disorders [178,122].

5.6 Effects of consanguineous marriage at the population level

Despite numerous studies, it has hitherto proved difficult to measure the genetic effects associated with customary consanguineous marriage at the population level. This is partly because of flaws in the assumptions underlying some studies, and partly because a variety of confounding factors can generate misleading results. Before discussing the data, it is necessary to consider these potential sources of bias.

First, when comparing populations without and with a tradition of consanguineous marriage, it is often assumed that the coefficient of inbreeding ($F$) is zero in the former. However, this is improbable. All endogamous\(^8\) societies

\(^8\) Societies in which partners are selected from within the group.
of finite size, whether small isolated communities (e.g. island populations or populations in inaccessible areas) or societies with strong social subdivisions (e.g. caste populations), exhibit some degree of random inbreeding because of restricted choice of marriage partner. Whether or not they favour consanguineous marriage, the average coefficient of inbreeding calculated for such populations is an underestimate.

Secondly, in societies with a long tradition of consanguineous marriage the true coefficient of inbreeding may substantially exceed that calculated for the present generation, because of antecedent consanguineous marriages.\textsuperscript{9}

Thirdly, postnatal morbidity and mortality is significantly higher in children of consanguineous parents, especially during the first year of life. Studies conducted in less developed regions do, however, face a major problem in diagnosing cause of death, and there is a consequent difficulty in partitioning mortality into genetic and non-genetic components with any real degree of confidence.

Fourthly, interactions between consanguineous marriage and social variables complicate assessment of its genetic effects. In most communities consanguineous marriage is commoner among the poorest and least educated, whose children are also at greatest risk of infant or childhood death from infectious and nutritional disease. Therefore, failure to control for such socioeconomic differentials can lead to exaggerated estimates of the adverse genetic effects of consanguineous marriage.

Despite these obvious difficulties, too often there has been uncritical interpretation of data in terms of the effects of deleterious recessive genes, without information on the specific socioeconomic profiles of the consanguineous and non-consanguineous groups studied. Conversely, in countries where consanguineous marriage is common, the almost universal failure to include it among the variables affecting infant and childhood mortality and morbidity must throw into question

\textsuperscript{9} In families for which credible multi-generation pedigrees are available, some attempt can be made to allow for the fact that the common ancestor may be the product of a consanguineous union by incorporating the term \((1 + F_A)\) into the calculation of \(F\), where \(F_A\) is the inbreeding coefficient for the ancestor, and measuring the probability that the ancestor carried two genes which were identical at a specific locus or loci [179]. The inbreeding coefficient for an individual in the present generation is then given by \(F = (1/2)^n \left(1 + F_A\right)\) where \(n\) is the number of individuals in the path connecting the parents of the individual under investigation (including the parents themselves) and the summation (\(\Sigma\)) is taken over each path that goes through a common ancestor. In practical terms, there is often insufficient depth in the pedigree to go back more than three to five generations, and in many populations with a history of consanguineous unions the task becomes extremely complex because of the many interrelated strands in the pedigree, necessitating extended and laborious computational analysis.
the reliability of existing perceptions of the roles of maternal education, birth order, and birth interval as determinants of postnatal survival.

5.7 Consanguineous marriage and fertility

It is often thought that consanguineous marriage reduces fertility, either by altering the prevalence of primary sterility, or though increasing the spontaneous abortion rate. However, survey results from a wide variety of sources have confirmed that fertility is greater in consanguineous marriages, with younger female age at marriage and first delivery identified as important contributory factors.

Surveys have also consistently shown reduced levels of sterility in consanguineous marriages [180,181]. This is thought to be due to increased immunological compatibility of mother and fetus, with lower predicted rates of potentially lethal conditions such as rhesus incompatibility [182] and pre-eclamptic toxaemia [183]. There is also little evidence linking consanguineous marriage to increased miscarriage rate [184,185,186,187] and no detectable effect on indirect indicators of fetal survival, such as multiple birth rates and sex ratio at birth [181,188,189]. Thus, there is no evidence that consanguineous marriage has any significant adverse influence on the incidence of recognized fetal loss at the population level. The data offer no support for the suggestion that when a couple share common human leukocyte antigens they may have increased difficulty in initiating pregnancies, and suffer an increased risk of recurrent spontaneous abortion [190].

In terms of gross fertility, usually greater numbers of infants are born to consanguineous than to non-consanguineous couples [150,176,191]. Bittles (in preparation) has analysed reported data on parental consanguinity and fertility in relation a) to the frequency of first cousin marriages and b) to all types of consanguineous union reported. A significant positive association between parental consanguinity and fertility was found at first cousin level in 25 of the 28 populations examined (sign test, \( P < 0.001 \)), with a mean excess of 0.24 (±0.9) live births per couple in the first cousin unions.\(^{10}\) In the equivalent meta-analysis based on all consanguinity categories, 25 of the 28 populations again revealed a positive association between parental consanguinity and fertility (sign test,

\(^{10}\) The coefficient of determination \( (R^2) \) measuring the goodness of fit of the linear regression was 0.61.
Thus, according to both measures, parental consanguinity was associated with a greater number of live births.

Social factors may be largely responsible for the greater fertility of consanguineous marriages. Prominent among these is younger female age at marriage which maximizes maternal reproductive span and increases child-bearing in the most fertile years. This pattern has been clearly seen in south India [176] and Pakistan [162]. In addition, the larger number of births in consanguineous marriages may represent compensation for increased infant and childhood mortality [192] operating either through a conscious decision by parents to achieve their desired family size, and/or the cessation of lactational amenorrhoea following the death of a breast-fed infant. In Pakistan, for example, a greater number of live births have been reported in families where childhood deaths have occurred [193], especially when the dead child was male [194].

Fertility is an important variable in assessing the biological effects of consanguineous marriage on mortality, since the larger the family size the greater the expectation that an affected child will be born to parents who both carry an autosomal recessive disorder (see Chapter 7).

5.8 Parental consanguinity and infant and childhood mortality

Many opinions and impressions concerning the genetic effects of consanguineous marriage stem from studies of geographical, religious, or ethnic isolates such as the Samaritans [195,196]. Even when there is no preference for consanguineous marriage, mutations which are rare in large populations can randomly reach a high frequency in such small groups within a few generations because of founder effects and random genetic drift. Many genetic disorders encountered in the Eastern Mediterranean Region are only found at high frequency in such small groups [197]. A particularly well-worked out example is the marked variation between tribes in the distribution of lysosomal storage diseases observed in Saudi Arabia [198]. Extrapolating from such studies to large continental populations is, however, of questionable academic or practical value.

To obtain representative data for large populations and different age intervals, studies on 38 (mainly urban) populations in east, south and west Asia, West Africa, South America, and western Europe have been analysed [199]. Together, the studies provided information on 622 188 pregnancies or live births, with a median follow-up of 10 years (range 1 month to 30 years). In 34 of the 38 studies there
was a positive association between parental consanguinity and mortality (sign test, $P < 0.001$). Mortality among the offspring of first cousins was on average 4.4% higher than in non-consanguineous controls (Figure 5.5).

The results may underestimate the total mortality associated with parental consanguinity because data on deaths in later childhood was absent from a number of studies. However, this is probably more than compensated for by the fact that in many of the studies analysed there was inadequate (or occasionally no) control
for socioeconomic variation, a deficiency that would tend to exaggerate the adverse effect of parental consanguinity on survival. The remarkably consistent results indicate considerably lower excess mortality in the offspring of first cousins than previously reported. These empirical studies have the advantage that any effects of antecedent parental consanguinity are included, so the resulting figure can be used in genetic counselling for consanguineous couples who are already married, or plan to marry.

5.9 Parental consanguinity and morbidity

Failure to control for socioeconomic variables may be an important source of extraneous variation in studies of the effect of parental consanguinity on morbidity and mortality. When social variables have been controlled, conditions with a polygenic/multifactorial pattern of inheritance appear to be little affected by parental consanguinity, and studies of anthropometric measurements at birth and in childhood frequently have failed to reveal any major, consistent effect. In the classic Japanese study conducted by Schull and Neel [177], it was possible to measure socioeconomic differentials, and to show that had they not been controlled, they would have inflated the calculated adverse effect of parental consanguinity on anthropometric measurements by approximately 20%.

Investigations of the influence of parental consanguinity on birth weight in the Eastern Mediterranean Region have produced mixed results, with reports of a decline in low and/or mean birth weight in small-scale studies in Kuwait [200], Iraq [201], and Pakistan [202] but not in Lebanon [203] or Saudi Arabia [163]. Given the importance of birth weight as a predictor of well-being and survival in childhood [204] this topic requires further studies, incorporating careful controls for socioeconomic variables.

Tests of intellectual capacity have shown only marginal declines in the mean scores attained by children of consanguineous parents [205,206]. It appears that parental consanguinity mainly leads to greater variance in IQ levels [207]. The greater part of this variance may be due to the expression of detrimental recessive genes in a small proportion of those tested. The occasional expression of recessives leading to exceptionally high intelligence has not been excluded. Offspring of consanguineous parents may be over-represented among individuals with severe mental retardation [208,209], with blindness [210], hearing impairment [211,212] or deaf-mutism [213].
Global studies have shown a significantly higher incidence of major congenital malformations in offspring of consanguineous parents [188,214,215,216]. However, surveys in Saudi Arabia [217] and Pakistan [218] were unable to detect a significant increase in perinatal mortality or birth defects respectively. In considering these results, it is important to recognize that most communities which favour consanguineous marriage are still economically developing, and under these circumstances it is difficult to ensure correct diagnosis of congenital disorders, or to differentiate between genetic and non-genetic determinants of morbidity.

These diagnostic problems do not apply in studies on British Pakistanis. In the present generation 50% to 55% of marriages in this population are between first cousins [219]. So observed genetic effects are likely to be more marked than in most Eastern Mediterranean populations. Mean perinatal mortality in this community (15.7 per 1000 births in 1988) significantly exceeded that in all other population groups of the United Kingdom [220,221] and was consistent across all socioeconomic classes [123,222]. Congenital anomalies accounted for 41% of all infant deaths among British Pakistanis during the period 1982 to 1985 [222]. In a multi-ethnic prospective study, serious malformations were diagnosed in 28.2 per 1000 British-Pakistani babies. However, only half of the excess mortality due to congenital malformations was associated with parental consanguinity, raising the possibility of additional environmental effects. Chronic disorders (many with a recessive mode of inheritance) were diagnosed in 41.5 per 1000 of those surviving the first month of life [223,221].

A preliminary survey conducted in Pakistan [224] suggested that some major diseases of adult life, including some forms of cardiovascular disease and cancer, may be more prevalent in offspring of consanguineous parents. This suggestion needs further investigation, keeping in mind the strong influence of social factors on the epidemiology of these disorders.

5.10 Conclusion

The demographic characteristics of Eastern Mediterranean populations—large family size with multiple consanguineous marriages—have a marked effect on the pattern of manifestation of genetic disorders, and will strongly influence the orientation of strategies for their diagnosis and prevention.

Single gene disorders cluster particularly markedly in Eastern Mediterranean families because the consanguineous marriage pattern tends to retain mutations
within affected families. This does not increase the overall frequency of dominant and X-linked disorders, but those families that are affected may contain an unusually high proportion of mutation carriers. The consanguineous marriage pattern increases the birth rate of individuals with recessively-inherited disorders, the effect being most marked for the rarest types. Whatever the inheritance pattern, when consanguineous marriage is common family studies starting from affected individuals may detect an unusually large number of carriers, who may benefit from information on how to reduce their genetic risk. The implication is that genetic counselling has a particular potential for providing help to families in the Region, and that genetics services should be strongly family-oriented.

For the moment, evidence that excess mortality among children of cousin marriages in the Eastern Mediterranean Region has a significant genetic component is largely dependent on statistical analysis. Standardized and comparable studies are needed in the countries of the Region to provide data that can be used in developing health policies. There is an urgent need for pilot studies in the countries of the Region of the feasibility of genetic diagnosis and counselling for the extended families of people with genetic disorders.
Part 3
Available approaches for prevention
Chapter 6
Approaches in primary health care

6.1 Introduction

Prevention of congenital and genetic disorders at the population level depends on a combination of basic public health measures, and the education and involvement of the primary health care network [9,225]. The public health approaches discussed below should be applicable in most countries. Genetic approaches appropriate at the primary care level include pre-conception information, screening and counselling, and identification and referral of individuals and families at increased genetic risk. Since the structure of primary health care and level of service provision differ widely between the countries of the Region, these approaches will need to be developed and implemented according to local circumstances and available resources: the situation in many countries allows immediate implementation, but in others prior planning is needed.

When the relatively simple and effective measures outlined in 6.2 are incorporated into primary health care, many serious disorders will be prevented from arising in the first place.

6.2 Basic public health approaches

6.2.1 Provision of appropriate family planning services

The incidence of chromosomal disorders and spontaneous abortion rises rapidly with maternal age after the age of 35 [59]. Women should be informed of these risks. When family planning is generally available, couples tend to curtail further reproduction once they have reached the desired number of children. This leads to a selective fall in births to older parents and a reduction of genetic risk. In western Europe for example, the proportion of children born to women over 35 fell from more than 20% to about 6% between 1950 and 1975 [9], although it has since risen again to about 10%. A similar change in the Eastern Mediterranean Region could be beneficial for reproductive health.
Figure 6.1 Risk of miscarriage in relation to maternal age and social class

Risks rise sharply after the age of 37 years. Variation in risk by social class probably reflects differences in the general health of the mother.

Miscarriage is strongly associated with maternal age [226]: after the age of 40 over one third of recognized pregnancies miscarry (Figure 6.1). Miscarriage is a common but often neglected cause of maternal morbidity, with associated blood loss and risk of anaemia. On this ground alone, increased use of family planning is likely to increase women’s well-being and ability to look after their family.

Between the ages of 40 and 50 the risk in each pregnancy of a liveborn child with a serious chromosomal anomaly rises from 1.5% to 8% and estimated data indicate that in some countries of the Eastern Mediterranean Region, almost 50% of Down syndrome children are born to mothers over 40 years of age. Figures 6.2 and 6.3 show reported maternal age distribution, population age profile and estimated births of children with Down syndrome, for two countries of the
FIGURE 6.2 Population–age distribution, maternal age distribution, and Down syndrome births by age of mother in the Libyan Arab Jamahiriya, 1984
Comparison of population age distribution, maternal age distribution, and Down syndrome births in two countries of the Region (Libyan Arab Jamahiriya 1984 and Cyprus 1989). In the Libyan Arab Jamahiriya 4.7% of births were to mothers over the age of 40, and these women are estimated to have had 26% of all children born with Down syndrome. By contrast, in Cyprus only 1.1% of births were to mothers over the age of 40, and this group is estimated to have had 13% of the children with Down syndrome.
Region. It confirms that the birth incidence of affected children can fall by over half when family planning is widely available.

In addition, a reduction in the proportion of older fathers reduces the rate at which new mutations enter the population and this initiates a gradual long-term decrease in the frequency of inherited disease [74]. The actual scale of this effect could be elucidated by epidemiological studies in the Region.

6.2.2 Optimizing women’s diet

It is a priority to ensure that women of reproductive age in the Region have an adequate diet. In view of the growing evidence that maternal health and nutrition can affect predisposition to common diseases of later life in the offspring [145], it is important to identify and correct maternal anaemia and malnutrition before, as well as during pregnancy.

Randomized controlled trials in areas with a high incidence of neural tube defects have shown that supplementing women’s diet with vitamins, including folate, prior to and in the first months after conception reduces the risk of fetal neural tube defect and of some other congenital malformations [46,47]. The folate intake necessary for full protection may be about 0.4 mg daily, and even diets in industrialized countries provide only 0.2 mg daily. Since it is difficult to reach the desired level by diet alone, vitamin supplements starting before conception are now recommended in many countries.

There is a need to consider whether dietary vitamin supplementation should also be recommended in the Eastern Mediterranean Region. Populations differ considerably in the relative frequencies of different types of congenital abnormality and presumably in the causative factors involved. There have as yet been no studies of the effects of vitamin supplements in the Region and it is unlikely that reliable data will become available in the next 10 years. However, the evidence from elsewhere is so strong that it is appropriate to inform women of the importance of a balanced diet including fruit and vegetables, and to consider vitamin supplementation. When fertility is high, as in most countries of the Region, it is not easy to identify a pre-conception period and it may be preferable to supplement women’s diet throughout the reproductive span. These issues might be clarified through a carefully planned demonstration project in one country of the Region.
6.2.3 Other aspects of diet

Iodine deficiency is highly prevalent in many countries of the Region, especially Afghanistan, Islamic Republic of Iran, Pakistan, Syrian Arab Republic, Sudan and Republic of Yemen. Severe iodine deficiency in the mother can lead to impaired fetal brain development, and is probably the most important cause of mental retardation in these countries. The beneficial effects of the current campaign for iodization of salt in the Region are likely to include a significant reduction of mental handicap [45].

Iron deficiency is also extremely common among pregnant women and children. Haemoglobin level is directly related to physical energy, and iron deficiency causes a measurable reduction of IQ levels in children [227]. Iron supplementation of basic foodstuffs might therefore be considered.

Though relatively few women of the Region smoke or drink alcohol at present, women should be informed about the increased risk of miscarriage, prematurity or low birth weight associated with smoking, and the risk of fetal alcohol syndrome associated with high alcohol consumption.

6.2.4 Immunization against rubella infection

Rubella infection is endemic in the Region. The limited data that exist for some countries suggest that from 60% to nearly 100% of girls are already immune by the time they reach reproductive age (see Chapter 2). It is now important to conduct studies in each country, to establish the proportion of non-immune adult women in relation to age.

The case for including rubella immunization in the regional Expanded Programme on Immunization has been considered. If over 90% coverage could be achieved and sustained, rubella immunization should be considered. However, since immunization interrupts natural transmission during childhood, coverage of less than 90% can create a risk of a future epidemic, and could lead to an increase in congenital rubella syndrome among infants of non-immunized susceptible women. Alternative approaches that should be considered include immunizing schoolgirls, or screening and immunizing non-immune women of reproductive age at or before marriage.
Further information is also needed on the extent of maternal immunity to toxoplasmosis, since if infection is diagnosed and treated during pregnancy, congenital abnormalities may be avoided [228].

6.2.5 Routine antenatal screening for rhesus blood group

Administration of anti-D immunoglobulin to rhesus negative women after childbirth, miscarriage or abortion has reduced mortality and chronic handicap due to rhesus haemolytic disease by over 95% in many countries [229]. A formal study is needed in each country of the Region, to confirm that screening for rhesus blood group and antibodies is a routine component of pregnancy care, and that adequate supplies of anti-D immunoglobulin are available. Figures are also needed on the proportion of rhesus negative women who become isoimmunized.

6.2.6 Better control of diabetes during pregnancy

Women with insulin-dependent diabetes mellitus have about a 6% risk of a seriously malformed child in each pregnancy. They can greatly reduce their risk by meticulous control of the blood sugar, which must be started before pregnancy begins because major malformations arise very early in embryonic development [230]. Appropriate advice for women and assistance in achieving the necessary standard of blood sugar control should be a routine part of diabetes care throughout the Region.

A similar risk is associated with certain drugs taken for epilepsy.

6.3 Pre-conception information and counselling

Primary prevention of genetic and congenital disorders depends largely on pre-conception information, screening, and counselling. Box 6.1 shows basic information that should be available to women prior to pregnancy.

The strong case for inclusion of pre-conception information and counselling in primary health care services in the Eastern Mediterranean Region is developed in Chapter 7.

Worldwide, primary health care services need strengthening in this important area. In each country, this calls for identification of an appropriate infrastructure, reinforcement of laboratory diagnostic services, development of educational
BOX 6.1 Information that should be available to women prior to pregnancy

1. The risk of miscarriage and newborn chromosomal abnormality rises with maternal age. These risks can be reduced by family planning.
2. Diet should be adequate in iodine, vitamins and iron, before, as well as during, pregnancy.
3. It is desirable to know your rhesus blood group.
4. It is desirable to be tested for immunity to rubella.
5. Risk of infection with toxoplasma or listeria can be avoided.
6. Smoking, alcohol, and medications for specific disorders can increase the risk of miscarriage, congenital abnormality and fetal growth retardation.
7. Genetic counselling is available for families with a history of repeated abortions, stillbirth, perinatal and infant death, congenital malformations, disability and unexplained childhood death.
8. Availability and implications of carrier testing for specific common genetic risks (e.g., haemoglobin disorders, G6PD deficiency).

materials for women and primary care workers, and training in basic genetic counselling for primary care workers. Incorporation of services into the maternal and child health programme can, in some countries of the Region, represent a great opportunity for the prevention of congenital and genetic disorders.

The appropriate infrastructure for pre-conception counselling will differ in different communities. It may be integrated into a comprehensive primary health care network where one exists. For example, in the United Kingdom, the primary care network of general (family) practitioners provides an appropriate framework [225]. A family planning programme may also provide a suitable focus for advice about future pregnancies. In Hungary, young couples who attend a dedicated “optimal family planning programme” run by nurses, have a significantly better pregnancy outcome than the Hungarian population in general [231]. The Hungarian experience also suggests that the stage when young people are setting up a family is an appropriate point for health promotion in general, including screening oriented towards avoiding common disorders, e.g., blood pressure measurement, counselling about lifestyle and screening for risk factors for common diseases. Implementation of WHO’s mother–baby package for safe motherhood could have a considerable potential for the prevention of hereditary disorders and congenital abnormalities, if the above-mentioned public health approaches are integrated into it.
6.4 Identification in primary health care of patients and families requiring referral for specialist genetic counselling

The organization of genetic counselling services in response to the clear need for them in the countries of the Eastern Mediterranean Region is discussed in Chapter 12. When specialist services exist, their usefulness to the community depends on appropriate awareness and referral by primary health care workers. In general, very little genetics was included in the training of existing health workers. The adjustments needed in the medical and nursing curricula, and the requirements for updating current primary care workers are discussed in Chapter 13.

Box 6.2 outlines the role of primary health care workers in community genetics.

In order to carry out these tasks, primary health care workers need the following training and information:

- Training in taking and recording a basic genetic family history, including for large families with multiple consanguineous marriages.

- Guidelines on detecting possible genetic risk, e.g. suspicion of diabetes, single gene disorders or a familial cancer, and on lines of referral.

---

**BOX 6.2 Role of primary care workers in basic community genetics**

1. Provide correct information on genetic risks that are common locally and ways to reduce risks.
2. Be aware of common genetic disorders and their management.
3. Be aware of local specialist centres, and refer affected children and couples at risk appropriately.
4. Be able to take a basic genetic family history, in order to identify people in need of specialist referral.
5. When services are available, arrange screening and counselling for carriers of common single gene disorders (e.g. haemoglobin disorders). Inform relatives of known carriers of their high chance of also being carriers and offer testing.
6. Give advice on reducing the risk of common disorders with genetic predisposition.
7. Understand the basic ethical principles and techniques of non directive genetic counselling.
• Training in methods for examining newborn children for congenital malformations, for timely specialist referral.
• Training in the basic ethical principles and techniques of genetic counselling.
• When genetic screening is available, e.g. for haemoglobin disorders, training in how to detect and counsel carriers and appropriately refer couples at risk.
• Access to appropriate information materials for patients and families and the general public.
• Information on specialist services available and on any family support associations that exist, and their role.

Medical geneticists have an important role in training primary health care workers in genetic aspects of disease and should have a long-term role in the education programme.

6.5 Health education for the public

All the above activities are aspects of health promotion. There is an associated need for public health education. Suitable materials need to be designed and widely disseminated, especially to women. Models exist, e.g. the United Kingdom Health Education Authority's *Pregnancy Book*, and outline information materials for haemoglobin disorders produced by the WHO [232], but all educational materials need to be adapted or designed locally, with the specific characteristics of local populations in mind. Some appropriate educational materials are already produced in the Region; such initiatives should be supported and extended.

6.6 Conclusion

Involvement of the primary health care system is essential if genetics services are to reach the general population. This calls for training and provision of educational materials for primary health care workers. This task should begin as soon as possible in view of the importance of introducing correct genetic information at the point of medical contact with the public. Training courses in community genetic counselling should be initiated in each country.

Since responsibility for health must be shared with the public, each aspect of a community genetics programme needs support with specific health education materials.
Basic public health measures that reduce the incidence of genetic disorders are mainly the responsibility of the primary health care services. Guidelines for the prevention of genetic disorders and congenital abnormalities in primary health care should be developed at the central level and implemented throughout the primary health care network. Patients and families who need specialist genetic counselling must also, in general, be first identified at the primary health care level. This calls for involvement of specialists in training and updating for primary health care workers. Finally, education of the population and of primary health care workers in relevant aspects of medical genetics must go hand-in-hand.
Chapter 7

Identification of genetic risk: family history and population screening

7.1 Introduction

There are two main approaches for identifying people who are at risk of developing a genetically-determined disorder themselves, or for passing one on to their children. The classical genetic approach is to study the families of people who present with a genetic disorder. A second approach is screening the whole population for individuals at increased risk.

The family-oriented approach and population screening differ in basic concepts, strategy, financial implications and associated ethical issues. They are complementary rather than alternatives. In the Eastern Mediterranean Region, the balance between them may differ from that in industrialized countries because of the characteristic family structure in the Region.

7.2 The family history or family-oriented approach

7.2.1 Diagnosis and counselling

A correct genetic diagnosis is necessary for affected individuals, to give guidance on the management, natural history and prognosis of the condition, and to allow families to make contact with the appropriate support associations (when they exist). A correct diagnosis is equally important for relatives, who may wish to know of any risk to themselves or their descendants. For example, in the case of a single gene disorder, 50% of first degree relatives are likely to be carriers, with a significant risk of passing the same disorder on to their children (Table 7.1).

There is good evidence that people generally prefer to know about a genetic risk if effective action can be taken to avoid it and that counselling often dispels misconceptions and alleviates anxieties. Medical geneticists, therefore, usually attempt to contact family members in order to offer genetic counselling and definitive carrier testing if suitable tests are available.
TABLE 7.1 Chances that relatives of a person known to carry a particular gene also carry the same gene

<table>
<thead>
<tr>
<th>Relationship to carrier</th>
<th>Chance of carrying the same gene (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent, brother, sister, child</td>
<td>50</td>
</tr>
<tr>
<td>Grandparent, uncle, aunt, nephew, niece</td>
<td>25</td>
</tr>
<tr>
<td>First cousin</td>
<td>12.5</td>
</tr>
</tbody>
</table>

The example of a couple at risk for having children with thalassaemia major, the commonest recessively-inherited disorder in the Region, may be used to illustrate the family implications of genetic reproductive risk (Figure 7.1).

7.2.2 Options for the parents

When both parents carry thalassaemia, in each pregnancy there is a 25% risk of an affected child, although there is no way of predicting the outcome for any given couple using this risk figure. Figure 7.2 shows that even when family size is large, a significant proportion of couples at risk escape having affected children, while others have more than the expected number.

When children with thalassaemia major are not diagnosed, most die of anaemia compounded by infection between 6 and 18 months of age. If the parents have no information on recurrence risk, they usually have further children in order to replace the lost child or children.

![Recessive Inheritance in the context of thalassaemia](image)

FIGURE 7.1 Recessive inheritance in the context of thalassaemia

Rarely, a carrier of a recessively-inherited disorder chooses a partner who carries the same recessive disorder. Then in each pregnancy there is a 25% chance that the child will be "normal", a 50% chance that it will be a healthy carrier, and a 25% chance that it will suffer from the major disorder.
Figure 7.2 Recessively-inherited disorders: risk of one or more affected children in relation to family size

Although each at-risk couple has a 25% chance of an affected child in each pregnancy, some couples have more than their “fair share” of affected children. Others escape without any affected children, even when final family size is greater than four. For instance, almost 20% of at-risk couples with six children escape having an affected child.

When facilities for diagnosis and treatment are available, parents are usually also informed of their 25% recurrence risk. Couples who already have healthy children often then decide not to undertake further pregnancies, if they have access to family planning services. The effect on the birth rate of affected children depends on the population norm for family size. In communities where the average completed family size is more than five, if all couples with one affected child had no more children, the affected birth rate could fall by as much as 50% [233]. However, the decision to have no (further) children is unacceptable to many couples, especially those who have no, or few, healthy children. Informed couples who wish to enlarge their family may knowingly “take the risk” in each
pregnancy, or make use of prenatal diagnosis if it is available. The implications of these choices for the family are discussed more fully in Chapter 8.

7.2.3 Genetic counselling for relatives

The parents of affected children should be informed of the fact that 50% of their brothers and sisters and 25% of their nephews and nieces may be carriers. Carrier testing is available for an increasing number of inherited diseases. When it is offered to members of a large extended family, many carriers can be detected. Especially where there are multiple consanguineous marriages, other couples at risk within the family may also be identified and counselled before they have any affected children. A study among Palestinian refugees in the Syrian Arab Republic suggested that between 20% and 30% of thalassaemic births might be foreseen, and possibly avoided, in this way (Dr F. Hamadeh, personal communication). Thus, the commonest kinship structure in the Region may offer particular opportunities for effective and efficient genetic counselling. Table 7.2 shows that a far higher proportion of the carriers in a population might be identified through family studies in the Eastern Mediterranean Region than in populations of industrialized countries.

However, there is little chance of exploiting the unique possibilities for useful genetic counselling in the Region if attitudes of health care professionals are unsympathetic to cousin marriage; large, closely-consanguineous families are

<table>
<thead>
<tr>
<th>Carrier percentage</th>
<th>Percentage of carriers detectable by family studies with:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Random mating</td>
</tr>
<tr>
<td>0.1</td>
<td>0.10</td>
</tr>
<tr>
<td>0.5</td>
<td>0.12</td>
</tr>
<tr>
<td>1.0</td>
<td>1.50</td>
</tr>
<tr>
<td>3.5</td>
<td>5.00</td>
</tr>
<tr>
<td>10.0</td>
<td>16.00</td>
</tr>
<tr>
<td>16.0</td>
<td>24.00</td>
</tr>
<tr>
<td>20.0</td>
<td>30.00</td>
</tr>
</tbody>
</table>

*Detection of six carriers per affected individual diagnosed is assumed throughout.

Note. The power of family studies to detect carriers depends on carrier frequency and on the frequency of consanguineous marriage. It is greater in populations where consanguineous marriage is common, especially when the genes involved are rare. The same applies for late-onset dominantly-inherited disorders, e.g. familial cancer syndromes.
unlikely to open themselves to genetic counselling if the counsellor is expected to criticize their preference for marrying kin. In-depth studies of the feasibility and effects of family genetic counselling are a high priority in the countries of the Region.

At the same time, family studies following the diagnosis of an affected person cannot identify everyone in the population who might benefit from genetic counselling. When carrier tests are available for a common condition, like the haemoglobin disorders, population screening can identify the majority of couples at risk before the first affected child is born into the family. Screening is also the only way to detect congenital malformations and chromosomal abnormalities which arise sporadically during pregnancy with no indication of increased risk from the family history.

7.3 Genetic population screening

A genetic population screening programme is a systematic attempt to identify and counsel as many people at genetic risk in a population as possible, whether or not they have a genetic family history [9]. The agreed general requirements for population screening [234] can be summarized as follows:

- a common and potentially serious condition
- a clear diagnosis in each case
- good knowledge of the natural history of the condition (permitting correct prediction of outcome)
- an effective and acceptable solution (treatment or prevention)
- affordable tests

The haemoglobin disorders satisfy all the above criteria in the majority of countries of the Region. Between 3% and 20% of most populations carry thalassaemia or sickle cell trait (see Table 3.2). The disorders are serious and management burdensome. Carriers can be identified by very simple methods in peripheral centres\(^\text{11}\) and definitive carrier diagnosis can be practically 100% accurate at expert centres. Carrier couples can be given clear information on their reproductive risk and the implications of the disease. The options then available to them are discussed more fully in Chapter 8.

\(^{11}\text{One tube osmotic fragility test for thalassaemia [234], sickling test for haemoglobin S [235].}\)
Neonatal detection and simple protective measures are strongly indicated for sickle cell disease [93,94], and could be particularly important when the prevalent form of the disorder is relatively mild, as in many areas of the Region.

Prevention programmes for haemoglobin disorders are feasible and cost-effective [236], and their organization has been described in detail in a WHO document [81]. Thalassaemia has been brought under complete control in Cyprus [237], thalassaemia screening has been initiated in the Islamic Republic of Iran, and screening for sickle cell carriers is under consideration in other countries. The discussion of costs and benefits of prevention programmes for the haemoglobin disorders in Chapter 11 suggests that screening for the haemoglobin disorders should be considered in all Eastern Mediterranean countries where they are prevalent.

A decision to undertake genetic population screening involves initiating a new type of service, with its own distinctive risks and benefits. It requires the support of the public health authorities and an appropriate health infrastructure, and should be investigated, planned and monitored systematically. Screening affects large numbers of people who are unaware of any risk, and can do more harm than good if implemented without appropriate preparation and public education. Genetic population screening requires the highest standards of diagnosis, quality control, information and counselling [9]. In particular, the need for training health workers in genetic counselling, and for information for the public, must not be underestimated.

Clearly, population screening must be delivered by health workers in primary health care and maternal and child health services, most of whom have had little or no education in genetics or the principles of genetic counselling. This presents an educational challenge, discussed in Chapter 13. Possibilities for ensuring regular collection, transport and storage of uncontaminated samples, laboratory organization, and recording and communicating results, also differ by country. Hence each new screening service should be introduced as a research project within the local medical and social context.

The boundary between family studies and genetic screening is not clear-cut. Taking a genetic family history is a screening method for identifying families which could benefit from referral to a medical geneticist. When a carrier is identified by population screening, their extended family should be offered carrier testing. Though most chromosomal anomalies and congenital malformations
arise sporadically, there are also family implications: women who have a child with a chromosomal disorder have an increased recurrence risk, and women who have a child with a serious malformation are usually considered to have a 2% to 6% recurrence risk in each subsequent pregnancy [1,238]. The figure may well be higher in the Eastern Mediterranean Region because some malformations are recessively inherited. Local studies are needed.

7.4 What is the best point in life for genetic screening?

A comprehensive genetic screening programme requires a combination of approaches because each individual approach has limitations and advantages. In contrast with the predominantly sporadic risk of a chromosomal disorder or congenital malformation, the risk of inherited disease is lifelong, detectable at any time, may affect every pregnancy and involves other family members. Ideally, people with such risks should be identified before they start a family, so that they can make an informed choice among the options available and prepare themselves for the associated stresses.

In most industrialized countries, screening for genetic reproductive risk is integrated into antenatal screening. The approach is considered efficient because only women who will actually have children are tested, at a time when the result is highly relevant to them. However, Box 7.1 shows that antenatal screening is unsatisfactory as the only screening approach. Its limitations are particularly

---

**BOX 7.1 Limitations of genetic screening in the antenatal clinic**

- The option of whether to undertake a pregnancy at all is no longer open
- Choice is unnecessarily urgent, difficult, and painful
- Some women come too late for prenatal diagnosis to be possible
- Most women are identified too late for first trimester prenatal diagnosis
- Some carrier tests are more difficult to interpret during pregnancy
- There is no time to correct clinical or laboratory errors
- Hurried decisions may be regretted later
- Rapid staff turnover and lack of staff with specific responsibility for screening make a consistent policy difficult

---
important in the Eastern Mediterranean Region, for social and religious reasons. What then is a better approach?

The experience of the Cyprus Thalassaemia Control Programme is informative on this point. About 16% of Cypriots carry β-thalassaemia trait, and carrier screening, with the option of prenatal diagnosis and selective abortion has proved generally acceptable in Cyprus [239]. A proposal to introduce mandatory pre-marital testing was discussed by the Cypriot parliament towards the beginning of the programme, but rejected as unconstitutional. Consequently, most couples were screened only during pregnancy (as in many industrialized countries). However, the Archbishop of Cyprus questioned the morality of screening only during pregnancy, because it leaves women little alternative to prenatal diagnosis and abortion of an affected fetus. His view was that couples should be made aware of their risk earlier, so that they could choose from the full range of possible options. He therefore decreed that all couples wishing to marry in church must show a pre-marital certificate. The premarital certificate does not give results, which are confidential. It simply certifies that the couple have been tested for thalassaemia in a government laboratory and counselled appropriately [237,239]. Thus, the Cypriot Church effectively imposed mandatory, but non-directive, pre-marital thalassaemia testing for ethical reasons.

The moral argument for pre-conception or pre-marital carrier testing may be particularly powerful in the Eastern Mediterranean Region, because of religious and cultural reservations about termination of pregnancy and the timing of termination. If couples are to consider the options of family planning or early prenatal diagnosis, they need to be aware of risk before they start a pregnancy. Information, screening, and basic genetic counselling should become part of primary health care (see Chapter 6).

7.5 Genetic screening tests in antenatal care

7.5.1 General

The antenatal screening tests that are routine in many industrialized countries (Box 7.2) include several aimed at preventing congenital and genetic disorders. Box 7.3 lists some tests that may be appropriate for antenatal screening in the Eastern Mediterranean Region.
BOX 7.2 Antenatal screening tests* that are routine in many industrialized countries

1. Ultrasound scan for fetal viability, number, dates. Exclude, for example, ectopic pregnancy, hydatidiform mole
2. Blood tests including: Haemoglobin
   - ABO and rhesus group
   - Rubella antibodies
   - Hepatitis B
   - Offer of HIV testing
3. Carrier screening for:
   - Haemoglobin disorders
   - Tay–Sachs disease
   - Cystic fibrosis (some centres)
4. Maternal serum screening for risk of neural tube defect or Down syndrome
5. Routine fetal anomaly scan

* Includes all routine tests at advanced centres. Some of these tests are provided for most pregnant women under most circumstances.

---

BOX 7.3 Suggested antenatal screening tests for the Eastern Mediterranean Region

- Scan for fetal viability, number, dates. Exclude ectopic pregnancy, hydatidiform mole.
- Blood tests including: Haemoglobin
  - ABO and rhesus group
  - Hepatitis B
  - Syphilis and toxoplasma
  - Iodine deficiency

(Rubella should be screened for prior to pregnancy: vaccine is available)

- Carrier screening for haemoglobin disorders (relevant to clinical management of the mother)
- Scan for fetal position to facilitate labour and to detect conditions amenable to early management after birth, e.g. urinary tract anomalies

---

7.5.2 Screening for risk of Down syndrome

Antenatal screening for risk of Down syndrome illustrates some of the issues involved in choice of a screening policy.
In industrialized countries, amniocentesis and fetal chromosome studies were initially offered to women at highest risk (pregnant women over 40 years of age, those who already had an affected child, or those who carried a chromosomal rearrangement). As laboratory capacity increased, the maternal age limit was lowered.

However, demographic change reduced the proportion of Down syndrome children born to older women in industrialized countries and led to a search for screening tests that could be offered to younger women. Complex maternal serum screening tests [240] are now becoming widespread. They arose from routine maternal serum alphafetoprotein screening for fetal neural tube defect: it was incidentally noted that when the pregnancy outcome was a child with Down syndrome, a low maternal serum alphafetoprotein had usually been recorded during pregnancy. It was subsequently found that serum unconjugated estriol was relatively low, and human chorionic gonadotrophin relatively raised, in stored maternal sera from these cases. For each pregnant woman, the results of two or all of these assays can be integrated mathematically with maternal age and ultrasound dating, to derive a statistical risk of Down syndrome in the fetus. A group of about 5% of pregnant women carrying about 60% of Down syndrome fetuses may be identified in this way [241] and offered definitive prenatal diagnosis.

Maternal serum screening is now requested by some women in Eastern Mediterranean countries, mainly for reassurance. However, several features of the test should be taken into account before considering it for use in the Region.

- Maternal serum screening is done at 16 weeks gestation, and therefore when positive leads on to mid-trimester amniocentesis, and selective abortion at around 20 weeks gestation.
- Over 95% of the 5% of women found to be at sufficiently increased risk for the offer of amniocentesis have a healthy fetus, i.e. the “false positive” rate is extremely high.
- The false negative rate is also high: about 40% of Down syndrome infants are born to women with a “negative” result.
- All laboratory methods involved must be accurate, with external quality control, and results must be integrated using a computer programme. The significance of results may differ in different populations, and standards for European populations cannot be assumed to apply in the Eastern Mediterranean Region.
• Unless a laboratory is doing a large number of tests, the results may be unreliable. There may also be strong commercial motivation to over-use maternal serum screening in private obstetric practice.

These facts can be difficult for health workers and patients to understand, and very careful information on the meaning of the test is necessary for both. Studies in the United Kingdom have revealed many problems associated with use of the test at the population level.

If the offer of pregnancy screening for Down syndrome were to be considered in the Eastern Mediterranean Region, maternal age appears to be a better indicator than maternal serum screening, in view of the very limited diagnostic facilities, and the large proportion of affected children born to older mothers. It also allows prenatal diagnosis in the first trimester of pregnancy. When individual younger mothers request maternal serum screening, they should be informed of the above limitations.

7.6 Conclusion

A family-oriented approach appears particularly suitable for detecting genetic risks in the Eastern Mediterranean Region populations due to their special family structure (large family size with multiple consanguineous marriages). The diagnosis of an affected person may permit screening of other family members for increased genetic risk. The first step towards detection of affected persons is sensitization of health care professionals in primary health care, secondary or tertiary care facilities, or special institutions for the mentally retarded, deaf-mute, blind, or other handicaps. The second step is referral to specialist centres with appropriate facilities for definitive genetic diagnosis.

Population screening may be considered for some common and potentially serious conditions for which cost-effective prevention and treatment strategies are available. This approach requires, as a prerequisite, adequate education of the public and proper training of the health care professionals involved. Early testing (e.g. premarital) provides a wide range of options where prenatal diagnosis and selective abortion are unacceptable.
Chapter 8
Genetic counselling

8.1 Introduction

Genetic counselling is inseparable from genetic diagnosis [1]. It aims to replace misunderstandings about the causes of genetic disease with correct information, and to increase people’s control of their own and the family’s health by informing them of the resources available for diagnosis, treatment, and prevention. Although counselling has a role in many medical consultations, it is particularly important in medical genetics because of the often predictive nature of genetic information, the implications for other family members, the difficult choices that sometimes have to be made, and the important ethical problems that can be involved.

Genetic counselling often relieves anxiety by excluding risk. For example, couples with a child with a congenital or genetic disorder, or who have lost a child, or who have such cases in the family, may hesitate to have (further) children because of worry about a recurrence. However, their reproductive confidence is restored if investigations show that the disorder is not in fact inherited, or that the risk of recurrence is small. On the other hand, genetic counselling may also inform people of risks that they hitherto knew nothing about, and can present them, and their advisers, with moral dilemmas that they may be ill-prepared to face.

8.2 Dilemmas in genetic counselling

Box 8.1 shows that specialist genetic knowledge, training in counselling skills, time, ability to communicate, and back-up by a medical geneticist or trained genetic counsellor are all needed for genetic counselling.

It is often assumed that medical training equips doctors to provide adequate genetic counselling, but in fact current teaching methods rarely prepare them to discuss complex issues with their patients in order to help the patients reach their own decisions (see Chapter 13). The responsibility involved in genetic counselling should not be underestimated. Genetic diagnosis is often difficult in
BOX 8.1 Main components of genetic counselling

1. A correct diagnosis in the presenting family member.
2. Explanation of the nature and prognosis of the disorder, and the treatment available and where to find it.
3. Estimation of genetic risk for parents and family members. This requires drawing up a family tree. It may also require investigations on other family members.
4. Communication of genetic risks, and the options for avoiding them:
   • the chances for parents and other family members of passing the disorder on to (other) children, and explanation of the risk;
   • options for avoiding (further) affected children: techniques, problems, risk of error, complications.
5. Support for the individual or couple in making the appropriate decision.
6. Accessibility for long-term contact: people at risk often need counselling and support at several points in their life.

view of the enormous diversity of the conditions involved, and misdiagnosis and misinformation can have disastrous consequences for individuals and their families. Furthermore, new medical possibilities created by the rapid advance of genetic technology may need to be included in genetic counselling, often before the ethical and moral dilemmas they involve have been adequately considered by society. The most obvious example for Eastern Mediterranean societies at present concerns the acceptability or otherwise of prenatal diagnosis and selective abortion, on account of genetic risk.

Table 8.1 summarizes the possibilities presently open to people who have been informed that they are at high risk of having children with a serious inherited disorder. It illustrates the challenges involved in genetic counselling, because all the available choices can involve difficult moral and social problems, and in most cases there appears to be no "right answer". On the other hand, once people understand their risk they cannot escape from choosing among the options in the table.

In practice, people's options are greatly influenced by the stage in life at which they learn of their risk, and by the availability and social acceptability of prenatal diagnosis. It is still unusual to learn of a major genetic risk before marriage, or before starting a family (though this is possible for carriers of haemoglobin disorders, Tay-Sachs disease, cystic fibrosis, and some relatives of
TABLE 8.1 Possible options for couples who find they are at risk of having children with an inherited disorder

<table>
<thead>
<tr>
<th>Time of discovering risk</th>
<th>Genetic abortion acceptable</th>
<th>Genetic abortion unacceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before marriage</td>
<td>Not marry</td>
<td>Not marry</td>
</tr>
<tr>
<td></td>
<td>Not marry another carrier</td>
<td>Not marry another carrier</td>
</tr>
<tr>
<td></td>
<td>Marry as usual</td>
<td>Marry as usual</td>
</tr>
<tr>
<td>After marriage</td>
<td>Separate and find a non-carrier partner</td>
<td>Separate and find a non-carrier partner</td>
</tr>
<tr>
<td></td>
<td>Have few or no children</td>
<td>Have few or no children</td>
</tr>
<tr>
<td></td>
<td>Have children as usual</td>
<td>Have children as usual</td>
</tr>
<tr>
<td></td>
<td>Use prenatal diagnosis and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>selective abortion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use assisted reproduction</td>
<td></td>
</tr>
</tbody>
</table>

Note: This table applies primarily for recessively-inherited disorders. The full range of choices listed here is not, and can never be, open to carriers of, e.g. X-linked or dominant disorders.

people with X-linked or dominant disorders). At present worldwide, most couples learn of their risk only after the diagnosis of an affected child. This limits their choices to those shown in the lower half of the table.

In most industrialized countries, it is now generally considered that couples at high genetic risk should have access to prenatal diagnosis, with the option of selective abortion, when this is feasible. It is also recognized that selective abortion is not an optimal or easy solution but simply the lesser of two evils, that early prenatal diagnosis is preferable to later prenatal diagnosis, and that not all couples at risk of having children with a serious disorder feel that prenatal diagnosis is the right choice. However, these attitudes have evolved only gradually, and in association with increased use of family planning and abortion law reform. It is difficult for people to deal with the idea of prenatal diagnosis unless they are already used to the concept of controlling their own reproduction, a social change that takes time.

When genetic diagnosis began to be developed in the 1950s, the options available to couples at reproductive risk were to ignore the information and hope for the best, to remain unmarried or separate, or to limit their reproduction using family planning, the same choices as those now available in most countries of the Region. It soon became clear that when options are so limited, most people choose either to avoid or ignore information on risk, or to limit the size of their family [242,243]. Family planning is only now becoming widely available in the
Eastern Mediterranean Region, and it is important to collect information on its use by couples at genetic risk in different countries.

### 8.3 Ethics in genetic counselling

Because the choices facing people at genetic risk can be so difficult, and can have lifelong consequences, experienced genetic counsellors generally consider that informed individuals or couples are themselves the best judges of what to do (see Box 8.2). Consequently, professional ethical practice in genetic counselling, as it has gradually evolved during the past 20 years, can be summarized under three simple headings [9,244], namely:

- the autonomy of the individual or couple
- their right to complete information
- the highest standard of confidentiality.

It is considered that genetic counselling should be non-directive, and that the genetic counsellor’s main role is to provide people at risk with full information.

---

**BOX 8.2 Reasons why genetic counsellors consider that genetic counselling should be non-directive**

- People at risk often have first-hand experience of the condition in question—unlike most of their advisers.
- People at risk have to learn all the facts, think the issues through, and actually reach a decision that they must live with for the rest of their lives.
- The “right” choice for given individuals among the options actually available is determined by many factors, including their social and religious attitudes, personal experiences, economic and educational level, and family and reproductive history.
- Since most situations involve a statistical risk, the “rightness” or “wrongness” of a particular choice can be assessed only in retrospect. For example, the majority of couples who take the risk of another pregnancy do not have an(other) affected child: in retrospect, this was the right choice for them.
- Genetic risks may take years to materialize, during which new and more acceptable approaches for avoiding them may become available (see Chapter 9). Irreversible “solutions”, such as change of partner or sterilization may therefore be regretted.
- Doctors and other professionals are no more, or less, qualified than their patients to make moral choices of the type generated by awareness of genetic risk.
give them time for consideration, and support them in making the decisions they feel to be morally right for themselves. Genetic counsellors may also assist in the evolution of public attitudes by reporting their patients’ views and choices back to society [9].

The ethical approach to genetic counselling in industrialized countries has been strongly influenced by the observation that genetic concepts are widely misunderstood and can easily be incorporated into harmful social prejudices, such as the concept of superior and inferior races, or into unacceptable coercive policies such as forcible sterilization. In order to avoid stigmatization of people with a genetic risk, genetic information is considered to be the highly confidential property of the individual and the family.

8.4 Genetic counselling in the Eastern Mediterranean Region

Sensitive services like genetic counselling cannot be transferred in entirety from one social context to another. In the Eastern Mediterranean Region, social and religious reservations about intervention in pregnancy could lead to a rather different evolution of opinion about who should make decisions and the range of services that should be available. The wide range of family and social structures, religious and legal conventions, and economic resources within the Region may also lead to different conclusions in different countries. One aim of this document is to assist development of attitudes and approaches by setting out the facts (including present experience with genetic counselling and prenatal diagnosis, and analysis of their costs and benefits) in as objective a manner as possible.

For this purpose it may be helpful to examine the options available for people with a genetic reproductive risk in more detail. The discussion will focus mainly on the haemoglobin disorders, because the fact that carriers can be detected and advised of any reproductive risk either before or after marriage opens a wide range of choices for consideration. There is also extensive experience of the choices that people make in practice. However, the variety of inheritance patterns should also be kept in mind. For example, a female carrier of haemophilia or Duchenne muscular dystrophy has (independent of the genetic make-up of her partner) a 25% risk of an affected child in each pregnancy, so any marriage would be at risk. In the absence of prenatal diagnosis, the only options open to such women are not to marry, not to have children, or simply to hope for the best.
How can information be obtained on approaches that are acceptable or unacceptable to a particular population? One possibility is through public meetings, discussions, and questionnaires addressed to interested professionals and the general public. However, this presupposes an informed public (which exists in very few countries worldwide at present) so the approach also requires a substantial component of public education. The most extensive such consultation exercise to date was carried out in the early 1990s by the Canadian Royal Commission on New Reproductive Technologies [245]. The results (like those of other surveys) showed that a large majority, including many who might not themselves use the service for religious or other reasons, approved of the availability of prenatal diagnosis and termination of pregnancy for serious genetic disorders.

A second possibility is to seek the views of informed people who are themselves at genetic risk. However, there is a difference between what people think they would do and what they actually do. A more objective approach is to observe and report the choices that people at risk actually make. Data obtained in all these ways is included in the discussion below.

Programmes for prevention of haemoglobin disorders in Europe and Cyprus now include the option of prenatal diagnosis and selective abortion, but in some countries carrier screening and genetic counselling was introduced either before prenatal diagnosis was possible [239,246,247] or before it was legal [247]. This early experience produced useful information on the acceptability of some alternative approaches in industrialized societies.

8.5 Premarital screening and choice of marriage partner

On first considering the facts, it often seems that affected births can be prevented if couples at risk are identified prior to marriage, on the assumption that they will then decide to separate and each find another, non-carrier partner. However, we understand too little of how most marriages come about to make any valid assumptions about the effect of genetic information on choice of partner. In all societies, marriage is a complex social phenomenon that involves many family members besides the prospective couple, and partners are usually selected because of a strong personal preference, for valid family reasons or for traditional reasons, or a combination of all three.
Before prenatal diagnosis was feasible, a research study of the effect on choice of marriage partner of informing young people and their families of their carrier status was carried out in the Arta area of Greece, where 20% of the population carry either thalassaemia or sickle cell trait. All young people of marriageable age were screened and counselled, and counselling contact was maintained for a two-year period. When the pattern of marriages was assessed at the end of this period, screening had had no measurable effect on choice of partner [246].

In the same period a similar approach was tried in Cyprus, with the addition that marriages between carriers were actively discouraged. This proved unacceptable to the population and was soon abandoned “because of evasions” [239]. Once prenatal diagnosis became possible for thalassaemia it was made available within the Cypriot health service and confidential premarital screening was mandated. It was then found that 98% of couples at risk detected prior to marriage proceeded to marry, even though Cypriot parents often have considerable influence on choice of partner. Nevertheless, couples used the information on genetic risk in a variety of ways to obtain a healthy family and the annual number of new births of thalassaemic children has fallen almost to zero in Cyprus. Less than 5% of this fall is due to separation of engaged couples, about 80% is due to prenatal diagnosis and selective abortion, and around 20% is because couples at risk have rather fewer children than couples not at risk [237]. In both Cyprus and Sardinia the population is now well-informed, and has gained confidence that the thalassaemia control programme involves little, if any, coercion. There is increasing popular demand for carrier testing in high schools, so that young people and their families can take information on carrier status into account at an earlier stage in the choice of marriage partner [248]. It will be of great interest to follow the long-term results of these Mediterranean social experiments.

In Canada, a programme of information and screening for carriers of Tay-Sachs disease or thalassaemia in high schools in Montreal has proved highly acceptable, and is also informative about pitfalls in predicting how people will use genetic information [249]. A sample of the young people screened were followed up with a questionnaire that included the questions, “Do you think that a couple planning to marry who found they were both carriers would change their marriage plans? Would you change your own marriage plans?” Interestingly, almost 80% thought that other couples would change their marriage plans, but only 10% thought they would change their own plans. Clearly, it is all too easy to
underestimate the importance of other people’s inner lives, and practical experience is the only reliable guide to how people are prepared to use information on genetic risk.

Thus, on the one hand there seems to be a strong case for early carrier diagnosis and genetic counselling so that couples at genetic risk and their families can make an informed choice whether to separate or stay together. On the other hand, knowledge of a genetic risk may be insufficient to change one of the most significant of all human decisions, choice of a lifetime partner.

Prenatal diagnosis is now available in all the countries whose experience has been drawn on above. Assessment of its desirability from the medical, religious and social points of view is only now beginning in the Eastern Mediterranean Region, and even if it were decided to make prenatal diagnosis available tomorrow, the decision would take years to implement because of the lack of trained personnel and facilities for genetic diagnosis in the Region. Therefore, for practical purposes the options for most couples at genetic risk in the Region are limited to those in the right hand column of Table 8.1.

In view of these circumstances, premarital testing for haemoglobin disorders with the aim of reducing the frequency of at-risk marriages may present itself as the most feasible approach at present for reducing the birth rate of thalassaemic children. Premarital screening is being considered in a number of countries and has effectively been mandated in some parts of the Region. Follow-up studies of counselled couples are essential to find out how they use knowledge of risk, both in choice of partner, and in subsequent reproductive behaviour. Although the experience summarized above showed little effect of premarital screening on the frequency of at-risk marriages, results may differ in societies with a different social and family structure, especially if a directive approach is adopted in genetic counselling. If the knowledge leads couples at risk to limit their family, it could have a very significant effect on the birth rate of thalassaemic children.

The developing thalassaemia control programmes in the Eastern Mediterranean Region have the potential to answer many questions on the social and ethical implications of genetic screening in the Region. Appropriate research studies would help to inform public and professional opinion, and contribute to policy decisions in the countries of the Region.
8.6 Choices for couples at risk detected by premarital screening

One possibility is to separate and each find a new, non-carrier partner. Research data are needed on the frequency of this choice, its relationship to the counselling approach adopted, and the short-term and long-term effects on individuals and families. Questions that need to be answered include the extent of the social embarrassment or stigma that rearranging a planned marriage can cause for young people and their families, and the risk of the problem recurring because one of the new partners found is also a carrier. This risk is not insignificant: if population carrier frequency is 6%, the chance that one or other of the new partners is a carrier is 12%—or higher if the new partner is a relative.

An important question when prenatal diagnosis is not available is whether decisions should be left to the young people and families concerned, or whether health workers should actively try to prevent carrier couples from marrying. Data is needed on views and practice at different centres, and long-term follow up of couples at risk who decide to marry, as well as of those who separate, is very important.12

A second possibility is to marry as planned, but avoid having children altogether. This choice is particularly difficult in a strongly family-centred society, as in most of the Eastern Mediterranean Region. It is also technically difficult unless high quality family planning is readily available. A more realistic option for married couples at risk is to limit their family size. If they limit themselves to two healthy children, 56% of them will never have an affected child (see Figure 7.2). With hindsight, these couples could feel they had made a good decision.

Another possibility is to marry, and wait to have a family until appropriate methods for prevention become available. For example, when Cypriot couples at risk were informed that prenatal diagnosis would become available in the near future, many postponed conceiving until they could use the service [239]. At present the average reproductive span of an Eastern Mediterranean couple is more than 20 years. Within this period, present methods for prenatal diagnosis may

---

12 For objective results in such delicate studies, follow-up should be conducted by someone perceived by the families to be highly sympathetic, and committed to confidentiality. If a directive approach has been used in genetic counselling, this person must be unconnected with the counselling team.
become more widely accepted and new techniques for fetal treatment or pre-implantation diagnosis will probably be developed (see Chapter 9).

A final possibility is to marry and have a family as usual. This seems to be a common choice in the absence of alternatives that are acceptable to families, but research data is very much needed.

8.7 Choices for couples at risk who are already married

In practice, at present, the majority of couples who seek genetic counselling in the Eastern Mediterranean Region are already married, and have one or more children with a (possible) genetic disorder (such as a rare metabolic disease, thalassaemia, cystic fibrosis, haemophilia or muscular dystrophy). Once a genetic diagnosis is made, the parents learn two main things.

- First, treatment is not available or is complex, expensive and lifelong, and may involve regular long journeys to an expert centre. Even when part or all of the medical treatment is provided free, there are heavy emotional and financial burdens for the family. Many families have inadequate resources to cope with the problems of obtaining treatment and must decide, implicitly or explicitly, to allow their affected child to die. However, an untreated or partially treated child may be ill for years before succumbing to the disorder, with all the sadness that entails.

- Second, there is a high (usually one in four) risk of the same disorder affecting any other child they may have. Even couples who can provide for one affected child may find it impossible to manage two, and the information is bound to have a major impact on their reproductive life.

It is instructive to consider the options available to them, with particular reference to the woman’s position.

A choice to have no further children may be relatively simple for couples who already have healthy children, but is extremely difficult for couples who only have sick children. The woman is likely to feel she cannot fulfil her expected role and is inferior to other women in the family, while, in some cases, her husband may be under pressure to divorce her or take a second wife in order to ensure healthy children. The decision to have no more children also requires access to reliable and highly effective family planning.
Another option is to continue to have children and take the risk. In the absence of prenatal diagnosis and ready access to family planning, this is the route that most families in the Eastern Mediterranean Region have had to pursue until recently. Some couples feel that this is the path God has laid down for them, but others suffer great anxiety and distress.

When a couple is unlucky and has further affected children, parents can become chronically anxious or depressed, and there may be family breakdown and intensified pressure for divorce. A father can to some extent escape these problems through his outside life, but the mother often has no means of escape, since she usually must look after the children. Despite the fact that (at least where autosomal recessive diseases are concerned) both partners are equally carriers, the problem is usually perceived as attached to the woman, a misconception that may be ironically confirmed when a second wife is not a carrier and her children are healthy.

Statistical information is needed on the relative frequency of divorce among couples at increased genetic risk in the Eastern Mediterranean Region: in industrialized societies there is no convincing evidence of an increased divorce rate among couples who discover a genetic risk after marriage.

Other options for having children while avoiding a known genetic risk, such as artificial insemination by donor, egg donation or adoption, have not so far proved popular in any society and are unacceptable in many communities of the Region.

Numerous families with, for example, children with thalassaemia, sickle cell disorders, haemophilia or muscular dystrophy attend clinics in the Region. They provide an opportunity for research on the counselling provided for retrospectively-detected couples and the extent to which they understand it, the availability of family planning and the extent to which they use it, the number of healthy and affected children that they have after they have been informed of the recurrence risk, and any effects on the stability of the marriage. It also seems reasonable to ask parents whether and how their difficulties might be reduced by the availability of prenatal diagnosis, and to inquire into their attitudes towards selective abortion.

---

13 In studies of this kind it is not enough to report the reproductive behaviour of the parents of affected children: controls are needed. The reproductive behaviour of older and younger siblings of the parents, who do not have affected children, may be a suitable control.
All medical programmes, including genetic prevention programmes, must operate within existing legal and social frameworks. However, technology can develop rapidly, while legal, social and religious attitudes evolve more slowly. This is the case with medical genetics at the moment, and it is a priority for interested professionals to produce research information that may be taken into account in development of social attitudes.

8.8 Genetic counselling and customary consanguineous marriage

The question of how to provide genetic counselling in the context of societies that favour consanguineous marriage also creates dilemmas for families and health workers. Clearly any genetics programme in the Eastern Mediterranean Region must adopt a sensitive and realistic approach, and should recognize the shortage of research information on the role of customary consanguineous marriage in the stability of the family and society in the Region.

Discussion of statistical associations between marriage type and mortality and morbidity, as in Chapter 5, can give the impression that any consanguineous marriage will participate to some extent in the negative effects described, but this is not the case. The great majority of families where the parents are related suffer no adverse effect. The observed increase in average childhood mortality and morbidity in such families is largely because relatively severe effects in a limited number of families shift the average figures for the whole group. It follows that medical attempts to help families with genetic problems should focus on identifying families at particularly high risk and providing them with genetic counselling and access to appropriate services.

Nevertheless, in some countries efforts have been made to discourage consanguineous marriage through public information programmes emphasizing the associated genetic risks. These programmes arise from the perception that recessively-inherited diseases (especially rare and unusual types) are indeed unusually common in Eastern Mediterranean populations. There is an urgent need for prevention, but appropriate genetic counselling services are rudimentary or non-existent. It may then seem that altering the traditional behaviour of the population is the only possible way to reduce genetic disease incidence.
In view of our ignorance of the social causes and consequences of customary consanguineous marriage (see Chapter 5), attempts to reduce its frequency in the population as a whole on genetic grounds run the risk of doing more harm than good. They disturb customary marriage arrangements when the majority of families would come to no harm in any case, and are incompatible with the concept of non-directive genetic counselling. Research in the Region is urgently needed because policies relating to consanguineous marriage should be firmly grounded in an understanding of its social, as well as its genetic, role.

Discussions in the United Kingdom with families who have had pressure put on them against consanguineous marriage [250] led to the conclusions shown in Box 8.3.

Individual case histories are also instructive. For example, a man married to his first cousin had three children, two with severe sickle cell disease. On being (mis)informed that the children were sick because he had married his cousin, he divorced her and took an unrelated wife. However, they had two further children with sickle cell disease. He became extremely distressed when the inheritance of the disorder was finally explained to him as he had not wanted to divorce his first wife and, at the least, with correct information he could have ensured his second wife was not also a carrier [251]. Another example is a kindred reported from

---

**BOX 8.3 Reasons for caution in mounting public information programmes aimed at discouraging consanguineous marriage**

- Pressure against cousin marriage rarely alters what people actually do, although it can make them feel uncomfortable about it.
- If people are told their children are sick because they are related, it causes great unnecessary distress, may alienate them, and makes it more difficult for them to understand the real explanation.
- Where cousin marriage is common, people are aware that most couples of cousins have perfectly healthy children. If they are told not to marry a cousin because their children may be sick, they may become confused and could lose confidence in medical advice.
- Avoiding cousin marriage does not guarantee that children will not have a congenital disorder. Unrelated couples who have affected children may lose confidence in medical advice.
- People do not attend genetic counselling if they think they will be criticized and their cultural conventions attacked.
Gaza, Palestine, with an apparently unique recessive form of progressive cone-rod dystrophy combined with amelogenesis imperfecta [252]. On the one hand, continuation of the tradition of consanguineous marriage is disadvantageous for this family, but on the other hand they may have little choice, since attempts to find a partner from an unrelated family are likely to fail, given the obvious detrimental symptoms of the disorder. Publicity focusing on the deleterious genetic effects of consanguineous marriage is only likely to increase the stigmatization of such families.

8.9 The clinical approach for consanguineous marriage

In advising related couples, or relatives who wish to marry, a geneticist always first draws up a detailed family tree. Families may then be seen to fall into two groups. The first and largest group consists of related couples who know of no evidence of a genetic disorder in the family. These couples may be informed of the observed average additional genetic risk associated with cousin marriage. In the industrialized world, most related couples who consult a clinical geneticist are planning to marry or are already married. There are no published reports on their subsequent choices, but the impression is that most find the genetic counselling reassuring, and proceed to marry and set up a family. Clear information on this point is particularly important in the Eastern Mediterranean Region, since so many families are involved.

The second, smaller group are those where it seems that a family member may have, or may have died from, a genetic disease. Investigations are then carried out to establish the true diagnosis, if possible. Often the condition in question proves to have a negligible recurrence risk, e.g. Down syndrome or a neural tube defect, or not to be inherited, e.g. a disorder due to a new mutation like osteogenesis imperfecta. In such cases the couple can be appropriately reassured.

If the relative does in fact suffer from a dominant, X-linked or recessively-inherited disorder, it may be possible to offer the couple carrier testing. They can then make a decision about whether to marry, or to have children, on the basis of definite information. Even when carrier testing is not possible, if the inheritance pattern is clear, the couple can be informed of their statistical risk of having children with the disorder in question. Figure 8.1 shows two examples of how such risks can be calculated for a recessively-inherited disorder, whether for
Example 1. Uncle or aunt has a recessively-inherited disorder

Example 2. Sibling of one partner has a recessively-inherited disorder

FIGURE 8.1 Calculation of genetic risk for consanguineous couples from family history

Example 1. Uncle or aunt has a recessively-inherited disorder

The number within each symbol shows the statistical risk to each relative of being a carrier on the basis of this relationship alone. The population risk must be added to this figure, and also applies to unrelated spouses.

Chance of healthy aunts and uncles being a carrier = 66%
Chance of each of their offspring being carriers = 33%
Chance that both first cousins are carriers = 33% of 33% = 10.9%
Chance in each pregnancy of a similarly affected child = 10.9 / 4 = 2.7%

Example 2. Sibling of one partner has a recessively-inherited disorder

The number within each symbol shows the statistical risk to each relative of being a carrier on the basis of this relationship alone. The population risk must be added to this figure, and also applies to unrelated spouses.

Chance of affected person's healthy sibling being a carrier = 66%
Chance that affected person's first cousin is a carrier = 25%
Chance that both the couple indicated above are carriers = 25% of 66% = 16.5%
Chance in each pregnancy of a similarly affected child = 16.5 / 4 = 4.1%
relatives of an affected individual or of a carrier detected, for example, by population screening.

Once a single gene disorder has been diagnosed within a family, over 50% of close relatives will also be carriers (see Table 7.1). It is, therefore, basic genetic practice to offer genetic counselling (and carrier testing when this is feasible) to as many family members as possible. The same approach is indicated whether consanguineous marriage is common or rare, so genetics services can be developed without undue emphasis on particular marriage patterns. This may be advantageous when efforts to discourage consanguineous marriage have created some popular confusion about the concepts of genetic counselling.

However, in principle, a convention of cousin marriage could make family-oriented genetic counselling particularly effective, for two main reasons. First, unusually large numbers of carriers of the presenting disorder may be detected within the family. Carrier testing may, for example, permit early detection of many individuals at risk for some conditions (such as family cancer syndromes) where surveillance and early treatment could be beneficial.

Second, when cousin marriage is common within the family, carriers of recessive disorders are at particularly high risk of making an at-risk marriage. Many carriers will already be married and some couples at risk may be identified in time for prospective reproductive counselling. Many will be children or not yet married, and early information on carrier status may be taken into account to avoid further at-risk marriages within the family.

Detection of a carrier by population screening also identifies a family at high genetic risk who could appropriately be offered extended family studies.

There is as yet very little published research on strategies for genetic counselling in the Eastern Mediterranean Region. A range of information is needed about the potential of a family-oriented approach, and common recessively-inherited disorders like thalassaemia and sickle cell disease (where carrier detection is feasible and cheap) provide a convenient model. Studies of a limited number of families with an affected child would allow calculations of the proportion of carriers and couples at risk who could theoretically be detected by extended family studies. The same research studies might also show what proportion of families would welcome extended family studies, and their views about how they could best use information on reproductive risk. A family-oriented approach is labour-intensive, but an analysis of costs and benefits is needed as it might yield exceptional benefits in an Eastern Mediterranean Region setting.
Even if it becomes clear that the regional kinship structure offers exceptional opportunities for effective genetic counselling, these can be exploited only if there are adequate genetic diagnostic facilities, and trained genetic counsellors who have the confidence of the population. The question therefore arises of how the limited existing resources can be used most efficiently. One possible policy may be to systematically encourage the earliest possible diagnosis of affected children, followed by genetic counselling for the extended family. The approach has important implications for paediatric services. Paediatricians need:

- Support in further developing their genetic diagnostic skills.

- Access to genetic laboratory services, including chromosome, DNA and biochemical studies, and postmortem diagnosis.

- The assistance of trained associate genetic counsellors, e.g. nurses, for taking genetic family histories, drawing pedigrees and providing genetic counselling for the numerous families who need it. Training courses for such genetic counsellors would need to be developed at an early stage.

8.10 Conclusion

There is a clear need for genetic counselling services in the Eastern Mediterranean Region, but the most appropriate and efficient approaches have yet to be defined. Research is needed in the Region on almost all aspects of genetic counselling.

The ethical principles governing genetic counselling need to be reviewed in the light of social and religious structures in the Region. This is particularly indicated for the issues surrounding prenatal diagnosis of genetic disease, and counselling in relation to customary consanguineous marriage.

Current legal and religious attitudes in the countries of the Region towards the options available to people at genetic risk should be reviewed.

Information is needed about the current views of professionals such as geneticists, paediatricians and obstetricians on whether genetic counselling in the Region should be directive or non-directive, on the range of options that are currently available, and the options that should be available to couples at high genetic risk.

The social impact of the genetic counselling at present provided to families with children with genetic disorders should be defined. Information is needed on
the counselling provided to the parents, their level of understanding of the information, and of the frequency of divorce, remarriage, use of family planning and further childbearing following genetic counselling. Information is also needed on the genetic counselling currently offered to members of the extended family.

The social impact of premarital screening for haemoglobin disorders should be investigated in those countries in which it is already practised. Identified couples at risk should be followed up to define the effect of information provided before marriage on the final choice of marriage partner, and subsequent reproductive behaviour. The social effects of the screening on the families should be defined.

The characteristic kinship pattern of Eastern Mediterranean societies suggests that an approach emphasizing correct diagnosis of the first presenting child (or adult) and genetic counselling for the extended family may be particularly appropriate and effective in the Region. This suggestion needs testing in different countries of the Region, through organized studies of families with specific disorders, using a common protocol.

A family-oriented approach has particular implications for paediatricians who need systematic updating in genetics and genetic counselling, access to genetic diagnostic services, and assistance with carrying out genetic studies of the extended families of the numerous children that they see with inherited diseases.

Appropriate counsellors should be trained in each country to undertake pilot studies of the feasibility of screening and counselling extended families, and of incorporating these approaches into paediatric and primary health care services.
Chapter 9
Prenatal diagnosis

9.1 Introduction

Prenatal diagnosis is recognized as an important option for couples at increased genetic risk in most industrialized countries [253,254]. However, the concept has only been accepted slowly over the past 25 years, and there is ongoing concern about its ethical and social implications [245]. The detection of fetal abnormality at any stage of pregnancy causes shock, guilt and grief for the parents and distress for medical and nursing staff. The decision whether or not to terminate an affected pregnancy is never taken lightly, even in communities where prenatal diagnosis and selective abortion are fully accepted. Selective abortion is performed only at the parents’ request and within the country’s general rules for therapeutic abortion, the main consideration being for the future and quality of life of the child. The aim of couples who request prenatal diagnosis is to obtain a healthy family: they see termination of pregnancy as the main cost of prenatal diagnosis, rather than its main benefit.

This chapter outlines the obstetric techniques commonly used in prenatal diagnosis, and touches on ethical issues and current research that could help couples at high risk to have healthy children in the future without recourse to the painful option of abortion.

In order to diagnose genetic disease in the fetus, it is usually necessary to obtain a sample of fetal tissue for analysis using an invasive procedure. The methods commonly used are chorionic villus sampling, amniocentesis and fetal blood sampling [253,255]. All require expert ultrasound guidance. So far, only chorionic villus sampling can be done reliably during the first trimester of pregnancy. Since this is particularly important in the Eastern Mediterranean Region, the timing of different procedures with respect to fetal age is given in Table 9.1.
TABLE 9.1 Timing of stages of pregnancy in relation to prenatal diagnosis

<table>
<thead>
<tr>
<th>Weeks from last menstrual period</th>
<th>Weeks of fetal life</th>
<th>Prenatal diagnostic test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st trimester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>Chorionic villus sampling feasible</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>→</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>2nd trimester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>12</td>
<td>Amniocentesis feasible</td>
</tr>
<tr>
<td>16</td>
<td>14</td>
<td>→</td>
</tr>
<tr>
<td>18</td>
<td>16</td>
<td>Maternal serum screening</td>
</tr>
<tr>
<td>20</td>
<td>18</td>
<td>Fetal blood sampling feasible</td>
</tr>
<tr>
<td>22</td>
<td>20</td>
<td>Fetal anomaly scanning</td>
</tr>
<tr>
<td>24</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>3rd trimester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

9.2 Fetal tissue sampling techniques

9.2.1 Chorionic villus sampling

The aim is to obtain a small sample of the developing placenta, which has the same genetic make-up as the fetus. Chorionic villus sampling can be done using either a catheter passed through the uterine cervix, or a needle inserted through the abdominal wall, at nine weeks of gestation onwards (Figure 9.1).

Advantages. Chorionic villus sampling has social advantages because it can be done in the first trimester of pregnancy. It also has technical advantages, since many fetal cells are obtained for analysis. DNA and biochemical methods can usually give a result for inherited diseases in a few days. Rapid diagnosis of abnormal chromosome number can also be achieved on direct preparations made immediately after sampling, or after between 24 and 48 hours in culture, so a diagnosis of Down syndrome or other abnormalities of chromosome number can
FIGURE 9.1 Chorionic villus sampling technique (CVS)

CVS at 9–12 weeks of pregnancy can be performed either transcervically using a catheter, or transabdominally. The procedure is always conducted under expert real-time ultrasound guidance. Microscopic examination of the material obtained at the bedside confirms that the tissue obtained is of fetal origin.

a) Transcervical CVS. A soft plastic catheter is inserted gently through the developing placenta under ultrasound guidance. Chorionic villi are aspirated using a syringe.

b) Transabdominal CVS. A needle is inserted under ultrasound guidance directly into the placenta, and villi are aspirated using a syringe.

Source. Reproduced from reference [225] with permission of the authors.
be reached by between 10 and 12 weeks gestation. However, between 10 to 20 days of culture are needed to obtain preparations of sufficiently high quality for detecting subtle changes such as chromosomal rearrangements.

Disadvantages. In a small proportion of cases, placental mosaicism can lead to a false-positive or false-negative cytogenetic diagnosis [255]. Therefore, most cytogeneticists use both direct and tissue culture preparations, which increases the expense of the test. In a few cases where some doubt remains, it is necessary to confirm the diagnosis by amniocentesis. This problem does not apply for biochemical or DNA analysis. Studies of the additional risk of fetal loss associated with chorionic villus sampling have given divergent results, ranging from 0.5% to 4.5% [256,257]. The wide range is thought to reflect variations in level of expertise at different centres: chorionic villus sampling requires an expert team. In experienced hands the fetal loss rate appears to be between 0.5% and 1% [258]. There is no evidence of an increase in obstetric complications. The possibility of an increased risk of limb malformation has been widely discussed [259]. There is evidence of an association between very early sampling (before the eighth completed week from the last menstrual period) and some fetal malformations [260] but any increased risk after the beginning of the ninth week of gestation has been virtually excluded [261]. It is therefore recommended to perform chorionic villus sampling only after the beginning of the ninth week of gestation at the earliest, and preferably only after the beginning of the tenth week of gestation.

9.2.2 Amniocentesis

The aim is to obtain a sample of amniotic fluid by transabdominal puncture (Figure 9.2).

Amniocentesis is conventionally done from 16 weeks gestation onwards. Between 15 ml and 20 ml of amniotic fluid are withdrawn, and the scanty fetal cells are separated and grown in tissue culture for between 2 and 3 weeks to obtain enough healthy cells for chromosome or DNA studies. Thus the result is usually obtained at between 19 and 20 weeks gestation.

Advantages. Amniocentesis is a tried and true procedure. It is simpler to perform than chorionic villus sampling, its risks are well known, and the cytogenetic

---

14 Although DNA diagnosis can be done directly on amniotic fluid cells, the failure rate is high because of the poor condition of most of the cells.
FIGURE 9.2 Procedure for obtaining a sample of amniotic fluid

Amniotic fluid is obtained by transabdominal needleling, usually at 16 weeks of pregnancy or later.

Source: Reproduced from reference [225] with permission of the authors.

make-up of the cells obtained reflect the fetus more directly than the placental cells obtained by chorionic villus sampling.

Disadvantages. The main disadvantage is the lateness of diagnosis. When amniocentesis is performed because of suspected abnormality following, for example, maternal serum or ultrasound screening, a diagnosis may not be reached before 20 weeks gestation or even later. Amniocentesis is considered to carry a 1% increased risk of miscarriage, and a slight increase in risk of respiratory distress and common mild, correctable orthopaedic deformities such as club foot [262].

With modern ultrasound guidance amniocentesis can be performed at 12 weeks gestation onwards, to achieve earlier diagnosis. Though amniotic fluid can be obtained at 11 weeks gestation, cells can be reliably cultured only after 12 weeks, giving a diagnosis at 15 weeks [263]. More information is needed about the risks of early amniocentesis, since one report suggests that the fetal loss rate may be higher than that associated with chorionic villus sampling [264].
9.2.3 Fetal blood sampling

Fetal blood sampling can be done safely only at or after 18 weeks of pregnancy. A fetal blood sample is obtained by ultrasound-guided transabdominal needle puncture of the fetal cord insertion (Figure 9.3).

At present, fetal blood sampling is most often used for rapid diagnosis of fetal chromosomal anomalies at 18 weeks gestation or more, since high quality chromosome preparations can be obtained from cultured fetal lymphocytes in three to four days. It has been found that between 10% and 30% of malformed fetuses detected by fetal anomaly scanning have a serious underlying chromosomal anomaly [265], so when a malformed fetus is detected, rapid fetal karyotyping may be indicated. Hence if an older woman presents late for antenatal care, or suspicion of chromosomal abnormality arises during fetal anomaly scanning at 19 weeks, a diagnosis can be obtained within the legal time limit for abortion in many countries. Fetal blood sampling is also used for a range of other indications, such as diagnosis of intrauterine infection by examining fetal antibodies [266].

Figure 9.3 Procedure for obtaining a sample of fetal blood

Fetal blood sampling is performed at or after 18 weeks of pregnancy. Fetal blood is usually obtained by needling the vessels in the placental insertion of the umbilical cord, under ultrasound guidance.

Source: Composite diagram based on reference [225] with permission of the authors.
### TABLE 9.2 Characteristics of techniques commonly used to obtain samples of fetal cells for prenatal diagnosis

<table>
<thead>
<tr>
<th>Method</th>
<th>Success rate (%)</th>
<th>Timing (weeks from last menstrual period)</th>
<th>Time to diagnose Karyotyping DNA</th>
<th>Fetal loss rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorionic villus sampling</td>
<td>&gt;89</td>
<td>&gt;×9</td>
<td>Hours to 10 days 48 hours</td>
<td>1</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>&gt;99</td>
<td>&gt;×15</td>
<td>14 days or more 2 to 16 days**</td>
<td>1</td>
</tr>
<tr>
<td>Fetal blood sampling</td>
<td>&gt;95</td>
<td>&gt;×18</td>
<td>3 to 4 days 48 hours</td>
<td>1–2</td>
</tr>
</tbody>
</table>

*At expert centre.
**May require cell culture.
Based on references [253,254].

**Disadvantages.** Fetal blood sampling is associated with late diagnosis, and requires a high level of expertise. At appropriate centres, the fetal loss rate is considered to be between 1% and 2% [254].

Table 9.2 summarizes the main advantages and disadvantages of current fetal sampling methods.

### 9.3 Ultrasound scanning for diagnosis of congenital malformations

A "dating" ultrasound scan is commonly used in obstetric practice for the limited purposes of confirming pregnancy, fetal viability and gestational age, for excluding ectopic gestation or hydatidiform mole, and for diagnosing multiple pregnancies. Only the grossest malformations can be detected by such “level 1” scanning. A formal “fetal anomaly scan” at around 19 weeks gestation when most fetal organs are well developed, taking time and using a check-list, is required to detect major congenital malformations [267]. Very careful training is needed, and a diagnosis of fetal abnormality should be confirmed by “level 3” scanning by an expert in fetal medicine.

Parents often request ultrasound scanning to exclude major fetal malformations, and in most cases fetal anomaly scanning provides the reassurance they seek. The finding of an abnormality by no means always leads to selective abortion; many abnormalities diagnosed before birth can have a good prognosis,
BOX 9.1 Indicators in pregnancy of increased risk of fetal malformation

- Maternal insulin-dependent diabetes
- Previous fetal abnormality
- Twins
- Raised maternal serum alphafetoprotein
- Exposure to teratogenic drugs (e.g., antiepileptic drugs)

especially if parents and doctors become aware of the problem in time to arrange delivery at a centre with paediatric surgery immediately on hand. Abnormalities of the renal tract, which are common and readily detected, are a good example: unilateral abnormalities can usually be successfully treated, but severe bilateral abnormalities such as renal agenesis are inevitably lethal. In such cases prenatal diagnosis allows the parents the option of terminating the pregnancy, when the laws of the country permit.

Fetal anomaly scanning is often offered to groups of women known to be at increased risk of having a malformed child (Box 9.1). However, most congenital abnormalities occur without any prior indication of risk. It has been shown that when fetal anomaly scanning is offered routinely to all pregnant women, up to 70% of major malformations can be detected [268]. Therefore, it appears that fetal anomaly scanning has more potential than any other approach for preventing congenital abnormality at the population level. In countries where prevention of fetal abnormality is a recognized component of health services, and selective abortion is an accepted option, routine fetal anomaly scanning is gradually becoming integrated into obstetric practice, especially at university centres.

Disadvantages. The main problems in fetal anomaly scanning are the risks of false-positive and false-negative diagnoses, and the difficulty in predicting the outcome in some cases. These problems are particularly important when routine scanning is offered to the whole low-risk population. False-positive and false-negative findings are more likely when large numbers of scans are done routinely, and quality training and expert back-up are required. It can also be difficult to interpret some findings detected by routine scanning. For example, agenesis of the corpus callosum is common in the normal population, but may also be associated with mental retardation. When it is found in a fetus screened because
of a family history of mental handicap, its implications may be clear; however, detecting it in the absence of a family history can lead to unresolvable anxiety for the parents [269]. Long-term follow-up studies will help to resolve such problems of interpretation.

9.4 Ethical issues in obstetric ultrasound scanning

Wherever obstetric scanning is performed, prenatal diagnosis unavoidably occurs incidentally and can confront obstetricians and parents with serious dilemmas. The spread of ultrasound is therefore leading to more general recognition of the moral and ethical dilemmas associated with prenatal diagnosis.

The time at which an abnormality is detected ranges from early to late in pregnancy, the range of abnormalities identified is very wide, the prognosis is sometimes unclear, and the main options when an abnormality is found are selective abortion or early neonatal treatment. In countries where selective abortion is not permitted, it is impossible to detect correctable abnormalities without detecting more serious uncorrectable ones. On the one hand, it is ethically unacceptable to withhold information on fetal abnormality from parents but on the other, informing them during pregnancy that the fetus has anencephaly, renal agenesis or multiple malformations, without the option of abortion being available, can cause great distress to parents, doctors and nurses. In view of the religious and ethical implications of prenatal diagnosis, consultation on the role of ultrasound in obstetric services in the Eastern Mediterranean Region is a priority.

9.5 Fetal treatment

Prenatal diagnosis can sometimes lead to effective fetal treatment. The commonest indication is blood transfusion for fetal anaemia due to rhesus isoimmunization or other causes, such as parvovirus infection or haemorrhage: blood is transfused directly intravenously via the placental insertion of the umbilical cord [261]. Up to 90% of treated fetuses survive. Platelets may also be infused to treat genetic or acquired thrombocytopenia.

Fetal surgery has so far met with very limited success, even at the most expert centres. “Closed uterus” procedures include needle aspiration, dilation of stenosed major blood vessels, and placement of chronic shunts for cystic lesions
of the chest or for urinary tract obstruction. "Open uterus" procedures (which so far have a very high failure rate) include surgery for diaphragmatic hernia, urinary tract obstruction, or sacrococcygeal teratoma.

In a limited number of situations, a drug can be administered to the mother to control a medical condition in the fetus. Examples include dexamethasone given to avoid virilization of a female fetus with congenital adrenal hyperplasia; vitamin B12 treatment for the B12 responsive form of methylmalonicacidemia; biotin supplementation for fetal multiple carboxylase deficiency; cardiac drugs for fetal arrhythmia; and maternal intravenous gammaglobulin administration for alloimmune thrombocytopenia.

9.6 Research areas in prenatal diagnosis

There is much research aiming to overcome the main problems in prenatal diagnosis, namely the late stage of gestation at which many diagnoses are made, the associated risks to the pregnancy, and the undesirability of selective abortion.

9.6.1 Fetal tissue transplantation

It is realistic to hope that some single gene disorders may be treated by intrauterine tissue transplantation in the future. These include the haemoglobin disorders and some metabolic disorders that are at least partly treatable by postnatal bone marrow transplantation [270]. Creation of chimerism in the fetus might be adequate to correct most manifestations of these disorders.

The main problems of bone marrow transplantation are infection (unlikely in utero), rejection of the graft, and graft-versus-host disease. The fetus does not develop full immunological tolerance until about 20 weeks gestation, so first trimester prenatal diagnosis of, for example, a major haemoglobin disorder leaves a window of some weeks where tissue grafting might be attempted. New methods for stimulating production of bone marrow stem cells in donors, leukopheresis and purification of selected types of white blood cells, permit preparation of highly concentrated bone marrow stem cells in a volume that is sufficiently small for infusion into the fetus. The risk of graft-versus-host disease is reduced by removing the majority of donor T cells. The approach might not be excessively expensive, and is being actively investigated [271].
9.6.2 Pre-implantation diagnosis

Diagnosis prior to implantation might allow couples at high genetic risk to ensure a healthy baby, without having to face the risk of selective abortion. Three different approaches for pre-implantation diagnosis, depending on in vitro fertilization techniques combined with DNA diagnosis on single cells, are being investigated [272].

1. Embryo biopsy. Eggs are fertilized and grown in vitro for 2–3 days, to the 6–10 cell stage. One or two cells are then removed and a diagnosis made using polymerase chain reaction and fluorescence enhanced hybridization techniques. One or two early embryos diagnosed as unaffected are returned to the mother. There is no apparent detrimental effect on subsequent embryonic development. By the end of 1996 this approach had been tried in 300 clinical cycles, leading to about 50 pregnancies and births of children free of genetic disorders.

2. Blastocyst biopsy. Fertilized eggs are allowed to develop in vitro to the blastocyst stage, when 10 or more cells may be removed for diagnosis. This may allow a more reliable result but has so far been tried in only one clinical case.

3. Polar body diagnosis. The first polar body, extruded from the unfertilized egg at ovulation, carries a full single set of maternal chromosomes. Eggs thought not to carry the mutation in question as a result of examining the first and second polar bodies may be Implanted using standard in vitro fertilization techniques. This technique has been tried in more than 500 cases of pre-implantation diagnosis, resulting in the birth of over 80 healthy babies.

Confirmation of pre-implantation diagnosis by chorionic villus sampling is indicated in all cases.

9.6.3 Non-invasive fetal sampling

Small numbers of fetal cells enter the maternal circulation during pregnancy, and prenatal diagnosis may be feasible by extracting and analysing them. Trophoblast cells, fetal lymphocytes, and nucleated red cells have all been found in maternal blood, and can be extracted by rather complex immunological methods. Diagnostic methods appropriate for use on a very few cells, e.g. fluorescence enhanced hybridization and polymerase chain reaction methods, may be used to make a provisional fetal diagnosis, though a really pure preparation of fetal cells is needed for diagnosis by the polymerase chain
reaction [273]. Present methods are cumbersome, expensive and experimental, but if successful may be made acceptably reliable and simple. If so, this could become a useful screening method. Women with a negative result, for example, for Down syndrome, might choose to forego prenatal diagnosis. Women with a positive result might request direct fetal sampling for definitive diagnosis.

9.7 Potential drawbacks in the use of prenatal diagnosis

Until recently, in countries where prenatal diagnosis is ethically and legally acceptable, the main problem was the inequitable delivery of the associated genetic screening and counselling services [9]. Over the past 10 years efforts have been made to achieve widespread population coverage with, for example, screening for risk of Down syndrome, neural tube defect and haemoglobin disorders, by integrating the service into antenatal care. This wider acceptance is in turn giving rise to further ethical questions [274]. Probably the most important of these is the difficulty of ensuring that counselling provided by doctors and nurses with little formal genetic training, conforms to the key ethical principles of genetic counselling. There is considerable concern among midwives in the United Kingdom, for example, that women are expected to undergo all available genetic screening tests without fully realizing the consequences if a fetal abnormality is suspected.

Another difficulty is that of ensuring objective, non-directive counselling for parents about the clinical picture of the wide range of disorders that may be diagnosed in the fetus by present techniques.

Although the vast majority of women consider abortion only in the case of severe fetal abnormality, a particularly anxious woman may request termination of pregnancy for a relatively small or treatable abnormality. There is, therefore, continuing concern about what the limits should be, and who should draw them. Commercial advertising already generates powerful social pressures to conform to an unrealistic standard of physical perfection: could such pressures be reflected in demand for abortion for cosmetic reasons, for example?

9.8 Conclusion

In industrialized societies, it has taken more than 20 years to define the role of prenatal diagnosis in the prevention of genetic and congenital disorders, and
its application is under continual review as new technologies appear. In view of rapid technical developments, the possibilities for fetal treatment and pre-implantation diagnosis in the prevention of certain genetic disorders need to be considered. However, there is already a need for each country to develop a clear strategy on prenatal diagnosis that is consistent with its social and religious norms, responsive to the needs of affected families, and governed by the country’s general health regulations.
Chapter 10

Neonatal screening

10.1 Introduction

A neonatal screening service involves organized examination of newborns in order to diagnose and treat specific disorders. It includes clinical and biochemical screening.

10.2 Clinical screening

Infants who are stillborn or die in the neonatal period should always be examined by an experienced paediatric pathologist. If a congenital abnormality is present or a genetic diagnosis is made, the parents should be informed and counselled on recurrence risk. In industrialized countries neonatal postmortem examination includes X-rays and an autopsy [275] but autopsy is unacceptable on religious and cultural grounds in many countries of the Eastern Mediterranean Region. New methods, such as ultrasound examination, are now available for non-invasive investigation of babies and fetuses [276]. In view of the importance for the family of a diagnosis, a standard protocol for non-invasive postmortem examination of deceased infants needs to be developed.

All liveborn babies should be examined systematically by a paediatrician or midwife using a check-list for congenital malformations.

It is considered to be particularly important to diagnose actual or potential congenital dislocation of the hip as this can be corrected simply by splinting in the first few months of life. However, current European studies of the outcome of neonatal screening using the Ortolani-Barlow manoeuvre at birth suggest that the efficacy of screening and the effectiveness of splinting differ widely, according to the level of expertise and supervision in each centre: inexpert examination and/or treatment may even damage a normal hip. It seems that a radical review of screening policies is needed, especially as other approaches such as ultrasound screening are currently under study [277]. The indications for screening for the disorder could usefully be investigated in the Eastern Mediterranean Region.
Information should be collected on the prevalence of the disorder in the populations of the Region, and on current policies with respect to screening adopted in different centres.

Available evidence indicates that metabolic diseases could be a significant cause of neonatal and infant death in the Region [122,198]. A metabolic disease should be suspected in infants with non-specific symptoms of acute illness such as otherwise unexplained acidosis, hypoglycaemia, alterations in level of consciousness, persistent breathlessness, failure to thrive or vomiting, particularly if a sibling has died unexpectedly in the neonatal period. However, a definitive diagnosis requires a specialist genetic biochemical service, and availability of such services in the Region is limited. A regional collaborative research study is needed on the prevalence and types of metabolic diseases in newborns: this could be based on the Guthrie system described below.

10.3 Biochemical neonatal screening

This service was first introduced in the 1960s for phenylketonuria, since a low phenylalanine diet started in the first weeks of life prevents severe mental retardation in affected babies. In most European countries midwives or nurses routinely take heel-prick blood samples when the baby’s metabolism has stabilized sufficiently for reliable results, at between 5 and 10 days after birth. The drops of blood are collected onto filter paper (the Guthrie card), which is posted to a central newborn screening laboratory. Once this system is set up, it becomes simple and cheap to screen for other conditions and to carry out epidemiological research.

Screening for phenylketonuria, congenital hypothyroidism, sickle cell and G6PD deficiency has been shown to meet the criteria for a screening service in a wide range of countries. Tables 3.3, 3.4 and 3.6 give the results of surveys of the frequency of these disorders in some countries of the Region. The figures suggest that when resources are available, neonatal screening would be indicated in many areas. However, the cost–benefit equation of neonatal screening services differs between countries, depending on the prevalence of relevant disorders and local circumstances. For example, testing for phenylketonuria is relatively cheap, but the diet needed for treatment is quite expensive and supplies may be irregular or non-existent. By contrast, testing for congenital hypothyroidism is expensive but lifelong treatment is easy, cheap and completely effective.
The feasibility of neonatal screening depends primarily on the local level of development of the health and communications infrastructure. The indications in the Region for neonatal screening for sickling disorders and G6PD deficiency require clarification.

10.4 Neonatal screening for research

Neonatal screening using Guthrie cards is a useful and relatively simple epidemiological research tool, especially as modern methods also allow DNA studies on dried blood spots [278]. Samples can be routinely collected in key obstetric services, stored at room temperature for years, tested locally, and/or posted for analysis or confirmation to specialist centres. The spectrum of conditions that can be screened for is being broadened dramatically by new technology (Tandem mass spectrometry) [279] which allows extremely rapid analysis of a large number of samples for multiple metabolic disorders.

Some countries of the Eastern Mediterranean may consider screening newborns for chromosomal abnormalities through cytogenetic techniques in order to assess the role played by factors such as parental age, parental consanguinity, drugs, infections and occupational exposure on the occurrence of chromosomal abnormalities.

10.5 Conclusion

This is an appropriate moment to initiate a large-scale research project aiming to use neonatal screening to define the basic epidemiology of some genetic disorders in the Region. The results would assist in planning appropriate genetic counselling services and determine the cost-effectiveness of neonatal screening for specific disorders.
Part 4
Prevention in practice
Chapter 11

Estimating costs and benefits of prevention: experience with thalassaemia

11.1 Introduction

In many countries of the Eastern Mediterranean Region, there is a clear need for planning and realistic funding of community-based programmes for the control of chronic handicapping disorders. An important element in programme development is analysis of the costs and benefits of different possible approaches [280]. There is good evidence that implementing policies for prevention of genetic disorders leads to significant financial savings [281], and that these are particularly marked in the case of thalassaemia [282,283,284,237]. However, an acceptable analysis must include health and social, as well as financial, criteria [9,285]. To illustrate this approach for inherited disorders, this chapter reviews experience with costs and benefits in existing control programmes for thalassaemia, the commonest inherited disorder in the Region. Since little direct data is yet available from the Region, the analysis is based on experience in other areas and the figures must be considered as extremely hypothetical. The aim is to illustrate the method, to stimulate collection of more realistic figures, and to show how such analysis can contribute to development of appropriate policies.

One of the most difficult questions for societies confronting the increasing importance of hereditary disorders is the acceptability or otherwise of prenatal diagnosis, at the individual and social level (see Chapter 8). Therefore a particular effort has been made a) to assess the relative effectiveness in terms of patient numbers and effects on the family, of policies that include or exclude the option of prenatal diagnosis; and b) to identify specific information (and therefore research) that is needed in order to develop policies appropriate for societies of the Region.
The aim of a genetic prevention programme is to inform people of an avoidable genetic risk, so that they can take the steps that are available to them, and that they consider appropriate, to reduce the associated suffering for affected individuals and their families. All calculations in this chapter assume that genetic counselling is non-directive, and that there is no pressure on couples at risk either to separate or to accept sterilization, abortion or prenatal diagnosis against their true wishes.

In the case of severe inherited childhood diseases such as thalassaemia, one important indicator of the effectiveness of a policy is a reduction in the birth rate of affected children. A minimum estimate of the current number of thalassaemic children born annually is available for each country of the Region (Table 3.2). This value, called \( N \), is a key baseline parameter in the calculations that follow. The following considerations must be taken into account in predicting the effects of different possible policies on the value \( N \).

- In many instances it is possible to calculate reliably the maximum possible effect of a given policy on the annual affected birth rate, taking account of objective factors, such as a) whether genetic counselling is provided retrospectively (i.e. only after the diagnosis of an affected child) or prospectively (i.e. to individuals and couples at risk without an affected child, detected through some form of population screening); and b) the mean final family size for the population (see Figure 7.2). The calculation of maximum possible effect does not predict the effectiveness of any policy in practice. It simply gives a figure that cannot be exceeded however thoroughly a given policy is implemented.

- The potential effect of a policy depends on its acceptability to the families concerned and to the society as a whole. If a policy involves measures that are unacceptable or unrealistic for families, it will have little or no measurable effect, in the absence of coercion. In European societies and in Cyprus, extensive data now exist about the relative acceptability of the options open to couples at risk for having children with thalassaemia or sickle cell disorders (see Chapter 8). The absence of equivalent information for the Eastern Mediterranean Region introduces considerable uncertainty into some calculations. For the purpose of this analysis it has been necessary to make hypothetical assumptions about the acceptability of some policies that have either not yet been fully explored elsewhere (such as screening in high schools) or that have proved unacceptable in European societies (such as premarital screening with the explicit objective of avoiding marriages between individuals at risk).
The effect of a policy depends on implementation. For example, in the United Kingdom, uneven delivery of screening to the ethnic groups at risk is the most important limiting factor in prevention of the haemoglobin disorders [286].

An effort is made below to distinguish between limits that are set mathematically and those that depend on unverified assumptions. Variations in implementation are not considered in detail here, but allowance is made for the fact that implementation of any health service rarely reaches 100%.

11.2 Policies for managing and preventing an inherited disease

A policy is a comprehensive approach to a problem. A health policy for an inherited disease includes both patient care and prevention, when the latter is feasible and acceptable.\(^\text{15}\) Five policies for thalassaemia that exist in different countries of the Eastern Mediterranean Region are considered in this section. The analysis led to consideration of a sixth possible policy. These six policies are shown in Box 11.1. Their estimated effects are compared in Tables 11.1, 11.2 and 11.3 and Figure 11.1. For the sake of simplicity, the maximum possible effects of each policy are presented. The calculations are necessarily oversimplified because of the uncertainties already mentioned.

Policy 1. In the baseline situation, since no treatment is available, most thalassaemic children die before their second birthday. The annual number of affected births is \(N\) or even more, because in the absence of any genetic counselling parents of affected children tend to have even more children than their peers, in order to replace the affected deceased ones ("reproductive compensation") [287]. Because most children die before 2 years of age, the total number of living patients in the population is less than \(2N\). Costs to health services are minimal (Table 11.1). The effect on families can be devastating [285].

Policy 2. With this and all other policies, the first step is to provide the best possible patient care. Since modern treatment leads to a life expectancy of at least 35 years, once it is initiated the cumulative number of living patients starts to rise.

\(^{15}\) A control programme for an inherited disorder has been defined as "a comprehensive approach that combines the best possible treatment with prevention by population screening, genetic counselling and the availability of prenatal diagnosis" [10].
BOX 11.1 Six possible policies for thalassaemia (Policies 1 to 5 are currently in existence in different countries of the Eastern Mediterranean Region)

Policy 1: a "baseline situation" in which no treatment, counselling, or prevention is available. This was the situation, until recently, throughout most of the Region, but in many countries there has been rapid progression towards policy 2 during the last 10 years.

Policy 2: The best possible patient care, plus retrospective genetic counselling after the first affected child is diagnosed. This is a common situation in many countries of the Region at present.

Policy 3: The best possible patient care, plus retrospective genetic counselling, plus the option of prenatal diagnosis in subsequent pregnancies. This is available for a limited number of families in the Region at present.

Policy 4: The best possible patient care, plus retrospective genetic counselling, plus prospective (premarital) carrier screening and counselling, but no prenatal diagnosis. This is already in place in some countries of the Region.

Policy 5: The best possible patient care, plus comprehensive prospective (premarital and antenatal) carrier screening and genetic counselling, plus availability of prenatal diagnosis. At present, the only country of the Region implementing this policy is Cyprus.

Policy 6: The best possible patient care, plus comprehensive prospective (premarital, and family-based and population-based) carrier screening, plus genetic counselling, but no prenatal diagnosis.

by the number born (= N) per year. In the absence of any prevention, numbers would rise at about this rate for at least 35 years.16

The associated expense causes serious concern wherever thalassaemia is common. The cost of treating thalassaemia in the United Kingdom was estimated to be about US$ 8250 per patient per year in 1985 [81], but the 1995 figure was between US$ 19 125 and US$ 22 500, due to increases in costs of hospital admissions, of preparing safe blood (testing for HIV, hepatitis B and hepatitis C), of deferoxamine and drug dispensing, and patient growth [288].17 Costs of providing blood and labour costs differ between countries, but the costs of drugs and disposables are relatively fixed. Therefore, treatment costs must be calculated

---

16 This figure is oversimplified, as it assumes treatment is started for all patients at once. The true rate of rise in patient numbers is more gradual, and is likely to last longer as new treatment possibilities will be developed in the intervening time.

17 The cost of treating thalassaemia is typical of the high cost of treating most inherited diseases. Modern management for cystic fibrosis, haemophilia, or most treatable metabolic disorders is even more costly [283].
individually in each country. A basis for the calculation is given in Annex 3. Here, an absolutely minimum figure of US$ 5500 per patient per year has been used.

Patient care includes genetic counselling for the parents. Once they become aware of the 25% recurrence risk in each pregnancy, many couples who already have healthy children consider it desirable to avoid further pregnancies. Figure 7.2 shows that when final family size is large, if parents have no more pregnancies at all after the birth of one affected child, their relative reproductive performance would fall by as much as 50%, and hence the birth rate of affected children would fall to about 50% of N [233]. In the United Kingdom, before prenatal diagnosis became possible, families with an affected child reduced their further reproduction by more than 70% through family planning backed up by abortion of accidental pregnancies [243]. However, retrospective genetic counselling can have an effect only if family planning is readily available [287]. Clearly, research is needed on its present effect in the countries of the Eastern Mediterranean Region. In the absence of direct observations, an estimated fall in the thalassaemia major birth rate of 40% (to about 60% of N) has been adopted in calculating the maximum effect of Policy 2 (see Table 11.1).¹⁸

| TABLE 11.1 Annual increase in requirements for treating thalassaemia with six different policies (estimated maximum possible effects only) |
|---|---|---|---|---|
| Policy number | Treatment | Retrospective counselling | Prospective counselling | Prenatal diagnosis | Estimated effects |
| | | | | | Births of baseline | Financial cost (US$) | Units of blood |
| 1 | 0 | 0 | 0 | 0 | 100 | Little | None |
| 2 | + | + | 0 | 0 | 60 | 3300 × N | 10.2 × N |
| 3 | + | + | 0 | + | 50 | 2750 × N | 8.5 × N |
| 4 | + | + | + | 0 | 50 → 25 over 20 years | 2750 → 1380 × N over 20 years | 8.5 → 4.3 × N over 20 years |
| 5 | + | + | ++ | + | <10 | 550 × N | 1.7 × N |
| 6 | + | + | ++ | 0 | 25 | 1380 × N | 4.25 × N |

⁰ = Nothing  
++; ++ = Intensive drive  
+= Service available  
→ Decreasing to

¹⁸ Since experience shows that couples with no healthy children tend to take the chance in order to achieve a family and, when family planning is unavailable or fails, many couples continue an at-risk pregnancy.
Policy 3. The option of prenatal diagnosis is also made available to parents of affected children. This enables many couples to complete their family without risking the birth of a second affected child. However, even with a 100% uptake of prenatal diagnosis, there is only a small additional reduction of the affected birth rate.\textsuperscript{19} Thus, the estimated maximum possible fall in the affected birth rate with Policy 3 is about 50% (a fall to 50% of \(N\)).\textsuperscript{20}

Policy 4. This approach, already being applied in some parts of the Region, is intended to allow for the fact that abortion on account of genetic risk is not accepted, or not available, in many parts of the Region. The policy combines the best possible patient care with a programme of community information, population screening prior to marriage, and genetic counselling (see Chapter 8). It is anticipated that prospective couples who are both found to be carriers will separate and each find a new, non-carrier partner, in order to avoid problems in the future. Therefore, the discussion here is limited to possible effects on partner choice. Effects on the reproductive behaviour of couples who marry knowing their risk are discussed under policy 6.

Evidence from industrialized countries suggests a relatively small effect of premarital screening on choice of partner (see Chapter 8), but there could be a larger effect in the context of the Eastern Mediterranean Region societies. The calculation used for Table 11.1 therefore includes a range of estimates for premarital separation of couples at risk, from 10% to 60%. If this is added to a 40% reduction in affected births due to retrospective genetic counselling (for couples who already have an affected child), the final fall in affected birth rate might reach between 50% and 80%. However, premarital screening focuses on couples at the start of a reproductive span of more than 20 years and any consequent fall in the affected birth rate will occur gradually over a 20-year period. This considerably limits the short-term efficiency of this policy, as indicated in Table 11.1.

Policy 5. This combines optimal patient care, family counselling, prospective premarital and antenatal population screening, and the availability of prenatal diagnosis. With this policy (almost) all couples at risk are detected and counselled

\textsuperscript{19} This is because a) the retrospective offer of prenatal diagnosis does not allow couples to avoid the birth of the first affected child, and b) in the absence of prenatal diagnosis informed couples may already have taken steps to avoid further births.

\textsuperscript{20} It is important to note, that as average final family size falls, the maximum effect of policies 2 and 3 on the affected birth rate fall markedly (see Figure 7.2). This has not been allowed for in these calculations.
in time to consider the option of prenatal diagnosis in every pregnancy. In European populations and in Cyprus, prenatal diagnosis is requested by 80% to 98% of counselled couples at risk, and the policy has led to a rapid, very large reduction in the number of new affected births. This is exemplified by the almost 100% fall in the thalassaemia birth rate in less than 10 years in Cyprus [237] and Sardinia [289]. However, such dramatic results are exceptional. In both these island communities thalassaemia is a recognized priority health problem, the population is well-informed, and the service is run by a handful of dedicated teams. Premarital screening is mandatory in Cyprus and well-organized in Sardinia, and in both populations is backed up by screening all pregnant women. Implementation is more difficult in larger populations: in mainland Italy and Greece for example, thalassaemia major births have so far fallen by about 80% [249].

With the exception of Cyprus, there is practically no information on the acceptability of prenatal diagnosis to families at risk for thalassaemia in the Region. For the sake of this discussion, it is assumed that even when prenatal diagnosis is available, most informed couples at risk in the Region would use family planning to limit their family. However, they would be able to consider prenatal diagnosis in the pregnancies they do undertake, either voluntarily or because family planning fails. A maximum possible uptake of 80% of prenatal diagnosis in these pregnancies is assumed. Table 11.1 shows that when the effects of prospective screening and prenatal diagnosis are added to a 40% fall in thalassaemia major births due to retrospective counselling, the affected birth rate could fall by about 90% (i.e. to about 10% of N).

Policy 6. A sixth policy suggested by the above considerations might be particularly suitable in the short term in the Eastern Mediterranean Region. This would aim to maximize the effect of genetic counselling on reproductive behaviour by using multiple approaches for identifying couples at risk, and providing them with access to family planning. Only two approaches to identifying carrier couples have so far been implemented in the Region. These are a) retrospective genetic counselling, which influences reproductive behaviour only after couples have already had at least one affected child, and b) premarital screening, which can influence couples at risk only slowly over the next 20 years. Figure 7.2 shows that during this interval, because of large average final family size, up to 50% of the baseline number of thalassaemic births will occur among couples at risk who were already married but had not had an affected child when
the prevention programme began. In countries where prenatal diagnosis is available, these couples are identified by routinely screening women during pregnancy. This is inappropriate when prenatal diagnosis is not available, but other ways can be found for providing timely genetic counselling to couples who have not yet had an affected child. For example, if women were offered carrier testing when they brought children for immunizations, many couples at risk could be counselled in time to avoid further pregnancies. In addition, the extended families of thalassaemic children, and of carriers identified by screening, could be offered carrier testing and counselling, as discussed in Chapter 8.

The combination of these approaches could identify almost all couples at risk, with or without an affected child. If most then limit their family to two healthy children, the thalassaemia major birth rate might fall by 75% (i.e. to 25% of N). This substantial result might be achieved in the absence of prenatal diagnosis and without exerting pressure on couples at risk to separate or to remain childless. It would require introduction of basic genetic counselling approaches into primary health care and maternal and child health services. Research is needed on its feasibility, acceptability and costs.

11.3 Effects of the six policies on the number of new affected births

Table 11.1 summarizes the maximum theoretical effect of each policy (calculated above) on the annual affected birth rate over the first 20 years, and on the cost of patient care.

The figures indicate the following conclusions.

- No policy can completely prevent a steady increase in costs of patient care. Therefore, the sooner a prevention programme is started, the greater the long-term savings.
- In order to achieve any significant reduction in annual affected births, a population screening programme is required to identify couples at risk prospectively.

11.4 Costs of the six policies

Table 11.2 summarizes the estimated costs of the six prevention policies, using the following figures. Details are given in Annex 3.
TABLE 11.2 Costs of prevention with six different policies

<table>
<thead>
<tr>
<th>Policy number</th>
<th>Retrospective counselling</th>
<th>Prospective counselling</th>
<th>Prenatal diagnosis</th>
<th>Annual cost (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Almost none</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>= 1200 N</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>= 4000 N</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>= 11200 N</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>= 8000 N</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>++</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

0 = Nothing
++ = Intensive drive
+ = Service available

Average (minimum) cost of patient care = US$ 5500 per patient per year. Minimum annual increase in cost of patient care in the absence of a prevention policy = US$ 5500 x N.

Annual cost of premarital screening = US$ 1000 x 4N

Annual cost of more comprehensive carrier screening = US$ 1000 x 8N.

Cost per prenatal diagnosis = US$ 1000

Table 11.3 summarizes the total costs of treatment and prevention associated with each policy. The figure given under treatment is for the annual increase in cost. In 10 years time this figure is 10 times that given, because each annual cohort of new patients survives and requires treatment for each subsequent year. By contrast, the annual cost of prevention is relatively constant. To show the

TABLE 11.3 Total costs of the six policies, including treatment and prevention

<table>
<thead>
<tr>
<th>Policy number</th>
<th>Annual increment in treatment costs (US$)</th>
<th>Annual cost of prevention policy (US$)</th>
<th>Cost per year, 10 years from start (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Approx. 0</td>
<td>Approx. 0</td>
<td>Approx. 0</td>
</tr>
<tr>
<td>2</td>
<td>3300 N</td>
<td>Small</td>
<td>33 000 N</td>
</tr>
<tr>
<td>3</td>
<td>2750 N</td>
<td>1200 N</td>
<td>28 700 N</td>
</tr>
<tr>
<td>4</td>
<td>2750 → 1380 N</td>
<td>4000 N</td>
<td>24 650 N</td>
</tr>
<tr>
<td>5</td>
<td>550 N</td>
<td>11 200 N</td>
<td>16 700 N</td>
</tr>
<tr>
<td>6</td>
<td>1380 N</td>
<td>8000 N</td>
<td>21 800 N</td>
</tr>
</tbody>
</table>

→ Decreasing to
evolution of costs with time, the table also shows total annual costs 10 years from the start of the programme.

Figure 11.1, which summarizes the projected evolution of total costs over the first 20 years from the start of each policy, supports the following conclusions. Policy 1 (do nothing) is no longer acceptable in many Eastern Mediterranean Region countries.

Policies 2 (patient care and retrospective genetic counselling only) and 3 (adding prenatal diagnosis for retrospectively diagnosed couples) are the most expensive both in the short term and long term.

Policy 4 (best possible patient care, and premarital screening and counselling) is potentially effective but requires 20 years to have its full effect.

Policy 5 (best possible patient care, antenatal and premarital screening and counselling, plus availability of early prenatal diagnosis to all couples at risk) is the most effective in bringing about a rapid reduction in the number of affected

---

**FIGURE 11.1** Evolution of total costs of treatment and prevention with six policies for thalassaemia
births, and in the number of families struggling with thalassaemia. Although it also appears the most expensive financially, costs may be recouped in two to three years from the start of the programme.

Policy 6 (best possible patient care, plus multiple approaches for identifying and counselling couples at risk) is potentially less effective than policy 5, but seems the best option where prenatal diagnosis is not available. It includes a large training component (of primary health care and maternal and child health workers) in basic medical genetics and the principles of genetic counselling) which has not been costed here. In fact, such training is a benefit of this policy in a region with a particular need for primary health care workers to be trained in basic genetic skills.

11.5 Conclusion

Experience with the haemoglobin disorders can provide useful general information on appropriate policies for preventing genetic disorders in the Eastern Mediterranean Region.

Comparison of the maximal possible effects of different approaches for preventing thalassaemia in the Region suggests that even when prenatal diagnosis is not available, a carefully-planned programme of genetic counselling could have substantial savings and health benefits. For example, an intensive effort to identify prospectively all couples at risk, and to make family planning available to them and to couples who already have affected children, might in itself lead to a fall of over 50% in the annual number of new affected births.

A common protocol should be developed to collect data on the financial and health costs and benefits of current policies for treating and preventing haemoglobin disorders, and other common inherited disorders such as haemophilia and metabolic diseases. The effects of these policies on the psychological and social well-being of families at risk for the disorders should be evaluated.

Evaluation is needed of the costs and effects of offering screening and genetic counselling to the families of patients with inherited disorders, and of introducing carrier screening into primary health care.
Chapter 12

Organization of community genetics services

12.1 Introduction

The progress made in sanitation and nutrition and the achievements in the control of communicable diseases of childhood over the last few decades have transformed the health scene in the Eastern Mediterranean Region. Although the burden of the unfinished agenda of infectious diseases remains considerable in many countries, analysis of the epidemiological situation clearly indicates that noncommunicable diseases, including hereditary disorders and congenital malformations, are rapidly becoming problems of major public health concern in the Region.

Irrespective of the degree of the epidemiological transition, the health care needs of most of the people of the Region leave no alternative but to address both groups of problems simultaneously. Moreover, great advances have been made in our knowledge concerning genetic disorders, and the principle of equity in health care demands that the gap between medical progress and health care services should be narrowed whenever possible.

Action is therefore required, in every country, to initiate activities to control hereditary disorders. The nature and sophistication of such activities, as well as the areas of emphasis, will no doubt vary from one country to another, but there is a pressing need to establish national programmes that are able to provide, in a cost-effective manner, basic services covering disease prevention, health promotion, and case management activities. Genetics services cannot be simply transposed from the societies in which they already exist. There must be appropriate research on which to base services that will match the unique demographic, religious and cultural features of the populations of the Region.

The broad scope of national programmes for the prevention of hereditary disorders, and the range of Eastern Mediterranean Region countries that need them, means that service requirements, organization and costs will differ widely.
Some countries have already developed a nucleus of genetic expertise while others have only basic primary health care systems. Nevertheless, important action to reduce the prevalence of genetic disorders and congenital abnormalities is possible in most countries. Even when the prospect of a comprehensive genetics service seems remote, the public health measures discussed in Chapter 6 can be implemented.

The planning and organization of community genetics services requires certain prerequisites, and adoption of realistic approaches and feasible interventions.

12.2 Prerequisites

Political will and commitment are essential. Policy-makers at the highest level should be well informed about the increasing dimensions of hereditary disorders as a public health problem and the need to initiate action. Government authorities can be positively influenced by national experts and motivated leading clinicians. Formation of parents' and patients' support associations in contact with international support associations creates a community resource capable of supporting the programmes in many ways.

The availability of reliable data demonstrating the magnitude of the problem is also important in convincing health authorities and in obtaining political support.

A basic situation analysis at the national level is also necessary to determine priorities. In the absence of reliable epidemiological data, preliminary information on trends and hospital statistics are useful. The analysis must take into account the nature of the health infrastructure in the country, the availability of basic laboratory facilities, and the extent to which genetics expertise has already been developed.

A minimum level of financial resources should be made available. This will vary according to the local situation. In the presence of firm commitment, no obstacles should be encountered in providing sufficient funding by the national authorities. However, the provision of additional resources should be sought from nongovernmental organizations. Universities and other academic institutions may be able to provide funding for basic data collection and epidemiological research initiatives.

No programme is successful without competent leadership and effective coordination between the various governmental and nongovernmental agencies concerned. A programme manager or coordinator is needed at the central level.
This person should be highly motivated, knowledgeable and acceptable to all parties concerned. In the case of national programmes, this key person should either be based in the ministry of health or work in close coordination with the health officers responsible.

12.3 Initiating a national programme

A national committee should be formed and assigned the responsibility of assessing the epidemiological situation, evaluating health care systems and planning a national programme for the control of genetically-determined diseases. The composition of the committee will be determined by each country according to the priorities defined and the availability of experts in various disciplines. However, it should include as a minimum requirement representatives of basic specialties such as medical genetics, paediatrics, haematology, community medicine and public health, family planning, maternal and child health, as well as health education. The national programme coordinator mentioned above should be the secretary of the committee. The responsibilities of the committee should focus on the formulation of policies, preparation of the national plan, and mechanisms for coordination. Specific tasks may have to be given to specialized subcommittees with full coordination with the national committee.

Data collection should form the preliminary phase of the national programme. The type of epidemiological and health systems research needed as a baseline will vary from one place to another depending on prevailing disease trends and the local situation. In addition to the data which is already available, information on the magnitude of hereditary disorders, data on trends and future projections should receive priority. Review of the health care system, existing facilities, and human resources is another priority for baseline data collection. Using the baseline data, indicators will be identified for monitoring the development and efficacy of programmes.

Priorities should be set in accordance with the local situation analysis. They relate to the disorders that are commonly encountered and their underlying risk factors. Examples of priorities that are already known to be relevant to countries of the Region are:

- prevention and control of haemoglobin disorders
- control of G6PD deficiency
- prevention of congenital malformations.
Other priorities will be identified through the recommended epidemiological studies.

12.4 Preparing a national plan

The general objectives of the programme should be determined. Examples of objectives include:

- primary prevention through various approaches, including community education;
- ensuring the availability of genetic diagnosis (clinical, biochemical, chromosomal, and DNA);
- providing genetic counselling services within the primary health care and maternal and child health services;
- ensuring care for children, adolescents, and adults with handicap or chronic disease, and their integration into society.

Based on the objectives and priorities agreed upon, specific achievement targets should be set. These targets should be translated into specific activities to be implemented within a time-frame.

Process measures should be developed. These may include conducting specifically planned data collection activities and research programmes, preparing health education material, establishing certain diagnostic services, and training of personnel in specific areas of health care needed by the programme.

Outcome measures should also be set. These may include the following items.

- Improvement in survival of patients.
- Number and age distribution of patients using ongoing patient registers.
- Improvement in quality of life of patients with congenital or genetic disorders, and their families. Measures of quality of life include educational status of patients as well as their work, marriage and reproductive life. Examples of relatively basic indicators are the amounts of drugs and equipment necessary for the management of patients purchased by the ministry of health, and the availability of special diets for conditions like phenylketonuria.
- Reduction in birth prevalence of avoidable congenital and genetic disorders (also assessed through patient registers).
- Impact on the family life of the parents (assessed, for example, by measuring the number of healthy children they have relative to the population norm).
The establishment and functioning of parents’ and patients’ support associations for various disorders.

It is of crucial importance to ensure that primary health care has a major role to play in all activities related to prevention and health promotion. Supported by an effective referral system, the medical, paramedical and community workers should be the resource persons for community genetics services. Responsibilities in implementing planned activities should be defined according to the level of health professionals in each country. Major issues to be addressed should include dispelling misconceptions among health care professionals about the role of inheritance in disease, and providing correct information on genetic risks that are common locally and ways to reduce them.

It is extremely important to coordinate at the planning phase with other health protection and promotion programmes like maternal and child health, and family health and reproductive health. Close coordination with the Expanded Programme on Immunization (e.g. on rubella vaccination), the nutrition programme (on correction of micronutrient deficiencies), and laboratory and blood transfusion services should also be ensured. Such collaboration and coordination should continue throughout the implementation and evaluation phases.

Educational institutions for health professionals, e.g. medical and nursing schools, should be at the forefront of the national programme and should be actively involved in preparing the national plan. They have two major roles, first in revising teaching curricula and methods to respond to current and future needs of the programmes, and secondly, to provide leadership in promoting preventive and clinical services, and human resources development.

Involving the community is of paramount importance. The public and the parents should be represented on the national committee and be involved in major initiatives during the planning, implementation and evaluation phases of the programme. Nongovernmental organizations should be actively involved in fundraising, and in public and professional education.

### 12.5 Addressing major needs

Each national programme should start with research on the frequency and distribution of the common genetic disorders and congenital malformations, the demographic structure of the population, frequency of consanguineous marriage, correlation between local mutations and severity of the corresponding disorders
(when feasible), and level of demand for diagnostic services. Continuing research is essential to ensure that the country keeps abreast of developments in treatment and prevention.

Training of professionals is urgently needed. Specialist training is required in clinical genetics, molecular biology, cytogenetics, registration of congenital abnormalities, management of thalassaemia and sickle cell disorders, perinatal pathology and fetal medicine, including ultrasound. However, the first step would be to recognize existing experts who are providing genetics services and to strengthen their capabilities.

It is important for primary health care professionals to acquire basic knowledge and skills. Examples include becoming aware of common genetic disorders and their management, ability to take a genetic family history in order to identify people in need of specialist referral, providing basic counselling for carriers of common single gene disorders and informing relatives of their high chance of also being carriers, and providing testing. They should also be able to advise on how to reduce the risk of common disorders with genetic predisposition.

At least one national centre for genetics should be established in each country, even in those with minimal resources. Such a centre would provide training in the various aspects of medical genetics and act as a focus for epidemiological and health system research as well as epidemiological surveillance.

It is also very important to promote collaboration with nongovernmental organizations. In places where such organizations do not exist, efforts should be initiated to establish them, with special emphasis on patients' and parents' associations.

National and international cooperation is necessary to maintain standards, to develop and test new methods in diagnosis and treatment, to establish difficult diagnoses and to contribute to knowledge of human genetics. Ensuring such cooperation is an important function of the national committee.

Laboratory diagnosis of inborn errors of metabolism may be particularly important in the Region, in view of the importance of rare recessively-inherited disorders. Some diagnoses may be made in a good biochemical laboratory, but the full range of genetic biochemical diagnoses requires a highly specialized service. Since samples can often be sent over long distances, a handful of specialist laboratories might provide a service for the entire Region.
A special and continuing effort is required to develop, produce, and disseminate information materials on relevant genetic disorders, appropriate for the needs of health professionals, families with affected members, healthy carriers of disease genes detected by family studies or screening, and the general public.

12.6 Strategies and approaches

The major approaches and interventions for the prevention and control of the various hereditary disorders and congenital malformations have already been discussed in earlier sections of this book.

Special emphasis has to be placed on basic public health approaches which include:

- promotion of reproductive health and family planning services;
- immunization against rubella infection;
- prevention of rhesus haemolytic disease of the newborn;
- informing women of the genetic risks associated with advanced maternal age;
- emphasizing the importance of balanced nutrition for women, including green vegetables and vitamin supplementation, before and during pregnancy;
- providing services for genetic screening that are appropriate to the local situation;
- prevention of maternal teratogenic infections and awareness of teratogenic drugs.

Public health specialists, obstetricians, nutritionists and family planners, as well as the primary health care professionals, should be involved in implementing such interventions, and in ensuring appropriate delivery and audit of these services.

The relative roles of the government and private sector, and the nature of the health care system, will undoubtedly affect the planning as well as the strategies adopted for providing community genetics services. The health care infrastructure, rather than the amount of money spent on health care, is the main determinant of the feasibility of community-based services. Experience shows the key role of nurses, midwives and other non-physician personnel in providing community genetic counselling services. Attention may therefore be paid to their training and involvement at an early stage. It seems feasible and appropriate to integrate public health strategies to prevent hereditary disorders and congenital malformations into
the existing maternal and child health network in Member States, thus incorporating community genetic services into an already successful programme which is widely available at the primary health care level.

In some countries, government services are confined to basic programmes, more advanced services being limited or available only on a private basis. In this case some genetics services may develop within the private sector and at academic centres in response to demand, so at least some families obtain access to diagnosis, treatment and counselling. Because of the severe shortage of fully-trained medical geneticists, the demand is usually met by paediatricians, obstetricians and physicians. Genetic screening tests may be provided in private practices by obstetricians, but the numerical benefits will be relatively small. It may be difficult to provide genetic population screening in these circumstances.

12.7 Evaluation of national programmes

Monitoring and evaluation are essential components of any health care delivery programme. Information systems should be developed within the programme to assist in evaluation. The process and outcome measures referred to earlier will also be used for this purpose.

A knowledge of, and continuing ability to follow, the epidemiology of congenital and genetic disorders is fundamental to evaluating the effectiveness of community genetic services.

A congenital anomaly register is a key tool for establishing the epidemiology of, and changes in the frequency of, many conditions.

Disease-specific registers for important genetic conditions may be developed through collaboration of interested clinicians, and with the help of patients’ and parents’ associations. Candidate conditions are thalassaemia, sickle cell disease, haemophilia, phenylketonuria, Down syndrome and congenital rubella syndrome. Once prevention services become available, changes in the frequency of the conditions may then be measured. The necessary, relatively small resources in staff and support costs should be made available, and, to achieve reliable recording and full cooperation, the information needed for registers should be requested by the ministry of health.
Chapter 13
Role of education in the control of genetic disorders

13.1 Introduction

The remarkable advances in understanding the genetic component in disease, and in genetic technology mean that if they are to provide appropriate services and to keep up with medical developments in the future, all health workers now need a basic understanding of genetics. Geneticists worldwide are concerned that the future impact of genetics on health is not yet appropriately addressed in the medical, nursing, or high school curricula. The population has an equal need to understand simple genetics concepts, so that they can use services as they become available. It is necessary to recognize that many common public misconceptions about inheritance are shared by many health workers. For genetics services to reach the community, such misconceptions must be replaced by clear and accurate concepts. Many countries are therefore reviewing genetics teaching for health professionals and for the general population. Such a review is particularly indicated in the Eastern Mediterranean Region because of the local importance of genetic disorders, the shortage of trained medical geneticists and the relative inflexibility of the medical curriculum in some areas.

It is often argued that physicians rarely encounter genetic disorders, but this holds true only for rare single gene or chromosomal disorders. The growing evidence for a genetic component in the etiology of most common diseases means that application of knowledge in human genetics now finds a place in many clinical specialities.

Prevention of multifactorial, chromosomal and single gene disorders would substantially reduce human suffering, morbidity and mortality. Prevention depends, among other factors, on knowledge of genetic background and basic molecular derangements, and appreciation of the range of variation of individual genetic susceptibility to diseases.

Even in developed countries with a major investment in the Human Genome Project, surveys show uneven and often inadequate genetics teaching for medical
students. For example, out of 140 North American medical schools, the medical genetics course was considered good to excellent in 21% of them, fair in 33%, and nonexistent or poor in 47%. Although the mean number of teaching hours was 18, the range was 0 to 40 hours. Only 19% of the medical schools had a genetics department responsible for the course. In 52% the principal teaching was in the paediatric department. In the remainder responsibility was divided among the departments of medicine, anatomy, biochemistry, microbiology, obstetrics and gynaecology, pathology, biomedical science and community medicine [290]. The situation is very similar in the United Kingdom [291]. In Japan, genetics is an independent structured course in only 51% of Japanese medical schools [292].

Although it is always difficult to add new material to the crowded medical curriculum, students must understand the basic concepts and modern applications of genetics, in order to keep pace with the current and future practice of medicine. Some adjustment might be made by changing the emphasis of present teaching, e.g. by emphasizing the clinical applications of genetics and paying less attention to aspects of less clinical relevance [293]. Some guidance on the topics perceived as most relevant by practising clinicians has been obtained by a survey of the views of clinical professors in medical schools of the United Kingdom [291].

It is also important to recognize that as nurses and midwives are responsible for a great deal of basic genetic counselling, their education in genetics is as important as that of medical students, but it is even more unsatisfactory. The same core curriculum and approaches may be adapted for teaching both types of professional, taking into account the more scientific orientation of the medical and the more psycho-social orientation of the nursing curriculum. Thus the discussion that follows applies equally to the medical and nursing curricula.

13.2 A modern medical genetics curriculum

The objectives of medical genetics education may be fulfilled if students can acquire the following.

- Sound basic knowledge of genetic mechanisms in health and disease, an understanding of new genetic technologies, and their application in medicine for diagnosis, prevention and treatment.

- An attitude of lifelong self-learning, particularly necessary in such a rapidly expanding field.
• Knowledge of the common genetic problems in the local population(s) and strategies for management and prevention.

• An understanding of the basic principles and approaches for genetic counselling, including a non-directive approach.

• Knowledge of the genetics services available in the community and how to refer patients for a genetic consultation.

These objectives may be achieved through teaching the following core curriculum.

• Basic molecular concepts: DNA, gene structure and function, mutation, and DNA techniques and their applications for diagnosis and possibly for treatment.

• Basic cytogenetics: the commonest chromosomal disorders.

• Mendelian patterns of inheritance.

• Multifactorial inheritance, genetics of common diseases including cancer, and how to assess risk from the family history.

• Congenital malformations and teratology.

• Consanguineous marriage: scope and effects, genes in populations. This subject needs clear, thorough, and deep scientific discussions with the students to dispel misconceptions and clarify advantages and disadvantages, keeping in mind that many students are offspring of a consanguineous marriage and many will make such a marriage themselves.

• Genetics of the inherited blood disorders: haemoglobin disorders and G6PD deficiency. The scope of molecular genetics and advances in the field can be discussed using these disorders as examples. Knowledge of their molecular basis is already widely applied in diagnosis, screening and prevention, and may in future be used in gene therapy.

• Prevention of genetic diseases:
  – diagnosis and risk assessment for family members
  – non-directive genetic counselling
  – genetic screening
  – primary prevention by avoiding environmental risk factors
  – the option of prenatal diagnosis.

• Ethical issues. Discussion of ethical aspects of present preventive measures should be encouraged. These may include premarital, antenatal and newborn
screening, non-directive genetic counselling, and the acceptability of prenatal diagnosis.

In addition, relevant genetic aspects should be included in the teaching of basic subjects such as pharmacology, immunology, neurology and psychology.

Medical genetics is best taught through a structured course. If this is not feasible, integration with other specialities can be achieved. These may be preclinical such as anatomy, biochemistry and pathology; or clinical such as paediatrics, obstetrics and medicine. A preclinical course would probably require between 15 and 20 theoretical teaching hours to cover most of the curriculum content. Practical sessions and seminars enrich the course and improve the students’ knowledge and performance. Enough credit must be given to the subject in examinations to emphasize its importance to the students.

It could be recommended to give a basic, clinically-oriented course to first or second year medical students, followed by integrated education on applied genetics within the clinical specialities. Integration of human genetics teaching into the clinical subjects can be accomplished through collaboration with relevant departments in the following ways.

- Ensuring genetic evaluation of patients in clinical sessions whenever applicable.
- Encouraging students to construct a family tree when taking the family history of a patient.
- Involving patients or members of support associations in teaching sessions.
- Guided practice of genetic counselling whenever feasible.
- Dedicating some sessions of journal clubs and case presentations and discussions to genetics topics.
- Inviting guest lecturers to present currently important genetics topics.
- Including genetics questions in examination papers of the clinical specialities.

Innovative teaching strategies have been extensively discussed for most medical disciplines, including medical genetics. Methods that have been evaluated and show improved results include:

- problem-solving strategies, which teach skills, attitudes and values, as well as knowledge;
• small group, student-centred and patient-centred tutorials encouraging self-education;
• use of videotapes, including patient-related videotapes;
• computer-assisted instruction materials;
• research papers for students to prepare, present, and discuss with other students;
• clinical case conferences.

In principle, medical genetics is particularly suitable for innovative teaching approaches. The diversity of genetic conditions and their precisely-known molecular basis make the subject particularly appropriate for interactive computer-assisted teaching, and several suitable programmes exist. Problem-solving in medical genetics involves not only reaching a diagnosis and prognosis, but also evaluating risk for relatives and developing attitudes on social and ethical issues. Students need to learn that in genetic counselling there is often no “right answer”, and decisions will often be made according to the family’s, rather than the doctor’s, perceptions of what is appropriate. Many major issues in genetics are still unsettled in the Eastern Mediterranean Region so there are excellent opportunities for group discussion of the social and ethical dimensions of medical practice.

13.3 Genetics teaching in medical schools of the Eastern Mediterranean Region

Genetics education varies from one country to another. Examples from Egypt, Iraq, Jordan, Tunisia and the United Arab Emirates were reviewed during the Regional Consultation on Community Genetics Services organized by WHO/EMRO in Alexandria, Egypt, in November 1994. In Egypt, there are between 10 and 15 hours of genetics per year for the first two academic years with emphasis on basic aspects. There are four theoretical hours and between four and eight practical hours of clinical genetics in the paediatric course in the fifth year. In Iraq, eight out of nine medical schools follow a unified system. First year students have between 10 and 15 hours of theoretical teaching (within biology) covering basic principles of genetics and an introduction to prevention. In the third year pathology course, there are six theoretical hours and between three and six practical hours of cytogenetics. There are also some small group discussions, and
students' presentations on important genetic topics. Between three and five more teaching hours of clinical genetics are integrated into paediatrics and medicine in the fourth and fifth years. In Jordan, human genetics is taught as part of biology in the first year, with strong reinforcement through an independent structured course in the third year. In the United Arab Emirates, a new medical curriculum has been developed. Genetics is integrated into the biological and medical science course in the third academic year [294]. In Tunisia, there are around 52 hours of theoretical and practical teaching on genetics.

Variations also include teaching methods, the student:teacher ratio, and the availability of teaching aids, references and text books.

Many medical schools in the Eastern Mediterranean Region still follow traditional teaching methods, including didactic lectures, and emphasize memorizing factual information rather than a problem-solving approach. The large number of students per class limits possibilities for small group teaching, and students are more concerned about their grades than about acquiring knowledge and skills.

A major problem in changing from traditional to innovative teaching methods is the attitude of students who, throughout their educational years, have been used to memorizing factual knowledge and regurgitating it in examinations. They therefore feel more secure with traditional lectures and examinations, and excellent implementation strategies are needed to enable them to appreciate new teaching methods.

The general shortage of trained clinical geneticists and the, as yet, limited availability of clinical genetics services are to some extent self-perpetuating. Thus, in most medical schools human genetics is taught by non-medical scientists who are often insufficiently aware of its clinical applications to make it attractive to medical students. The lack of clinical genetics practice means that curriculum committees may not appreciate the importance of the subject. Limited representation in the curriculum and particularly in the examinations, means that students may not take the subject seriously. Those who do may lose interest and enthusiasm because of the limited opportunities for applying modern preventive approaches. To change the situation it is necessary to recognize the problem, and in each country to plan and implement appropriate adjustments.

In developing an appropriate programme, the following questions need to be answered for each country.
• How much do students entering medical college already know about genetics? A number of countries in the Eastern Mediterranean Region have recently introduced genetics in senior school biology classes, including DNA structure, protein synthesis, Mendelian inheritance and some examples of human genetic disorders. It is advisable for medical geneticists to become involved in formulating courses for senior school students, and in updating the knowledge and teaching methods of biology teachers, through specific programmes.

• How much does the public know about genetic diseases, and what is the public knowledge of and attitude to the possibilities for prevention? The different attitudes of individual families to genetic counselling, and the very inadequate understanding of genetic concepts within society should be clarified to students, in order to facilitate their future practice.

• What are the prevailing misconceptions about genetics? Misconceptions common among doctors as well as the general public include the ideas that genetic conditions are rare, affect only a few families and are a matter for specialists, and that health workers must discourage consanguineous marriages on genetic grounds. A primary task in medical genetics education is to identify and neutralize such misconceptions among the students.

• What are the most prevalent genetic diseases in the population? The curriculum should focus on these common genetic disorders and their burden on health and society.

• What genetics services are currently available and what is the future potential?

Each country has a characteristic pattern of common genetic disorders, and many issues associated with the practice of medical genetics have particular aspects in the Region, so that the curriculum cannot simply be adopted from elsewhere. It requires serious reconsideration and planning in each country. Since medical geneticists cannot themselves do all the necessary teaching, they need to focus efforts on assisting other teachers to teach appropriately and providing teaching aids to help them.

Finally, it is important to recognize that as medical genetics teaching improves, an increasing number of students may seek guidance on the possibility of genetic problems within their own family. It is important for medical schools to have specialist advice available for these students.
13.4 Continuing education for existing health professionals

Physicians, nurses and social workers who have already been trained and are in practice need to be informed of new technologies and approaches, and encouraged to incorporate them into everyday practice. Specialized journals and meetings can disseminate such information, but this is not enough as most health workers think genetics is too difficult, and in any case only a limited number can attend up-dating courses. At the same time, most are interested in the Human Genome Project and attracted by ideas such as gene therapy, and would like to understand DNA.

How can the new molecular and cytogenetic technologies be translated into understandable terms for primary health care professionals? How can they be trained in the principles and practice of genetics counselling? These questions are urgent because in the absence of appropriate teaching, existing misconceptions about inheritance are likely to become more widespread.

A number of different approaches are needed for continuing education of doctors and nurses in genetics.

- Providing lectures in genetics to physicians and other health professionals such as nurses and social workers. However, this approach cannot reach all those who need to know more about medical genetics.

- Newsletters, e.g. a teratology newsletter [295], are a useful way to inform interested professionals throughout the country, despite limitations by geographical factors. A medical genetics newsletter would be an ideal source of information on principles of genetics and medical applications of recent advances. Brief and frequent articles are easier for busy medical staff to read.

- Selected genetic topics may be regularly aired in existing up-dating courses, and in medical journals and newspapers, including the free, throw-away, magazines supported by advertising.

However, it is increasingly understood that effective introduction of new verified medical practices requires active training of doctors and nurses to implement them, and easy availability of the necessary tools. In some countries and organizations a structure exists for continuous in-service training of primary care professionals in, for example, obstetrics, paediatrics, family planning and immunizations. This framework can be used for teaching the appropriate genetics component of each service, as discussed earlier. This will require the development of packages of very clear and simple information for the teachers and the health
workers. It also calls for development of tools, e.g. for assisting in drawing a family tree or identifying family cancer risks, and production and dissemination of appropriate information materials for patients. Thus liaison with, and education of, health education workers is an important early step. Where no such formal structure exists, specific courses with similar content and objectives are needed for workers in primary health care, maternity care, family planning and child care.

Obviously, not every primary health care worker can attend a course, but the aim may be to train a core group, e.g. one midwife from each midwifery unit. Participants should be carefully selected, and providing training and back-up for the other members of their unit (i.e. teaching teachers to teach) should be one clear-cut aim of the course. Such courses should include an examination and a certificate in community genetic counselling. Those qualified need to be given time to teach and use their skills, and encouraged to form a national association of genetic counsellors, with a regular annual meeting. This type of approach has been developed in North America and Europe. Clearly, existing medical geneticists must play a key role in the educational enterprise. Although the task is large, many of the packages needed could be used throughout the Region. Regional medical geneticists may therefore be encouraged to collaborate, for example, with each other, with nurses and with specialists in health education and public health, in planning an appropriate approach and developing appropriate materials.

Similar higher level courses, tools and materials may be developed within relevant medical specialties, such as paediatrics, obstetrics, haematology and oncology. Regional and national professional associations should be approached, with a view to including sessions on the growing role of genetics in professional meetings, and developing relevant training courses.

Finally, health education materials produced for the population, and simply-written booklets on specific topics produced by lay support associations for their members, are incidental but powerful means of informing health workers.

13.5 Genetics education in schools

In the long run, genetics education for the public can best be achieved through education in schools. It is also worth noting that because of the young age structure of most populations of the Eastern Mediterranean Region, education (and other) efforts focused on schools can have a relatively greater and more rapid
Role of education in the control of genetic disorders

impact than in most more industrialized societies. The scientific community in universities must take greater responsibility in the reform of school curricula, and in working with schoolteachers to revise school science texts and formulate an ideal science curriculum for each stage that addresses concepts and principles and not just the delivery of factual knowledge. Scientists in universities can also make themselves available as consultants to education.

Experiences from industrialized countries should be sought and reviewed in the light of regional circumstances. Teacher/scientist partnerships developed in intensive summer programmes have been very successful. In Kansas, United States of America, a programme of 60 contact hours (including lectures on basic human genetics, genetic disorders, genetic counselling, ethical issues and new technology) has been aimed at leading high school teachers in human genetics, who in turn can train others. The teaching was enriched by laboratory sessions, with visits to chromosome and recombinant DNA laboratories, computer-assisted instruction and use of videotapes [296].

It is important for some genetics information to reach every pupil. It is therefore important to define the fewest, simplest pieces of information that should be included in biology teaching in schools, and the most appropriate stage for teaching them. Some agreement is developing that the recessive mode of inheritance is the single most important message to introduce, because it shows that anyone may be a carrier without having an affected individual in the family (i.e. genetics involves us all), and it prepares students for later offers of screening.

Special high school educational programmes in human genetics have been introduced in North America. In the United States of America, a module for teaching the Human Genome Project has been incorporated into the general high schools biology programme [297], and in the United Kingdom the revised national curriculum requires some teaching on genetics technology for all students. In Canada, a two-decade experience in introducing genetics science to high school students has proved highly successful. It involved teaching, followed two weeks later by the offer of voluntary genetics screening for carrier status for Tay-Sachs disease, β-thalassaemia and cystic fibrosis for 60 000 students. The programme “converts public abstractions about heredity into private facts about genotypes, and converts general statements about prevalence and variation into specific statements about personal identity and risks”. It increased the students’ knowledge about genetic diseases in general and about specific diseases in
particular, and revealed favourable attitudes of students towards the educational and screening experiences [298].

Despite the fact that similar programmes are difficult to implement in some countries because of limited resources, combining educational goals with community genetics services may prove very valuable in countries of the Eastern Mediterranean Region. For example, carrier screening for common genetic disorders offered to high school students could be a form of premarital screening, meet the ethical need for the early offer of testing, and constitute an important step towards prevention of hereditary disorders.

When adequate services are available, there is every reason to provide information to the public whenever and wherever possible, and particularly in schools.

13.6 Information for families with affected members

The diagnosis of a serious genetic disease in a family can indicate a lifelong problem. Families need the fullest possible written information on the problems that can arise through the whole course of life and how to cope with them. This is especially important when medical services and access to professional genetics advice are limited.

Parents’ and patients’ support associations can provide invaluable support for the medical services, especially by producing suitable information materials for families. The emergence of support associations for numerous individual genetic disorders in more industrialized countries has led to the formation of corresponding international associations interested in promoting the dissemination of correct information. Excellent materials for families may be obtained from these organizations and adapted for local needs. The availability of these materials also has an important part to play in the clinical genetics education of health workers, because they give a clear picture of families’ interests and needs.

13.7 Information for the public

The traditional ideas about inheritance that exist in every society are a complex mixture of true perceptions and folklore. Some examples are given in
BOX 13.1 Some common MISCONCEPTIONS about congenital and genetic disorders

- They are rare
- They may be contagious
- They are a punishment for the sins of the parents
- They are the responsibility of the mother
- They are caused by consanguineous marriage
- There is no treatment and no prevention
- Families with affected members have been cursed by God
- If your parents had a medical condition, you are also likely to develop it

Box 13.1 In any society it is a difficult task to displace such common misconceptions and half-truths with correct insights.

Today's adults were not exposed to any significant genetics teaching at school. They may subsequently acquire some genetics knowledge through physicians, the workplace, television news and documentaries, newspapers and magazines, but one of the most important sources remains family and friends. Knowledge picked up in this way is usually fragmentary and unsystematic, and often is inaccurate or sensationalized.

Communicating science to the public requires expert communicators who can shape the correct information according to the population's perceptions. Education of the public outside school, therefore, depends partly on education of the media. Health education materials for the public, and particularly the simple booklets produced by parents' associations, are an efficient means for conveying basic correct information to journalists and other professional communicators. Many such materials are available through international and national support associations, and may be adapted for use in the Eastern Mediterranean Region. Some excellent television documentaries on genetics also exist, and might be considered for adaptation for countries of the Region.

A second, and ultimately equally important, way of informing the public is to ensure that the individual members of the public who need them are given correct information and appropriate educational materials. For instance, when full and precise written and verbal information is provided to all carriers detected by
screening for thalassaemia, they are placed in the position to convey correct information to other family members and friends. The same is true for all families provided with correct genetic counselling. Thus, gradually, popular culture is changed by capillary information, and training health workers in primary health care centres to provide basic genetics counselling is ultimately one of the most effective ways of informing the general population.

13.8 Conclusion

It is urgent to start to train a new generation of clinical geneticists, and for existing medical geneticists in the Eastern Mediterranean Region to pool their efforts to generate appropriate advice, and teaching materials, on the teaching of medical genetics to medical and nursing students, to health workers now in practice and to the general public. Teaching of medical genetics assumes particular importance in the Region because of the high frequency of genetic problems. Because of the shortage of medical geneticists, for a long time to come most of the responsibility for teaching medical genetics will fall to non-medical scientists, interested clinicians or trained non-medical genetic counsellors. However, each medical and nursing school should aim at having some teaching input from trained medical geneticists. There is also an urgent need to include basic human genetics, including common hereditary diseases, in the curriculum of teachers’ training colleges, and to ensure that appropriate simple genetics information is included in the school curriculum at points where it may reach every child.
Chapter 14
Conclusions and recommendations

14.1 Epidemiology

The available evidence shows a particular need for genetics services throughout the Eastern Mediterranean Region. Additional needs are related to the high frequency of advanced parental age, haemoglobin disorders, and customary consanguineous marriage. In many countries medical services have reached a standard where many patients who would formerly have died are treated and are surviving. Consequently, the number of children with chronic disorders and costs for their treatment are rising progressively, with important future resource implications.

These conclusions are based on classical genetic epidemiological data from industrialized countries, together with local studies, but there is a general lack of accurate and standardized epidemiological data for the Region. Epidemiological studies are needed in each country in order to estimate present and future service needs. Some countries already have plans to establish registers of congenital anomalies and of specific genetic diseases. These, and other relevant research studies that have been initiated in a number of countries, should be promoted and extended more widely.

Newborn screening is also a useful research tool for establishing the frequency of congenital hypothyroidism, sickle cell disease and metabolic disorders, which are likely to be particularly important in the Region. The availability of new technologies for rapid large-scale detection of a broad spectrum of metabolic disorders in the newborn makes this an appropriate moment to consider a regional collaborative research project on newborn screening.

---

21 This chapter summarizes the conclusions and recommendations of the WHO Regional Consultation on Community Genetics Services, 17-21 April, Alexandria, Egypt.
Recommendations

- Basic demographic data relevant to the frequency of genetic disorders should be collected by appropriate expert centres in each country. Such data should include, for example, parental age distribution, and prevalence and types of consanguineous marriage.

- Registers of patients with common congenital and genetic disorders, such as Down syndrome, haemoglobin disorders and other congenital abnormalities should be established in each country, as an ongoing activity.

- National or regional registers of congenital anomalies should be established in countries of the Region, with the aim of establishing the epidemiology of the component congenital anomalies in the Region and comparing the data with that from other regions (see Annex 2).

- To facilitate definitive diagnosis, a standardized protocol for non-invasive postmortem examination of late miscarriages, stillbirths, and infant deaths should be developed for use throughout the Region.

- Data should be collected in each country on the relation between consanguineous marriage and morbidity and mortality at birth, in childhood and in adult life.

- Standardized methods for data collection should be developed and used throughout the Region, to generate comparable data and allow collaborative studies.

- Data collection should take account, whenever possible, of local population characteristics, such as geographic and ethnic factors, and should permit micro-mapping of disorders.

14.2 Consanguineous marriage

Consanguineous marriage is customary throughout the Region, and is an important integral part of cultural and social life in many areas. It can be beneficial for family and social stability and female status.

Consanguineous marriage can lead to an increase in the birth rate of children with rare recessively-inherited disorders. However, the extent of this effect in the population as a whole has been exaggerated. Although there is an increased risk regarding morbidity and mortality, the magnitude of the potential adverse effect does not, in general, seem sufficient to warrant any organized effort to intervene in this deeply rooted social practice at the population level.
**Recommendation**

The genetic implications of customary consanguineous marriage should be addressed by providing genetic counselling for individual families. Because of the characteristic population structure in the Region, it may be highly effective in this situation. Development of appropriate genetic counselling services is a high priority in the Region.

**14.3 Prevention of genetic disorders**

The experience available shows that over half of congenital and genetic diseases can be prevented, but this requires a variety of approaches.

*Basic public health approaches.* Some simple public health approaches (rubella immunization, prevention of rhesus haemolytic disease, correcting iodine deficiency, and family spacing) are effective and are already being implemented in some countries of the Region.

A relatively large proportion of children in the Eastern Mediterranean Region are reported to be born to older mothers (between 16% and 19% to mothers over 35; between 1% and 7% to mothers over 40).\(^{22}\) Family planning, when widely available, is particularly used by older couples, and can reduce the prevalence of genetic problems related to parental age. Ensuring access to family planning for older couples would be consistent with the objectives of the Regional Reproductive Health Programme: “to ensure that all women will have access to appropriate health care, all through their lives, that will enable them to go safely through pregnancy and childbirth, and provide married couples with the best chance of having a healthy baby”. In the Eastern Mediterranean Region, general availability of information and family planning would lead to a significant reduction in the frequency of miscarriage, and the frequency of new cases of Down syndrome could fall by up to 50%.

*Maternal nutrition.* Women need a balanced diet that is adequate in iron, vitamins including folate, and iodine where appropriate, throughout the reproductive years, and particularly pre-conception. There is strong evidence that an optimal diet reduces the frequency of unsuccessful pregnancy outcomes and severe congenital malformations.

\(^{22}\)Latest available figures, 1991 United Nations Demographic Yearbook (see Table 2.7).
Special control programmes for the haemoglobin disorders. These, including population screening, are being adopted by many countries of the Region, and these disorders have come under complete control in Cyprus.

Availability of genetics services. Genetic diagnosis and counselling should be available to all families where there is the possibility of congenital or genetic disorders. The benefits of genetic counselling are substantial. It permits diagnosis, prognosis and guidance on management of affected people. It replaces misinformation and misconceptions with correct information, often provides reassurance for family members, and allows reproductive and other relevant decisions to be made on an informed basis. Genetic counselling is most effective when it is available to the whole population at risk, and when it is delivered prospectively (i.e. before a couple have started to have children).

A nucleus of specialist genetic counselling services exists in some countries, but in general genetic counselling is currently limited to some families with an affected child. Its impact is also limited by lack of awareness among health workers. Key laboratory services exist in some centres, but prenatal diagnosis is available on a very limited scale.

Newborn screening. This is an effective means of preventing morbidity due to some disorders, such as phenylketonuria, congenital hypothyroidism, and sickle cell disease and G6PD deficiency when relevant. Each country needs to decide which disorders to screen for, on the basis of local epidemiological studies.

Recommendations

- Information on the genetic risks associated with advanced parental age, and access to family planning facilities, should be available to all women in the Region.

- The case for supplementing basic foods with iron, vitamins and folate should be considered throughout the Region.

- Women should be informed through the maternal and child health and health education systems of the steps they can take to maximize their chances of healthy children.

---

23 For example, limitation of further reproduction, as a result of genetic counselling alone, could have an important impact on the birth prevalence of many inherited disorders.
The health care system should be developed to make genetic counselling available to all families who need it. The role of the paediatrician in identifying families at risk and providing genetic counselling is crucial. There is a need for training of experts in medical genetics, of non-medical genetic counsellors to work with paediatricians and other specialists, and of workers in primary health care.

In all countries of the Region, disease-oriented prevention programmes should be considered for locally prevalent conditions such as the haemoglobin disorders.

When resources permit, newborn screening demonstration and research programmes should be established. The decision on which disorders to screen for in practice should be based on the results of these projects. Research protocols, methods and training should be standardized throughout the Region.

Intercountry collaboration should be established to make most efficient use of the genetic diagnostic resources available in the Region.

Information should be collected from all countries of the Region on availability of services for genetic counselling and diagnosis, on genetics education in medical schools, and on existing patients’ and parents’ support associations. A regional directory of services should be created.

14.4 Education

Despite the fact that medical genetics assumes particular importance in the Eastern Mediterranean Region because of the high frequency of genetic disorders, medical genetics education currently faces major obstacles hindering the educational process. Such obstacles include inadequate specialized personnel experienced in medical genetics, lack of emphasis on genetics in the medical curriculum, lack of integration between medical genetics and other related clinical specialties, and lack of effective teaching methods. There is also a considerable gap in the provision and availability of appropriate information on the genetic aspects of disease, for health professionals and the community.

Recommendations

Medical schools and academic institutions should be urged to reconsider the status of genetics education and its relevance to optimal health care, in relation to genetically-determined diseases. It should be recognized as a medical
discipline in its own right. At the same time, efforts to integrate it in an effective manner with other relevant clinical specialties in the curriculum should be intensified.

- Health authorities and medical education institutions should strengthen national capacities in medical genetics. Training programmes should be promoted to increase the number and experience of appropriately qualified geneticists. Emphasis should also be placed on acquisition of the required knowledge and skills related to genetics in postgraduate programmes of other specialties like paediatrics and obstetrics.

- Emphasis should be placed on collaboration with the ministry of education on revising and updating the genetics component of the school curriculum.

- It is appropriate to consider methods of training of other health workers such as maternal and child health workers, midwives and nurses in basic genetic counselling, with the aims of ensuring timely referral of families for specialist genetic counselling, assisting paediatricians, obstetricians and other clinicians to provide genetic counselling, and supporting primary health care physicians in genetic counselling.

- Proper genetics information can be introduced to the population in general through health workers in maternal and child and other primary health centres, as well as through scientific media documentaries.

### 14.5 Organization of genetics services

#### Recommendations

- In each country a national committee should be formed, and assigned the responsibility of assessing the epidemiological situation, evaluating health care systems, and planning a national programme for the control of genetically-determined diseases. The composition of the committee will be determined by each country according to the priorities defined and the availability of experts in the various disciplines. However, it should include, as a minimum requirement, representatives of basic specialties such as medical genetics, paediatrics, haematology, community medicine and public health, family planning, maternal and child health, and health education. An appropriately qualified and highly motivated national manager should be appointed to coordinate the activities of the committee and to ensure continuity of work and follow-up. The committee would be responsible for preparing a national plan focusing on priority problems and the achievement of the targets set.
At least one genetics centre should be established in each country, even those with minimal resources, to provide medical services, train health professionals in the various aspects of medical genetics, and perform research studies. Up-to-date diagnostic techniques should be introduced, step by step, as national resources permit.

The role of primary health care in the delivery of genetics services will vary from one country to another, but certain basic services should be generally available. These include appropriate counselling for common problems including consanguineous marriage, provision of maternal and child health services including advice on maternal nutrition, and pre-conception and pre-pregnancy counselling. They should also include taking a genetic family history, advice in relation to advanced maternal age, and assisting in screening programmes for common conditions such as the haemoglobin disorders.

The role of paediatricians is crucial in diagnosis and family counselling for congenital anomalies. Paediatricians need continuous up-dating in the range of genetics services that are available and provision of trained support staff for assistance with genetic counselling.
Annexes
ANNEX 1 Details of the calculation of the annual number of infants born with Down Syndrome in some Eastern Mediterranean Region countries (data on maternal age distribution from the 1991 UN Demographic Yearbook[68])

<table>
<thead>
<tr>
<th>Country</th>
<th>Annual births per 1000</th>
<th>Thousands of births to mothers aged</th>
<th>Total Down births per year</th>
<th>% of births to mothers</th>
<th>% Down to mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;24</td>
<td>25-29</td>
<td>30-34</td>
<td>35-39</td>
<td>40-44</td>
</tr>
<tr>
<td>Down births per 1000</td>
<td>0.52</td>
<td>0.83</td>
<td>1.13</td>
<td>4.43</td>
<td>14.08</td>
</tr>
<tr>
<td>Bahrain 1990</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Births</td>
<td>13.4</td>
<td>3.4</td>
<td>4.43</td>
<td>3.35</td>
<td>1.57</td>
</tr>
<tr>
<td>Down births</td>
<td>1.77</td>
<td>3.7</td>
<td>3.8</td>
<td>6.96</td>
<td>6.05</td>
</tr>
<tr>
<td>Cyprus 1989</td>
<td>10.4</td>
<td>3.93</td>
<td>3.65</td>
<td>1.96</td>
<td>0.67</td>
</tr>
<tr>
<td>Births</td>
<td>2.04</td>
<td>3.0</td>
<td>2.21</td>
<td>2.97</td>
<td>1.55</td>
</tr>
<tr>
<td>Down births</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Egypt 1988</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Births</td>
<td>1913</td>
<td>446.3</td>
<td>578.9</td>
<td>403.3</td>
<td>242.3</td>
</tr>
<tr>
<td>Down births</td>
<td>232</td>
<td>480</td>
<td>456</td>
<td>1074</td>
<td>1094</td>
</tr>
<tr>
<td>Kuwait 1987</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Births</td>
<td>52.4</td>
<td>15.17</td>
<td>14.99</td>
<td>10.9</td>
<td>6.33</td>
</tr>
<tr>
<td>Down births</td>
<td>7.9</td>
<td>12.4</td>
<td>12.3</td>
<td>28.0</td>
<td>23</td>
</tr>
<tr>
<td>Libyan Arab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jamahiriya 1981</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Births</td>
<td>118.2</td>
<td>39.59</td>
<td>28.23</td>
<td>21.96</td>
<td>13.82</td>
</tr>
<tr>
<td>Down births</td>
<td>20.6</td>
<td>23.4</td>
<td>24.8</td>
<td>61.2</td>
<td>77.7</td>
</tr>
<tr>
<td>Pakistan 1988</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Births</td>
<td>3195</td>
<td>1081</td>
<td>903.7</td>
<td>589.9</td>
<td>389.4</td>
</tr>
<tr>
<td>Down births</td>
<td>562</td>
<td>750</td>
<td>666</td>
<td>1725</td>
<td>2392</td>
</tr>
<tr>
<td>Qatar 1990</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Births</td>
<td>11.0</td>
<td>3.56</td>
<td>3.41</td>
<td>2.35</td>
<td>1.26</td>
</tr>
<tr>
<td>Down births</td>
<td>1.85</td>
<td>2.83</td>
<td>2.66</td>
<td>5.58</td>
<td>4.36</td>
</tr>
<tr>
<td>Tunisia 1989</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Births</td>
<td>199.5</td>
<td>49.89</td>
<td>55.73</td>
<td>41.07</td>
<td>21.6</td>
</tr>
<tr>
<td>Down births</td>
<td>25.9</td>
<td>46.3</td>
<td>46.4</td>
<td>95.7</td>
<td>80.4</td>
</tr>
<tr>
<td>United Arab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emirates 1982</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Births</td>
<td>42.0</td>
<td>15.49</td>
<td>13.0</td>
<td>6.97</td>
<td>2.79</td>
</tr>
<tr>
<td>Down births</td>
<td>8.0</td>
<td>10.8</td>
<td>7.88</td>
<td>12.36</td>
<td>10.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Down births per 1000</th>
<th>% of births to mothers</th>
<th>% Down to mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>35+</td>
<td>40+</td>
</tr>
<tr>
<td>232</td>
<td>18.1</td>
<td>5.4</td>
</tr>
<tr>
<td>1116</td>
<td>15.8</td>
<td>3.7</td>
</tr>
<tr>
<td>4452</td>
<td>18.0</td>
<td>6.3</td>
</tr>
<tr>
<td>295</td>
<td>18.0</td>
<td>6.3</td>
</tr>
<tr>
<td>8811</td>
<td>19.4</td>
<td>7.2</td>
</tr>
<tr>
<td>22</td>
<td>15.1</td>
<td>5.6</td>
</tr>
<tr>
<td>346</td>
<td>14.3</td>
<td>5.5</td>
</tr>
<tr>
<td>62</td>
<td>9.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>
Annex 2

Registers of congenital abnormalities

Introduction

Many countries in the Eastern Mediterranean Region, being aware of the clinical importance of congenital and genetic disorders, are considering initiating registers of congenital abnormalities. Since this is an important first step in obtaining the epidemiological data needed for service planning, this chapter outlines the basic functions of, and requirements for, such registries.

A congenital anomalies registry can be defined as a system for the collection, storage and application of data on cases affected with congenital anomalies.

The first function of a registry is to obtain baseline data on the local epidemiology of congenital abnormalities. It takes several years to obtain adequately reliable data for this purpose. A second important function of the registry is then to measure changes in the frequency of the disorders in response to environmental or dietary changes, exposure to teratogenic agents, and programmes for the prevention of congenital abnormalities.

Population-based or hospital-based registers

There are in principle two ways to select population samples for study. One is to choose one or more small, geographically-defined areas and set up a register that completely covers them. Alternatively, a sample of the whole population may be drawn from a number of hospitals over the target area. The South American hospital-based programme samples births from selected hospitals scattered throughout the countries of Latin America. The Hungarian population-based register obtains data from the obstetrical, paediatric and pathological records of every Hungarian hospital.

In countries or areas of moderate size and where local conditions permit, congenital anomalies registers with total population coverage may be most useful. Such population-based registers exist, for instance, in the Scandinavian countries, each one with less than 100,000 annual births. This approach may be feasible in some of the smaller countries of the Eastern Mediterranean Region.
If it is necessary to cover a much larger population with a register, a sampling procedure is likely to provide better quality data than a total population register.

There are advantages and disadvantages to both approaches. In a small country, a total population register may take years to provide statistically-reliable data. When the country is large, local samples may not be representative. This problem can be overcome to some extent by joint analysis of a number of population-based programmes. This methodology increases the risk of variable ascertainment and diagnostic inaccuracy, but may be the best solution, when applicable, for the problem of covering a large population like that of Egypt, the Islamic Republic of Iran or Saudi Arabia.

Ideally, the selection of participating hospitals in a hospital-based programme should ensure a sample that is as representative as possible of the population. Selection of specialized hospitals may increase the proportion of complicated pregnancies with an increased risk of congenital abnormality. Selection of public but not private hospitals may result in social bias. On the other hand, selection often includes hospitals with a particular interest in congenital abnormalities, and this may increase ascertainment and accuracy.

Hospital-based sampling systems by definition do not cover defined populations, and are less suitable for registration of the many types of congenital abnormality that cannot be diagnosed until a considerable time after birth.

Within a large country, a number of population-based systems covering restricted areas can coexist with a hospital-based sampling system, the latter acting as an umbrella organization coordinating the data from the hospital-based sampling system. The strategy, complicated as it may be, might represent the best solution for the surveillance of congenital anomalies in a large population.

The optimum size of a congenital anomalies register is difficult to estimate and depends on local conditions: large size gives greater statistical power, but usually decreased accuracy.

**Need for background data and confounders**

Background data are obviously needed for interpreting the findings in a congenital anomalies register. The total number of births in the target population is the denominator in the calculation of rates.
In general, prevalence \( P \) is calculated as follows:

\[
P = \frac{N}{n} \times 1000
\]

where \( N \) is the number of cases with congenital anomalies and \( n \) is the number of total births (i.e. still births and live births).

The detailed information is needed for full utilization of the register data. First, general epidemiological characteristics like maternal and paternal age and parity, parental consanguinity, residence and ethnicity are needed. Second, medical and social information, e.g. data on maternal disease, therapy, occupation or marital status, may be of value. Third, ideally, information on other pregnancy outcomes such as ectopic pregnancies or spontaneous and induced abortions should be sought.

In some programmes only the data of liveborn infants are available. Inclusion of stillbirths, i.e. late fetal deaths, in addition to live births considerably changes the rates for many congenital anomalies. The inclusion of stillbirths seems particularly important in the Eastern Mediterranean Region, in view of the probability of an increased rate of lethal congenital malformations in association with parental consanguinity. However, at present, the low rate of postmortem examination of stillborn infants and those dying in the neonatal period jeopardizes the validity of this information. A standardized and validated protocol for minimally-invasive postmortem examination of babies is a key prerequisite for a valid congenital abnormalities register.

**The problems of ascertainment**

At first glance, 100% ascertainment in a congenital anomalies register appears necessary, but this ideal situation can probably never be reached. Even the best registers in the world do not achieve more than 90% ascertainment and often it is less.

When initiating a register, it may be realistic to aim just for the fullest possible ascent of a limited number of easily diagnosed abnormalities, e.g. neural tube defects, limb reduction defects and multiple malformations, and work progressively towards better ascertainment of the full range of significant abnormalities.

It is not necessary to have 100% ascertainment. Lower ascertainment reduces the sensitivity of the register to changes, but can still be quite effective, providing
it is reliable. A register with 100,000 births and 75% ascertainment has the same statistical power as a register with 75,000 births and 100% ascertainment. The real problem with less than 100% ascertainment is the possibility, or even likelihood, of changes in ascertainment, that could lead to an apparent but false increase in the birth prevalence of a congenital anomaly, or hide a true increase. The effect of such changes can of course be greater with lower ascertainment. Changes in ascertainment have the most marked effect for rather common events, but play a minor role for rare events. In the former group, even relatively small changes in ascertainment can lead to statistically significant changes in rates, resulting in alarms. In the latter group, random variation in numbers will be much larger than changes in ascertainment. It is therefore important to strive for good ascertainment. Though the ideal 100% goal cannot be reached for all congenital anomalies in any register of reasonable size, it may be achievable for specific conditions, such as anencephaly, and spina bifida.

Ascertainment can be increased by multiple-source case finding. In most registers, data are collected at or a short time after the birth of the malformed infant, usually from delivery units or paediatric services associated with delivery units. By adding information for other paediatric sources, e.g. general inpatient and outpatient clinics or paediatric surgical clinics, child cardiology centres, further cases can usually be identified, and more complete ascertainment can be obtained. A third possible source of data includes pathological institutions if data on embryopathological examination, infant autopsies, or other postmortem examinations are available. Genetic diagnostic laboratories (cytogenetic, biochemical, DNA) can be a particularly useful additional source of information, as can prenatal or postnatal screening programmes. Multiple-source systems are more complicated than straightforward data collection from the delivery units, and it usually takes time before data are complete. They can, however, give better ascertainment and increased accuracy. Thus, for instance, cardiac congenital anomalies are often incompletely ascertained and ill-characterized in reports from the obstetrics service, but good data can be obtained from paediatric cardiology centres.

The degree of ascertainment that can be reached also varies with the type of congenital anomalies studied. Obviously, identification of a gross congenital anomaly like anencephaly is easier than that of a cardiac congenital anomaly or a congenital anomaly of the urinary tract. However, experience shows that when a malformed infant is not registered, this is more often due to failure of reporting than to lack of primary diagnosis.
Every surveillance system should try to evaluate its ascertainment level by internal checks such as comparing rates of notification from different hospitals, comparisons with textbook rates, and comparing data from other systems. Special studies can be made in order to evaluate underascertainment and overascertainment, i.e. mistaken registration of an infant as malformed.

Thus, there is a balance between the need for speed in registration, accuracy of diagnosis, level of completeness, and size; the latter factor determines the statistical power of the system.

Many current congenital anomalies register systems are single-source, e.g. in Norway and in many hospital-based programmes. Other programmes, as in Canada, Hungary or in Sweden are multi-source. Some are based on compulsory notification of congenital anomalies (Hungary and the Scandinavian countries) but most are based on voluntary notification (England, Italy, Latin America, Mexico, Spain). It seems reasonable to assume that compulsory notification provides more complete coverage, and voluntary notification assures more reliable information. This general rule may, however, not be applicable in a specific country or region.

Several existing congenital anomalies registry systems have a special input document, a notification form to report abnormalities to the registry. Other congenital anomalies registers centralize and tabulate information gathered through health or vital statistics systems. In other programmes, personnel from the registry scrutinize all medical records in the area that can be related to congenital anomalies.

Special notification forms for congenital anomalies seem to assure the most direct and reliable flow of information between the affected child and the congenital anomalies register system. This may be a good strategy, though it is more expensive to run than using already recorded and stored data.

**Diagnosis, coding, data handling**

The data should be computerized and the diagnoses stored as codes (most programmes use the standard W110 International Classification of Diseases (ICD), 10th revision)\textsuperscript{26}, together with the other data mentioned above. However, as it is

\textsuperscript{26} For special purposes, other codes can be contemplated, e.g. the McKusick catalogue numbers for genetic diseases and the International Federal Society for Cardiology (IFSC) code for cardiovascular congenital anomalies.
not possible to foresee all the information that will be needed in the future, the original report forms and records should be stored in a way that permits easy access.

The important fact is that all the congenital anomalies diagnosed can be described and coded in such detail that specific types of congenital anomaly can be evaluated and studied without needing to review the original data and records. Thus, the coding system used should be designed to permit a hierarchy of classification of congenital anomalies, e.g. limb congenital anomalies, limb reduction defect, radial defect, unilateral defect.

Most codes used are descriptive codes. Codes can also be constructed to focus on the aetiology of the congenital anomaly to be surveyed. Thus, it is important to differentiate isolated and multiple congenital anomalies.

It is often suitable to have the material coded centrally, as the same condition may be interpreted in different ways at participating centres. A central coding process also carries a component of critical evaluation of the data, and often leads to requests for further information. It can give feedback to notifying hospitals, with suggestions for diagnoses and syndrome identification, and so can support development of genetic diagnostic skills.

Data analysis

The primary goal of a congenital anomalies register is to evaluate the occurrence of congenital anomalies in a population during a finite time period. The time period will depend on the size of the programme. Even in small registers, the material should be followed at monthly or bimonthly intervals. Continuous handling of the material will also increase the quality of the data.

A first task is to obtain baseline figures for the prevalence of congenital anomalies in the areas under study, as prevalences differ in different populations. An apparent gradual increase in prevalence with time is to be expected, due to improving ascertainment as the register becomes established.

Baselines figures may change over time for other reasons. Alterations in parental age distribution can cause quite marked changes in the birth prevalence of chromosomal disorders. Changes in the birth prevalence of conditions due to new mutations are also to be expected in association with changing paternal age distribution. Changes in the mutation rate can be monitored by paying particular
attention to the registration of sentinel abnormalities. These are a limited number of conditions (including achondroplasia, Apert syndrome and osteogenesis imperfecta) that are readily diagnosed at birth and are mostly due to a new mutation. Such conditions should be among those selected for complete ascertainment when setting up a register.

There may also be changes in birth prevalence of other types of abnormality. For example, there has been a steady decline in the birth prevalence of neural tube defects in many parts of the world during the last two decades. Similarly, long-term slow increases, e.g. hypospadias in Hungary, must be evaluated by some sort of regression analysis. The likelihood of such trends must be taken into consideration when estimating expected numbers for a specific time period. When baselines are stable, the comparison between observed and expected numbers can usually be made quite simple, e.g. based on a Poisson mode.

Another phenomenon that should be detectable in the surveillance system is a clustering in time of unusual cases. Simple statistical modes, e.g. Cusum, exist to estimate the probability of such occurrences by chance. It should be stressed, however, that if enough variables are followed for long enough, the laws of statistics are such that clusters of remarkable strength will occur by chance.

**Detecting outbreaks**

For each period, the observed number of cases is compared with those expected, as estimated from previous occurrences (baselines). Not only population differences in rate may exist, but also differences in ascertainment. Such baseline data therefore should be collected in the same system using the same technique during a period long enough to permit reliable estimates. Obviously, when an outbreak of a very rare condition occurs (similar to what happened in the thalidomide-Contergan epidemic), an accurate baseline is not needed, but only a rough estimate perhaps based on information available in the literature.

Although data studies shortly after the events are usually provisional, marked outbreaks, clusters or “epidemics” can be detected quite early, especially with unusual diagnoses. A more complete analysis usually necessitates a longer time period in order to increase numbers and reduce statistical variation, and to be as thorough as possible. In most cases it is probably a good idea to make a series of monthly, quarterly, and annual analyses. Only the annual analysis will be based on final figures.
Feedback and production of statistics

In time the register should produce final statistics. Such statistics are often based on annual data and usually tabulate a number of defined congenital anomalies that occur often enough to permit meaningful comparison. This does not mean that only such congenital anomalies are evaluated. The surveillance function of a congenital anomalies register should deal with all types or groups of congenital anomaly, including the important multi-malformed infants. The annual report from the register should also contain analyses of long-term trends and unusual events occurring during the year.

The quality of the data entered in the register depends mainly on the quality of the data sent in from the notifying units. It is difficult to keep up an interest in the periphery for this type of activity if the persons who do the actual notification are not continuously informed on what happens with the notified data. A regular annual report as feedback may help keep up the interest. Such reports are not necessarily based on final data but should be distributed soon after the events.

International cooperation in congenital anomalies registers

The advantages of international cooperation within the field of congenital anomalies surveillance have been stressed repeatedly and are briefly summarized here.

- Comparisons between different birth registries increases the awareness of congenital anomalies within each individual register.

- When rare events are studied, the sample size must often be increased beyond what is possible within one congenital anomalies programme. If a new teratogen appears, its effects may be more rapidly detected if comparisons can be made between many different surveillance systems.

- In case of alarms within one congenital anomalies register, the baselines used can be compared to those of other surveillance programmes and signs for parallel increases in other locations can be sought.

- Studies of different populations may help to overcome problems in causal analysis of environmental and population genetic (e.g. consanguinity) factors.
Concerns about new causal factors that arise with an independent congenital anomalies register may have a more effective impact on regulatory authorities if they can be channelled through an international organization.

There are two supranational organizations of congenital anomalies registry programmes. The European Registration of Congenital Anomalies system bases its registration on about 200 000 annual births and samples from 14 small population-based programmes within the European Community countries in Europe and is funded by the European Community. This multinational programme tries to standardize the diagnoses and the notification of congenital anomalies for a collection of relatively complete data, representative of the areas from which the samples are drawn.

The International Clearinghouse for Birth Defects Monitoring System is an organization for collaboration between 24 congenital anomalies surveillance programmes around the world. Some cooperative surveillance is performed (e.g. multi-malformed infants), but the main activity is the exchange of information collected within each programme using the technique of that particular programme. The primary goal is a worldwide surveillance and the time factor is important. Preliminary data are collected within three months after the end of each quarter, but final annual data are also produced. A close contact is maintained between the two organizations and some programmes submit data to both. They act in parallel with slightly different scopes.

Conclusion

Many Eastern Mediterranean Region countries have plans to establish registers of congenital anomalies and of specific genetic diseases. The main purposes of these registers are the prevention of congenital and genetic disorders and the improvement of care. International experience shows that such registers can:

- help to plan medical and social services and to check the efficacy of different preventive programmes;
- detect the temporal and/or spatial clusters of congenital anomalies, and help to identify their causes and prevent them;
- provide materials for research projects.
An important requirement for developing registers of congenital abnormalities in the Region is development of a protocol for non-invasive postmortem examination.

Requirements for a national register include the need for 5000 total live births and stillbirths per year, routine medical examination (by obstetricians and/or paediatricians), a standardized format for recording congenital anomalies, and a small staff (full time clerk, part time statistician, medical doctor [geneticist—teratologist]).

**Recommendations**

The following steps could be taken.

- Establishment of national or regional registers of congenital anomalies in countries of the Region;

- The use of the guidelines of the International Clearinghouse for Birth Defects Monitoring System after modifications to suit local needs;

- Inclusion of only visible congenital anomalies in the register initially, and then widening of the spectrum of entities included step by step.
Annex 3

Calculation of costs of treatment and prevention of thalassaemia

Introduction

Although costs vary widely in the Eastern Mediterranean Region according to the services provided, it is necessary to use average figures for the costs of patient care, carrier screening, and prenatal diagnosis for the calculations presented in this chapter. These average figures have been derived as outlined in the following sections.

Costs of treatment

Estimates on the requirements for treatment for thalassaemia are shown in Table A.1 [81].

The cost of the recommended treatment for the average patient in the United Kingdom in 1995 was calculated at between £8153 and £10 217 per year (US$ 12 230–US$ 15 300) [288]. Estimated figures for the Eastern Mediterranean Region are given in Table A.2. In reaching these estimates, the following have been taken into account.

Depending on country, four levels of treatment for thalassaemia are found in the Region.

- No treatment. Costs to the health service minimal. Patient life expectancy is less than 2 years. This level is not considered here.

- Monthly blood transfusions only. Mean patient life expectancy is 15 years.

- Monthly blood transfusions plus some deferoxamine treatment (assumed to be 50% of recommended dose). Mean patient life expectancy is 25 years.

- Full recommended treatment (monthly transfusion, including white cell filters, etc., and the recommended deferoxamine dose of 45 mg/kg per day). Mean patient life expectancy is at least 35 years.
**TABLE A.1** Basic annual requirement for treating one patient with thalassaemia major, related to age

<table>
<thead>
<tr>
<th>Age group</th>
<th>Mean weight (kg)</th>
<th>Units of donor blood per year*</th>
<th>Deferoxamine (kg, at 45 mg/kg per day)</th>
<th>Cost in 1993 at US$ 12 per gram**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5</td>
<td>15</td>
<td>10</td>
<td>0.22</td>
<td>2 600</td>
</tr>
<tr>
<td>6–10</td>
<td>25</td>
<td>17</td>
<td>0.37</td>
<td>4 400</td>
</tr>
<tr>
<td>11–15</td>
<td>40</td>
<td>27</td>
<td>0.58</td>
<td>7 000</td>
</tr>
<tr>
<td>16–21</td>
<td>55</td>
<td>37</td>
<td>0.8</td>
<td>9 600</td>
</tr>
<tr>
<td>Adult</td>
<td>60</td>
<td>40</td>
<td>0.88</td>
<td>10 500</td>
</tr>
</tbody>
</table>

*At about 300 ml/kg per year; 1 unit = 450 ml donor blood.

**1993 cost of deferoxamine = US$ 4.2 to US$ 4.6 per 500 mg vial, depending on area.

**TABLE A.2** Costs for treatment of thalassaemia in the Eastern Mediterranean Region: estimates for one patient aged between 7 and 11 years (range given = costs for a 2 year old and an adult)

<table>
<thead>
<tr>
<th>Item</th>
<th>Minimum treatment (US$)</th>
<th>Full treatment (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs other than iron chelation</td>
<td>375</td>
<td>375</td>
</tr>
<tr>
<td>Day transfusion: hotel and nursing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion × 12 per year</td>
<td>1088 (600–1575)</td>
<td>2250 (1390–3150)</td>
</tr>
<tr>
<td>Investigations</td>
<td>135 (135–435)</td>
<td>278 (278–870)</td>
</tr>
<tr>
<td>Occasional costs (operations, etc.)</td>
<td>150</td>
<td>645</td>
</tr>
<tr>
<td>Medical time</td>
<td>300</td>
<td>620</td>
</tr>
<tr>
<td><strong>Total, if no deferoxamine therapy</strong></td>
<td>2040 (1560–2835)</td>
<td>*</td>
</tr>
<tr>
<td><strong>Deferoxamine therapy</strong></td>
<td>3080 (1440–4725)</td>
<td>6165 (2880–9450)</td>
</tr>
<tr>
<td><strong>Total, with deferoxamine therapy</strong></td>
<td>5130 (3000–7560)</td>
<td>10 335 (6190–15190)</td>
</tr>
</tbody>
</table>

*Full treatment has to include deferoxamine therapy.

Cost estimates for all these situations are included in Table A.2, to allow each country to make their own estimates.

Costs in countries able to provide full treatment are assumed to be the same as in the United Kingdom. Minimal costs are those estimated for countries that can provide a) monthly transfusions but only part (estimated at 50%) of the recommended dose of deferoxamine, or b) monthly transfusion but no deferoxamine. The calculations for these countries assume that cost of personnel, etc. is about two-thirds of the United Kingdom costs.

All calculations assume that patients are transfused in a dedicated day-transfusion unit (the cheapest option). Cost of drugs, for example, is assumed to
be invariant. A minimum cost for deferroxamine of US$ 4.2 per 500 mg with no added dispensing costs has been assumed throughout.

Because the average patient in the Eastern Mediterranean Region is younger than in the United Kingdom, Table A.2 gives figures for a patient of between 7 and 11 years of age, with the range for younger and adult patients in brackets. It was necessary to reach a single figure to use in the simplified calculation presented in this chapter. The table shows that US$ 5500 per patient per year is a reasonable estimate of the minimum cost of treatment in the Region.

In the absence of a prevention programme, in each country treatment costs are expected to rise annually by at least US$ 5500 multiplied by \( N \) (\( N = \) annual thalassaemic births). Country figures for \( N \) can be found in Table 3.2.

When data are collected in the Region, costs may prove higher than this estimate. This will not alter the relative cost-effectiveness of the policies considered here, but it will increase the total cost-effectiveness of prevention.

**Costs of prevention**

The discussion below shows that the cost of carrier screening depends on many variables such as the strategy adopted, the laboratory methods used, local labour costs, and the level of information of the population.

**Cost of laboratory diagnosis**

In general, screening for carriers of haemoglobin disorders depends on a simple primary screen to detect people who may be carriers, followed by more complex definitive tests of those with a positive result. Costs vary depending on the range of abnormalities screened for, the prevalence of carriers, the degree of tolerance of false negative results and the number of tests, as shown in Table A.3 [81, and Dr Peiman Abidi (personal communication)]. Costs may also be lower at large screening centres because of economies of scale.

In industrialized countries, expensive equipment such as automated red cell analysers and high performance liquid chromatography are routinely used [299], and labour costs are high. When such sophisticated equipment is used, primary screening gives fewest false-positive and false-negative results. However, costs need not be so high in countries of the Eastern Mediterranean Region, as very cheap and simple primary screening methods such as a simple one-tube osmotic
TABLE A.3 Reported costs of current thalassaemia screening programmes in different countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Strategy</th>
<th>Estimated cost per person tested (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greece</td>
<td>All samples tested for thalassaemias and abnormal HbS.</td>
<td>30–40</td>
</tr>
<tr>
<td></td>
<td>HbA2 measured on all samples</td>
<td></td>
</tr>
<tr>
<td>Sardinia</td>
<td>All samples tested for thalassaemias and abnormal HbS</td>
<td>20–30</td>
</tr>
<tr>
<td></td>
<td>HbA2 measured on all samples. Economies of scale.</td>
<td></td>
</tr>
<tr>
<td>Iran, Islamic</td>
<td>Samples tested for thalassaemias only (red cell indices)</td>
<td>2–3</td>
</tr>
<tr>
<td>Republic of</td>
<td>Selected HbA2 measurement when marked microcytosis</td>
<td></td>
</tr>
</tbody>
</table>

fragility test for thalassaemias [300], and a turbidity or sickling test for sickle cell disease [234] are more than 90% efficient in detecting possible carriers. These tests can be carried out on the spot on fingerprick blood, and are suitable for use in a primary health care setting.24 When a possible positive is found, a venepuncture sample must then be sent for definitive diagnosis to an expert centre with quality equipment. The approach has not yet been tested in the Region.

Clearly, it is impossible to derive a single estimate for the cost of screening for calculations in this chapter, on the basis of the above data. An estimate was therefore derived by an alternative route. The cost of carrier screening is related to the frequency of the disorder. In the United Kingdom, for example, the national cost of screening and counselling approximately equals the national cost of providing prenatal diagnosis for all at-risk pregnancies [299]. It is simple to calculate the annual number of at-risk pregnancies for a population, as in principle it is \(4 \times N\). This figure can then be multiplied by the (hypothetical) cost per prenatal diagnosis in the Eastern Mediterranean Region (US$ 600 to US$ 1000), to reach an estimate of the cost of detecting an annual cohort of couples at risk, whether before or after marriage. Thus for each country, the basic cost of screening one annual cohort = \(N \times 4 \times \text{US$ 1000}\).

The number of tests required annually depends on the screening strategy.

- Premarital screening. The annual number of tests is one or two times the annual number of marriages, and remains fairly constant with time. The decision on whether both or only one partner is screened initially can depend

---

24 Costs of primary screening can be further reduced, e.g. by screening both members of a couple at once, and proceeding to a definitive diagnosis only if both have a positive result on primary screening.
on a variety of factors. The annual cost of this strategy is the annual cost of screening one annual cohort which is $N \times 4 \times \text{US} \$ 1000$.

- Antenatal screening or screening when children are brought for immunization in order to detect couples already married requires a greater investment in the first years. In most countries of the Eastern Mediterranean Region, the initial requirement would be between 5 and 8 times more than for premartial testing, because the annual number of pregnancies equals the annual number of marriages multiplied by the average final family size. However, a couple once screened do not need to be screened again, and after a few years the annual requirement would fall to the basic cost of screening one annual cohort. Thus the initial annual cost of this strategy is $N \times \text{US} \$ 1000 \times 24$, falling to $N \times \text{US} \$ 1000 \times 4$ over about 10 years.

Family studies must be considered under two headings. When laboratory resources are very limited, providing family studies for the relatives of affected children may be a particularly cost-effective way in the Eastern Mediterranean Region of detecting carriers and couples at risk (see Chapter 8).\textsuperscript{25} When there is a population-screening programme, family studies following the identification of a carrier would involve up to 10 to 20 additional tests per carrier diagnosed, and so could double the requirement for laboratory testing. It is assumed that when relatives of carriers are tested, the total cost of screening an annual cohort might be doubled (to $N \times \text{US} \$ 1000 \times 8$).

For the sake of simplicity for the calculations in this chapter, it has been assumed that the:

- Annual cost of premartial screening = cost of screening one annual cohort = $N \times 4 \times \text{US} \$ 1000$
- Annual cost of population screening = twice the cost of screening one annual cohort = $N \times 8 \times \text{US} \$ 1000$

**Cost of information and genetic counselling**

The requirement for counselling varies with the proportion of carriers in the population and the number of couples at risk detected. In the United Kingdom, Greece and Sardinia the majority of carriers are detected during pregnancy, and

\textsuperscript{25} The efficiency of family studies (compared with general population screening) would theoretically be greatest when carrier frequency is low and consanguineous marriage is common.
require face-to-face counselling by a health professional. This is estimated to take about half an hour, costed at about US$ 20 per carrier. Specialist counselling for couples at risk takes at least twice as long. These figures are included in the overall estimate based on number of at-risk pregnancies, above.

However, counselling costs can be reduced by investing in health education. In Cyprus, where both the population and health workers are very well informed on thalassaemia through a public education programme (with dedicated sessions in all state schools, annual publicity through an anti-anaemia week, etc.), individual carriers are simply given written information, and require face-to-face counselling only when there is a specific problem.

Genetic counselling for the parents of affected children is usually done by the staff looking after the patients, and costs are relatively small. By contrast, providing carrier testing and counselling for their extended families is labour intensive. The approach has yet to be costed, but would certainly require at least one fully-trained counsellor attached to each treatment centre. If it is decided to offer testing to the relatives of carriers detected by screening, there will also be a major increase in cost, family studies being labour-intensive. However, the high yield of carriers detected might more than justify the additional cost.
References


References


References


[95] Cao A et al. *1992 management protocol for the treatment of thalassemia patients*. Obtainable from Cooley's Anemia Foundation, 105 East 22nd St, New York, NY 10010 (fax 212 944 7327) and the Thalassemia International Federation, PO Box 8503, Nicosia, Cyprus (fax 02 429141).


References


References


References


Community Control of Genetic and Congenital Disorders

With socioeconomic development and the decline in the incidence of primarily environmental diseases of childhood, congenital and genetically determined disorders come to account for an increasing proportion of morbidity, disability and death. This pattern, which has existed for some time in the industrialized countries, has recently become apparent in many countries of the Eastern Mediterranean Region and genetic disorders are therefore emerging as major health problems in these countries. The increasing importance of genetic disorders will have a significant impact on requirements for, and cost of, health services.

This publication critically reviews the data available on the epidemiological characteristics of congenital and genetically determined disorders and evaluates their present magnitude within the Region. It aims to increase, among health policy-makers and the health professions, awareness of these disorders as an issue of increasing concern to public health. Feasible interventions and public health approaches for prevention are discussed, with particular emphasis on the role of primary health care. In order to respond to the pressing need for action to control these disorders in Member States, a structure and guidelines for the establishment of prevention and control programmes within the existing health care systems are proposed.