Historical Background

The name Bahrain means the land of life or the sacred land, as mentioned in the Sumerian Legends, and it was so named for the presence of water and agriculture, a rarity in the Arabian Gulf. The state of Bahrain is made up of an archipelago of 40 Islands in the Arabian Gulf. The Kingdom of Saudi Arabia is on the west and Qatar on the East. The total land area of the kingdom is 720.14 km². The largest island among these 40 islands is the island of Bahrain, which represents 85% of the total land area (Central Statistics Organization, 2006).

The geographical, religious and socio-cultural aspects of Bahrain play an important part in the influence of genetic association with environmental factors on the people of Bahrain. History clearly shows that from the Stone Age until the advent of Islam, Bahrain was influenced by the Babylonian, Assyrian and Greek civilizations amongst other Ancient civilizations. The eastern coast of the Arabian Peninsula was the one most influenced by these cultures; the Greek influence extended to the southern-most part of the Arabian Gulf, profoundly affecting Bahrain. The Sumerian Legends gave a clear mention of the Bahrainis as the people of Dilmun. However, around 500 B.C., Greek and Roman geographers called Bahrain as "Tylos". It is maintained that it was basically the pearls and precious stones of Bahrain that gave the Island its name and fame.

The Arabian Gulf was responsible for carrying out sea trade and from the dawn of time Bahrain became an important commercial centre on the major trade routes between the East and West. With geographic explorations and acquisition of overseas colonies by the Europeans, Bahrain became a battlefield and was occupied by the Portuguese in 1907. At the time when India became an important part of the British Empire, Bahrain was strategically located on the route to India. With the passage of time, its location contributed to an increased exchange with various parts of the world. Rapid economic progress with the advent of Independence in 1971 made Bahrain a diversified industrial base and a major banking centre with a number of reputable international and offshore banks. Bahrain is now (1) an important communication centre between the East and West, and has been (2) an important military base from the 2nd World War till today. All these factors highlight an infiltration of foreign cultures and civilization through time, giving a cosmopolitan blend of genes mingling with the local population.

The foundation of the modern health services dates back to 1900 when the first hospital was established. The first Government doctor was appointed in 1925 and a full- fledged government clinic was set up 11 years later. In 1968, a comprehensive health services development plan was drawn up by the government in co-operation with the W.H.O, and this was put into operation in 1970. The present Government provides free comprehensive health care to all the residents of Bahrain, citizens and non citizens in a two-tier system. Primary Health Care Centers are drained into various clinical set ups such as Salmaniya Medical Complex (SMC).
A Public Health Directorate is responsible for the prevention and control of diseases. Comprehensive programs for general sanitation, water purification, hygiene, health, and education, have led to a decreasing trend in various contagious diseases.

Presently, the Health system delivery maintains a partnership between both the government and private sectors. In line with this, the Ministry of Health (MOH) has concomitantly played a major role in the provision, improvement, and sustenance of quality health care services. Health facilities have improved rapidly during the past five years. This can be witnessed clearly through the remarkable evolution with regard to the type and quality of the services offered at Salmaniya Medical Complex (the major hospital in Bahrain).

The construction work on the new King Hamad General Hospital in Al Muharraq Governorate was initiated in February 2006. This hospital project is anticipated to be a huge training medical centre for the adjacent Medical University, which will be built later in the future. The expansion of the services in Bahrain was not limited to the Secondary Health Care, but it even catered to the Primary Health Care in order to maximize the capacities and accessibility to the services in Primary Health Care.

In brief, Bahrain has been subjected to various influences from a number of different civilizations due to its geographic location. Mingling of populations over generations has led to various social and cultural customs in the Bahraini people. An inherent desire of this small country to preserve its identity as well as its religious and social culture may have planted the seeds of consanguineous marriages leaving behind its genetic footprints on the sands of time (Central Statistics Organization, 2006; Bahrain Health Statistic Reports, 1985-2005).

Demographic Data

According to the demographic data of 2005, the population of Bahrain was estimated to be 724,645; close to the data of 586,110 in 1995. The proportion of Bahrainis to Non Bahrainis has remained relatively constant over the last 10 years. In 2005, Bahrainis made up 61.9% of the population, whereas 38.1% were non-Bahrainis. The crude birth rate in 2005 was 20.9/1000. The infant mortality rate of live births was 8.9/1000. The percentage of people under 15 years was estimated as 40.3% while in the 15-64 age groups it was 56%. However, in the age group of above 65, it was 3.4%.

Non-communicable diseases, especially genetic diseases, are assumed to be a major cause of morbidity and mortality. Genetic disorders are a significant burden on health care delivery systems. Their chronic nature requires life-long medical attention, expensive supportive and symptomatic therapy and specialized care. Effective control of these diseases requires that their natural history, frequency and distribution be studied (Bahrain Health Statistics Reports, 2005).

In 1983, a genetic unit was established at the Salmaniya Medical Complex (SMC). A national committee for the control of hereditary diseases was established in 1993. The aim of the committee was to conduct population studies on the prevalence of genetic diseases within the country, and to improve management and treatment standards of patients suffering from these diseases. During these years, many studies have been carried out.
Consanguinity in Bahrain

Consanguineous marriage has been a historically long-standing practice among the different social classes of Bahrain. Several studies were performed to determine the rate and to study the trend to see if the frequency of cousin marriages has changed over time. The following are the observations of some of these studies conducted.

In 1990, the first study was performed on a group of 500 young married Bahraini women in which each participant was asked to complete a standard questionnaire, which included questions about the family relationship between the husband and the wife, and the relationship between their parents. The questionnaire thus provided information about 1000 couples back to the grand parents’ generation. The rate of cousin marriage was estimated to be 39.4% in the present generation (fathers and mothers) and 45.5% in the previous generation (grand fathers and grand mothers), indicating a high rate of consanguinity, with a significant decrease over time. The rate of first-cousin marriage was evaluated as 21% (Al-Arrayed, 1995).

In 1998, through a National Family Health Survey (BNFHS ‘95), a total of 4,166 households were interviewed, including 26,723 participants. The overall consanguinity rate was estimated at 32%, including 24% for first cousin marriages, hence marking a significant gradual decline in the rate of marriages between relatives (BNFHS, 1995).

The third study was a neonatal screening for hemoglobinopathies performed in 2002, including a questionnaire with the intent to gather information about consanguinity. Marriage between relatives occurred at the rate of 20%, while the rate of first-cousin marriages was 12.5%. Marriages between distant relatives comprised a total of 7% (Al-Arrayed, 2005).

The fourth figure came from the premarital counseling study conducted in 2006, where 500 couples participated in the study, which revealed the consanguineous marriage rate to be 20%, with 11.4% being marriages among first cousins, and 8.6% among distant relatives (Table 5.1). About 80% of couples were non-related; hence, a gradual decline in the consanguinity rate was observed (Al-Arrayed and Al-Hajry, unpublished observations).

Genetic Blood Disorders

Bahrain has been one of the first countries in the region to tackle the issue of genetic

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<td>n=2,000</td>
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<tr>
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<td>20%</td>
<td>20%</td>
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<tr>
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<td>21.0%</td>
<td>24%</td>
<td>12.5%</td>
<td>11.4%</td>
</tr>
<tr>
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<td>7.8%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Distant relatives</td>
<td>7.1%</td>
<td>6.8%</td>
<td>8%</td>
<td>7%</td>
<td>8.6%</td>
</tr>
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</table>

Table 5.1. Prevalence of consanguineous marriage in Bahrain (adapted from Al Arrayed, 1995; BFHS, 1995; Al Arrayed, 2005; Al Arrayed and Al Hajry, unpublished observations).
Blood disorders since 1986. Genetic blood diseases are frequent in Bahrain as in all the Middle Eastern countries. A history of malaria characterized the gulf region where it was endemic until eradicated in 1970, resulting in frequent manifestation of malaria related diseases.

**Sickle Cell Disease**

Previous neonatal screening in 1984-1985 showed that the birth prevalence of SCD was estimated to be 2.1%, with SCT being 11% and glucose-6-phosphate dehydrogenase (G6PD) deficiency being 25% (Mohammed et al., 1992; Nadkarni et al., 1991). In 2004, (SCD) was found to be the first cause of admission to SMC. The number of hospital admissions due to SCD gradually increased with 2600 patients admitted during 2005, which formed 6.5% of the total admissions to SMC (Bahrain Health Statistics Reports, 2004-2005).

Several studies have been conducted on genetic blood disorders in Bahrain. One such study depicted the nature of SCD among the population. The finding revealed exposure to cold to be the principal precipitating factor of painful crisis (45% of cases), followed by fever (35%), and exhaustion (35%) being the next most common. Moreover, the most common symptoms were pain and fever. The main signs were anemia (92%), hepatomegaly (64%), jaundice (64%), and urinary tract infection (30%; Al-Arrayed et al., 1994; Al-Arrayed et al., 1995).

Another study sought to evaluate the clinical presentations, and management of 200 Bahraini SCD patients who attended the SMC Accident and Emergency Department for Vaso-occlusive crisis during the period January-March 1994. The male: female ratio was estimated to be 2:1, with 60% of the group in the age range 15-30 years. Extremity pain was the most common presenting feature (86% of patients), followed by pain in the abdomen/generalized body ache (71%). Most patients (83%) responded to treatment with hydration, narcotic analgesics or non-steroidal anti-inflammatory drugs, and were discharged from hospital. The manifestations suggested that the Bahrainis have a mild form of SCD (Al-Arrayed and Hamza, 1995).

Molecular genetic studies were undertaken to determine the haplotypes of chromosomes carrying the sickle cell allele in Bahraini patients, and hence to consider the possible origin of these alleles (Al-Arrayed, 1995). The beta S gene was found to be linked to the Asian haplotype in 90% and to the S2 haplotype in 5% of the cases. The Bantu haplotype was found in few patients (only 2.5%), and the haplotype was found in association with β-thalassemia chromosomes in 2.5% of the cases only. The study showed that the Asian haplotype which is linked to a benign form of sickle cell disease is predominant in Bahrain (Al-Arrayed et al., 1995).

Jassim and Al-Arrayed (2006) reported on the molecular basis of the benign form of sickle cell/beta-thalassemia syndrome in two healthy Bahraini patients. The aim was to study the different molecular determinants that might cause an extremely mild form of sickle cell/beta-thalassemia syndrome among the population. Two healthy Bahraini students belonging to two unrelated families with normal clinical pictures were noticed to have the sickle cell/beta-thalassemia syndrome through hemoglobin electrophoresis. Different molecular genetic techniques were employed to study blood samples from these girls. Three different molecular determinants were found in these students:
compound heterozygosity for the sickle cell mutation and beta thalassemia mutation. Their corresponding haplotypes were the Saudi-Indian haplotype for the sickle cell mutation and 88 (C-to-A) beta-thalassemia mutation. Alpha-globin gene mapping revealed homozygosity for the rightward deletion (−α3.7/−α3.7/) for both the students. The study concluded that different molecular determinants were found in association with the mild form of sickle cell/beta-thalassemia disease, namely inheritance of a mild β+-thalassemia mutation, an HbS haplotype-associated high HbF expression, and coinheritance of alpha-thalassemia. All of these modulators were responsible for such a mild state of sickle cell disease in these patients.

**Beta Thalassemia**

Studies have indicated that the incidence of beta-thalassemia among Bahraini students is 0.02% while the trait rate remains between 2.5 and 3.5% (Al-Arrayed et al., 2003). The number of Bahraini babies born with beta thalassemia has shown a decline from four babies annually to two during the same period of 20 years.

Jassim and colleagues (2000) studied a total of 80 Bahraini individuals of whom 35 were transfusion-dependent beta-thalassemia major patients, 37 presented with the trait and eight were sickle cell/beta-thalassemia patients. The application of different molecular techniques on 67 beta-thalassemia alleles identified 12 different mutations. However, IVS-I-3’ end (−25bp), CD 39 (C-to-T), IVS-II-5 (G-to-C), IVS-II-2 (G-to-C), and IVS-II-2 (G-to-A) accounted for more than 80% of the total studied alleles. Other mutations common both to the Mediterranean basin [IVS-I-1 (G-to-A), IVS-II-1 (G-to-A), IVS-I-110 (G-to-A)] and the Indian subcontinent [CD8/9 (+G), CD 15 (G-to-A), CD 41/42 (−TCTT)] were also reported.

**Alpha Thalassemia**

Newborn screening in 1985 showed a high frequency of alpha-thalassemia in Bahrain at about 24% (Mohammed et al. 1992; Nadkarni et al., 1991), but only a few patients presented with manifestation of Hemoglobin H (HbH) disease. There were no reported cases of hydrops fetalis.

Jassim et al. (1999 and 2001) reported on the molecular basis of α-thalassemia in Bahrain. Various polymerase chain reaction (PCR)-based methodologies were involved, namely differential PCR amplification, PCR-restriction fragment length polymorphism (PCR-RFLP), and direct PCR-amplified genomic DNA sequencing. Five alpha-thalassemia determinates were identified, which included three deletional types, the rightward 3.7 kilobase (kb) deletion, the leftward 4.2 kb deletion, and the penta nucleotide deletion in 5’ splice donor side of intron I in the alpha 2-globin gene (GGTGAGG…), and two non-deletional alpha-thalassemia determinants, the Saudi type polyadenylation (polyA) signal mutation (AATAAA→AATAG) and the Turkish type polyA signal mutation (AATAAA→AATGAA) in the alpha 2-globin gene. The study concluded that the three alpha-thalassemia mutations, the Saudi type polyA signal mutation, the penta-nucleotide deletion and the rightwards 3.7 kb deletion accounted for 97% of all alpha-thalassemia determinants in Bahrain. Clearly, the interaction between the deletion alleles and the non-deletion alleles provides a complex picture in the phenotype.
Al-Mukharraq (1999) studied hemoglobin H (HBH) disease in 26 Bahraini patients, followed by an assessment of the severity of anemia. The mean age at diagnosis was estimated to be 6.7 years. The mean hemoglobin was 8.1 g/dl, and the mean HBH was 17.4%. Fifty percent of these patients required blood transfusion, seventeen children had average growth, while nine were below average. There were no significant thalassemic bone changes or splenomegaly observed; thus depicting a mild to moderate clinical picture.

Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, a genetic defect underlying a biochemical red cell abnormality, occurs worldwide with variable incidence and clinical presentation among different ethnic groups. The disease may express itself as a drug-induced hemolytic anemia with neonatal jaundice, hemolytic anemia following infection, chronic non-spherocytic hemolytic anemia, favism or may be asymptomatic. G6PD-deficiency is a sex-linked disorder. The incidence of G6PD-deficiency has been observed to be higher in the Arab World, and is in the range of 8% to 50% in different populations. The frequency in Bahrain is between 20-23%, but with little clinical problems (Bhagwat and Bapat, 1987; Mohammed et al., 1992; Al-Arrayed et al., 2003).

Al Momen et al. (2004) reported on the molecular homogeneity of G6PD deficiency in Bahrain. DNA extraction was done for 83 G6PD-deficient subjects and 80 normal controls. Combinations of PCR-RFLP and PCR-DGGE procedures were employed to uncover the sequence variations at nt 563 and nt 1311 in both subjects with deficient and normal G6PD activity. The study showed that nearly 90% (93/102) of the X chromosomes from G6PD deficient subjects had nt 563 (C-to-T; G6PD Med) mutation, whereas ~9% of the X chromosomes from G6PD deficient subjects might have had other G6PD variant(s) or normal X chromosomes in heterozygote females. Ninety-six percent (89/93) of the G6PD Med-bearing X chromosomes showed thymine (T) at nucleotide position 1311. In contrast, 70% (82/117) of the normal X chromosomes showed cytosine (C) at nucleotide position 1311, while it was thymine (T) in 30% (35/117) of the normal X chromosomes. The study concluded that the vast majority (91%) of X chromosomes from G6PD-deficient subjects in Bahrain are harboring the nt 563 (C-to-T) mutation. The G6PD Med variant in Bahrain is in tight linkage disequilibrium with thymine (T) at nt 1311. These data revealed a high molecular homogeneity of G6PD-deficiency in Bahrain.

Hemophilia

Hemophilia is an X- linked condition common in some Arab countries, but not common in Bahrain. Currently, only 10 patients are under treatment at SMC.

Frequencies of ABO Blood Groups and Rh Types

Al-Arrayed and colleagues (2001) estimated the frequencies of ABO and Rh phenotypes along with the respective gene frequencies in two study groups: (1) 5675 Bahraini school students in the age group of 16-20 years and (2) 7362 adult Bahraini blood donors. The frequencies of ABO groups in both study groups showed Group O>Group B>Group A>Group AB; where group O contributed to nearly
50% of the total. Both study groups also showed >90% frequency of the RhD positive phenotype. In conclusion, the frequencies of ABO and Rh phenotypes in Bahrain were similar to those reported from other countries in the Arabian Gulf region. These frequencies appear to be intermediate between the frequencies seen in Europe and Southeast Asia.

Campaign to Control Hereditary Blood Diseases

Bahrain successfully implemented a campaign to control hereditary blood diseases. This campaign included education and public awareness events, as well as antenatal, carriers, students, premarital, newborn, and prenatal screening methods followed by genetic counseling.

Information booklets were prepared and distributed widely in schools and to the public in an attempt to increase awareness. In 1991, the Bahrain Hereditary Anemia Society was established to further strengthen these efforts. In 1993, a premarital counseling (PMC) service was started, and in 1998, a student-screening project was initiated (Al-Arrayed, 1997). Additionally, attempts aiming at screening Bahraini newborns for these genetic diseases will soon be put into practice. Also, a molecular genetic laboratory has been established to study the genotype of difficult cases. As a consequence of all these efforts, which continued for about 20 years, evidence has shown a decline in the incidence of sickle cell disease by 50-60% from 2.1%-0.9%

Premarital Counseling Services

Premarital counseling is intended to identify couples at high risk, by subjecting all the couples intending to marry to undergo screening by history taking, physical examination and further laboratory investigations. In 1993, a voluntary premarital counseling (PMC) service was established, which successfully contributed towards reducing the number of affected newborns, thereby reducing morbidity and mortality rates. More recently a law (Government Gazette, 2004) has been passed by the Bahraini Government which requires all Bahraini couples planning to marry to undergo a mandatory premarital counseling. Any citizen about to get married, even if the spouse is non-Bahraini, must now undergo a premarital check up, which includes hereditary, infectious and other diseases according to the regulation issued by H.E. the Minister of Health. According to the results of the check-up, couples are given advice to undergo further investigation if needed, including treatment, health education, and counseling. Couples at risk of hemoglobinopathies are referred to the genetic department of SMC.

In addition, couples are subjected to counseling regarding high-risk behaviors, including those related to HIV, Hepatitis B, and other infectious diseases, which facilitate early detection and treatment of some sexually transmitted diseases, and help providing immunizations, as required. It also promotes awareness regarding reproductive health, family planning, and healthy lifestyles, and provides couples with medical, social, and psychological support, when needed.

After successful counseling of both partners, certificates are issued, therefore leaving the decision of marriage to the couple even if they are not inclined to take the advice with respect to the genetics aspect. At-risk couples are followed upon, if they decide to marry and all sorts of medical care are extended to their children.
The development of this law included wide consultation with all stakeholders to ensure that socio-cultural mores, theological issues, and aspects of human rights had been considered. The possibility of issuing a law making the premarital counseling obligatory was raised by the Ministry of Health with the Shura Council (a consultative body) after a thorough discussion, with the subsequent approval of the ministerial cabinet and was then forwarded to the Parliament, to pass into law in 2004. In view of its high degree of sensitivity, the draft law was subjected to extensive consultation involving a wide range of stakeholders, and subsequently it received positive support and backing from the Islamic clergy. The WHO guidelines and recommendations (WHO, 1983) were followed at all stages of the project. In addition, the recommendations of the Genomics and World Health Report (WHO, 2002), providing guidance on the ethical, legal and social implications (ELSI) in genetic screening, while laying stress on the key points of the informed consent, confidentiality, stigmatization and discrimination, were carefully considered prior to implementation of the new law.

During 2005, which was the first year of the implementation of the law, 9107 clients underwent observation. Out of these, 97 (1%) cases presented with sickle cell disease and 1176 (12.9%) were carriers of the disease. A beta-thalassemia major status was reported in 19 patients (0.002%) and 239 individuals (0.03%) were carriers for beta-thalassemia. In addition, G6PD deficiency was reported in 2037 patients (22%). These frequency figures were similar to those obtained from a student screening program (Bahrain Health Statistics Reports, 2005; Al-Arrayed, 2006).

Student Screening

The student screening for genetic blood diseases started in 1999. Covering about 50,000 students until now, the aim of the program is to raise awareness among the younger generation about these diseases through a comprehensive educational campaign, followed by screening. It also identifies carriers, thereby empowering them to make informed reproductive decisions in the future. The project operates for about six months on an average every year for planning, education sessions, blood collection, laboratory testing, and data processing, distribution of report cards, data analysis, and delivery of results.

The public was initially resistant to the screening program, because they feared that girls identified as carriers would not be able to find a husband. The education campaigns, therefore, stressed that (a) all people carry some defective genes; (b) carriers could avoid the risk of giving birth to an affected child if they married a non-carrier; and (c) no one, including carrier–carrier couples, would be prevented from marriage. Broad based public campaigns were also required to encourage parents and students to agree to undergo screening.

The screening is equally applicable for both male and female students. Testing is stated to be voluntary and permission of the parents is sought before screening, or directly from the students in case they are eighteen years or older. So far, approximately 80–85% of parents and students have voluntarily agreed to be tested each year.

In order to maintain privacy, test results are returned to students on a standardized official medical report card and are delivered via their school in a sealed
envelope. In order to further protect their privacy and confidentiality, students are encouraged to open their envelopes at home with their families. Certainly, this system also helped them in choosing their appropriate future partners.

Each school receives reports on the prevalence of the three diseases in their student body. At the same time, the program also ensures that the Ministry of Health obtains accurate and updated statistics, which assists them in planning for future services. The Ministry of Education also observes the prevalence of these diseases among students, enabling them to take necessary steps to ensure improved health of the students. The study also yields important information about the frequencies of different types of abnormal hemoglobin levels among the population (Al-Arrayed et al., 2003; Figure 5.1). The study showed that the frequencies of HbD A= 0.66%, HbD D= 0.02%, HbE E= very rare, and HbE A= 0.13%. Surely, the benefits and effects of these measures will be seen in the improved genetic health of present and future generations (Al Arrayed, 2005).

Congenital Abnormalities

The incidence of congenital abnormalities in Bahrain was observed in two different periods. The first study was carried out to determine the incidence of these anomalies in Bahrain by referring to the Ministry of Health statistics for the 11-year period, 1980 to 1990, while the second study looked at the same abnormalities in the period 1991 to 2000 (Tables 5.2 and 5.3).

![Figure 5.1. Prevalence of sickle cell disease (SCD) and sickle cell trait (SCT). Data obtained from the student screening program for genetic blood disease (1999-2004).](image)

Table 5.2. Average annual incidence rates of congenital anomalies (per 1000 births) in Bahrain for the periods between 1980-1990 and 1991-2000.

<table>
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<tbody>
<tr>
<td>Neural tube defects</td>
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</tr>
<tr>
<td>Coron heart defects</td>
<td>1.32</td>
<td>3.35</td>
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<td>0.26</td>
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<td>Cleft palate</td>
<td>0.35</td>
<td>0.9</td>
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<tr>
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<td>Goniourinary</td>
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<tr>
<td>Skin</td>
<td>-</td>
<td>0.3</td>
</tr>
<tr>
<td>Others</td>
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<td>1.6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>27 per 1000</strong></td>
<td><strong>16 per 1000</strong></td>
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The incidence of congenital anomalies in the first study was found to be 2.7% of live births, while it was found to be 1.7% in the second study. A study of each anomaly separately showed that anomalies of the musculoskeletal system had the highest incidence (2.28 per 1000 and 3/1000), followed by the genitourinary system (2.13 per 1000 births and 2/1000). The incidence of chromosomal disorders in the first study was 0.9 per 1000 births while in the second it was 1.2/1000, (Al-Arrayed, 1995).

Metabolic Diseases

Al-Arrayed (1995) highlighted the frequency of metabolic diseases. In line with this, a neonatal metabolic screening pilot study was performed on 1000 neonates, in which electro spray tandem mass spectrometry was applied. Blood samples were collected on Guthrie cards from the heels of infants on the 3rd to 5th days of their birth. The dried samples were mailed to the mass spectrometry laboratory at King Faisal Specialist Hospital, where they were analyzed for more than 20 metabolic diseases, such as amino acids, organic acids and carnitine esters. The results showed a high incidence of metabolic diseases. Annually, we expect approximately 100 neonates to be affected by metabolic diseases such as maple syrup urine disease, medium-chain acyl-Co-A dehydrogenase deficiency, primary carnitine deficiency, methylmalonic acidemia, and methylene tetrahydrofolate reductase deficiency. Many of these affected babies died within the first or second week, even before the diagnosis can be established.

Al Jishi (unpublished observations) found an approximate prevalence of 1/10,000 for PKU, propionic acidemia, and fatty acid oxidation defect (CPTII); 2/10,000 for MSUD, isovaleric acidemia, 3-methylglutaric acidemia, and glutaric aciduria 11; and 6/10,000 for methyl malonic acidemia, glycemic acidemia, and arginosuccinic aciduria.

Some other metabolic diseases that are frequently observed in Bahrain are mucopolysacharidosis (MPS), Niemann-Pick disease, GM2 gangliosidosis, Sanfilippo disease, I cell disease, glycogen storage disease, biotinidase deficiency, and mitochondrial disorders, but further studies are needed to determine their prevalence (Al-Arrayed et al., 1999).

These diseases have also been reported from other Arab countries. Ozmand et al. (1990) reported that certain lysosomal

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**Table 5.3.** Annual incidence rates (per 1000 births) of different anomalies observed between 1991 and 2000 (adapted from the Bahrain Health Statistics Reports, 1991-2000).

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<td>2.6</td>
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storage diseases including. MPS type 1VA, Morquio disease, Multiple sulphatase deficiency, Niemann-Pick disease type B, GM1 gangliosidosis type “0” (Sandhoff disease), and ceroid lipofuscinosis (Jansky Bielschowsky and Batten Spielmeyer Vogt syndrome) are more frequent in Saudi Arabia. Another study (Benson, 1988) found that MPS type II (I cell disease) was found to occur more frequently in Arabs than in any other ethnic group. Circumstances demand that frequencies of these diseases is kept track of, since most of these diseases may be diagnosed in the prenatal period, and affected individuals could receive potentially treatment by bone marrow transplantation (Whitley et al., 1980; Schaison et al., 1989; Teebi et al., 1987; Wraith et al., 1987).

Chromosomal Abnormalities

The incidence of chromosomal abnormalities was found to be relatively low in Bahrain. The incidence of Down’s syndrome among Bahrainis in 1993 was found to be 0.9 per 1000, compared with 1.4 per 1000 internationally while in 1991-2000 it was found to be 1.2 per 1000 (Al-Arrayed, 1996). The number of confirmed trisomy 21 cases in the Cytogenetic laboratory during 2004 and 2005 among 15000 newborns was 12 and 17 respectively, indicating a prevalence of 0.8/1000, and 1.1/1000, respectively.

Al-Arrayed and Rajab (1995) studied the data collected retrospectively of 104 Bahraini patients presenting with Down’s syndrome from hospital records during the period 1989-1993, which included all patients suffering from Down’s syndrome admitted to the main hospital in Bahrain during the 5-year period. Cytogenetic analysis had been performed on 89 patients. The mean age of patients admitted was 5 years, with 60% of patients under 1 year of age; the oldest patient was 31 years old. The most common complications were chest infections, congenital heart disease, increased susceptibility to all types of infection, anemia, and ear, nose and throat and eye complications. Karyotype analysis showed that 97% of those studied had free trisomy, 2% had translocation and one patient had a mosaic karyotype.

A slight increase in trisomy 13 and trisomy 18 births has been noticed during the last few years. Fragile X syndrome was reported in five Bahraini families (Al-Arrayed, 1990).

Al Arrayed (1996) also reported on cytogenetic studies on 500 Bahraini patients suspected of having chromosomal abnormalities on the basis of physical and/or developmental clinical features. Almost 27% of these patients were found to have abnormal karyotypes. Numerical abnormalities (including trisomy 21) were found in 19% of patients, whereas structural abnormalities manifested in 7%.

Al-Arrayed (2003) studied inheritable chromosomal abnormality causing recurrent fetal wastage and abnormalities in children. Cytogenetic studies were performed on Bahraini patients suspected of having chromosomal abnormalities. Ten families inheriting different chromosomal abnormalities were reported.

The first family studied had one child and had six abortions. The chromosomal analysis showed interesting results. Both wife and husband presented with different chromosomal abnormalities. The wife had 45, XX, der (13; 14) (q10; q10), whereas the husband had 46, XY, inv (3) (p25q21). However, their child was phenotypically normal, though he inherited abnormal
chromosomes from both parents. The second family had three mentally retarded children with Trisomy 21. The third family had a male child with 46, XY, rec (8), dup p, inv (8) (P23.1 q 24.2). He inherited the abnormal chromosome from his mother. In the fourth family, the patient was married to her first cousin. She had 4 p 3 D 2 A1L1. Both the wife and the husband had the same balanced reciprocal translocation, t (6; 10) (q 15; q 21.2). Their retarded baby girl presented with the same chromosomal abnormality. The fifth family had an encephalic stillbirth and an abortion. The husband had a pericentric inversion of the Y chromosome. The sixth family had two children with trisomy 21; the mother presented with mild Down’s syndrome features. The seventh family had four children, all mentally retarded with fragile X syndrome. The father was declared as the transmitting parent. The eight family had a mentally retarded child with fragile X syndrome. The mother and five of her sisters were carriers for fragile X and the grandfather was observed to be the transmitting parent. In the ninth family, the father’s karyotype was 46, XY, inv. per. (2) (p12.q14). He had a balanced pericentric inversion of chromosome 2. His first child was abnormal with trisomy 13. In the tenth family, the father had 46, XY/46,XY,rea (2). The family had three abnormal mentally retarded children and had two abortions. This indicates that inherited chromosomal abnormality is not a rare condition, and that cytogenetic studies should be conducted for any family with abnormal children and with recurrent fetal wastage.

Al-Arrayed (1990 and 2003) reported on a consecutive series of fifty couples with history of fetal wastage. They were cytogenetically studied with current banding techniques. Fetal wastage was defined to be occurring in the couples who had had more than two early abortions, stillbirth(s), or live-birth(s) with multiple congenital anomalies. One couple was found to be carriers for a balanced reciprocal translocation. A woman was found to have Robertsonian Translocation, while another woman was found to be a mosaic (46, XX, 47, XXX). Moreover, one husband was found to have pericentric inversion of Y chromosome. These findings reveal that parental chromosome abnormalities account for fetal wastage in 8% of couples having such a history.

Cystic Fibrosis

Cystic fibrosis is a hereditary multi-system disease transmitted as an autosomal recessive disorder. It leads to chronic pulmonary diseases, pancreatic enzyme deficiency and abnormally high concentrations of electrolytes in sweat (Khan, 1985).

Al-Arrayed and Abdullah (1996) performed an intensive retrospective search for patients with cystic fibrosis from clinical data and hospital records from SMC, with the aim of determining the prevalence of cystic fibrosis in Bahrain. The survey included 27 patients confirmed as having cystic fibrosis, born during the period 1978—1994. Almost 200,000 children were born in Bahrain during this period. Diagnosis was established by the presence of high sodium and chloride (≥ 70 mmol/L) concentrations in sweat. The mean incidence during this period was found to be 1 in 7700. All cases were diagnosed during the first year of life, and 60% were diagnosed in the first 3 months of life. The male:female ratio was 14:13. The incidence of meconium ileus was 16%. Mortality in the neonatal period was 60%. The first–cousin marriage rate among these families was 63%. Another study in 1998 reported the incidence of cf as 1/5800. The gene
frequency seems to be low in Bahrain, while it is high in Caucasian population where the carrier frequency is about 1:20 to 1:25 (Warwick, 1978).

Eskandarani (2002) undertook a genotypic study to characterize the cystic fibrosis transmembrane regulator gene mutations (CFTR) in the Bahraini cystic fibrosis (CF) population using a polymerase chain reaction-based direct gene test to search for 15 common CF mutations amongst Arabs. During the period October 2000 to May 2001, 19 patients from 13 families were recruited in the study. Patients were diagnosed as having CF, based on a typical clinical picture and sweat chloride levels (> 60 mmol/l). Eight mutations were detected in 21 of the 26 alleles examined of the eight mutations detected, four were common among Bahrainis (2043delG > 548A-to-T > 4041C-to-G = F508, in order of decreasing frequency), accounting for 66 % of the Bahraini CF alleles. However, four different heterozygous mutations were also detected, namely: 1161delC, 1756G-to-T, 3120+1G-to-A, and 3661A-to-T, accounting for 16 % of the Bahraini CF alleles.

Congenital Blindness

According to Al-Arrayed, 1992; Ahmed and Selvyn, 1988; and Al-Alawi et al., 1998, the most common eye condition leading to low vision and blindness in Bahrain are cataract, followed by glaucoma and corneal diseases. The following causes of congenital blindness were reported in Bahrain: Retinal dystrophy, congenital glaucoma, congenital cataract, retinopathy, macular degeneration, mesodermal dysgenesis, optic nerve dystrophy, retinitis pigmentosa, Leber’s optic dystrophy, while oculocutaneous albinism was observed to causes poor vision among some families.

Ahmed and Selvyn (1988) found that consanguinity rate was positive in 42% of families with children with visual disability, but the consanguinity rate in the general population at that period was estimated to be 40%.

Hereditary Deafness

Jamal examined 196 children presenting with deafness and speech delay, who were referred to hearing impaired children clinic at SMC for over a period of 10 years from 1989-1996. The incidence of profoundly deaf children was estimated as 1.1 per 1,000 live births. Children with positive history of deafness in the family due to genetic causes constituted 37.8%. Reviewing the consanguinity rate among parents illustrated that 48.5% were first cousins, whereas 12.2% were far related which indicated high rate of consanguinity among parents. In one family, Connexin 26 was found to be the responsible gene. However, further molecular studies are needed in this field (Jamal, 2000).


The Salmaniya Medical Complex (SMC) is the main hospital for secondary and tertiary care in Bahrain. All rare, chronic and difficult cases are referred to this hospital. The records of patients admitted to SMC and diagnosed with genetic diseases and were studied. The record system was based on the WHO International Classification of Disease (ICD) 9 until 2002, when it was upgraded to ICD 10. The results highlight the magnitude of morbidity caused by each of these genetic diseases.

The number of patients admitted into SCD during this period was estimated to be around 7000. On the contrary,
the number of patients presenting with thalassemia did not exceed hundred, whereas other genetic diseases occurred at lower frequencies, and were not recorded in more than dozens or less.

During this 17-year period, 14 patients admitted with congenital hypothyroid, and the estimated prevalence for this disease was 1/2000. Patients with hemolytic anemia due to ABO were evaluated to be 21 in number. About 19 patients with leukodystrophy, 511 with disorders of lipoprotein metabolism, 138 with congenital hydrocephaly, 106 with anomalies of spine, 10 with Alzheimer’s, 15 with cerebral lipidodsis, 65 with Huntington’s disease, and 103 patients with multiple sclerosis were reported.

The numbers of cases presented does not accurately reflect the epidemiology of these disorders in Bahrain, as there is no referral basis that ensures the investigation of all possible genetic diseases. It does, however, give an idea of the common genetic disorders among Bahrainis.

Some other disorders reported include neurofibromatosis, epidermolysis bullosa, ichthyosis, G syndrome, polycystic kidney, polycystic ovaries, Parkinsonism, osteogenesis imperfecta, porphyria, hereditary 1,25 dihydroxyvitamin D-resistant rickets, and malignant hyperthermia (Khan et al., 1996; 1987; Al-Jishi, 2004; Al-Arrayed, 1999; Aldeen et al., 1999; Kooheji, 1988; Zayyani, 1987; Mohammad and Ebrahim,1985; Al-Ansari, 1984).

Spino muscular Atrophy

A significantly increasing number of families were found to present with spino muscular atrophies. Four families were reported with spino muscular atrophy, of which three had acute infantile type (Werdnig- Hoffmann or SMA1), while one presented with chronic childhood SMA. Apparently, there was an increased frequency of SMA among Bahrainis as three to four deaths occurred every year in the pediatric wards due to SMA1. One of the mothers had neuromuscular disorder manifested in diplopia and hoarseness of voice. Her younger brother and three of her male children had died in infancy.

SMA1 carrier frequency in the Caucasian population was shown to be 1:80, and that of chronic childhood SMA was 1:90 (Pearn, 1973). However, the frequency of carriers is very high in some communities (Schaap, 1985; Moosa and Dawood, 1990; Czeizel, 1989; Czeizel and Hamula, 1991). In the Occupied Territories, Fried and Mundel (1977) have found high incidence of SMA1 in the Egyptian Karaite community where the frequency of heterozygotes was about 1:20. Chronic childhood SMA has now been mapped to chromosome 5q11.2-13.3 with the gene of SMA1 located in the same general area (Brzustowicz, 1990; Melki et al., 1990; Melki, 1991).

Noonan Syndrome

Noonan syndrome (NS) is an autosomal dominant dysmorphic syndrome characterized by hypertelorism, a downward eye slant, and low-set posteriorly rotated ears. Other features include short stature, a short neck with webbing or redundancy of skin, cardiac anomalies, epicanthic folds, deafness, motor delay, and a bleeding diathesis.
Ten cases of NS have been reported from Bahrain. Four of them were Bahraini boys, and six were Pakistani girls (3 alive and 3 deceased). One of the Bahraini boys was a sporadic case, while the other three were siblings of one family. It was conjectured that the father could be the transmitting parent as he had ptosis, but was normal mentally. A changing phenotype with age was found to manifest in this family (Allanson et al., 1985). The 2-year-old boy had more severe edema, ptosis and a round face whereas the eldest boy had EEG abnormality and seizures. Lemmi (1983) reported that 71% of NS patients had electroencephalogram-graphic abnormalities, and that 82% had some type of neurological anomalies. In the cases of NS reported in the Pakistani family, all the affected girls had pulmonary stenosis. The mother had short stature of about 142 cm, but she was normal mentally, and could be the transmitting parent.

**Lawrence–Moon–Bardet–Beidl Syndrome**

Two consanguineous Bahraini families with Lawrence Moon Biedl syndrome (LMBBS) were also reported from Bahrain. Out of these two families, one presented with Bardet Biedl syndrome (BBS) with two siblings manifesting the typical clinical picture of this syndrome (Al-Arrayed and Al-Arrayed, 1991). On the contrary, the other family had Laurence Moon syndrome (LMS).

In 1977, Toledo et al. suggested the splitting of LMBBS into LMS and BBS as different but interrelated autosomal recessive disorders. Apparently, there is an increased frequency of this autosomal recessive syndrome among Arabs. Kalabian in 1956 reported the first case of this condition in an Arab boy. Other cases were reported by Abdel Aziz in 1972, and Temtamy and Shalash in 1975. In Jerusalem, Ehrenfeld et al. (1970) reported 18 cases of BBS. These cases were descended from 12 families, with 3 of them being Arabs and 9 being Jewish. Farag and Teebi (1988 and 1989) reported high incidence of BBS among Bedouins in Kuwait. They estimated the incidence in a mixed Arab population of Kuwait to be as high as 1:36,000, which was much higher than the prevalence of this disease in Switzerland (Buyse, 1979; Klien and Amman, 1969). Amongst 36 cases, 24 were Bedouins. They estimated the prevalence among Bedouins to be 1:13,000. The rest of the cases were from Saudi Arabia, Iraq, Syria, and Palestine (Temptamy and McKusick, 1978; Pagon et al., 1982; Bauman and Hogan, 1973; Hurley et al., 1975; Massof et al., 1979).

**Carpenter Syndrome**

Two of the families had Carpenter syndrome, with one family from Egypt and the other one from Iran. In both the families, the affected individuals were the products of consanguineous marriages. The affected presented with acrocephaly, peculiar facies, brachydactyly, and syndactyly in the hands, and preaxial polydactyly and syndactyly of the toes.

**Goldenhar Syndrome**

Two other families had babies with Goldenhar syndrome. One of them was Pakistani. The mother in the other family was Bahraini and the father Palestinian. The etiology of this syndrome is unknown, it is usually sporadic but some familial cases have been reported. The risk for first degree relatives is about 2 percent (Burck, 1983; Wilson, 1983).
Other Observed Syndromes

- Brachmann-de Lange syndrome
- Smith-Lemli-Opitz syndrome
- Seckel syndrome
- Retinoblastoma
- Achondroplasia
- Wolman disease

Non-Communicable Diseases

Health problems in Bahrain are those generally experienced by countries passing through a stage of transition from developing to developed nations. Over the years, communicable diseases have shown a declining trend as the major causes of mortality and morbidity. They are being replaced by non-communicable ones such as cardiovascular diseases, cancer, metabolic diseases, congenital anomalies and accidents, as compared to spontaneous abortion/miscarriages that were the most common complications in pregnancies throughout the word.

The National Family Health Survey (NFHS) in 1995 reported a dramatic increase in non-communicable diseases (NCD), such as cardiovascular disease (CVD), diabetes and cancer in Bahrain. Cardiovascular diseases and cancer were the leading causes of death. Diabetes prevalence was estimated to be between 20 and 30% depending on the study. This represented a common global trend, which affected the Arabian Gulf and the Eastern Mediterranean Region exponentially. The share of non communicable diseases of the region’s disease burden is expected to rise to 60% by the year 2020. The incidence of hypertension in the EMR area is 26% and diabetes ranges between 7-25%. The burden in terms of suffering and health costs is also immense.

NFHS also reported that: the most frequently reported chronic condition for both men and women were high blood pressure, joint disease and cardiac disease. Prevalence of these conditions rose steadily with age, among those aged 50 and over. Hypertension was the most common (15% for men and 27% for women), followed by diabetes (14% for men and 19% for women) and joint disease (7% for men and 18% for women), while heart disease prevalence was 7% for both men and women.

The Ministry of Health statistics for 2005 reported also on Mental Health. It showed that mental illnesses are increasingly becoming a universal problem in their distribution due to the rapid changes in the country’s socio-economic status, education and life style. Although Bahrain is a considerably small country, it has its own share of problems in terms of frequency distributions of socio-demographic characteristics, patterns trends and their relationship. A study was conducted on the data of inpatients at the Psychiatric Hospital over the past five years. The Psychiatric hospital is the only hospital in the country, which provides mental health care. In 2005, the distribution of discharges (1,159) according to the principal diagnosis showed that 24.2% of patients admitted were diagnosed as schizophrenics, 23% were depressed, 22% were drug dependent, and 30.8% suffered from other mental disorders. About 67% of all the discharges were among male patients. It was clear that throughout the selected four age groups, males of age group 15-44 years took the bulk of the total discharges at 44.2%. These statistics indicate that the Non communicable diseases (NCD’s) such as cardiovascular diseases, cancer, and diabetes are leading causes of morbidity and mortality in Bahrain.
Diabetes

Studies on the epidemiology of diabetes in Bahrain reported a prevalence of about 25% in those aged 20 years and over in a primary care-based study (Zorba, 1996) and 30% in people aged 40-69 years in a population-based study (Al-Mahrous, 1998). On the other hand, the study of Bahrain Family Health Survey, showed a total prevalence of 5.5% of diabetes mellitus and 6.3% of hypertension.

Cardiovascular Diseases

Cardiovascular disease (CVD) is considered the leading identifiable cause of death in Bahrain. They were reported to be responsible for 28.24% of deaths in 2003. The Health statistics Report for 2005 report states that cardiovascular diseases constitute the highest single cause of mortality in Bahrain, representing 69.9 per 100,000 of the population, accounting for more than 22% of total deaths at Salmaniya Medical Complex. The rate of deaths from circulatory disease distributed by gender showed 60.6 mortalities per 100,000 males and 59.1 mortalities per 100,000 females. This trend however, did not change dramatically since the seventies. Coronary heart disease (CHD; ICD: I20-25) seems to be the predominant type of cardiopathy encountered in Bahrain. CHD was also found to be the fourth leading cause of discharges from SMC in 2003. Coronary heart disease (CHD) and stroke are the predominant type of CVD encountered in clinical practice.

Known risk factors for CVD such as smoking, and raised blood cholesterol, and risk factors, such as lack of physical activity, obesity, and alcohol consumption are expected to have increased in Bahrain over the last two decades. In addition to that, the continuing rises in the incidence of the cardiovascular diseases is also association with the rise in the size of the over-sixty-five-years-of-age-population, who represent nearly 2.5% of the total population.

Cancer

Cancer is the third leading cause of death in Bahrain, accounting for 11.9% of all deaths (Annual Health Statistic Reports, 2004; Table 5.4). The age-standardized

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Table 5.4. Frequency of different malignancies among the male and female groups in Bahrain (adapted from Ministry of Health Cancer Statistics, 2004).
rate for incidence of cancer in Bahrain is 167 and 141 per 100,000 males and females, respectively. However, these rates are considerably lower than the corresponding figures reported in industrialized countries. More than 300 individuals are diagnosed with cancer annually with an estimated incidence rate of 66/100,000 population.

Lung cancer is the leading type of causes among males accounting for 14.5% of registered cases in 1998, and 17.25% of Bahraini patients. The crude incidence rate was 6/100,000 of the population, and among Bahrainis it was 11.6/100,000 (Table 5.4). Breast cancer is the leading cancer among females, accounting for 30% of all new cases diagnosed in 1998 and 27% of Bahraini patients. The crude incidence was 17/100,000 of the female population and 18/100,000 of Bahraini females.

**Recommendation**

In general, health care in Bahrain has improved during the last two decades, and gradually the problems of genetic disorders are becoming the subject of interest. We conclude that much has to be done to study and reduce the rate of these genetic disorders among Bahrainis.

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