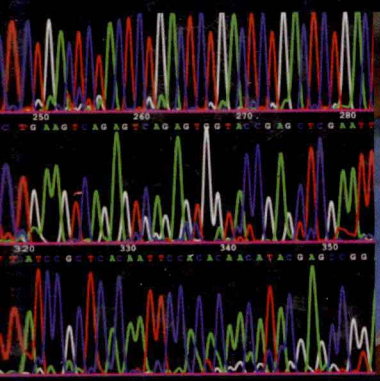
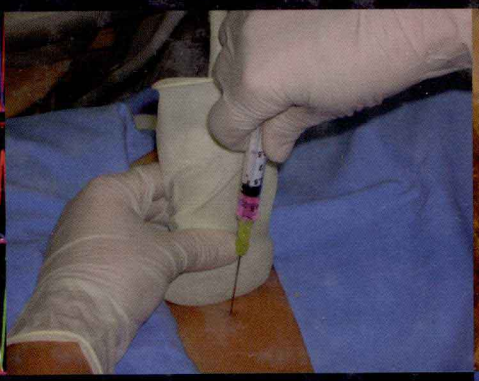
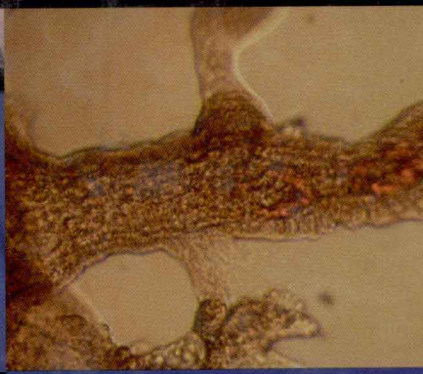
Genetic Disorders and the Fetus

Diagnosis, Prevention and Treatment







SIXTH EDITION

Aubrey Milunsky
and Jeff M. Milunsky

WILEY-BLACKWELL

Genetic Disorders and the Fetus

Diagnosis, Prevention and Treatment

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Preface

In the search for accurate and reliable information, a discerning reader would welcome a source that reliably dispenses evidence-based facts embellished by knowledge, experience and wisdom. This precious distillate, tinctured with recommendations and guidance born of long experience, is not reachable by the most avid electronic voyeur. Sifting through mountains of unfiltered, irrelevant, unreliable or misleading information, electronic searches simply spawn reams of paper, mostly lacking critical analysis of the subject in question. At best, authors will describe "limitations" in their studies, while awaiting guidance from their clinical Colleges or Societies, which often takes years.

Fortunately this volume, a major repository of facts about prenatal diagnosis, provides a critical analysis and synthesis of established and new knowledge based on the long experience of authorities in their respective fields. The guidance provided and the insights and perspectives of these authors make this volume a valuable and indispensable resource for all whose focus is securing fetal health through prenatal diagnosis.

A broad international perspective is presented in this volume with authoritative contributions from authors in nine countries. All chapters have been revised and updated, new guidelines emphasized, and three new important chapters added. The first addition is the use of chromosomal microarrays in prenatal diagnosis. Clinical trials, now underway, will help determine the frequency of detecting a microdeletion/duplication of clinical significance which would have otherwise been missed by routine cytogenetics. At the same time, a clear measure should emerge of how often copy number variations of uncertain significance are determined and how often they are deemed "probably benign". Compounding the normal anxiety expectant mothers experience during prenatal diagnosis with significant degrees of uncertainty will not only be unhelpful, but may cause harm if unnecessary pregnancy termination is pursued. Major reservation is expressed in this chapter about application of this new technology, which is constantly being refined, to preimplantation genetic diagnosis (PGD). The second addition is the chapter that is focused on the social, legal and public policy issues with special reference to international approaches to prenatal diagnosis. The third addition expands previous coverage of the important peroxisomal and related fatty acid oxidation disorders.

The fundamental pillars of this sixth (and earlier) edition(s) are represented by the other 32 chapters which are replete with the factual basis of prenatal diagnosis, synthesis, critical analysis and guidelines. In the opening chapter, the principles and practice that underscore preconception, prenatal and perinatal genetic counseling is presented in detail with emphasis on lessons learned since the inception of prenatal genetic diagnosis. An enormous factual base is provided in a chapter on amniotic fluid function and constituents including pesticides, carcinogens and other environmental contaminants, while the essentials of cell culture for prenatal diagnosis are provided in another. Chapters on amniocentesis and fetal blood sampling, and chorion villus sampling are anchored by authors with a lifetime of experience. Prenatal chromosome diagnosis, the bedrock upon which this subject was built, is again captured in an authoritative extensive chapter that is pertinent to all engaged in prenatal diagnosis, and enhanced by a separate chapter on molecular cytogenetics and the use of fluorescent in situ hybridization.

Clear guidance is provided for the genetic counseling and management following the frequently incidental prenatal diagnosis of a sex chromosome disorder, while the Fragile X syndrome is extensively addressed by pioneers. Recent and continuing advances in molecular genetics now command a central role in prenatal diagnosis reflected by the many serious monogenic disorders amenable to early detection. Comprehensive, authoritative and important chapters on biochemical genetics encompass much that is known about the prenatal

diagnosis of the lipid storage disorders, the mucopolysaccharidoses, the organic and amino acid and related disorders of metabolism, the disorders of carbohydrate metabolism, the peroxisomal and related fatty acid oxidation disorders and the disorders of folate and cobalamin metabolism.

Revised and updated chapters on cystic fibrosis, congenital adrenal hyperplasia and the primary immunodeficiency disorders are followed by a masterly discourse on the hemoglobinopathies. New advances combining molecular genetics and fetal imaging provide valuable information in the re-written chapter on connective tissue disorders. An extremely thorough exposition of maternal serum screening for neural tube defects, Down syndrome and chromosome abnormalities, occupies two chapters reflecting current practice. Biochemical screening for neural tube defects heralded previously as one of the most important advances in prenatal diagnosis, may well be largely replaced soon by ultrasonography once the technical skills have been universally mastered.

Sophisticated ultrasonic imaging for fetal structural and functional abnormalities are superbly covered in two updated chapters, while the growing importance of fetal magnetic resonance imaging in resolving difficult diagnostic quandaries is expertly covered in a re-written chapter.

Any attempt at prenatal diagnosis must be preceded by counseling at which time the provider must be fully informed about the details if induced abortion will need to be considered. An updated expert revision of a chapter on the subject provides the necessary facts and guidance to be shared with a patient. Avoidance of abortion is facilitated by preimplantation genetic diagnosis (PGD) which is fully updated in a revised chapter detailing a remarkable array of achieved diagnoses. Screening for aneuploidy prior to implantation seems common sense, but uniform supportive data are lacking, some concluding that randomized controlled trials are needed, while others maintain that sufficient data exists to indicate an unfavorable practice. Clearly, more definitive research is required.

Among the most anticipated and exciting developments is non-invasive prenatal diagnosis by analysis of fetal DNA and RNA in the maternal circulation. The technological innovations, now developing rapidly and including shot-gun sequencing of fetal DNA, are described and assessed in a re-written expert chapter.

Advances in fetal therapy, either directly or via the maternal circulation, have continued and require attention given opportunities to intervene, especially where surgical or medical treatment can save the fetus, as described in two re-written and revised chapters. Cogent issues of law, ethics and public policy as they apply to prenatal diagnosis are explored in depth by acknowledged experts in the three last chapters. Greater public awareness of genetics has alerted many to the opportunities of preventing adverse outcomes in pregnancy. One consequence has been escalating litigation by those deprived of the chance to avoid harm, which is also discussed in the first chapter.

This reference text, with contributions uniquely first authored by senior professors and directors, is a veritable repository of information on prenatal genetic diagnosis, is very heavily referenced, full of guidance and reflective of the lifetime experience and wisdom of the authors. This addition encompasses 162 tables, 129 figures, including 14 color plates, and nearly 9000 references. An extensive table of additional disorders amenable to prenatal diagnosis is added as an appendix. A valuable index will enrich the reader's search for specific information.

Exciting progress marks the 45th year since the introduction of prenatal cytogenetic diagnosis by amniocentesis and cell culture. Major recent advances include significant progress in the development of chromosomal microarrays, gene discovery and fast next-generation gene sequencing, fetal imaging, non-invasive prenatal diagnosis and preimplantation genetic diagnosis. We hope that this edition will once again provide evidence-based guidance, insight and perspective, combined with an enormous factual base. Recognition of many new and unresolved challenges should provide inspiration for novel research initiatives. Mostly however we hope that the progress mirrored in this volume and the anticipated progress will help reassure many parents at risk that they can avoid either conceiving offspring with serious/lethal genetic disorders or having affected offspring that could have been detected prenatally.

Aubrey Milunsky and Jeff M. Milunsky
Boston

Acknowledgments

Only rarely does one encounter a major reference text in which every chapter is written by an acknowledged authority or internationally recognized expert. Such is the nature of this sixth edition in which outstanding physicians, scientists and academicians have again considered it worthy to have taken the time to share their expertise, experience, and wisdom. Readers in many disciplines in which fetal and maternal health and welfare are paramount will be the beneficiaries of the information and guidance proffered. We are extremely grateful to all our authors for their superb contributions.

We are also most grateful to my senior executive secretary, Mrs. Marilyn McPhail, who yet again effectively demonstrated the art of multi-tasking.

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Contents

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1 Genetic Counseling: Preconception, Prenatal and Perinatal

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Advances in molecular genetics and fetal imaging have enriched our ability to secure early prenatal diagnosis of a rapidly enlarging spectrum of genetic and developmental disorders. *Pari passu*, a newly added layer of diagnostic uncertainty has dawned created by an extant lack of knowledge about polymorphisms and developmental structural and functional variations. Cognizance of "normal" has always been important and is especially critical in the evolution of fetal health. Analyses via chromosomal microarrays and whole-genome sequencing make mandatory the need to first delineate normal variation, if erroneous decision making is to be avoided.

The widening scope of molecular diagnostics and fetal imaging has increased opportunities for predictive, preconception, preimplantation and prenatal diagnosis. Consequently, genetic counseling for prenatal diagnosis can be expected increasingly to involve newly recognized microdeletion and microduplication syndromes (see Chapter 10), early adult-onset malignancies, neurodegenerative, cardiovascular and other fatal genetic disorders, as well as those with significant morbidity.

Against this background, physicians in all specialties are expected to be cognizant of new developments in genetics that facilitate the prevention or avoidance of genetic or acquired defects. In context, women at risk for having progeny with defects expect to be informed about their odds and options, preferably during preconception counseling. Their concerns are serious, given the significant contribution of genetic disorders to morbidity and mortality in children and adults.

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The incidence, prevalence and burden of genetic disorders and congenital malformations

Various measures reflect the population burden of genetic disease and congenital anomalies. Common assessments include the incidence or prevalence of the disorder/defect, the associated morbidity and mortality, the degree of disability and suffering, life expectancy and economic burden. Indeed, many factors influence efforts to accurately determine the incidence or prevalence of congenital anomalies or genetic disorders. Box 1.1 encompasses the majority of known etiologic categories, discussed below, which help explain sometimes striking differences among major studies. It is almost impossible to account for all these potentially confounding factors in a study and rarely has any one study come close.

Incidence and prevalence

Estimates of aneuploidy in oocytes and sperm reach 18–19 percent and 3–4 percent, respectively.[1] Not surprisingly, then, about one in 13 conceptions results in a chromosomally abnormal

Box 1.1 Factors that influence estimates of the incidence or prevalence in the newborn of a congenital malformation (CM) or genetic disorder

Availability and use of expertise in prenatal diagnostic ultrasound
Case selection, bias and ascertainment
Consanguinity
Definitions of major and minor congenital anomalies
Economic level in developed or developing world
Family history
Frequency, inclusion and exclusion of stillbirths, fetal deaths and elective pregnancy termination
Frequency of certain infectious diseases
History of recurrent spontaneous abortion
In vitro fertilization
Incidence and severity of prematurity
Intracytoplasmic sperm injection
Later manifestation or onset of disorder
Maternal age
Maternal alcohol abuse
Maternal diabetes and gestational diabetes
Maternal diet
Maternal epilepsy, lupus erythematosus and other illnesses
Maternal fever or use of hot tub in the first 6 weeks of pregnancy
Maternal grandmother's age
Maternal obesity
Maternal use of medication
Multiple pregnancy rate
Paternal age
Previous affected child
Previous maternal immunization/vaccination
Season of the year
Training and expertise in examination of newborns
Use of chromosomal microarray
Use of death certificates
Use of folic acid supplementation
Use of maternal serum screening for Down syndrome
Use of maternal serum screening for neural tube defects
Use of prenatal necropsy
Use of registry data

conceptus,[2] while about 50 percent of first-trimester spontaneous abortions are associated with chromosomal anomalies.[3] Clinically significant chromosomal defects occur in 0.65 percent of all births; an additional 0.2 percent of babies are born with balanced structural chromosome rearrangements (see Chapter 6) that have implications for reproduction later in life. Between 5.6 and 11.5 percent of stillbirths and neonatal deaths have chromosomal defects.[4]

Congenital malformations with obvious structural defects are found in about 2 percent of all births.[5] This was the figure in Spain among 710,815 livebirths,[6] with 2.25 percent in Liberia,[7] 2.03 percent in India,[8] and 2.53 percent among newborn males in Norway.[8a] The Mainz Birth Defects Registry in Germany in the 1990–1998 period reported a 6.9 percent frequency of major malformations among 30,940 livebirths, stillbirths and abortions.[9] Factors that had an impact on the incidence/prevalence of congenital malformations are discussed below.

More than 12,000 monogenic disorders and traits have been catalogued.[10] Estimates based on 1 million consecutive livebirths in Canada suggested a monogenic disease in 3.6 in 1,000, consisting of autosomal dominant (1.4 in 1,000), autosomal recessive (1.7 in 1,000) and X-linked-recessive disorders (0.5 in 1,000).[11] Polygenic disorders occurred at a rate of 46.4 in 1,000 (Table 1.1).

At least 3–4 percent of all births are associated with a major congenital defect, mental retardation or a genetic disorder, a rate that doubles by 7–8 years of age, given later-appearing and/or later-diagnosed genetic disorders.[12,13] If all congenital defects are considered, Baird et al.[11] estimated that 7.9 percent of liveborn individuals have some type of genetic disorder by about 25 years of age. These estimates are likely to be very low given, for example, the frequency of undetected defects such as bicuspid aortic valves that occur in 1–2 percent of the population.[14] The bicuspid aortic valve is the most common congenital cardiac malformation

Table 1.1 The frequencies of genetic disorders in 1,169,873 births, 1952–1983[11]

Category	*Rate per million livebirths*	*Percentage of total births*
A		
Dominant	1,395.4	0.14
Recessive	1,665.3	0.17
X-linked	532.4	0.05
Chromosomal	1,845.4	0.18
Multifactorial	46,582.6	4.64
Genetic unknown	1,164.2	0.12
Total	53,175.3	5.32[a]
B		
All congenital anomalies 740–759[b]	52,808.2	5.28
Congenital anomalies with genetic etiology (included in section A)	26,584.2	2.66
C		
Disorders in section A plus those congenital anomalies not already included	79,399.3	7.94

[a] Sum is not exact owing to rounding.

[b] International Classification of Disease numbers.

and in the final analysis may cause higher mortality and morbidity rates than all other congenital cardiac defects.[15] A metropolitan Atlanta study (1998–2005) showed an overall prevalence of 81.4 per 10,000 for congenital heart disease among 398,140 livebirths.[16] These numbers lead to a significant genetic disease burden and have accounted for 28–40 percent of hospital admissions in North America, Canada and England.[17,18] Notwithstanding their frequency, the causes of over 60 percent of congenital malformations remain obscure.[19,20]

The availability of prenatal diagnosis and maternal serum screening for neural tube defects (NTDs) and Down syndrome (DS) has also affected the birth frequency of these two most common congenital defects. One French study of the impact of prenatal diagnosis over a 21-year period (1979–1999) in a well-defined population showed a drop of 80 percent in the birth prevalence of DS.[21] A later report from the Paris Registry of Congenital Anomalies (2001–2005) noted a "fairly stable prevalence of DS (7.1 per 10,000 livebirths) over time."[22] A study from Newcastle, England, based on ascertainment of all cases of NTDs revealed a twofold reduction in the birth prevalence between 1984–1990 and 1991–1996.[23] A Scottish study aimed at assessing the impact of prenatal diagnosis on the prevalence of DS from 1980 to 1996. Both births and pregnancy terminations were included. Pregnancy terminations for DS rose from 29 percent to about 60 percent.[24] In contrast, the prevalence of DS noted by the Dutch Paediatric Surveillance Unit in 2003 was 16 per 10,000 livebirths, exceeding earlier reports and thought to reflect an older maternal age cohort.[25] In the US, a DS prevalence rate of 13 per 10,000 was found in metropolitan Atlanta (1979–2003).[26]

The effect of folic acid supplementation, via tablet or food fortification, on the prevalence of NTDs, now well known to reduce the frequency of NTDs by up to 70 percent,[27,28] (see Chapter 23) has only recently been assessed in this context. A Canadian study focused on the effect of supplementation on the prevalence of open NTDs among 336,963 women. The authors reported that the prevalence of open NTDs declined from 1.13 in 1,000 pregnancies before fortification to 0.58 in 1,000 pregnancies thereafter (see Chapter 23).[29]

In a population-based cohort study by the Metropolitan Atlanta Congenital Defects Program, the risk of congenital malformations was assessed among 264,392 infants with known gestational ages born between 1989 and 1995. Premature infants (<37 weeks of gestation) were found to be more than twice as likely to have been born with congenital malformations than infants at term.[30] Twins have long been known to have an increased rate of congenital anomalies. A UK study of 2,329 twin pregnancies (4,658 twins) and 147,655 singletons revealed an anomaly rate of 405.8 per 10,000 twins versus 238.2 per 10,000 singletons (relative risk (RR) 1.7).[31] The prevalence rate of anomalies among known monochorionic twins (633.6 per 10,000) was nearly twice that found in dichorionic twins (343.7 per 10,000)(RR 1.8).

A key study of homozygosity in consanguineous patients with an autosomal recessive disease showed that on average, 11 percent of their genomes were homozygous.[32] Each affected individual had 20 homozygous segments exceeding 3 cM.

Incidence/prevalence rates of congenital defects are directly influenced by when and how diagnoses are made. Highlighting the importance of how early a diagnosis is made after birth, the use of echocardiography and the stratification of severity of congenital heart defects, Hoffman and Kaplan[33] clarified how different studies reported the incidence of congenital heart defects varying from 4 in 1,000 to 50 in 1,000 livebirths. They reported an incidence of moderate and severe forms of congenital heart disease in about 6 in 1,000 livebirths, a figure that would rise to at least 19 in 1,000 livebirths if the potentially serious bicuspid aortic valve is included. They noted that if all forms of congenital heart disease (including tiny muscular ventricular septal defects) are considered, the incidence increases to 75 in 1,000 livebirths.

The frequency of congenital defects is also influenced by the presence or absence of such defects in at least one parent. A Norwegian Medical Birth Registry population-based cohort study of 486,207 males recorded that 12,292 (2.53 percent) had been born with a congenital defect.[8a] Among the offspring of these affected males, 5.1 percent had a congenital defect, compared with 2.1 percent of offspring of males without such defects (RR 2.4).

Maternal obesity also has the potential for increasing the prevalence of congenital anomalies.[33a] In a population-based case–control study excluding women with pre-existing diabetes, Watkins et al.[34] compared the risks of selected congenital defects among obese women with those of average-weight women. They noted significant odds ratios for spina bifida (3.5), omphalocele (3.3), heart defects (2.0) and multiple anomalies (2.0). Others[35] found a 2.2-fold increased risk of spina bifida in the offspring of obese women. Our own studies[36,37] have pointed in the direction of a prediabetic state or gestational diabetes as the biologic mechanism accounting for the increased rate of congenital anomalies in the offspring of obese women. In contrast, markedly underweight women reportedly have a 3.2-fold increased risk of having offspring with gastroschisis.[38] Young nulliparous women have an increased risk of bearing a child with gastroschisis, those between 12 and 15 years of age having a more than fourfold increased risk.[38a]

The frequency of congenital hypothyroidism, now known to be associated with up to a fourfold increased risk of additional congenital malformations, represents yet another factor that may influence incidence/prevalence rates of congenital anomalies. A French study of 129 infants with congenital hypothyroidism noted that 15.5 percent had associated congenital anomalies.[39] Nine of the infants had congenital heart defects (6.9 percent).

Women with epilepsy who are taking anticonvulsant medications have an increased risk of having offspring with congenital malformations, noted in one study as 2.7-fold greater than those without epilepsy.[40] The possible reduction of other congenital malformations as a result of folic acid supplementation remains to be proved.[41]

Congenital malformations and infant morbidity and mortality

The leading cause of infant death in the United States in 2005 was congenital malformations, deformations and chromosomal abnormalities, accounting for 19.5 percent of all infant deaths.[42] Survival is clearly dependent on the severity or lethality of the congenital defect. The Centers for Disease Control and Prevention assessed mortality rates for infants born with trisomy 13 and trisomy 18. Using death certificates and other source data, the authors identified 5,515 infants born with trisomy 13 and 8,750 born with trisomy 18. The median age at death for both trisomy 13 and trisomy 18 was 10 days. Survival to at least 1 year occurred in 5.6 percent of those born with trisomy 13 or trisomy 18.[43] A regional study in The Netherlands noted lethal congenital malformations in 51 percent of stillbirths and 70 percent among those who died during the neonatal period.[44] A Scottish study focused on the survival of infants with congenital anomalies up to the age of 5 years. They used a population-based and systematically validated registry of congenital anomalies containing 6,153 anomalous livebirths. Survival rates for these infants to the age of 5 were: chromosomal anomalies (48 percent), neural tube defects (72 percent), respiratory system anomalies (74

percent), congenital heart disease (75 percent), nervous system anomalies (77 percent) and DS (84 percent).[45] The survival rate among males with congenital defects was 84 percent, compared with 97 percent in those born unaffected.[8a] Liu et al.[46] examined temporal changes in fetal and infant deaths caused by congenital malformations in Canada, England, Wales and the United States. They concluded that the major factor responsible for the accelerated decline in infant deaths was prenatal diagnosis and elective abortion of fetuses with abnormalities. Given the frequency of DS, a more detailed discussion follows. NTDs are discussed in Chapter 24.

Down syndrome

The special problems and associated defects in DS are well known, as is the increasing life expectancy. Studies from Japan,[47] Denmark,[48] England,[49] Australia,[50] and Canada[51,52] highlight the increased life expectancy with DS. Baird and Sadovnick[51] reported a large study of 1,610 individuals with DS identified in more than 1,500,000 consecutive live-births in British Columbia from 1908 to 1981. They constructed survival curves (Figure 1.1) and a life table (Table 1.2) for DS and for the general population.[53] Their estimates show that 44.4 percent and 13.6 percent of liveborn individuals with DS will survive to 60 and 68 years, respectively, compared with 86.4 percent and 78.4 percent of the general population. In another report,[54] these authors have analyzed the causes of death in DS, highlighting congenital defects and cardiovascular and respiratory illnesses as the most important.

Additional studies of mortality rates in individuals with DS revealed that those up to about 35 years of age were little different from others who were mentally retarded. Subsequently, however, mortality rates in DS doubled every 6.4 years, compared with 9.6 years for other mentally retarded individuals.[54] Life tables constructed by these authors indicated a life expectancy of 55 years for a 1-year-old patient with DS and mild/moderate retardation and a life expectancy of 43 years for a 1-year-old patient with DS and profound mental retardation.

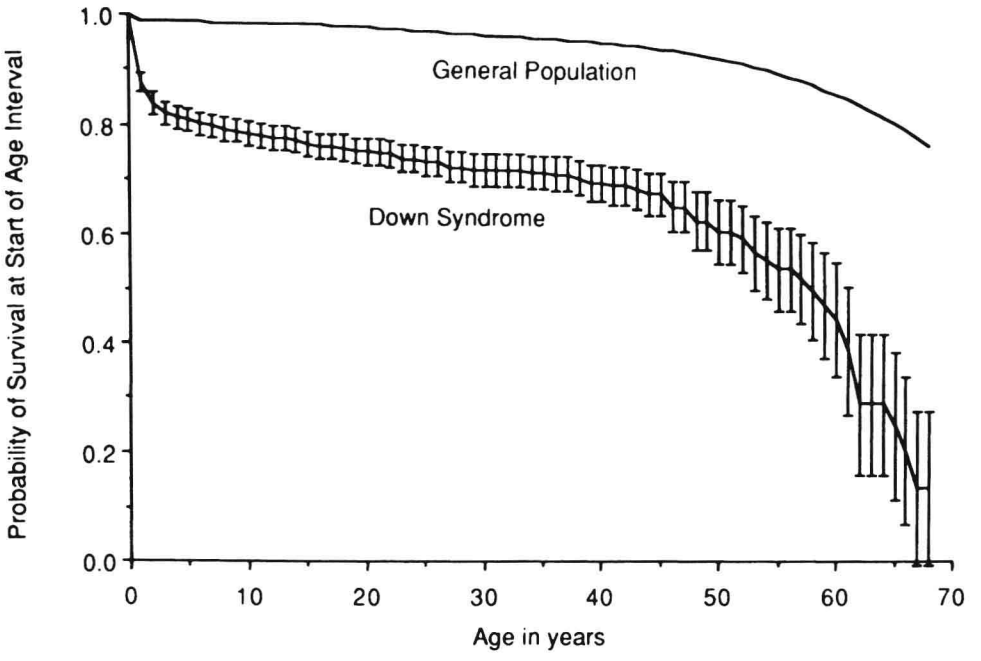

Figure 1.1 Survival curves for Down syndrome and for the general population of British Columbia. (Reproduced with permission from Baird and Sadovnik, 1987.[51])

Table 1.2 Life expectancy with Down syndrome, to age 68 years[51]

Age	*Total*	*Deaths*	*Withdrawals*	*Survival at start of age interval (%)*
0	1,337	164	0	100.00
1	1,173	51	0	87.73
2	1,122	23	0	83.92
3	1,099	10	29	82.20
4	1,060	5	35	81.44
5	1,020	10	33	81.05
6	977	5	37	80.24
7	935	6	20	79.82
8	909	3	30	79.31
9	876	7	28	79.04
10	841	2	27	78.40
11	812	4	28	78.21
12	780	2	34	77.82
13	744	3	21	77.61
14	720	6	35	77.30
15	679	3	41	76.64
16	635	1	34	76.29
17	600	1	26	76.16
18	573	4	36	76.03
19	533	1	35	75.48
20	497	1	46	75.34
21	450	1	26	75.18
22	423	5	40	75.01
23	378	0	38	74.08
24	340	2	50	74.08
25	288	0	46	73.61
26	242	3	38	73.61
27	201	0	36	72.62
28	165	1	36	72.62
29	128	0	37	72.12
30	91	0	35	72.12
31	56	0	30	72.12
32	26	0	26	72.12
33	255	1	19	72.12
34	235	0	27	71.83
35	208	1	7	71.83
36	200	0	12	71.48
37	188	2	21	71.48
38	165	2	12	70.67
39	151	0	15	69.78
40	136	1	8	69.78
41	127	0	11	69.25
42	116	1	17	69.25
43	98	1	5	68.61
44	92	0	6	67.89
45	86	3	4	67.89
46	79	0	5	65.47
47	74	3	4	65.47
48	67	0	4	62.74
49	63	2	4	62.74