THE PREVENTION OF DOWN'S SYNDROME

PRENATAL DIAGNOSIS AND SELECTIVE THERAPEUTIC ABORTION IN THE PREVENTION OF DOWN'S SYNDROME - AN EVALUATION EMPHASIZING MEDICAL & ECONOMIC ISSUES

By

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ABSTRACT

The organization of Health Care in Canada is such that many of the crucial decisions affecting the health of our population are made by politicians whose previous experience has not been in the health sector. This thesis is an attempt to present some of the medical and economic issues related to the prenatal diagnosis of disease in a form which can be readily understood by individuals who are neither physicians nor economists.

The technology responsible for prenatal diagnosis has developed very rapidly over the past few years and now the need for an evaluation of the potential role of these techniques in the prevention of serious genetic disease is widely recognized. This thesis evaluates the effects of prenatal diagnosis on Down's Syndrome, which is the most common serious genetic disease identified in this way, but many of the findings can be applied to other serious genetic disorders.

The extent of the problem presented by Down's Syndrome was evaluated by reviewing the literature related to the medical, developmental and epidemiological characteristics of the disease. The findings indicate that this serious disorder is fundamentally irreversible despite the major effects that are made to provide special medical, educational and residential facilities for affected individuals. In addition, Down's Syndrome is a relatively common disorder and it is estimated that there are approximately 130 affected infants born each year and that there are 9,000 affected individuals in Ontario at the present

time. The specific cause of the disorder remains unknown although the increasing incidence of affected infants with advancing maternal age is well recognized. The new techniques of prenatal diagnosis and selective abortion offer the only effective method of preventing the birth of these seriously and irreversibly handicapped infants.

The procedures involved in obtaining a prenatal diagnosis are reviewed in some detail and it is concluded that the techniques are both medically safe and diagnostically reliable when provided by experienced personnel. Parents are offered a therapeutic abortion when a defective fetus is identified and although a mid-trimester abortion is associated with some morbidity and mortality, the risks are not greater than those associated with a full-term delivery. These findings suggest that prenatal diagnosis could be made available to all those parents who would benefit from health information of this sort without imposing unacceptable health hazards.

A major section of this thesis is devoted to the evaluation of the economic effects of a program providing prenatal diagnosis, using the technique of cost-benefit analysis. The implications of several diagnostic and patient management policies are examined and the results indicate that prenatal diagnosis should be offered to all women aged 35 years or more. The use of less conservative estimates would suggest that the service could be extended to younger women and still remain economically feasible.

The final conclusion, based on medical, economic and administrative considerations is that the existing prenatal diagnosis programs should be expanded to provide this service to all women aged 35 or over as soon as possible.

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INTRODUCTION

In the past, when childhood mortality rates were high, parents were thankful when their children survived childhood diseases to reach adulthood. Today, however, survival through childhood is almost taken for granted and many parents are becoming concerned with the quality of survival, and not just survival in itself. Many serious disorders of childhood which used to be associated with early mortality and impaired quality of survival are now fully responsive to modern treatment methods. However, for disorders which are caused by an abnormality in the basic genetic constitution of the individual, treatment has been less successful and there is no early prospect of a cure. Since genetic diseases are frequently associated with serious congenital malformations and severe mental retardation they continue to present a major challenge to those who are concerned with the quality of life experienced by all children.

The recently developed technique of prenatal diagnosis, which enables the diagnosis of some genetic disorders to be made early in pregnancy, represents a major advance in the management of genetic disease, since it offers parents the opportunity to selectively abort a fetus which would otherwise develop into a seriously and irreversibly handicapped infant.

There are more than sixty genetic disorders which can be identified in this way and the technological advances necessary to reach a prenatal diagnosis for additional disorders are being made rapidly.

At the present time, however, the procedure is most frequently performed for parents at risk of having a child with Down's Syndrome - the commonest of the genetic disorders which result in mental retardation and congenital malformations.

Until recently, prenatal diagnosis has been regarded as an experimental procedure and its use has been restricted to "high-risk" pregnancies. However, as the reliability and safety of the procedures have improved there has been considerable interest in the possibility of extending the availability of these techniques in order to provide a prenatal diagnosis for parents whose pregnancies are at less risk.

Before a new procedure such as this moves from the experimental phase to the service phase, it is obviously important that the proposed program be thoroughly evaluated and that careful consideration be given to the likely effects and implications of the program. The objective of this thesis is to contribute to an overall evaluation of prenatal diagnosis by examining the characteristics and probable effects of a prenatal diagnostic program whose primary goal is the prevention of Down's Syndrome.

Although, the problems associated with the evaluation of such a prenatal diagnostic service are multiple and complex, the basic requirements are simple. They are to ensure that:

a) the disorder to be prevented is serious and cannot be treated successfully,

b) the disorder is quantitatively significant in our society,

c) the diagnostic procedure meets acceptable criteria for safety, sensitivity and specificity,

d) the preventive measure is safe and acceptable,

e) the procedures are compatible with existing moral, legal and ethical standards,

f) the service is economically feasible, and that

g) the service is administratively feasible in terms of the availability of equipment and personnel.

In order to evaluate the significance of Down's Syndrome and the effectiveness of present patterns of treatment and care, it was necessary to review the literature dealing with the characteristics and management of this disorder. Down's Syndrome is an intriguing and complex disorder which has been the focus of many publications. However, since much of the literature relevant to this evaluation has been published in specialty journals and is therefore not widely known, the major findings have been reviewed and are presented in Chapter One. Our present understanding of the epidemiology of Down's Syndrome is also discussed in this chapter since knowledge of the epidemiological characteristics of the Syndrome is necessary in order to identify those groups who are most likely to benefit from a prenatal diagnostic program.

In Chapter Two, the various procedures involved in reaching a prenatal diagnosis of Down's Syndrome are considered in some detail since they have been recently developed and are not widely known. Particular attention is paid to the safety, reliability and acceptability of the procedures and special consideration is given to those measures which seem to improve the safety and reliability of prenatal diagnosis. The moral, ethical and legal considerations raised by such a program are discussed briefly at the end of this chapter.

In Chapter Three the techniques of cost-benefit analysis are used to examine the economic implications of offering a prenatal diagnostic service to parents in various 'risk' categories. In this analysis the costs associated with prenatal diagnosis and therapeutic abortion are compared with the costs of raising an affected individual. Much of the fairly detailed information presented in the first two chapters is used in assessing the economic implications of providing a prenatal diagnostic program, and the effects of various diagnostic and management policies are examined. The administrative characteristics of the program are considered following the economic analysis and possible future trends are discussed briefly.

In the final chapter the findings of the study are summarized and the conclusions are presented.

CHAPTER ONE

DOWN'S SYNDROME - THE EXTENT OF THE PROBLEM

Historical Background

More than one hundred years ago, John Langdon Haydon Down, a physician at a large institution for the mentally retarded in Britain, observed that about 10 per cent of his patients resembled the normal members of the Mongolian race. In 1866, he published the first description of these patients whom he referred to as "Mongolian idiots".

Down was an observant clinician and part of his original paper is reproduced here as an introduction to the disorder of Down's Syndrome:

> "A very large number of congenital idiots are typical Mongols and they present such a close resemblance to one another in mental power, that I shall describe an idiot member of this racial division, selected from the large number that have fallen under my observation.
>
> The hair is not black, as in the real Mongol, but of a brownish colour, straight and scanty. The face is flat and broad, and destitute of prominence. The cheeks are roundish, and extended laterally. The eyes are obliquely placed, and the internal canthi more than normally distant from one another. The lips are large and thick with transverse fissures. The tongue is long, thick, and is much roughened. The nose is small. The skin has a slight dirty yellowish tinge, and is deficient in elasticity, giving the appearance of being too large for the body.
>
> They have considerable powers of imitation, even bordering on being mimics. They are humorous, and a lively sense of the ridiculous often colours their mimicry. They are usually

> able to speak; the speech is thick and indistinct, but may be improved very greatly by a well-directed scheme of tongue gymnastics. The co-ordinating faculty is abnormal, but not so defective that it cannot be greatly strengthened. By systematic training, considerable manipulative power may be obtained.
>
> The circulation is feeble, and whatever advance is made intellectually in the summer, some amount of retrogression may be expected in the winter. Their mental and physical capabilities vary directly as the temperature.
>
> The life expectancy is far below the average and the tendency is to tuberculosis, which I believe to be the hereditary origin of the degeneracy." [1]

Since it is now known that the similarities which Down observed between these patients and true Mongols are only superficial and since the commonly used terms "Mongol", "Mongoloid" and "Mongolism" have racist overtones the alternative term of Down's Syndrome has been suggested and is gradually gaining public acceptance.

Present Understanding of Down's Syndrome

Today, Down's Syndrome is recognized as a common congenital disorder that occurs throughout the world with a frequency of approximately 1 in every 800 live births.[2] It is characterized by multiple abnormalities and almost every organ system of the body is affected both structurally and functionally to a greater or lesser extent.[3] Although the general medical problems associated with this disorder are serious, the most incapacitating feature of the disorder is the severe mental retardation which characterizes all patients with the syndrome.

Developmental Patterns

The infant with Down's Syndrome is usually recognized in the

newborn nursery. There are a number of easily identified physical features, none of which are distinctively characteristic of this condition, but which, if present in combination, can lead to a virtually certain clinical diagnosis of Down's Syndrome within the first weeks of life.(Appendix A) Infants with Down's Syndrome tend to be smaller at birth than normal infants of the same gestational age;[4] their growth remains slow throughout infancy and childhood and as adults they rarely exceed 5 feet in height.[3]

Several investigators have found that the retarded development of intellectual skills in a child with Down's Syndrome becomes increasingly apparent with age.[5,6,7] In 1973, Melyn and White made a cross-sectional study of 612 of these children, ranging in age from birth to 16 years, and established the mean IQ at each year of age.[7] Their findings are displayed in Table 1.

It can be seen from this table that Melyn and White also found an overall tendency for the IQ scores of children with Down's Syndrome to decrease with age. Although they noted considerable individual variation among the children, they derived an equation which predicted the mean age-specific IQ for 14 age groupings of Down's Syndrome children, with fair reliability. The prediction formula they established was as follows:

$$Y = -1.80\,x + 59.13$$

where x is the chronological age

Y is the predicted IQ

The apparent decline in intellectual function is thought to be due, at least in part, to the characteristics of the tests used. In

TABLE 1

ACTUAL AND PREDICTED AVERAGE IQ'S FOR 14
AGE GROUPINGS OF DOWN'S SYNDROME CHILDREN

N	MIDPOINT (years)	ACTUAL AVERAGE IQ	PREDICTED AVERAGE IQ
70	.5	58.28	58.23
75	1.5	58.10	56.43
75	2.5	54.46	54.63
73	3.5	54.40	52.83
76	4.5	49.35	51.03
76	5.5	48.26	49.23
66	6.5	45.36	47.43
36	7.5	44.25	45.63
34	8.5	45.36	43.83
28	9.5	43.38	42.03
15	10.5	41.53	40.23
9	11.5	37.40	38.43
6	12.5	33.66	36.63

TABLE 2

MOTOR AND SPEECH DEVELOPMENT DATA
FOR CHILDREN WITH DOWN'S SYNDROME
adapted from Melyn and White[7]

SKILL	AV. AGE (mths)	RANGE (mths)	N.	"NORMAL" -Denver Scale -modified
Rolls Over	6.4	1-60	332	3.6 mths
Sits up unsupported	11.8	5-72	468	6.5 mths
Stands Up	20.8	7-84	284	12.5 mths
Walks unassisted	24.4	7-74	430	13.5 mths
Speaks first word	24.2	6-84	322	9.0 mths
Speaks first sentence	52.1	17-132	139	22 mths

infancy, the tests depend heavily on motor skills (such as sitting, walking, and the use of hands) and some children with Down's Syndrome achieve these skills by the normal time.(see below) The tests used in later childhood have an increasingly verbal and abstract component and the findings in Down's Syndrome reflect their disabilities in these areas.

The developmental pattern of motor skills in children with Down's Syndrome has been studied by several investigators[5,7,8] and some typical findings are presented in Table 2.

Again, wide variation is present and in some cases motor development may appear to be normal during the first few years. The motor handicaps of the child with Down's Syndrome become more apparent in later childhood as physical movements become more complex and require better coordination. Impaired muscle control[3] (hypotonia) may persist into adulthood and jeopardise employability by limiting an individual's capacity to perform the simple manual tasks which he/she can master intellectually.

Children with Down's Syndrome can usually attend the special schools for retarded children and participate in special recreational programs. With careful training, most of them can learn to look after their basic personal needs (feeding, dressing, toileting) with minimal supervision. Most adolescents and adults can talk using simple sentences, a few can count to 5 or 10 and the occasional individual can write a few words. As adults they are suitable candidates for sheltered workshops where they are said to be "good workers" apparently content with simple repetitive tasks and achieving a measure of productivity.

Physical Abnormalities

In addition to the problems of mental retardation, patients with Down's Syndrome also suffer from multiple physical abnormalities. Many of these abnormalities are readily apparent at birth and sometimes they are life-threatening.

Congenital heart defects are particularly common, affecting 30 to 40% of these infants.[9,10] Some of the defects are not amenable to surgery (e.g. endocardial cushion defects) but in other cases cardiac surgery has been performed.

Abnormalities of the gastrointestinal tract are common[11,12] and some of these conditions are also fatal without surgical intervention in the newborn period.(e.g. duodeno atresia)

A number of skeletal abnormalities may be present necessitating orthopedic care if the child is going to be able to walk.[13]

Abnormalities affecting the eyes are so common in Down's Syndrome that they are extremely useful in establishing the diagnosis at birth.[14] It is less widely recognized that about 5% of adults with Down's Syndrome are functionally blind as a result of congenital cataracts, severe refractive errors, untreated strabismus and recurrent corneal infections.[3,14]

The skin of Down's Syndrome infants is relatively inelastic and loose. The major and minor skin markings (dermatoglyphics) are quite distinctive and provide useful diagnostic clues.[15] The best known of these characteristics is the "simian" crease which is found in about half these infants.[15,16]

The neurological signs of Down's Syndrome are not distinctive. Anatomically, the brain is small and asymmetrical, and its structure

resembles that of the lower animals. The most striking microscopic finding is the paucity of cells in the brain tissue and the relative simplicity of the communications between the cells.[17] Clearly these defects are unlikely to be successfully modified in the foreseeable future.

In infancy and early childhood these children are unusually susceptible to infections,[9,18] particularly the common childhood infectious diseases of measles and chicken pox which may be fatal. Respiratory infections are also very common and until the advent of the antibiotic era many of these children died of pneumonia in childhood.[19,20]

The unusual susceptibility to infections suggests that patients with Down's Syndrome have an impaired immune response to disease and the available evidence supports this theory.[21] In addition, there are a number of morphological abnormalities in the blood cells and the incidence of leukemia is increased about 20 fold in young children with Down's Syndrome.[22]

Extensive literature exists on the pathology of the endocrine glands in Down's Syndrome, particularly the thyroid and pituitary glands. There is no doubt that disorders of the thyroid are common in Down's Syndrome patients but therapy to correct thyroid malfunction does not seem to alter the overall prognosis for these patients.[3,23]

Sexual maturation is slow in both sexes and the genitalia are usually underdeveloped. Although male patients with Down's Syndrome are infertile, some female patients have reproduced.[3] Among the few cases reported both normal and Down's Syndrome offspring have resulted in about equal frequencies.[23,24]

Dentition is usually delayed and the teeth are irregular in size, shape and position. Occlusal anomalies and orthodontal disorders are common.[25] In addition, because of the patient's retardation it is difficult to provide routine preventive and curative dental care, and frequently such patients must be admitted to hospital for dental care.

Finally, degenerative changes affecting the brain and cardiovascular system are often apparent by the mid 30's in patients with Down's Syndrome. The functional and pathological changes which are indistinguishable from Alzheimer's disease, are not specific to Down's Syndrome since they are associated with "normal" aging, but in Down's Syndrome the changes occur much earlier than expected.[26]

In the presence of so many physical disorders it would be surprising if individuals with Down's Syndrome did not use acute health care facilities more frequently than the general population. However, firm evidence in support of this hypothesis is lacking.

Several investigators have been interested in establishing the proportion of childhood hospitalization that can be attributed to genetic disorders including Down's Syndrome. In one Canadian study of admissions to the Montreal Children's Hospital between 1969 and 1970, it was found that 11.1% of admissions to the hospital could be attributed to genetic disorders. This group estimated that children with genetic disease were hospitalized about 8 times more frequently than their counterparts in the general population.[27]

No study dealing specifically with the hospital or health care utilization patterns of patients with Down's Syndrome is available but

several pediatricians working with these children felt that Scriver's estimate was consistent with their experience.

Life Expectancy

The decreased life expectancy of infants with Down's Syndrome has been recognized for over 100 years. In recent years, however, a number of authors have published life tables for children with Down's Syndrome or have described their mortality experience in other ways.[19,20,28-31] The results of some of the major studies are summarized in Table 3.

The first attempt to describe the mortality experience of these children was made by Record and Smith in 1955.[28] These investigators developed a life table based on the survival of 252 Birmingham-born children with Down's Syndrome who were carefully ascertained from the records of maternity hospitals, the children's hospital, general hospitals and the local authorities mental health records.

In 1958, Carter prepared a life table for children with Down's Syndrome based on the mortality experience of 725 children seen at the Hospital for Sick Children in London between 1944 and 1955.[19] It was his opinion that the sample was not significantly biased despite the source of the cases.

Collman and Stoller based their life table on 729 Down's Syndrome patients born between 1948 and 1957 in Victoria, Australia, and also ascertained cases from many sources.[29]

In the most recent study, Fabia & Drolette ascertained 2,469 children with Down's Syndrome who were born alive in Massachusetts between January 1, 1950 and January 1, 1967.[31] This study was carefully done, sources of ascertainment included maternity and pediatric hospitals,

TABLE 3

SURVIVAL RATES FOR DOWN'S SYNDROME

STUDY CHARACTERISTICS	PERCENTAGE SURVIVING TO:				
	1 mth	6 mths	1 yr	5 yrs.	10 yrs
Record ans Smith-Birmingham, U.K., 252 births, 1942-1952 (1955)[28]	69%	-	50%	44%	-
Carter-London, U.K., Hosp., Sick Children 725 births, 1944-1955 (1958)[19]	70%	-	47%	40%	37%
Collman and Stoller, Vict. Australia 729 births, 1948-1957 (1963)[29]	-	76%	69%	49%	46%
Fabia and Drolette, Mass. U.S.A. 2421 births, 1950-1966 (1970)[31]	93%	83%	76%	68%	64%
Canadian General Population 1966 Male Female[148]			97.5m 98f	97.1m 97.6f	96.8m 97.4f

TABLE 4

CHANGES IN INFANT MORTALITY WITH TIME

TIME PERIOD	DOWN'S SYNDROME	GENERAL POPULATION
1948-1952	354.9	22.14
1953-1957	269.0	19.65

Percentage decrease - general population 11%
Percentage decrease - Down's Syndrome 24%
after Collman and Stoller[29]

Massachusetts Department of Public Health, Massachusetts Department of Mental Health, private nurseries and schools for mentally retarded children, genetics laboratories, birth and death certificates, and several other sources. Most subjects were ascertained more than once, averaging 2.02 times per subject.

The basic findings of these four studies are presented in Table 3 and it is clear that, while survival is still obviously decreased in comparison to the general population, there has been a marked trend towards increased survival for children with Down's Syndrome. Collman and Stoller also presented their data separately for the two time periods 1948 to 1952 and 1953 to 1957. Using their data it can be shown that there was a 24% decline in infant mortality for Down's Syndrome between these two time periods, with the change being mainly attributable to the increased survival in the first six months of life. The infant mortality for the general population declined 11% in the same time period. (see Table 4)

A complete life table for Down's Syndrome is not available at present. The mortality experience for patients after the age of 10 years is usually based on the experience of institutionalized patients and is commonly expressed as a multiple of the equivalent age-specific mortality rate for the general population. Most investigators have reported factors of between 2 and 24 for adult patients with Down's Syndrome although an average figure would be a mortality rate of 5 to 6 times that of the general population.[30,32,33]

Although patients with Down's Syndrome are subject to early degenerative changes, an increasingly large proportion are living until

the 5th or 6th decades of life. We can no longer think of Down's Syndrome as a disorder of childhood, we must plan to care for the majority of these patients into adulthood and old age.

Current Management of Down's Syndrome in Canada

Historical Background

In order to understand the present patterns of care for individuals with Down's Syndrome, it is helpful to review the historical development of the services for the mentally retarded in Ontario. The first asylum in Ontario opened in 1841 at the Old York Jail in Toronto and the first Hospital Training School for "feeble minded" children was opened in Orillia in 1876. Additional facilities were opened in subsequent years and there are now more than 7,000 beds available for mentally retarded persons in the large government-run institutions known as Schedule I Facilities, with an additional 1,000 beds in smaller residences such as the Board-run Schedule II Facilities.[34]

Until the mid 1960's the services available for retarded persons reflected earlier policies which recommended that mentally handicapped persons be segregated from the general community. Consequently, the handicapped were placed in geographically and socially isolated institutions established in rural settings where the residents were supposedly free of the stresses and strains of everyday living. The policy of segregation was reinforced by those professionals and members of the public who felt that retarded persons represented a menace to the general population in that they were prone to drift into pauperism and petty crime if they remained in the general community.

During this period families were strongly advised to institutionalize their newborn Down's Syndrome children immediately after birth. Implicit in this recommendation were the assumptions that:

i) the presence of such a child resulted in severe family problems and serious detrimental effects on other members of the family,

ii) a severely retarded child would not benefit in any substantial way from care in a conventional family structure.

Present Trends

In the late 50's and early 60's, several investigators published the results of studies which seemed to indicate that children with Down's Syndrome developed faster when cared for in their own homes (or small foster homes) than they did in large institutions.[35,36] The findings of these studies had much intuitive appeal and they certainly highlighted the deplorable conditions that existed in the large, overcrowded and understaffed institutions of the time. However, in retrospect the results of the studies are difficult to interpret since the studies frequently lacked appropriate control groups and they did not show that the speedier development noted in home-reared children was sustained into adulthood or that it substantially improved the individual's ultimate functional capacities.

Recognizing that the relative merits of institutional group home and familial care remain unclear, additional studies are currently in progress in Britain to try to clarify some of these points and to examine the effects of different types of residential care on patients,

families, communities and staff.[37]

Organized parent groups, dissatisfied with the care available to their children in the large institutions also began to apply pressure on government to upgrade the services available to the mentally retarded in the early 1960's. Some of these families wished to care for their handicapped children themselves and they pressed for appropriate community facilities to allow them to do so.[34]

As a result of the combined activities of parent groups and concerned professionals, task forces and commissions were set up to review the existing programs and to make recommendations for improved patterns of care for the mentally retarded. In general, their recommendations emphasized the right of the retarded person to be a participating member of the general community and it was felt that, as far as possible, the retarded should live outside hospitals and institutions.[34,38]

A principle which subsequently became known as "normalization" emerged as a major contribution to the changing patterns of care for the mentally retarded. In 1970, Bengt Nirje wrote: "the normalization principle means making available to the mentally retarded, patterns and conditions of everyday life which are as close as possible to the norms and patterns of the mainstream of society".[39] The proponents of the normalization principle raise a number of objections to traditional institutional care. They consider that there are many aspects of normal human life which are experienced incompletely by children and adults living in institutions and that "normal" behaviour cannot be encouraged in these "abnormal" environments. They recommend parents should be encouraged to care for their retarded children at home whenever possible,

and that those handicapped individuals who cannot be adequately cared for within their own familial homes should live in small hostels or foster homes within the general community.

The normalization principle has gained wide acceptance throughout the Western world, and in Ontario, major revisions and reorganizations of government bodies have already taken place in order to provide a more co-ordinated community-based service for the mentally retarded.[38]

At the Interprovincial Conference of the Ministers of Social Development held in Winnipeg in September 1974, the Minister of Community and Social Services for Ontario, the Honorable Rene Brunelle, restated Ontario's policy as follows:

> "To achieve the community living policy, the Province of Ontario intends to expand and diversify many of the programs that presently exist.... Clearly, the task at hand is to reorient the former system that emphasized institutional care. By expanding and developing community-based services available to individuals and families, we will reduce the flow into institutions. By changing the role of institutions from long-term care to rehabilitation, we will increase the outflow into normal community living."[40]

This policy is also in keeping with the recommendations of the Williston Report which was prepared for the Government of Ontario in August 1971.[34]

Family Care & Residential Placement

As a result of these dramatic changes in policy, any family whose newborn child has been diagnosed as having Down's Syndrome is now strongly advised to keep the child within the nuclear family for as long as possible.

For parents expecting the birth of a normal child, the arrival of an infant with Down's Syndrome is obviously a major disappointment. Initial grief reactions are usually marked and the family needs a great deal of support from their families, friends and the health professionals who are involved in this initial period. The fact that these children require extra care and supervision all their lives, and are always dependent on others to a very large extent, may also result in significant long-term emotional stress for the family. Such families may become socially isolated and the burden of constant care may become intolerable and lead to maladaptive behaviours. Eventually, some families seem to make a surprisingly good adjustment and manage to alter their own life style and their expectations for the child to a remarkable degree.[41]

The presence of a handicapped child also results in extra expenses for the family although it is difficult to document the extent of these private costs.[34] These costs include payments made for instructural alterations to the house, additional fencing, out-of-pocket health care costs, babysitting charges and transport of the child to the various services which he requires. In some instances, a mother who may have planned to return to the work force after the birth of her child may find it impossible to do so after the birth of an infant with Down's Syndrome. It is difficult to know what proportion of these mothers would have returned to work under different circumstances, but in any event a great deal of a parent's time must be devoted to the care of a retarded child - time which could otherwise have been spent in alternate activities.

Regardless of the type of residential care provided for the

retarded child, when the mentally retarded person reaches adulthood, it is considered desirable to provide facilities which allow the individual as much independence as possible.[34] This means providing a suitable residential facility so that the mentally retarded adult can leave the familial home and establish himself as an independent individual at the age when most children leave the parental home. The knowledge that the handicapped child will have an independent existence outside the family home may encourage parents to care for their child during the formative years and certainly will do much to relieve fears about the long-term management of the child.

It has been suggested that the needs of retarded adults could best be met in small family-type units which are separate from but reasonably close to the main sheltered workshops in which many of the adults would be employed during the day.[34,42] The Government of Ontario is planning to meet the needs of these people by providing group homes which will serve from 8 to 18 residents each.[40]

Community Services

Increasingly, our communities are beginning to accept the fact that a society which strongly advises parents to maintain their handicapped child at home has a responsibility to provide that family with the material and social support it needs to carry out such a task. Many city communities now provide a wide range of supportive services including nursery schools, day care centres, special schools and workshops but it is clear that an even broader range of services is needed if families of severely handicapped children are not to bear an unjust burden. Day care facilities are being expanded and new services

providing for parent counselling, short-term vacational leave, specialized babysitting, habilitative equipment, continuing education in "life skills" and recreational programs are being considered.[34,40]

Ideally it would seem that parents in this difficult situation should be able to make an informed personal choice knowing both that suitable residential care is available and that those parents who decide to care for their children at home will be adequately assisted by their community and by society as a whole.

Education for Severely Retarded Children

A major advance in the last ten years has been the development of highly specific educational techniques directed towards increasing the skills and decreasing the inappropriate behaviour of the severely mentally retarded child.

With the growing realization that more and more mentally retarded children are reaching adulthood and the appreciation that many of them can function to some extent in the community with special education and training, educational programs for the mentally retarded have undergone a substantial change in emphasis.

To prepare a retarded child for an adult role, the educational program is directed towards achieving a measure of self sufficiency and occupational competence. Instead of teaching the elements of traditional subjects modern educators have stressed that the subnormal should be taught different skills including:

(a) how to co-operate with others

(b) how to accept a work situation and give reasonable satisfaction

(c) how to manage money

(d) how to make use of public services and

(e) how to manage leisure time [43]

As far as reading is concerned the prevailing practice is to teach severely retarded persons a "social sight vocabulary" which includes such words as Ladies, Gentlemen, Wet Paint, Danger, Exit, Entry, etc. The typical person with Down's Syndrome can be taught an average of 45 words in this way.[44]

It is obvious that the successful implementation of these special programs requires the services of skilled teachers and high teacher-student ratios. Predictably, the cost of "special" education greatly exceeds the cost of education for normal children and these costs will be considered in more detail later in this paper.

In Ontario, prior to 1947, children with I.Q. measurements of under 50 were excluded from the public school system. The first school for retarded children in Ontario was opened at Kirkland Lake, as an experimental project supported by parents, service clubs and the Community Chest. The Government gradually assumed major responsibility for the schools and the Department of Education now administers a large program with more than 127 "schools for the trainable retarded" serving more than 5000 pupils. Since September 1972 any retarded child aged between 5 and 21 years has been able to attend these schools and the attendance regulations are now the same as for normal children in the public school system. In addition, the Special Education Branch operates Opportunity Classes in the public schools, for the "educable retarded" and almost 30,000 children are registered in these programs.[34]

Education & Employment for Retarded Adults

It is important to note that education for the mentally subnormal should be continued after the conventional educational period has come to an end.[43] The acquisition and maintenance of those skills which assist a retarded person in coping more competently with everyday situations cannot be left to chance or informal learning.

The Department of Community and Social Services has recognized this and has proposed the development of a "Life Skills Program" to provide appropriate learning opportunities for retarded adults.[40]

In 1954, Tizard and Loos showed that a group of severely subnormal adults, selected because they were thought to be virtually unemployable in an institution workshop, showed significant improvement in their ability to perform simple spatial tasks as a result of individual training, rewards, and repetition.[45] As other workers substantiated their findings,[43] the traditional assessment of the severely retarded as unemployable had to be revised, and the concept of the Sheltered Workshop developed.

The 86 Sheltered Workshops currently operated by the Association for the Mentally Retarded in Ontario provide a supportive and protected environment for about 3,500 retarded adults who are capable of work but who are not able to compete successfully with people of average intelligence.[34,40] Although a few persons may be able to proceed to employment in the regular work force as a result of special training in this type of program, most of the clients require long-term employment in a workshop environment.

The kind of work that seems suitable in these programs includes basic industrial assembly work and simple packaging. Administrators find that clients with Down's Syndrome are "good workers" and perform repetitive tasks well and with apparent enjoyment. Some have been taught to count to 5, a skill used to advantage ih packaging.

The emphasis placed on "work" for retarded persons should not be misunderstood. It is felt that retarded adults who can work, even if only in a limited way are more likely to be treated as adults. In addition, a workshop program can make a social life possible and assist in integrating the retarded person into the wider community. Thus the emphasis in a contemporary workshop is less on establishing an efficient profit-making organization and more on the provision of a service which meets the social and cultural needs of the clientele.[43]

Income Maintenance

When a retarded person reaches the age of 18 years he becomes eligible for Family Benefits. Evidence of "mental impairment which is likely to render them permanently unemployable and disabled" must be supplied but persons with Down's Syndrome are always eligible and receive an allowance of $225.00 per month, an amount which the Department claims is adequate for retarded persons who are boarding at home or residing in a community residence.[40]

One of the difficulties with the Family Benefit program is that recipients of this allowance are only permitted to earn an additional $24.00 per month before their allowance is proportionately reduced. The major effect of this policy is, of course, to restrict the total income receivable by a retarded recipient, but in addition,

it renders meaningless any financial incentives offered to encourage productive work. Administrations of workshop programs feel that some flexibility in this area would assist them in developing good work habits in their clients.

It should be noted that, in Canada, no special allowances are available to families who care for their retarded child at home. The care of a child with Down's Syndrome results in special food and clothing requirements, extra medical and dental costs and difficulties in obtaining suitable babysitters and vacation services. While few of these problems are insoluble, the extra costs involved may result in economic hardship for the family. In addition, the constant supervision that at least one parent, usually the mother, must provide may prevent her from obtaining an outside job and making a contribution family income. In Scandinavian countries the Government recognizes these additional private costs to families and an allowance is made to assist them with the care of their handicapped child. Such a policy does not exist in Ontario at present although it has been suggested and is currently being studied.[40]

Health Care

Most health professionals feel that those patients who are living in the general community receive adequate attention for their physical problems including congenital heart disease, digestive abnormalities and recurrent respiratory infections. The major difficulty is that, despite the relatively immense capacity to sustain biological life, our ability to secure an improved quality of personal life for these patients is extremely limited.

Children and adults who are cared for in an institution also receive adequate basic health care but it seems likely that some services such as cardiac or orthopedic corrective surgery, speech therapy and physiotherapy are less likely to be offered to these patients. In addition, it is likely that certain medical disorders such as pneumonia or serious feeding problems may be successfully treated in an institutional setting whereas they would probably require hospitalization in the case of the child being cared for at home.

Conclusion

The objective of the new programs for the mentally retarded is to provide an environment which will optimise the limited potential of these people, and while this goal may be applauded, it is important to recognize the implications of these policies for the individual, the family, and the community. A community should seek to provide those services which will minimize the suffering of affected persons and their families while remembering that even with the deployment of the most advanced treatment teams and educational resources, the underlying abnormality in Down's Syndrome is not reversible.

There is no doubt that Down's Syndrome is a serious and therefore qualitatively significant disorder for which prevention should be the ultimate goal.

The Epidemiology of Down's Syndrome

Incidence, Prevalence and Significance

The foregoing description provides an indication of the extent to which Down's Syndrome may affect a particular patient and his family,

and it is apparent that the disorder represents a major problem on an individual basis. In order to establish the quantitative significance of Down's Syndrome for our whole society, we need to derive incidence and prevalence rates for Down's Syndrome. One might expect such measures to be readily available for a disorder such as Down's Syndrome - a definite diagnostic entity with such incapacitating consequences - but reliable measures have been difficult to obtain.

The Incidence of Down's Syndrome

Although Down's Syndrome is characterized by a number of distinctive physical features such that a clinical diagnosis can usually be made in the newborn nursery, surveys of birth certificate data are not a useful source of incidence figures. It seems that some physicians who suspect a diagnosis of Down's Syndrome shortly after birth are reluctant to identify the infant as having the disorder until the diagnosis is conclusive. Thus, when Hay and Barbano surveyed more than 8 million births occurring in 29 states of the U.S.A. between 1961 and 1966, they found that only 4,130 births of infants with Down's Syndrome were reported - less than half of the expected number.[46]

Since birth certificate data is incomplete, studies of the incidence of Down's Syndrome must be specially conducted using data obtained from many sources including maternity hospitals, obstetric wards, neonatal nurseries, special schools, mental retardation associations, psychiatric hospital admissions, records of Public Health Departments and death certificates. One of the most comprehensive studies was done by Collman and Stoller in Victoria, Australia, between 1942 and 1957[47] and every available source was contacted in order to obtain

as complete an enumeration of cases as possible.

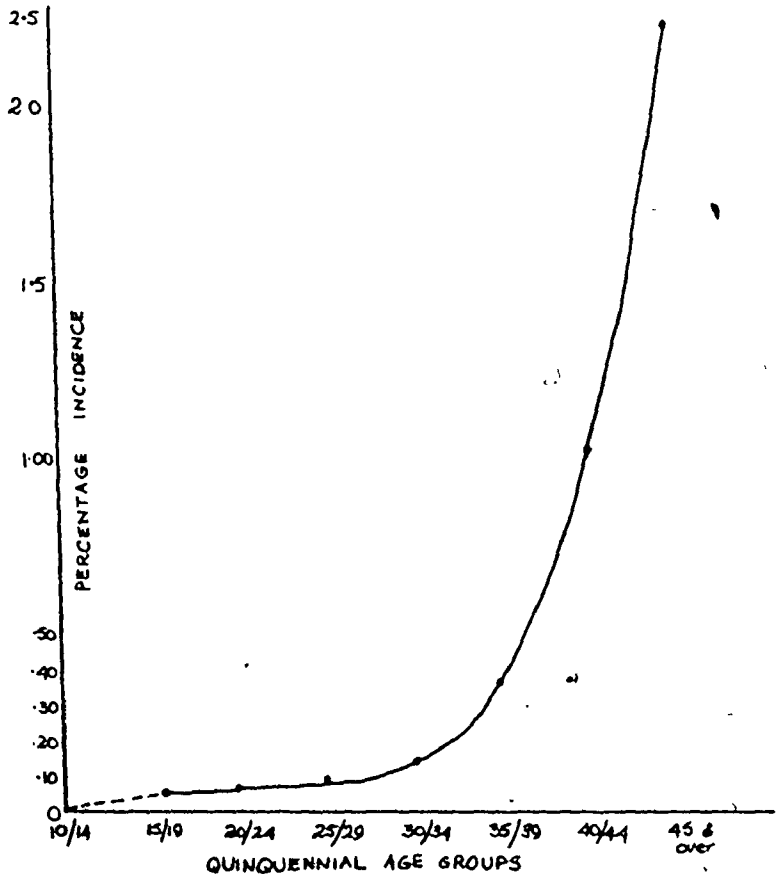
Prior to this study several investigators had identified the strong association of Down's Syndrome with advancing maternal age but precise incidence figures were not available. The maternal age-specific incidence rates for Down's Syndrome developed by Collman and Stoller in 1962 have been repeatedly confirmed[2,48,49] and are now widely used to calculate the theoretical number of infants with Down's Syndrome that can be expected from a population of pregnant women whose ages are known. The age-specific incidence rates derived by Collman and Stoller are shown in Table 5 and the same data is displayed graphically in Figure 1. It should be noted that the incidence rises slowly until the 30 to 34 year quinquennium, but after this point the rates increase rapidly with advancing maternal age.

TABLE 5

MATERNAL AGE-SPECIFIC INCIDENCE RATES FOR DOWN'S SYNDROME - COLLMAN AND STOLLER (1962)[47]

MATERNAL AGE GROUP	INCIDENCE RATE/1000 LB.
15 - 19	0.43 (~1/2300)
20 - 24	0.62 (~1/1600)
25 - 29	0.83 (~1/1200)
30 - 34	1.15 (~1/900)
35 - 39	3.50 (~1/300)
40 - 44	9.93 (~1/100)
45 +	22.0 (~1/45)

FIGURE 1



THE VARIATION IN THE INCIDENCE OF DOWN'S SYNDROME BIRTHS WITH MATERNAL AGE, VICTORIA, AUSTRALIA 1942-1957

- after Collman and Stoller

The age-specific rates derived by Collman and Stoller can be applied to the corresponding quinquennial maternal age distributions for live births in order to estimate the numbers of Down's Syndrome infants born in any given year. Thus, for 1973, the latest year for which Ontario's natality statistics are available, the estimate is made as follows:

MATERNAL AGE GROUP	NUMBER OF BIRTHS	AGE-SPECIFIC INCIDENCE OF DOWN'S SYNDROME PER 1000 LIVE BIRTHS AFTER COLLMAN & STOLLER	EXPECTED NUMBER OF DOWN'S SYNDROME INFANTS
Under 15	108	0.43	6.56
15-19	15,156		
20-24	41,044	0.62	25.45
25-29	42,854	0.83	35.67
30-34	17,481	1.15	20.10
35-39	5,759	3.50	20.16
40-44	1,306	9.93	12.97
45+	68	22.0	1.47
TOTAL	123,776		122.38

INCIDENCE OF DOWN'S SYNDROME/1000 LIVE BIRTHS = 0.99

OR 1 DOWN'S SYNDROME INFANT IN 1011 LIVE BIRTHS

In order to demonstrate the pattern in previous years, the equivalent data for the years 1925-1972 are presented in Table 6. The variation in the number of Down's Syndrome infants born in each year is attributable to changes in the absolute numbers of live births and to the changing proportion of the infants who are born to older mothers. The effects of recent changes in fertility rates will be discussed in a later section, but it should be noted here that approximately 130

TABLE 6

ESTIMATED CHANGES IN THE INCIDENCE OF DOWN'S SYNDROME:

ONTARIO 1925-1973

YEAR	ESTIMATED NUMBER OF INFANTS WITH DOWN'S SYNDROME BORN PER YEAR	RATES PER 1000 LIVE BIRTHS
1925	123	1.75
1930	119	1.67
1935	103	1.63
1940	100	1.45
1945	117	1.48
1950	147	1.36
1955	192	1.37
1956	194	1.36
1957	205	1.36
1958	204	1.34
1959	210	1.34
1960	214	1.36
1961	214	1.36
1962	210	1.35
1963	209	1.35
1964	207	1.36
1965	190	1.34
1966	174	1.32
1967	159	1.25
1968	151	1.19
1969	149	1.15
1970	147	1.09
1971	136	1.04
1972	126	1.01
1973	122	0.99

infants with Down's Syndrome are born in Ontario each year.

Trends in Incidence

It has been estimated that about 15% of all recognized pregnancies end in spontaneous abortion, usually in the first trimester of pregnancy.[50] Careful study of the abortuses however, has demonstrated that Down's Syndrome occurs much more frequently in abortuses than in live births, and it has been estimated that only one in every five Down's Syndrome conceptuses survives through a pregnancy.[2,51] If changing patterns of obstetric care result in a reduction of this high rate of attrition, the incidence of Down's Syndrome could rise substantially.

On the other hand, the incidence of Down's Syndrome can be expected to decline further if parents choose to complete their families at younger ages.

If present fertility patterns continue it is likely that the overall trend will continue to be a slight annual reduction in the incidence of Down's Syndrome.

The Prevalence of Down's Syndrome

The prevalence of Down's Syndrome is more difficult to establish, even on a theoretical basis. Although the value of a province-wide Registry for Congenital Malformations has been recognized and will probably provide some prevalence data in the future, a direct measure of the prevalence of Down's Syndrome is not currently available.

In 1973, an Act was passed making it compulsory for mentally retarded children to attend school[38] and as this Act takes complete effect, data from this source may help to provide accurate prevalence rates for Down's Syndrome among school-age children.

Although an attempt was made to enumerate all the cases of Down's Syndrome in Wentworth County, a complete ascertainment was impossible due to the constraints of both time and funds. The cases that were ascertained are presented in Table 7 together with the major sources of the cases. It is relatively easy to enumerate those persons with a clinical diagnosis of Down's Syndrome who are using recognized services for the mentally retarded, e.g. nurseries, day care centres, special schools and workshops, but the important ratio of users to non-users is unknown. In addition, the data for Wentworth County may be seriously affected by the effects of inter-county migrations, as families relocate in communities where special services are available for their children.

The Hamilton School Board provided much of the information relating to the Down's Syndrome children of school age in Wentworth County and although the data is subject to the limitations outlined above, it is nonetheless interesting to note that the prevalence of Down's Syndrome among school-age children in Wentworth County is approximately 1.087/1000 or 1/920, rates which are similar to those obtained from larger British studies. (Table 8)

AGE GROUP	GENERAL POPULATION*	ASCERTAINED CASES DOWN'S SYNDROME	PREVALENCE
5-13 years	62,797	75	1 in 837.3
14-18 years	39,316	36	1 in 1,092
5-18 years	102,113	111	1 in 920

*Figures obtained from the Planning Dept., City Hall, Hamilton.

TABLE 7

PERSONS WITH DOWN'S SYNDROME IN WENTWORTH COUNTY
-ascertained cases. 1974

AGE GROUP	NO. OF CASES
0-4	13
5-9	44
10-14	42
15-19	36
20-24	19
25-29	6
30-34	2
35-39	5
40-44	1
45-49	1
50-54	0
55-59	1
TOTAL	170

SOURCES OF CASES

-The Hamilton Board of Education, (Special Services)
-The Hamilton & District Association for the Mentally Retarded (Nursery Schools and Workshop)
-The Children's Aid Society
-Southwestern Regional Centre
-Cedar Springs - Palmerston
-Huronia Regional Centre, Orillia
-Brantford Sanitarium
-The Robert Mac Home
-Rygiel Home
-Hamilton Psychiatric Hospital
-Hamilton & District Health Unit
-St. Peter's Hospital

TABLE 8

CHANGES IN THE PREVALENCE OF DOWN'S SYNDROME:
SELECTED BRITISH REPORTS 1905-1965 AND ONE COMPARISON CANADIAN STUDY

YEAR OF BIRTH	AGE AT SURVEY (YR.)	AGE-SPECIFIC PREVALENCE-RATE PER 1000	PROPORTION OF SEVERELY RETARDED (%)	INVESTIGATOR
1895	10	0.01	5	Tredgold[62]
1920	10-14	0.34	9	Lewis[63]
1930	10-14	0.46	..	Penrose[64]
1940	10	1.06	..	Carter[19]
1947	17	1.04	29.4	Kushlick[65]
1950	10	1.14	31.5	Goodman and Tizard[60]
1958	7	0.8*	33	Davie et al.[66]
1958	10	0.87	23	McDonald (Canada)[67]

* The investigators state that this figure is an underestimate as more cases have been discovered as the cohort has grown older.

Ascertainment was obviously so incomplete in both pre-school and adult age groupings that an estimate of the prevalence of Down's Syndrome in the total population was not made.

Many persons with Down's Syndrome are known to be residents of Ontario's psychiatric hospitals and hospital schools but the statistics that are prepared for these institutions tend to categorize patients by degree of mental retardation rather than by specific diagnostic categories. Special studies would therefore be required in order to enumerate all the patients with Down's Syndrome in these facilities. Casual estimates from administrators and government sources indicate that Down's Syndrome is responsible for the admission of about 10% of the residents of these hospitals.

The best estimates of the prevalence of Down's Syndrome are derived indirectly and are based on the findings of large population surveys designed to assess the prevalence of mental retardation in the general community.

Mental retardation is a surprisingly common phenomenon - it has been estimated that 3% of Canadians are mentally retarded.[34,52] Fortunately almost all of these individuals are only mildly affected and can, with extra supervision, learn to take their place in society as ordinary citizens participating in the labour force. The severely retarded, about 0.4% of the population,[53,54,55] present a much greater problem to the community. They are much more likely to be retarded on an irreversible organic basis and tend to have physical as well as mental handicaps.[55] Many can participate in the programs of sheltered workshops with special education and training but they usually remain dependent on others

throughout their lives.

The boundary line between mild and severe mental retardation is difficult to define; an individual's performance may change as a result of special training or the amelioration of physical handicaps, and the final categorization is often a matter of judgment. The World Health Organization Experts Committee on Mental Health has recommended the use of an Intelligence Quotient of 50 as the cutoff point[56] and despite the obvious problems of standardization, calibration, reliability and dependence on an Anglo-Saxon culture which are inherent in such a scale, most clinicians find this measurement to be a useful criterion especially when it is used in conjunction with the social and personal assessment of the individual.

Almost all patients with Down's Syndrome are severely retarded - about 5% have I.Q. values of less than 25 and about 5% patients have I.Q. values in the 50 to 60 range.[57,58] Down's Syndrome is now the single most important cause of severe mental retardation and is responsible for 25 to 35% of the individuals in this group.[3,59] (Table 8)

If we use this figure in conjunction with the available estimates for the prevalence of mental retardation in the Ontario population, we can develop a measure of the extent of the problem of Down's Syndrome in this province. Thus, it can be estimated that there are 240,000 mentally retarded individuals in Ontario (3% of the population) of whom about 36,000 (0.4% of the population) are severely retarded and within this group between 9,000 and 12,600 (25-35% of 36,000) will have Down's Syndrome.

Down's Syndrome has not always been such a prominent cause of

severe mental retardation, and a number of factors have contributed to its increasing importance. Trends in the prevalence of severe mental retardation are dependent on the trends in the incidence, survival rates and prognosis of persons who are classified as being severely mentally retarded. Several studies suggest that there has been a marked decline in the incidence of some of the causes of severe mental retardation, a decline which has been attributed to better antenatal and obstetric care, increased use of immunization techniques (particularly for Rubella and Rubeola), prevention of Rh sensitization of the fetus in Rhesus-negative women, and increasing attention to the nutritional needs of pregnant women and children.[60,61] In addition, the societal trend towards the completion of families at younger parental ages has probably also contributed to the decline in incidence of many causes of severe mental retardation since we know that obstetric difficulties and most congenital abnormalities increase with advancing maternal age.

Although it can be shown that there has also been a significant decline in the theoretical incidence of Down's Syndrome, the decline has not been so marked in the case of this syndrome as it has been for other disorders and Down's Syndrome has therefore become relatively more important.

While the incidence of severe mental retardation (all causes) has been declining over the past decades, the survival and life span of the mentally retarded has been steadily increasing over the past two decades.[32,33] The net effect of these two changes is that the prevalence of severe mental retardation has remained almost constant as can be seen in the studies listed in Table 8.

In contrast to the constant prevalence for severe mental retardation attributable to any cause, the rise in the prevalence of Down's Syndrome is striking. British data which spans this century is also presented in Table 8.

The rise in the prevalence of Down's Syndrome has definitely over-shadowed the reduction in incidence that has occurred and since this disorder is playing an increasingly important role among the causes of severe mental retardation, the discovery of its cause or the development of effective preventive measures are of major consequence.

Chromosomes and the Etiology of Down's Syndrome

The next major advance in our knowledge of Down's Syndrome came with the discovery that the syndrome is always associated with a major abnormality in the chromosomal constitution of all the body cells.

Background Information

For many years it has been known that in man, as in other organisms, hereditary information is transmitted from generation to generation by genes collected together in units known as chromosomes, present in the nucleus of each body cell. The techniques which permitted study of the human chromosomes were only developed comparatively recently; it was only in 1956 that Tjio and Leven combined a number of processes together and conclusively established that the normal human chromosome complement was 46 chromosomes.[68] The chromosomes cannot be visualized in the functioning cell but during the process of cell division (mitosis) the chromosomes contract and become visible as deeply staining bodies (chromos, color; soma body). In one phase of cell division they arrange themselves in an almost two-dimensional pattern known as the metaphase

plate and during this stage they are much easier to analyze. Using these preparations the 46 human chromosomes can be classified into 22 pairs of autosomes, which are alike in males and females and an additional pair of chromosomes, the sex chromosomes, which are different in males and females. The gametes (ova and sperm) are the only normal human body cells which do not have 46 chromosomes. During their formation, a special type of cell division (meiosis) results in these cells having only 23 chromosomes. After fertilization the embryo again has 46 chromosomes with one member of each pair being contributed by each parent. Conventionally, the chromosomes are identified and named on the basis of size and structure, according to the Denver Classification in which the 22 autosome pairs are placed into 7 groups (A, B, C ... G) arranged in order of decreasing length. When the Denver classification was devised in 1960, it was impossible to classify the chromosomes individually within the groups but recent developments in staining techniques which result in the appearance of characteristic cross-bands on the chromosomes allow the individual identification of each chromosome pair.[24]

A systematized array of the chromosomes prepared either from a drawing or from photographs of a metaphase spread is called a karyotype. A metaphase spread of the chromosomes from a normal male is shown in Figure 2 and a karyotype prepared by cutting up a photograph of the chromosomes and sorting them into pairs and groups is shown in Figure 3. The effect of "banding" is shown in Figure 4 and the differences between the members of each group can be observed.

Abnormalities of the chromosomes may be either numerical or structural and may affect either the autosomes, sex chromosomes, or,

FIGURE 2

THE CHROMOSOMES OF A NORMAL MALE IN A METAPHASE SPREAD

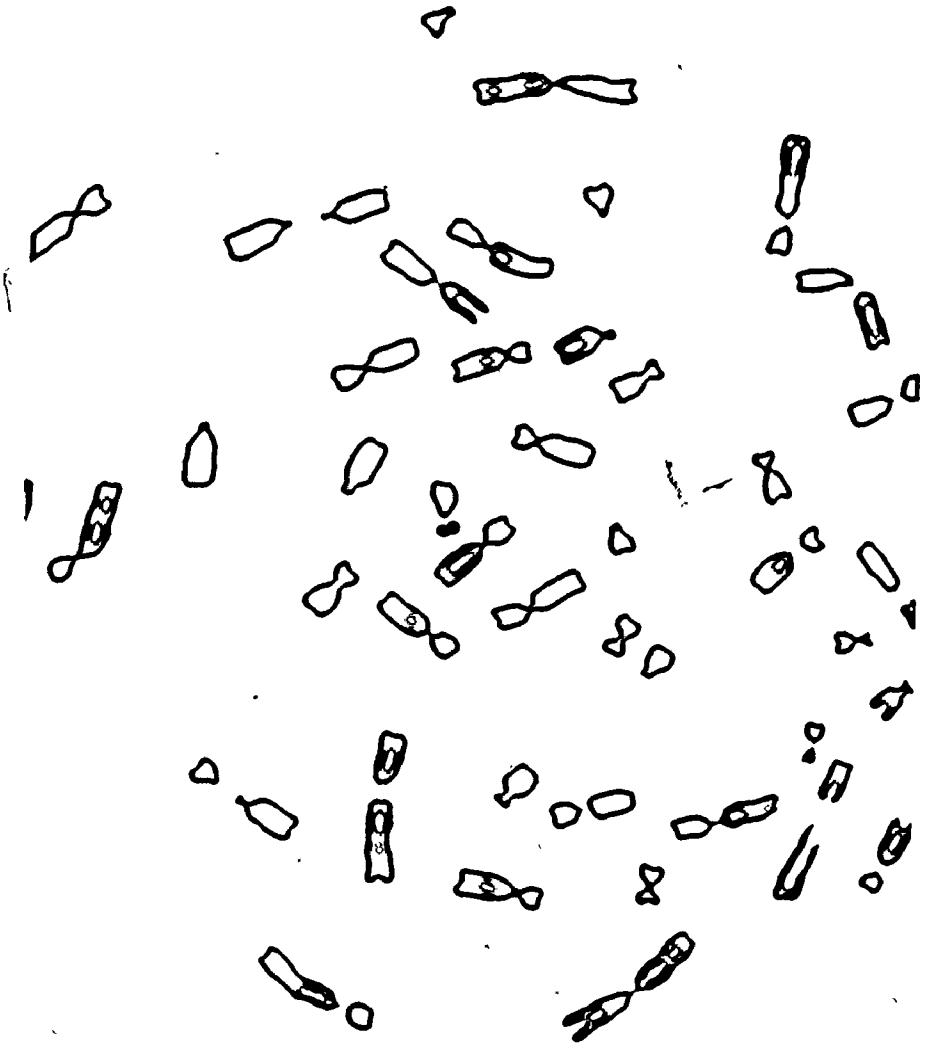


FIGURE 3

THE KARYOTYPE OF A NORMAL MALE

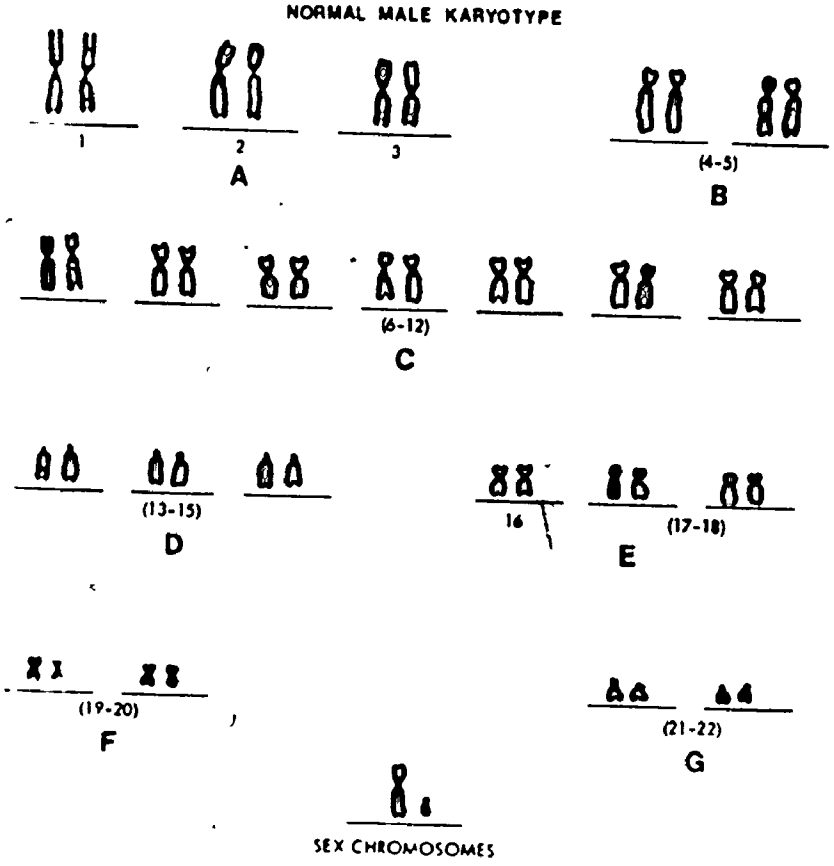
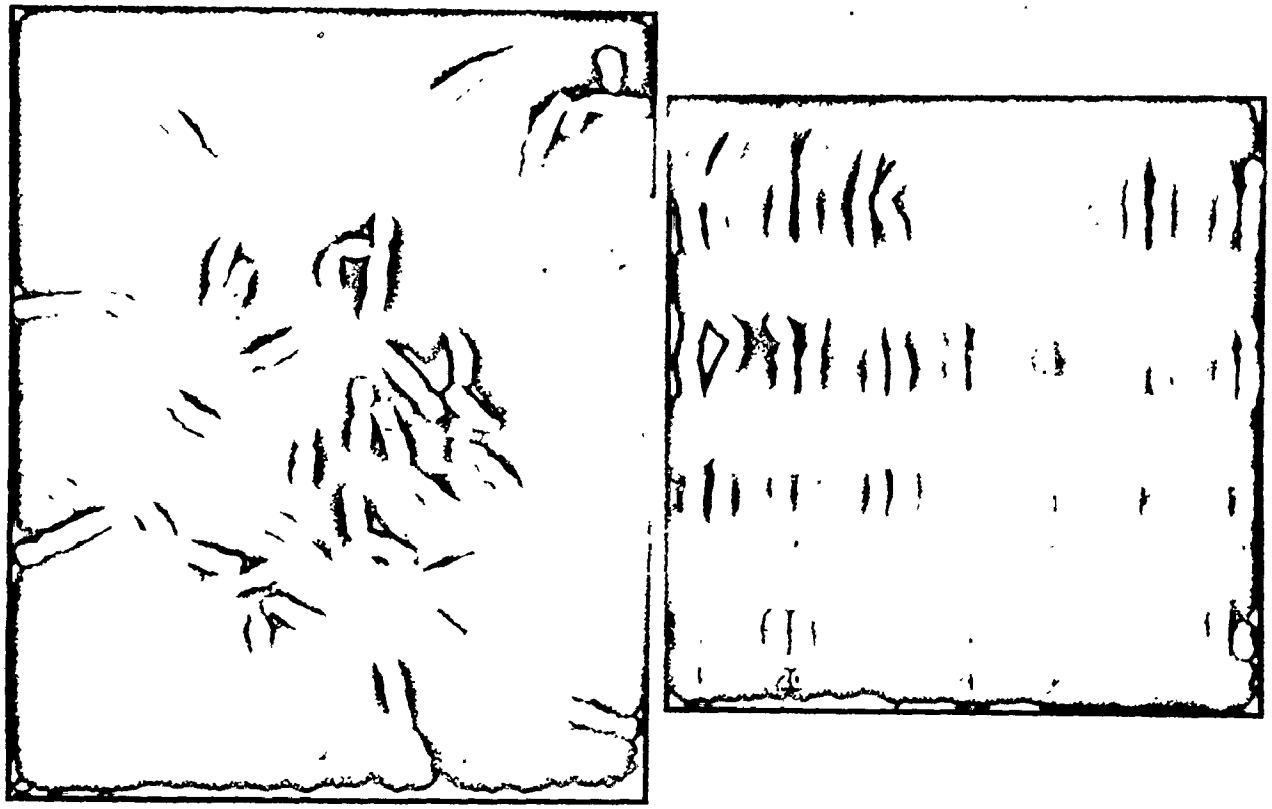


FIGURE 4

THE CHROMOSOMES OF A NORMAL MALE - FLUORESCENT BANDING



rarely, both in the same karyotype. To be recognizable with ordinary staining techniques, chromosomal aberrations must be abnormalities of number or gross abnormalities of structure; even with the use of "banding" many structural defects are beyond the limits of resolution.[24]

It has been shown that almost any abnormality of autosomal number or structure which is large enough to be detected by present methods is likely to cause mental retardation together with other congenital anomalies. Aberrations affecting the sex chromosomes seem to be somewhat better tolerated than those affecting the autosomes. Severe mental retardation is not a constant feature of these disorders but other serious congenital abnormalities may be present and sexual development is often disturbed.[69]

Alterations in a number of chromosomes arise chiefly through a process called non-dysjunction which is a failure of the paired chromosomes to separate normally during cell division. If non-dysjunction occurs during meiosis (the cell division that leads to the formation of the gametes) the resulting gametes receive an abnormal number of chromosomes, e.g. 24 instead of the normal 23. Fertilization of such an abnormal gamete by a normal one with 23 chromosomes results in an embryo with 47 chromosomes. The processes involved are described diagrammatically in Figures 5A-C.

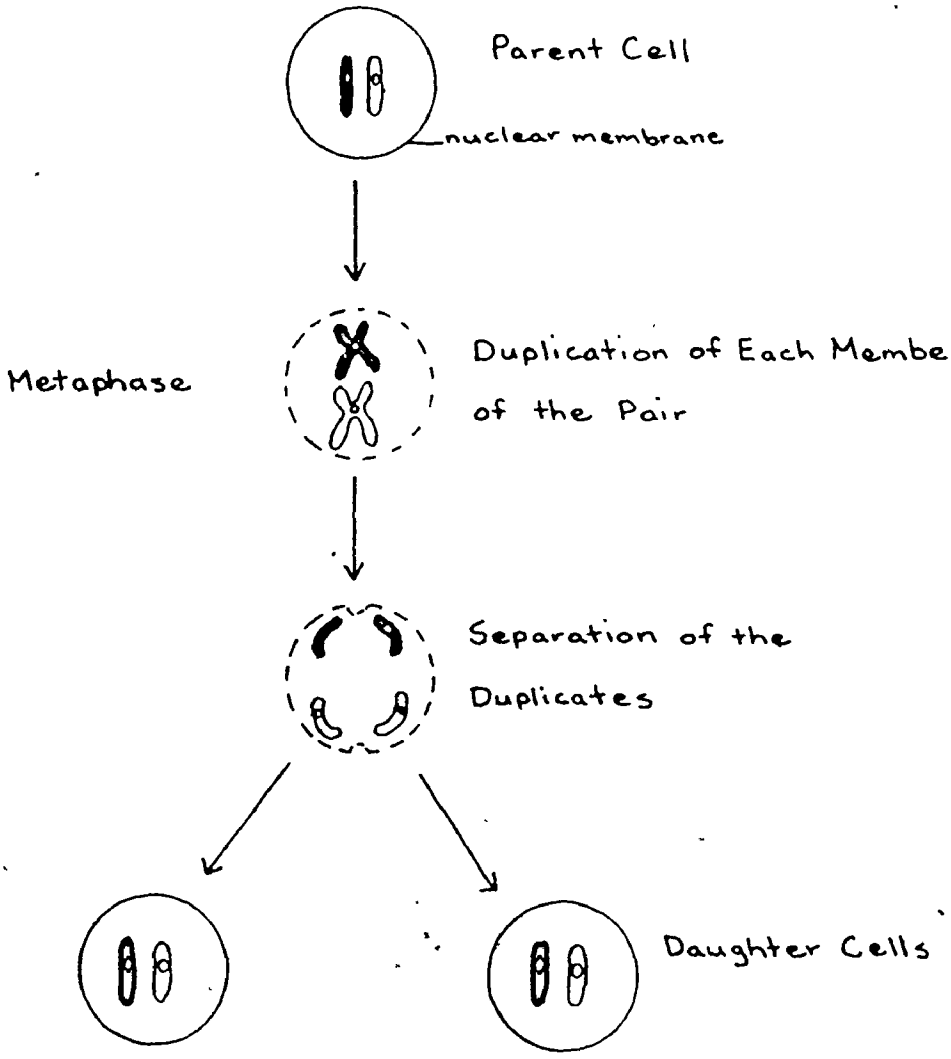
The Chromosomes in Down's Syndrome

Trisomy 21

A major advance in our understanding of Down's Syndrome was made in 1959, when Lejeune and Turpin demonstrated that "Les enfants Mongoliens" have 47 chromosomes in each body cell instead of the normal

FIGURE 5A

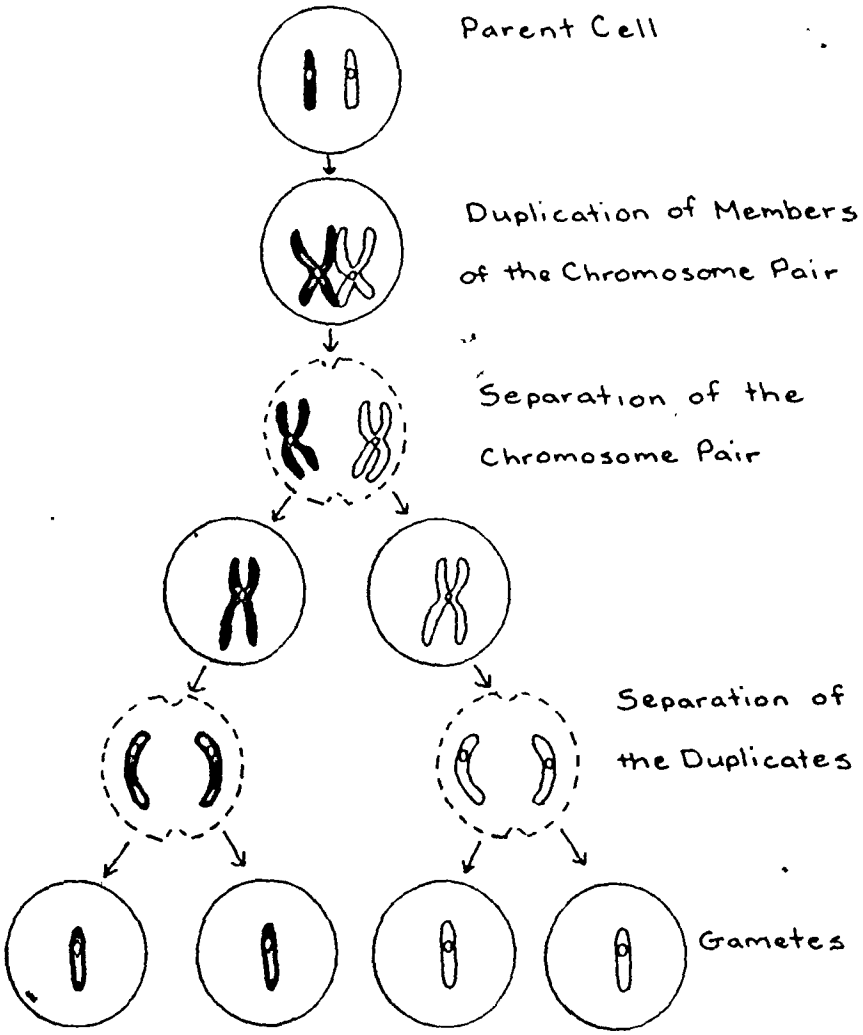
MITOSIS



The behaviour of a pair of chromosomes in the normal process of cell division to form two daughter cells.

FIGURE 5B

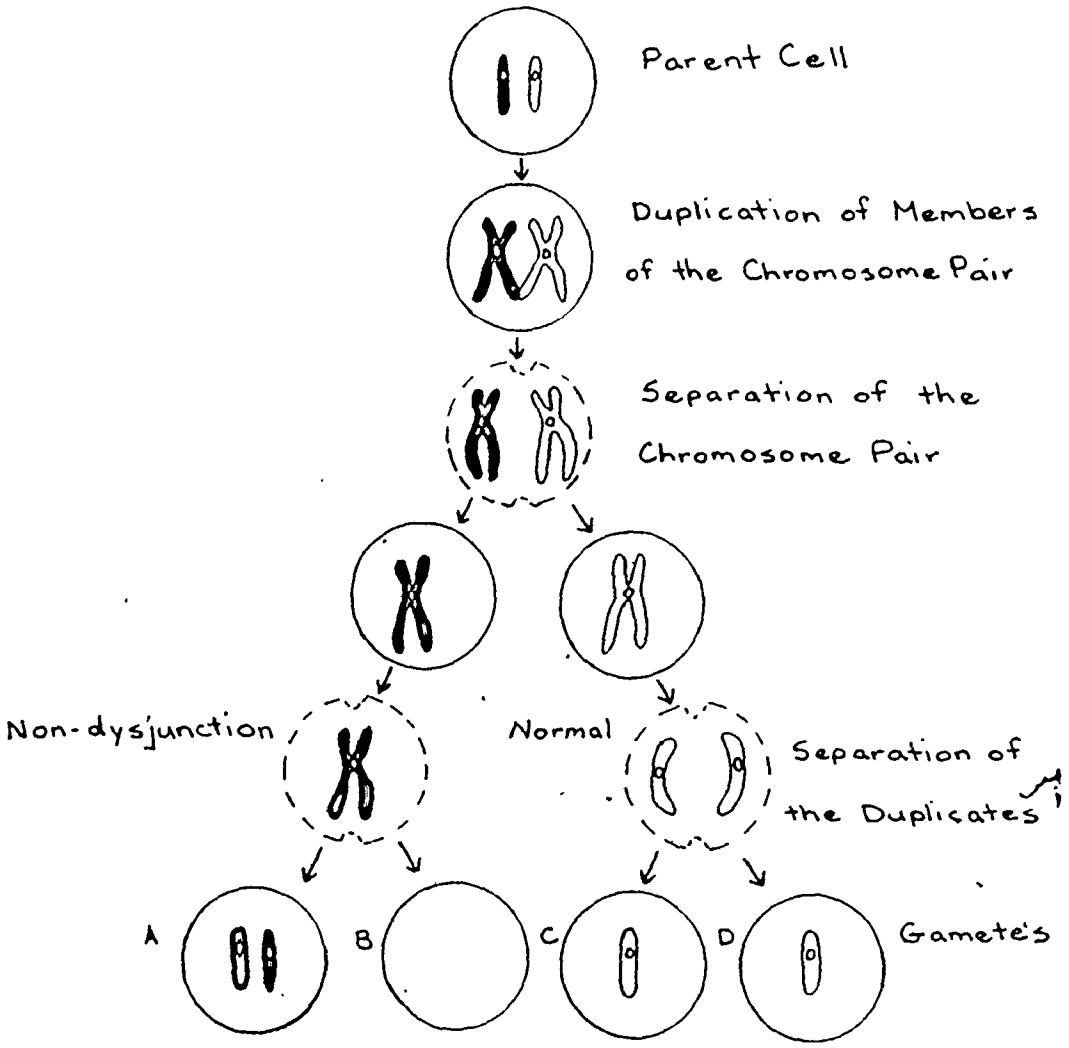
MEIOSIS



The behaviour of a pair of chromosomes in the normal process of cell division to form four gametes.

FIGURE 5C

NON-DYSJUNCTION



The chromosome pair does not separate normally in the last phase of meiosis. The resulting gametes A and B will produce trisomic or monosomic fetuses respectively. Gametes C and D are normal.

46 chromosomes.[70] The extra chromosome in Down's Syndrome is a small autosome belonging to the G group, now conventionally regarded as Chromosome 21. (Fig. 6) This discovery resulted in two more synonyms for Down's Syndrome, namely Trisomy G and Trisomy 21. (Trisomy is the term used when a chromosome is present in triplicate instead of duplicate) Down's Syndrome is considered to arise as a result of non-dysfunction in the formation of one of the gametes and because of the strong association of Down's Syndrome with advancing maternal age, the ovum rather than the sperm has been implicated.

Translocation

Trisomy 21 accounts for about 95% of all cases of Down's Syndrome.[64,71] In a small minority of cases, the body cells are found to have only 46 chromosomes but the karyotype is still abnormal because, by a process known as translocation, a considerable portion of an extra number 21 chromosome is fused with another autosome, usually chromosome number 15 or 22. (Fig. 7) This variety of Down's Syndrome is clinically indistinguishable from Trisomy 21. Although the translocation type is rare, its importance lies in the fact that in about 40% of cases, the disorder is familial, and one of the parents is found to be a carrier.[64] In the carrier parent, the total amount of chromosomal material is normal but it is arranged in only 45 chromosomes as a result of translocation. The presence of a balanced translocation in the parent greatly increases the risk of Down's Syndrome in the children and it is in this situation that we may find multiple cases of the syndrome in a single family group. In addition, the parent with a balanced translocation is also at risk of transmitting the carrier state to future generations.

FIGURE 6

THE KARYOTYPE OF A MALE WITH TRISOMY 21

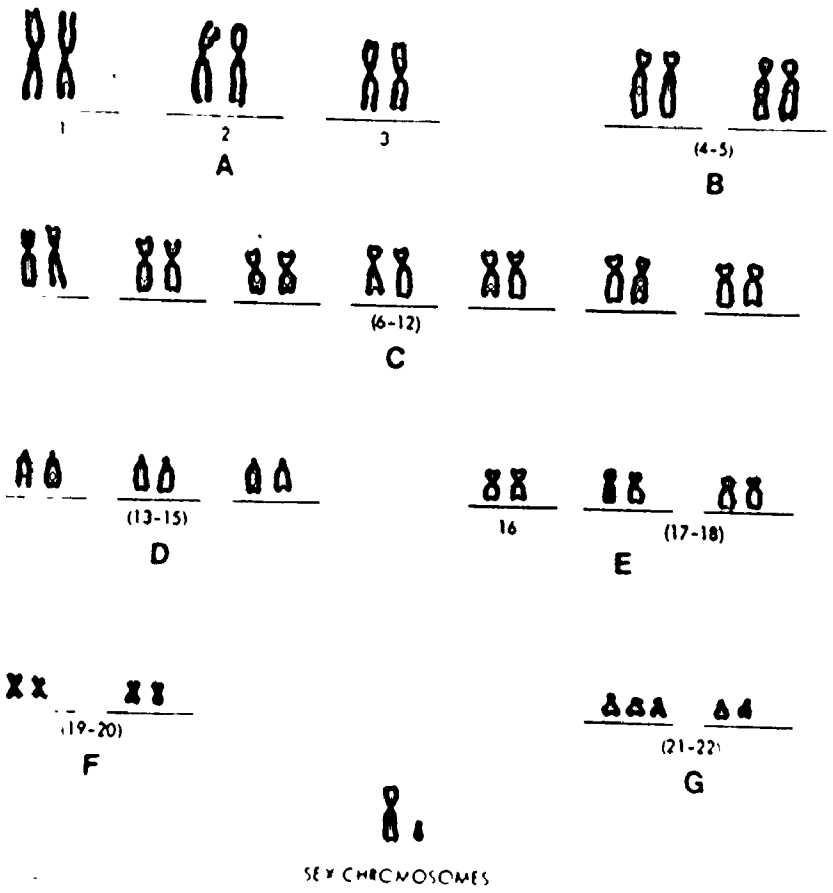
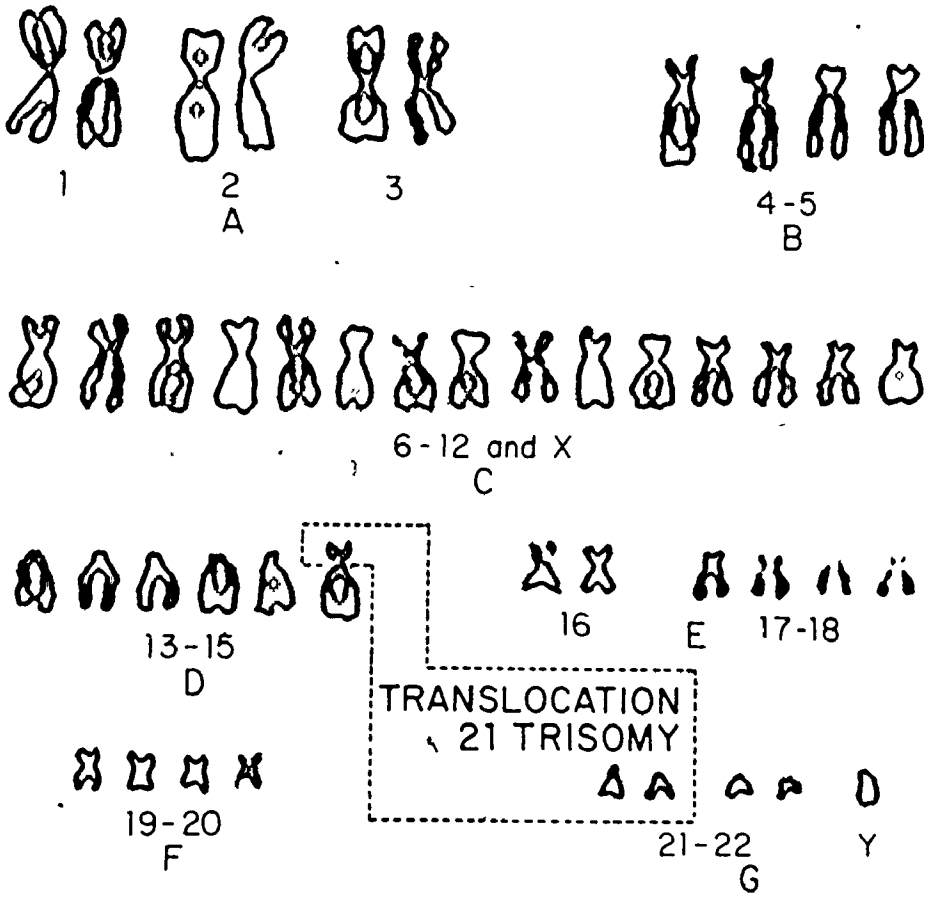


FIGURE 7

THE KARYOTYPE OF A MALE WITH TRANSLOCATION DOWN'S SYNDROME



Although translocation Down's Syndrome only accounts for between 3 and 4% of all cases of Down's Syndrome,[64,71] its importance varies according to maternal age. About 9% of children with Down's Syndrome born to women under 30 have the disorder on the basis of translocation, whereas for mothers over 30, translocation is present in only 1.5%.[24]

Mosaicism

Another minor chromosomal variation in Down's Syndrome which is responsible for less than 1% of cases is mosaicism,[71] in which some cells have a normal chromosome complement and others show the typical Trisomy 21. This variety of Down's Syndrome is thought to occur as a result of an error in cell division during early embryonic life and may also be associated with advanced maternal age. Generally, mosaics are less severely affected than individuals in whom all the cells have an extra chromosome, but unfortunately, the degree of mosaicism observed in laboratory cell cultures does not correlate well with the clinical severity of the disorder.[24,64,72]

The Search for the Cause of Down's Syndrome

Prior to Lejeune & Turpin's discovery of the chromosomal basis of Down's Syndrome in 1959,[70] a review of the literature revealed approximately 40 different theories for the cause of the disorder.[3] As early as 1932, Waardenburg,[73] an ophthalmologist, and Bleyer,[74] a pediatrician, had both deduced the presence of a chromosomal abnormality based on their observations of the wide-spread nature of the disease - "the more one looks, the more one sees" and on their observations of the pattern of the disorder in twins. (Identical or monozygotic twins were concordant for Down's Syndrome and non-identical or dizygotic twins were discordant

for Down's Syndrome.)

Subsequent to the work of Lejeune and Turpin, many of the theories that had been developed could be disgarded and the quest for the etiological factors in Down's Syndrome could be concentrated on those circumstances or events which could theoretically lead to an abnormal distribution of the chromosomes during gametogenesis. Although the discovery of the chromosomal basis of Down's Syndrome represented a major breakthrough it is important to recognize that we are still far from understanding the cause of the chromosomal abnormality.

Much of the recent work attempting to determine the cause of Down's Syndrome deals with the findings of large epidemiological studies and although the cause (or causes) of Down's Syndrome has not been identified, some of these studies have resulted in the identification of persons at "high risk" of having a child with Down's Syndrome.

Advanced Maternal Age and Maternal Health

Shuttleworth, in 1909, was the first to point out the relatively advanced age of many mothers at the time of the birth of their mongoloid children.[75] This observation was confirmed by many subsequent studies. In 1938, Bleyer showed that the peak maternal age at the birth of 2,822 children with Down's Syndrome was 41 years whereas in the general population the peak was found to be at 24 years.[74] These findings were confirmed by Penrose, who also showed that paternal age and the birth order of the child had no apparent independent effects.[76,77] Other researchers have demonstrated that the incidence of the disorder does not seem to be related to race, geographic location, season of birth, socio-economic class, or sex.[2,9,55,64,78]

As a result of the well-recognized association of mongolism with maternal age, interest has been focussed on the role of maternal health - particularly reproductive, hormonal and constitutional factors - as well as on the circumstances and events around the time of conception. Several studies of maternal reproductive performance both before and after the birth of a child with Down's Syndrome have been made but no consistent abnormalities in menstrual history, fertility experience, (including the frequency of spontaneous abortions), duration of the marriage or pregnancy free intervals have been observed.[9,71]

Since many endocrine disorders are known to have an effect on ovarian function, endocrine diseases have been suggested as possible etiological factors. For many years, laboratory and animal studies have shown that disorders of the thyroid gland may result in abnormal chromosome distribution during cell division and several studies reporting on the thyroid function of the mothers of mongoloid children have been presented.[79] Unfortunately most of the studies have been inadequately controlled and have presented conflicting evidence on the frequency of thyroid dysfunction among these mothers.[2]

Thyroid Antibodies

Reflecting an interest in thyroid disorders and the possible influence of autoimmunity (a situation in which the body develops antibodies against itself) in the etiology of chromosomal disorders, Fialkow and Uchida reported that the mothers of children with Down's Syndrome were more likely to have thyroid antibodies than were the control mothers.[80] Additional analyses indicated that the difference is essentially limited to mothers under 35 years of age. Their findings are presented in

Figure 8, Table 9 and Table 10. Their findings suggest that the presence of thyroid disease, on the basis of autoimmunity, may be differentially responsible for translocation, non-disjunction and mosaicism but since Fialkow and Uchida do not relate their findings to the cytogenetic variety of Down's Syndrome, it is not possible to explore this hypothesis further. Several other authors have confirmed the association between thyroid antibodies and Down's Syndrome and further support for this theory has come from a large prospective study of chromosome abnormalities in which it was reported that mothers with a history of thyroid disease had a greatly increased risk of bearing a child with a chromosomal abnormality.[81] Although the evidence linking thyroid disorders to Down's Syndrome is inconclusive at the present time, a history of thyroid disease in a pregnant woman should alert physician to the possibility of a chromosomal defect in the infant.

The association of Down's Syndrome with advanced maternal age has overshadowed all other epidemiologic findings but there has also been considerable interest in the risk of recurrence of Down's Syndrome in the family that already has one affected child.

In those cases where a familial translocation is identified the risks of recurrence are much higher than for the non-dysjunction form of Down's Syndrome. The precise risks depend on the type of translocation present and on whether the carrier is the father or the mother. Data summarizing the risks in translocation Down's Syndrome are presented in Table 11. It can be seen that the observed risks are substantially less than theoretical risks. This has been attributed to the decreased "fertilization potential" of defective gametes and to

FIGURE 8

AGE-SPECIFIC PREVALENCE OF THYROID ANTIBODIES IN MOTHERS OF PATIENTS WITH DOWN'S SYNDROME COMPARED WITH CONTROL FEMALES

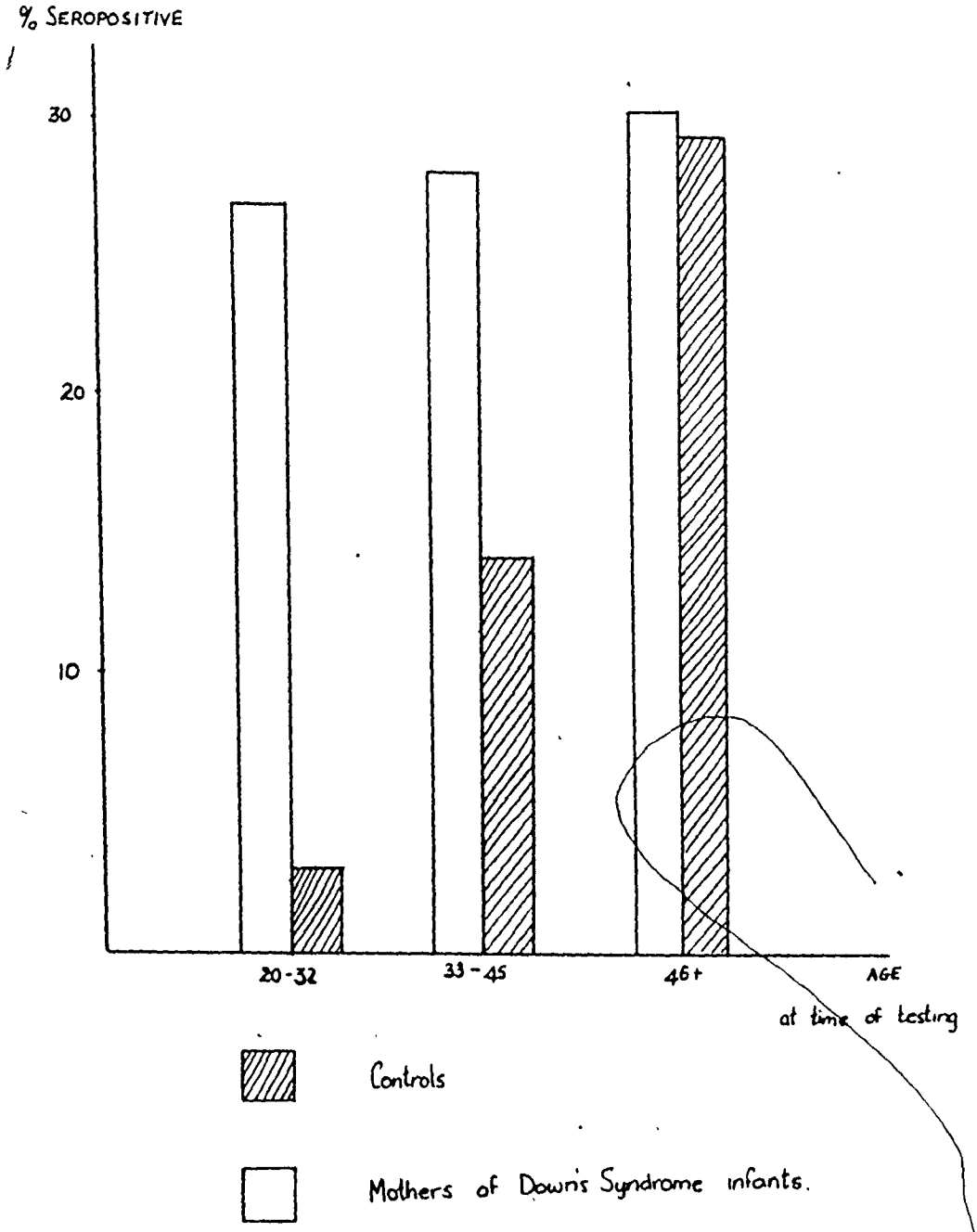


TABLE 9

AGE RANGE AT TIME OF TESTING (YEARS)	MOTHERS OF PATIENTS WITH DOWN'S SYNDROME		CONTROL FEMALES		x^2	p
	No. Tested	No. Positive	No. Tested	No. Positive		
20-32	66	18 (27%)	66	2 (3%)	13.3	<0.001
33-45	97	27 (28%)	97	14 (14%)	4.5	<0.05
45 +	79	24 (30%)	79	23 (29%)	-	-
Total	242	69 (29%)	242	39 (16%)	10.0	<0.005

Thyroid antibodies in mothers of patients with Down's Syndrome compared with control females in relation to age at the time of testing.

(after Fialkow and Uchida[80])

TABLE 10

MATERNAL AGE AT BIRTH OF DOWN'S CHILD (YEARS)	NO. TESTED	NO. POSITIVE		x^2	p
		OBSERVED	EXPECTED		
18-34	120	34	11.5	12.5	<0.001
35+	122	35	27.5	0.91	>0.3

Maternal thyroid antibodies in relation to age at time of birth of child with Down's Syndrome.
(after Fialkow and Uchida[80])

TABLE 11

RISKS OF RECURRENCE IN TRANSLOCATION CARRIERS

- after Thompson[24]

	Infants who are carriers		Affected infants	
	Expected	Observed	Expected	Observed
Mother D/G carrier	33%	40%	33%	11%
Father D/G carrier	33%	59%	33%	2%
Mother G/G carrier	33%	52%	33%	1%
Father G/G carrier	33%	66%	33%	N.S.

the increased risk of prenatal death in the chromosomally abnormal fetus.[24,51]

The risks of recurrence in later children when the affected child has Trisomy 21 are somewhat uncertain because of the fact that early studies failed to differentiate between the translocation and non-dysjunction varieties of Down's Syndrome. One of these early studies suggested that the risk of recurrence was twice or three times the expected age-specific risk in women under 35 years and many genetic counsellors used these estimates in advising prospective parents.[82] However, later cytogenetic studies have demonstrated that almost all the previously observed increase can be explained by the presence of translocation carriers in this group. The chromosomal disorder in Trisomy 21 is thought to arise as a result of a random mutation and it now appears that the risk of a further trisomic infant, when the parents are themselves chromosomally normal, is not significantly increased.[83] In the few cases where a recurrence has occurred it is possible that the mother is an unrecognized mild mosaic for Trisomy 21. Further, there is some evidence that the women who are later found to be mild mosaics were born when their mothers were in the later child-bearing years, so that advanced grandmaternal age can be added to the list of possible risk factors.[71]

The finding that the risk of recurrence is not appreciably increased for the mother of a classical Trisomy 21 infant leads one to question the role of transient environmental factors in the causation of Down's Syndrome and a number of hypotheses have been suggested.[84,85]

Viruses

The Australian epidemiologists, Collman and Stoller compared

the annual incidence of Down's Syndrome with the annual incidence of reported infectious diseases over a 16 year period.[86] They found a concordance of Down's Syndrome with infectious hepatitis 9 months earlier and they postulated a viral etiology for the disorder arguing that the aging ovum was more susceptible to attack by a virus or th at an immunological reaction to the infection might affect the stability of the nucleus of the ovum. Subsequent studies have not confirmed this suggestion, however, and further analysis suggests that their conclusions were based on a chance finding.[2] A viral etiology is attractive in many respects because of the known association of viral diseases with chromosomal breaks but despite several attempts it has been impossible to demonstrate their etiologic role in Down's Syndrome.[9]

Radiation

In view of the known relationship of ionizing radiation to chromosomal non-dysjunction in laboratory studies with Drosophila, several investigators have tried to determine if the mothers of mongoloid children had been exposed to unusual amounts of diagnostic or therapeutic radiation in the conceptional period. Once again, the evidence has been conflicting and further research is required.[84,87,88] There is, however, enough consistent evidence to warrant maternal fluoroscopic and therapeutic radiation being regarded as risk factors for Down's Syndrome.

Drugs and Fluoride

Several researchers have looked at the question of maternal drug use early in an affected pregnancy but no unusual patterns have been reported.[9] However, Rapaport has suggested that there is an

increased incidence of Down's Syndrome in cities where the water is fluoridated.[89] Unfortunately, the sources of ascertainment resulted in a selection bias which undermine his analysis and his findings have not been substantiated by the more complete study of Needleman et al.[90] The present evidence indicates that fluoridation of water supplies at the usual level of one part per million does not result in an increase in the incidence of Down's Syndrome (unless the induction period is longer than 3 to 5 years).

Summary

In summary, it is evident that inspite of a major research effort, little progress has been made toward establishing the cause or causes of Down's Syndrome. However, it has been possible to identify certain individuals who are at a particular risk of producing a mongoloid infant:

1) translocation "carriers", most of whom will not be identified until after the birth of an affected child,
2) mild mosaics, who are also unlikely to seek advice until after the birth of an affected child,
3) women who have a history of:
   a) thyroid disease,
   b) the presence of thyroid antibodies,
   c) recurrence spontaneous abortions in the absence of any gynecological explanation (the abortuses may have been chromosomally abnormal and the mother may be a translocation carrier),
   d) diagnostic fluoroscopy,

e) therapeutic radiation,

f) advanced grand-maternal age and

4) advanced maternal age.

The only situation where the increased risk has been quantified is in the case of advanced maternal age and as was indicated earlier the risk increases rapidly after the age of 35 years. (Fig. 1)

The few individuals who fall into categories 1-3 are at special risk and the geneticist must take these factors into account when reaching a decision about the expected outcome of the pregnancy, and the advisability of prenatal diagnosis. By far the largest proportion of the mothers of infants with Down's Syndrome cannot be identified prenatally at the present time since they are at risk simply on the basis of advanced maternal age. In order to significantly reduce the incidence of Down's Syndrome a preventive program should be directed to this group of women.

The Prevention of Down's Syndrome

Programs directed at the prevention of disease may be focussed in three areas:

1) primary prevention - preventing the development or expression of the disease by modification of health behaviour, vaccination, presymptomatic treatment, etc.

2) secondary prevention - preventing the full expression of the usual characteristics of the disease by active treatment programs, e.g. antibiotic therapy in pneumonia,

3) tertiary prevention - modification of the effects of the disease by rehabilitating the patient, e.g. the use of prosthesis for

amputees and job retraining programs.

Until recently, the major emphasis in preventive programs relating to Down's Syndrome has been on secondary and tertiary prevention in that every attempt has been made to optimize the potential of affected individuals, rehabilitate institutionalized patients, and minimize the suffering of patients and their families. However, since the underlying abnormality is irreversible, these efforts have not been very successful and it is clear that an ideal preventive program for Down's Syndrome would offer primary prevention of the disorder.

Ideally, one would wish to prevent the conception of a fetus with Down's Syndrome but review of the literature suggests that our understanding of the causation of Down's Syndrome is inadequate for this to be an efficient solution to the problem.

Attempts to prevent the conception of infants with Down's Syndrome include:

a) voluntary family limitation following the birth of an affected infant,

b) genetic counselling of "at risk" families.

In addition, present fertility trends, while not specifically directed at the prevention of Down's Syndrome have substantially reduced the incidence of this disorder.

While prenatal diagnosis and selective therapeutic abortion is not an ideal method of primary prevention and does not represent a basic advance in our understanding of Down's Syndrome it does offer a realistic method of preventing the birth of affected infants. The effectiveness of each of these methods in preventing Down's Syndrome

will be considered in more detail in the following pages.

Voluntary Family Limitation and the Primary Prevention of Down's Syndrome

It is a clinical impression that many parents are unwilling to have further children following the birth of a severely handicapped child. Since family limitation can be regarded as a form of primary prevention, the determinants and effectiveness of the decision to limit family size will be considered in more detail.

The birth of an infant with Down's Syndrome may affect parental decisions about further children in a number of ways. Regardless of whether the child with Down's Syndrome was born as a result of a planned or unplanned pregnancy the parents may decide to:

a) avoid further pregnancies because they now have the desired number of children (or more),

b) avoid further pregnancies despite the fact that they had planned more children because of the additional burden of the child with Down's Syndrome,

c) avoid further pregnancies despite the fact that they had planned more children because they are unwilling to risk having further affected infants,

d) plan further pregnancies with the total number of desired children unchanged by the birth of the Down's Syndrome infant,

e) plan an additional pregnancy to "replace" a child with Down's Syndrome recognizing the reduced life expectancy and the severity of the mental retardation associated with the disorder.

Usually, the child with Down's Syndrome is born late in the child-bearing years and it is therefore difficult to establish the

effect of the birth of a child with Down's Syndrome on family limitation. Some writers have reported that parents tend to limit their family after the birth of a retarded child but the conclusions have usually been based on small uncontrolled studies whose findings are difficult to interpret.

One of the larger studies was a British survey reported in 1958. Holt interviewed over 200 families who had a retarded child born in the years 1939 to 1955.[91] Among those families where a further pregnancy was theoretically possible, he found that 6.9% planned no further pregnancies because they had already achieved the desired number of children, 35.6% planned no further children because "the defective child required so much work, or because the mother wished to give the defective child all her attention", 20.6% planned no further pregnancies because they were unwilling to face the risk of having further affected infants, 12.5% were indifferent, and 24.4% wanted more children. Of this latter group, 18% of the families had decided to have more children only after they had been assured that there was little chance of their having another retarded baby and 10% wanted more (normal) children to help the retarded child develop.

These findings seem to indicate a very significant reduction in planned family size as a result of the birth of a retarded child but, because a large proportion of parents did not use effective birth control methods further pregnancies were only reduced by an estimated 21%. Holt demonstrated that two factors were significantly associated with the decision about future child-bearing - a mother who was under 30 and those for whom the retarded child was the first born were more likely to desire a further pregnancy. Nevertheless, his finding that almost 60%

of mothers under 30 whose retarded child was a first born did not want more children is striking.

Although some families may plan to "replace" a defective infant, the overall effect of family planning decision after the birth of a Down's Syndrome infant is probably to decrease the number of subsequent pregnancies. Since the risk of recurrence is very low (it is probably not increased at all when the parents are found to have a normal chromosome constitution as in 95% of cases), the effect of family limitation in this situation is to prevent the birth of normal children without reducing the incidence of the disorder.

Genetic Counselling and Primary Prevention

Professional activities whose objective is primary prevention of Down's Syndrome have not been very successful. Until recently, the main tool of health professionals in trying to achieve primary prevention has been genetic counselling.

The characteristics of a disorder that can be effectively prevented by genetic counselling are:

1) the disease is a definite diagnostic entity with severely incapacitating consequences,
2) the parents can be identified as being at "high risk" before the birth of an affected child on the basis of either family history or the health history of the parents,
3) the risk must be quantifiable and
4) the risk must be high enough to persuade the majority of parents to avoid a further pregnancy.

Down's Syndrome certainly has the first characteristic but

because the abnormality usually arises as a random new mutation, the parents cannot be identified prior to the birth of an affected child. Further, since the risk of recurrence is low, genetic counselling serves to reassure the majority of parents and has no impact on the overall incidence of the disorder.

Where Down's Syndrome is the result of translocation, however, the situation is different. Although most "carrier" parents are also unlikely to seek genetic counselling prior to the birth of an affected child, subsequent genetic counselling may result in family limitation, which would slightly reduce the incidence of the disorder.

Another approach to the primary prevention of Down's Syndrome might be to inform families of the risks of the disorder at various maternal ages. However, since the risks are relatively low (approximately 1 in 300 at 35-39 years and 1 in 100 at 40-44 years), most parents would be willing to take a chance if they really wanted more children.

In summary, genetic counselling has not played a major role in primary prevention of Down's Syndrome except in those cases where a translocation carrier has been identified. In most cases, the geneticist can reassure parents of the low risk of recurrence so that they can proceed with the desired number of pregnancies.

Fertility Trends and Primary Prevention

In contrast to the impact of genetic counselling, recent societal trends towards the earlier completion of families and reduced family size have resulted in a very significant decline in the theoretical annual incidence of Down's Syndrome. (See Table 6) Two

demographic factors have been responsible for this decline:

1) a reduction in the total number of children born and
2) the marked decline in the age-specific fertility rates among older women.

The relative impact of these two factors is examined in Table 12. Column 2 shows the trends in the absolute numbers of live births in Ontario between 1953 and 1973. Column 3 lists the number of infants with Down's Syndrome that would be expected from the total births in each year if the maternal age distribution remained constant at that observed in 1953. Column 4 shows the theoretical estimates of infants born with Down's Syndrome allowing for the annual changes in both the total number of births and the maternal age distribution. The two factors have been almost equally responsible for the decline in the incidence of Down's Syndrome since 1960.

The age-specific fertility rates have decreased in all maternal age-groups since 1960 but the decrease has been particularly marked in the older age-groups as can be seen in Figure 9 and Table 13. The percentage of live births born to women of 35 and over has declined from 13.4% in 1961 to 5.9% in 1973 and since the risk of Down's Syndrome is so much higher in these "older" women, this trend has had a major effect on the overall incidence for Down's Syndrome (Table 12).

The precise reasons for the dramatic decline in age-specific fertility rates that has been observed since 1963 is unknown, but factors which may be responsible for the change include the availability of effective birth control methods and therapeutic abortions, the increasing participation of married women in the work force, the change

FIGURE 9

AGE-SPECIFIC FERTILITY RATES – TRENDS 1955 – 1972

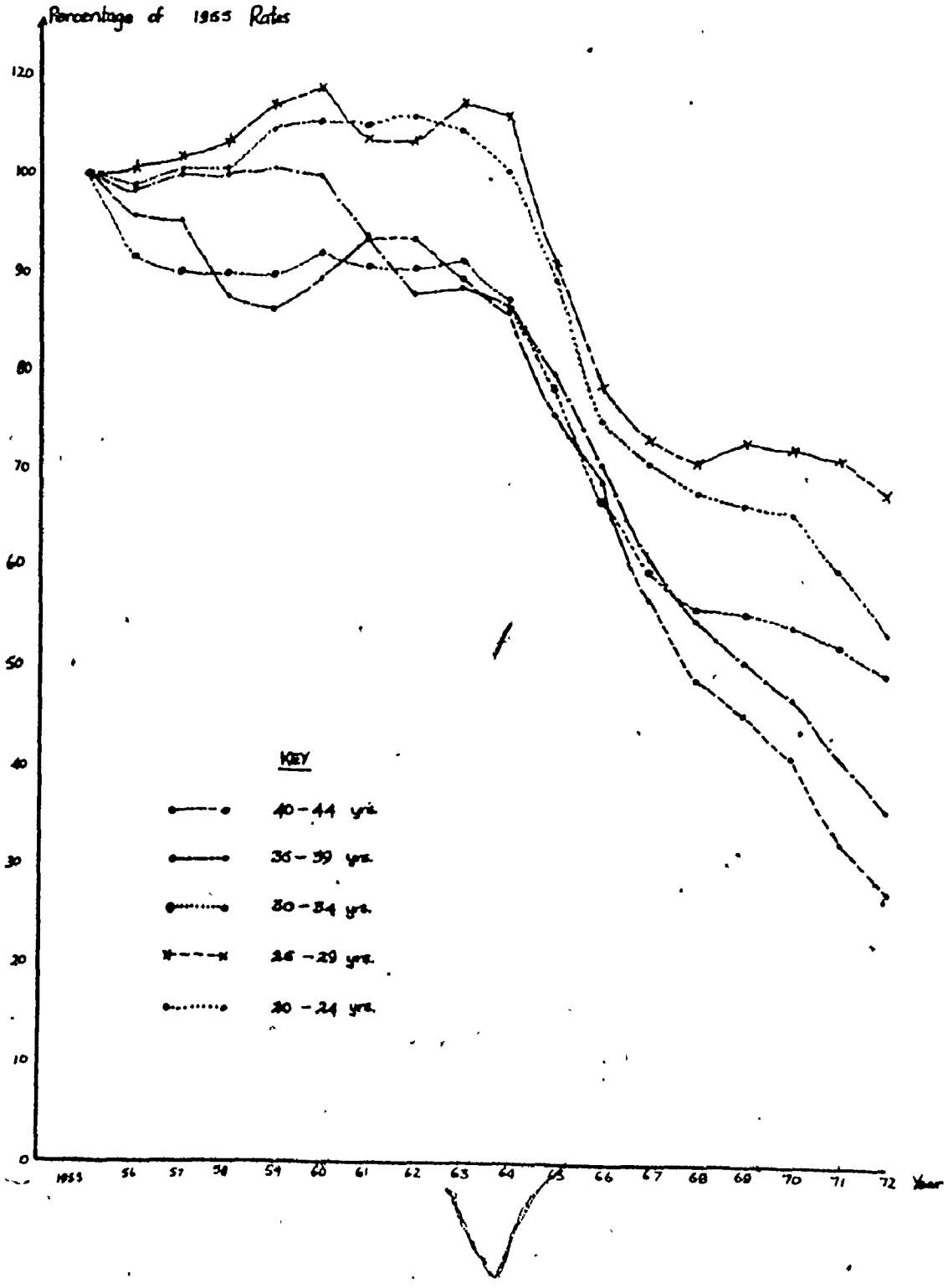


TABLE 12

THE IMPACT OF CHANGING FERTILITY PATTERNS ON DOWN'S SYNDROME

YEAR	TOTAL LIVE BIRTHS	NUMBER OF DOWN'S SYNDROME INFANTS EXPECTED BASED ON INCIDENCE RATE OF 1953	NUMBER OF DOWN'S SYNDROME INFANTS EXPECTED BASED AGE-SPECIFIC RATES APPLIED TO EACH YEAR
1953	129,771	173	173
1954	136,361	182	185
1955	139,554	186	192
1956	143,516	192	194
1957	150,920	201	205
1958	152,637	204	204
1959	157,124	210	210
1960	159,245	213	214
1961	157,663	210	214
1962	156,053	208	210
1963	155,089	207	209
1964	152,729	204	207
1965	141,610	189	190
1966	131,942	176	176
1967	127,509	170	159
1968	126,257	169	151
1969	130,398	174	149
1970	134,724	180	147
1971	130,395	174	136
1972	125,060	167	126
1973	123,776	165	122

TABLE 13

AGE-SPECIFIC FERTILITY RATES TRENDS 1955-1972, ONTARIO

MATERNAL AGE GROUP	LIVE BIRTHS PER 1000 WOMEN PER YEAR 1955	1965	1972
20-24	228.5	192.9	122.2
25-29	204.4	180.6	138.6
30-34	148.2	114.5	72.8
35-39	74.5	59.3	27.2
40-44	23.6	17.8	6.4
45-49	1.6	1.5	1.0

in the perception of a woman's role, economic constraints, and consumer awareness of the increased maternal and fetal risks associated with pregnancy and delivery in the later child-bearing years.

Penrose noted that in 1939 approximately 60% of Down's Syndrome infants were born to women of 35 years or older and it was clear that if women could be persuaded to complete their families before this age, many cases of Down's Syndrome could be prevented.[92] As we have seen, societal trends have been in this direction and current estimates show that only 28% of Down's Syndrome infants are born to women 35 years and over. However, it is likely that there will always be a proportion of parents who, for a variety of reasons, wish to have children in the later years, and it is for this group that prenatal diagnosis is of great importance.

Prenatal Diagnosis and Primary Prevention

The approach to the primary prevention of Down's Syndrome has been dramatically altered by recent developments in the field of prenatal diagnosis. The most important procedure in this field is called amniocentesis and involves obtaining a sample of the fluid that surrounds the fetus (the amniotic fluid). The fluid and its cells can then be analyzed to provide precise diagnostic information able a specific pregnancy. The first prenatal diagnosis of Down's Syndrome was made by Valenti in 1968,[93] and the usefulness of the test is becoming increasingly apparent as its safety, reliability and accuracy are demonstrated. At the present time the test is offered, by a few special centres, to women in "high risk" categories. In most centres this "high risk" group includes prospective mothers of 40 years of age and over, but as the

safety of the test is established, it can be anticipated that many clinicians will want to obtain this diagnostic information for patients whose pregnancies are at lesser risk. Since Down's Syndrome obviously has such major implications for both the affected infant and his family, a clinician in this situation is usually more concerned with the safety availability and accuracy of the procedure and may feel that consideration of such factors as the "cost" of prenatal diagnosis are irrelevant.

Although one can argue for a complete prenatal diagnostic screening program on humanitarian grounds many other factors must be considered. It is clearly important to establish that the test meets accepted medical criteria for safety, sensitivity and specificity, but it is also important to establish that it is economically and administratively feasible and that it is compatible with current moral, legal and ethical principles. These issues will be considered in more detail in the following chapters.

CHAPTER TWO

PRENATAL DIAGNOSIS AND THERAPEUTIC ABORTION

Historical Background

Human beings have probably always wanted to be able to predict the characteristics of an unborn child. Aristotle, in his "History of Animals", refers to the possibility of being able to predict the sex of the unborn child by such criteria as the side on which movements are felt or the general condition of the mother.[94] It is only in recent times, however, that precise techniques have been developed that allow the study of the human fetus "in utero".

As early as 1882, Schatz suggested that certain characteristics of the fetus could be determined by study of the amniotic fluid surrounding the infant,[95] but it was not until 1919 that the procedure of amniocentesis was actually used and reported.[96] By 1930 amniocentesis was being used as part of an X-ray procedure to locate the position of the placenta,[97] but subsequent to the discovery that X-rays were carcinogenic to the developing fetus, the use of X-ray investigations during pregnancy was severely curtailed and amniocentesis was not widely used again until the early 1950's. At this time, analysis of the amniotic fluid became a valuable method of monitoring the affected pregnancies of Rhesus negative mothers. (Rh. disease)[98] Large numbers of third trimester amniocenteses were performed in this clinical situation and it became apparent that the procedure was accompanied by very low risk to the mother or fetus.[99]

In 1956, several investigators reported, almost simultaneously, that fetal sex could be determined prenatally by studying the characteristics of the nuclei of amniotic fluid cells and amniocentesis became of increasing interest to geneticists.[96] Unfortunately, the amniotic fluid cells proved to be extremely difficult to culture for full chromosome analysis and it was not until 1966 that Steele and Breg reported the first successful karyotype preparation of human amniotic cells.[100] At first, the culture techniques were only successful in a small proportion of cases but recent advances have made it possible to reach a prenatal diagnosis in almost 100% of those cases seen in established centres.[101,102] In addition to chromosomal disorders it is now possible to diagnose many congenital biochemical disorders in the fetus and occasionally there is the possibility of instituting prenatal treatment.[101] Progress is also being made in the prenatal diagnosis of neural tube defects.[103,104] The potential of these techniques for genetic counselling was immediately apparent - instead of advising parents in terms of probilities, a definite prediction could be made about the presence or absence of an abnormality in a particular pregnancy.

The excitement generated by the rapid scientific advances in prenatal diagnosis was intensified with the recognition that changing societal and legal attitudes to abortion made selective therapeutic abortion a possible alternative to the birth of a severely defective child. Prenatal diagnosis has thus become a means by which these serious disorders can be prevented.

Although the potential of prenatal diagnosis for the prevention of Down's Syndrome is evident, a number of questions must be answered

before the procedure ceases to be experimental and becomes part of normal clinical practice.

1. What are the processes and procedures involved in the prenatal diagnosis of Down's Syndrome?
2. At what stage of pregnancy should the amniocentesis be performed?
3. What is the sensitivity and specificity of the test?
4. What are the maternal and fetal risks associated with the procedure and what are the maternal risks of a mid-trimester therapeutic abortion?
5. How much does the procedure cost? and
6. To whom should the procedure be offered?

These questions will now be considered in more detail.

Prenatal diagnosis is a time-consuming process dependent on information from several different sources and the complete results are usually not available for about 2 weeks after the amniocentesis has been performed.[53]

Genetic Counselling & Obstetric Assessment

The process is usually initiated by a referral to a Prenatal Diagnosis Clinic and at the present time most couples are referred by an obstetrician because they seem to be at particular risk of having a defective child. At this initial visit, the couple is seen by a geneticist who obtains a complete family and individual medical history, reviews the previous medical assessments and establishes the approximate risk for the present pregnancy. Each clinic selects its own "risk" criteria and if a particular pregnancy meets these criteria the geneticist

discusses the procedure of amniocentesis with the parents, informing them of the risks involved and of the nature of the diagnostic information that can be obtained. It is stressed that although many disorders can now be detected prenatally, a normal karyotype does not guarantee that a child will be "normal". The availability of a therapeutic abortion for those cases where an abnormal fetus is diagnosed is also discussed, although few clinics now require that parents should be committed to this option prior to the performance of the amniocentesis. The decision for or against a therapeutic abortion in the presence of a positive diagnosis of a severely defective infant is obviously an extremely difficult and personal one. Most clinicians feel the couple need time to carefully consider the options available to them and for this reason the possibility of a therapeutic abortion is raised at the initial visit. If the couple wish to proceed with amniocentesis they are also seen by an obstetrician at this visit. An important part of the obstetric assessment is the estimation of the duration of the pregnancy since the optimal timing for an amniocentesis is between 15 and 16 weeks gestational age. Some Canadian clinics also request a blood specimen from both parents in order to prepare parental karyotypes. The main justification for this investigation is that the parental karyotypes are sometimes needed for comparison with the fetal karyotype. There is considerable variation in the appearance of normal karyotypes and minor structural abnormalities are often present in normal people as the so-called "normal variants". These variants sometimes appear in several members of the same family and knowledge of their presence in a normal parent is useful in interpreting the significance of a similar

abnormality observed in the fetal karyotype. In addition, the parental karyotypes may reveal an unsuspected translocation carrier state and while this finding has little effect on the management of the present pregnancy it indicates that the parents should be offered prenatal diagnosis for all subsequent pregnancies.

Although an argument can be made for restricting the preparation of parental karyotypes to those cases where abnormalities of doubtful significance appear in the fetal karyotype, the timing of prenatal diagnosis is already uncomfortably tight and the delay of 3 or 4 days may make a therapeutic abortion legally impossible.

Amniocentesis

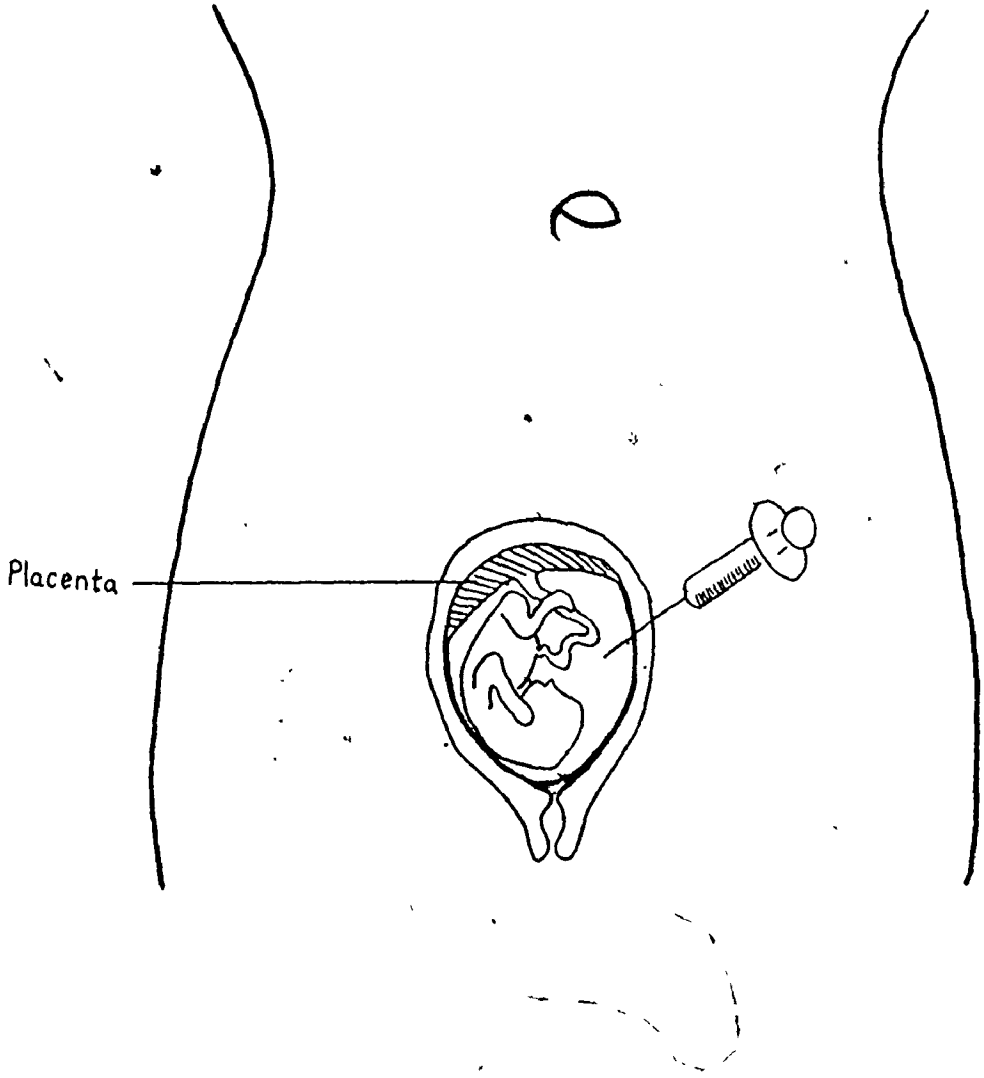
The actual technique of amniocentesis takes 15-30 minutes and can be performed in any out-patient department or doctor's office where sterile conditions can be maintained. The patient lies on her back, the abdominal skin is cleansed with an antiseptic solution, and surgical drapes are placed over the patient's abdomen. The skin and abdominal wall overlying the chosen puncture site are anaesthetized using local anaesthetic and a spinal needle with a stylet in place is then passed directly into the amniotic cavity.(Fig. 10) The stylet is removed and 10 to 20 ml of amniotic fluid is drawn into a sterile syringe. The stylet is then replaced, the needle withdrawn and a colloidin or sterile dressing applied to the puncture site. The patient remains under nursing observation for one or two hours after the procedure and can be discharged home later the same day.[105,106]

The Characteristics of Amniotic Fluid

The developing fetus is surrounded by amniotic fluid contained

FIGURE 10

AMNIOCENTESIS AT 16 WEEKS



Amniocentesis is the name of the procedure by which a sample of amniotic fluid is obtained using a hypodermic syringe. It is described in more detail on page

in the amniotic sac. (See Fig. 10) The amniotic fluid is thought to be formed by the fetus and both the volume and composition of the fluid change as the pregnancy progresses. Regulation of the volume and composition of the fluid is probably achieved by a balance of excretion and reabsorption from the fetal kidneys, gut and respiratory tract. The cells in the fluid are known to be fetal in origin and although many are dead, a percentage are viable and these are the cells that can be cultured to provide a prenatal diagnosis.

The Timing of the Amniocentesis

Knowledge of the anatomic, physiologic and developmental changes that occur in both the fetus and the mother suggested that the optimal time for a genetic amniocentesis was between the 14th and 16th weeks of gestation. Experience with genetic amniocenteses confirmed this prediction and most centres now schedule amniocenteses for the 15th-16th week.[53,105-107] The time at which the procedure is carried out is a compromise since the technique itself becomes progressively easier as the pregnancy advances yet aspiration must be carried out early enough for termination to be possible should it be indicated.

Anatomically, the uterus starts to enlarge out of the pelvic cavity 10 weeks of gestational age but by 16 weeks the fundus reaches approximately half way to the umbilicus and is therefore readily accessible for transabdominal puncture.[108] Although amniotic fluid can be obtained by a transvaginal route earlier in pregnancy, this approach is technically more difficult and since it has been associated with greater risks of infection and of spontaneous abortion,[105,109] it has not been widely adopted.

The amount of amniotic fluid present at the various stages of pregnancy is also an important determinant of the timing of amniocentesis. In an eight week pregnancy the amniotic cavity is less than 3/4" in diameter and contains about 3 ml of amniotic fluid. The uterus grows rapidly in the early weeks and by 16 weeks there is about 200 ml of amniotic fluid surrounding the 4" fetus,[110,111] (Fig. 11) and the chances of successfully locating the amniotic sax and of obtaining an adequate specimen of amniotic fluid are much higher at this stage. Although no complications have been attributed to the physical removal of the fluid the sudden deflation of amniotic fluid pressure is also a potential source of fetal damage and it seems sensible to defer the amniocentesis until the specimen removed represents a smaller proportion of the total fluid volume.

The majority of the cells in the amniotic fluid are of fetal origin[96,105] and although the total number of cells per millilitre of amniotic fluid is relatively high, (Fig. 12) approximately 80% of the cells are dead and the proportion of viable cells that survive to form colonies of cells in culture is exceedingly small and only about 15 colonies are obtained from most amniotic fluid samples.[96,112] Despite this, culture success rates are high as long as a sample of at least 10 ml is available for analysis.[53]

A final reason for timing the amniocentesis for 16 weeks of gestational age follows from our present understanding of the natural history of pregnancy. About 15% of all recognized pregnancies end in fetal death as a result of spontaneous abortion (approximately 12%) or stillbirth (approximately 3%). The probability of fetal death increases

FIGURE 11

THE VOLUME OF AMNIOTIC FLUID IN EARLY PREGNANCY

- after Emery[96]

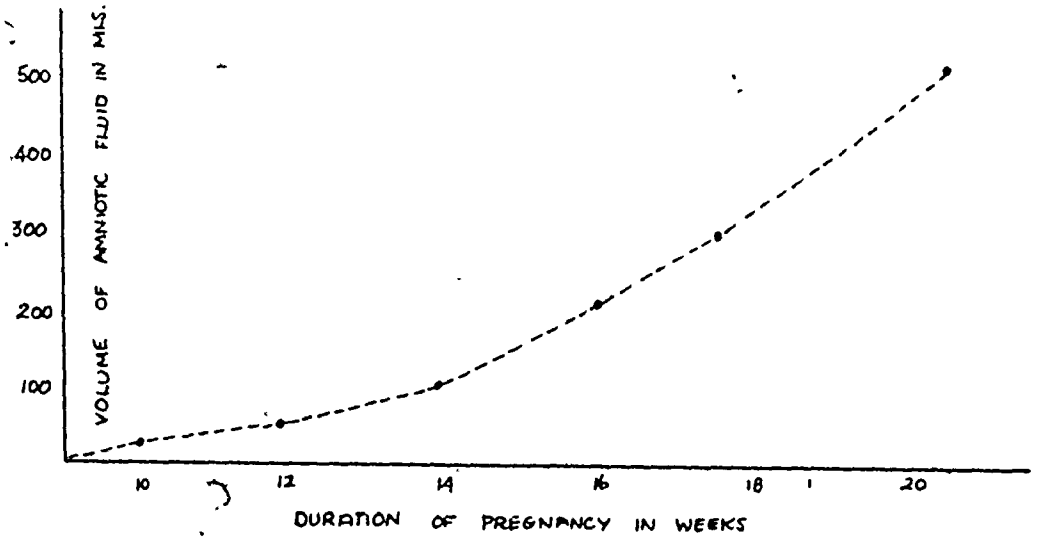
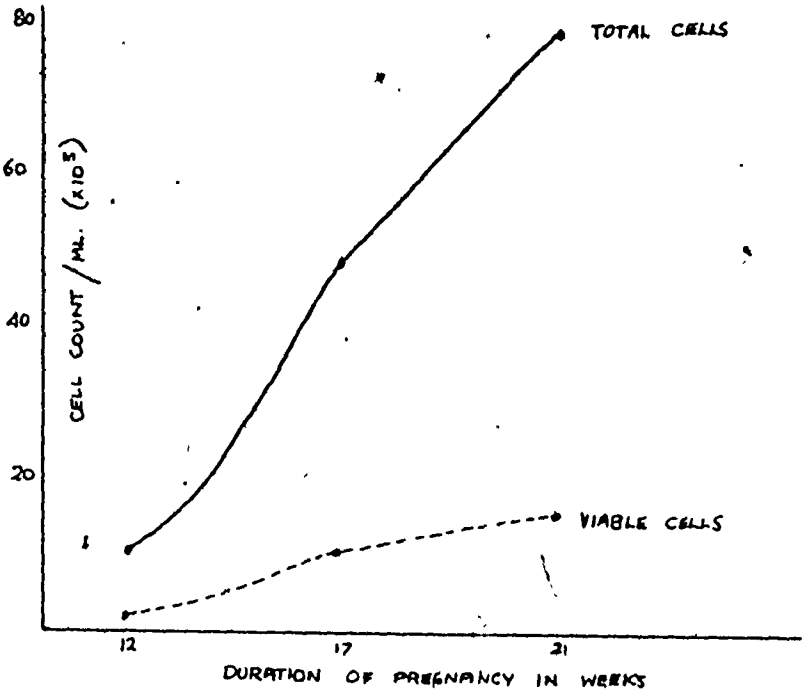


FIGURE 12

VIABLE CELLS IN AMNIOTIC FLUID

- after Emery[96]



with advancing maternal age and in women 35 years of age or over 22% of all recognized pregnancies end in fetal death. The gestational-age-specific rate of spontaneous abortion reaches a peak at 10 weeks of gestation and 70% of spontaneous abortions occur in the first 12 weeks of pregnancy. By the 16th week the rate has sharply declined and 92% of the expected spontaneous abortions will have occurred.[50] Thus, by postponing amniocentesis until the 16th week some "unnecessary" amniocenteses (and therapeutic abortions) are avoided.

The Risks of Amniocentesis

Amniocentesis would appear on superficial examination to be a potentially hazardous procedure for both the mother and the fetus but recently acquired evidence from prenatal diagnosis clinics indicates that the risks are very low.

The theoretical risks to the mother include trauma, hemorrhage, infection and abdominal pain.[113] Maternal structures that could be damaged during the procedure are the urinary bladder, the uterine wall and the maternal portion of the placenta. Bladder puncture should obviously be avoided although if the bladder is inadvertently damaged, there are unlikely to be any long term effects. Contamination of the amniotic fluid with maternal urine and cells, however, may interfere with culture success rates.[106] Some obstetricians prefer to perform an amniocentesis directly after the patient has voided and others find a full bladder to be useful in stabilizing the uterus[96] - the precise method is probably of less significance than experience with the chosen technique. There have been no reports of bladder damage following transabdominal genetic amniocentesis.

The uterine wall is also unlikely to sustain any permanent damage as a result of being punctured. Uterine muscle is arranged in a complicated network and irritation of the muscle results in a muscular contraction, thus controlling any bleeding that might have occurred at the puncture site. Jacobson studied 50 uterine specimens at hysterectomy following an amniocentesis and was unable to find the puncture site in any of the specimens.[114]

The risk of a significant maternal hemorrhage is slight but bleeding may occur in the veinous sinuses of the uterine muscle. The total blood loss is usually insignificant but amniotic fluid samples are sometimes grossly blood-stained with maternal blood and the presence of maternal blood in the sample may interfere with efficient cell culture.[53,106] There is clear evidence that the number of blood-stained specimens can be markedly reduced if the placental site is localized prior to the amniocentesis so that the placenta can be avoided when inserting the needle.[106] The placenta can be localized using one of several techniques but the technique using ultrasound is the procedure of choice in this situation and will be discussed in more detail later in this chapter.

Infection is a risk in amniocentesis as it is with all surgical procedures, however, as long as the procedure is done by experienced personnel, with careful attention to aseptic technique, the risk of infection is slight.[115]

There is the potential risk of initiating or aggravating blood group sensitization in the mother.[115] This is of particular significance to rhesus negative women in whom sensitization could theoretically

complicate subsequent pregnancies. Blood groups sensitization arises when fetal blood escapes into the maternal circulation (a feto-maternal hemorrhage) and stimulates the maternal production of antibodies. The antibodies then cross the placenta and destroy fetal blood cells, sometimes with fatal results. A small feto-maternal hemorrhage occurs in about 10% of amniocenteses but the precise risks of blood group sensitization are unknown.[115] Some investigators feel that consideration should be given to administering anti-D-immunoglobulin to these patients as is done for spontaneous abortions or full-term delivery. However, the effect of this treatment on the developing fetus is not clear and the recommendation remains controversial.[53] Once again, avoiding the placental site substantially reduces the incidence of this complication.[116]

In a few cases the amniotic fluid has continued to leak for a few days after an amniocentesis but in all the reported cases the pregnancies continued uneventfully and normal infants were born.[106,117,118]

Finally, a small proportion of women experience abdominal pain and some uterine cramping after the procedure but this is usually transient, rarely severe and does seem to dissuade patients from amniocentesis. In a recent study where the patient's opinions were solicited, 100% of the women said they would recommend the test to others.[117]

In summary, although there are a number of theoretical risks to the mother undergoing an amniocentesis, actual complications are extremely rare. No maternal deaths or significant morbidity had been reported following transabdominal amniocenteses performed before the 20th week of gestation in established Prenatal Diagnosis Clinics.[53,119] The theoretical risks can be minimized by careful timing of the procedure

pre-puncture localization of the placenta, attention to aseptic techniques and, presumably, experience.

Potential fetal complications of amniocentesis include trauma, hemorrhage, infection and spontaneous abortion. Trauma to the developing fetus has not be described in genetic amniocenteses though fetal damage has been documented in a few cases in third trimester amniocenteses.[115,120]

Theoretically, a hemorrhage resulting from trauma to the placenta, umbilical vessels or the fetus could result in the fetus being exsanguinated. One such case has been reported after late amniocentesis[121] but again there have been no reports of serious fetal hemorrhage in mid-trimester amniocenteses. However, Blajchman, et al. using techniques that permitted the detection of fetal bleeds greater than 0.25 ml showed that 15% of 26 early amniocenteses resulted in fetal bleeds,[122] so that care should be taken to avoid the placenta on this account as well.

Infection of the amniotic cavity (amnionitis) was found to be contributary to three fetal deaths in a series of 21,000 amniocenteses done after the 20th week. (Amnionitis was followed by a fatal septicaemia in one mother and this was the only maternal death in this series.)[115] Amnionitis has not presented a problem in early prenatal diagnosis but it is possible that mild cases of amnionitis resolve in a few days and are therefore not detected.[123]

The concern that amniocentesis may increase the risk of spontaneous abortion has been one of the major reasons for limiting amniocentesis to extremely high risk pregnancies. The usual experience of Prenatal Diagnosis Clinics has been that approximately 3% of the

pregnancies that are tested end in fetal death, and while this figure is similar to the expected rate in women 35 years and older, fears about the risks of amniocentesis have lingered.[106,117]

The National Institute of Child Health and Human Development in the United States have recently presented the results of their four year collaborative study - the Amniocentesis Registry Project. In this study, 1,040 amniocentesis cases were matched with 992 controls for a variety of factors and observations were made on the pregnancy outcome, the one-year development of the child, frequency of malformations, etc. The two groups were not strictly comparable, (members of the test group were older and had born more children prior to the index pregnancy) but despite these differences biasing the results in favour of the control group, fetal loss occurred in only 3.6% of the cases and 3.2% of the controls. There were also no significant differences between the two groups in the frequency of maternal morbidity, congenital malformations, neonatal problems or development at one year of age. There was no maternal mortality. Although this data is not conclusive, it indicates that the maternal and fetal risks associated with amniocentesis are extremely low; in particular, the risk of spontaneous abortion if present, is slight.[119] Calculation of the precise risks will require much larger sample sizes than are available at present.

Failure to Obtain Amniotic Fluid at Amniocentesis - "Dry Taps"

In a small proportion of cases the obstetrician is unable to obtain a sample of amniotic fluid particularly if the patient is obese, is tested before 16 weeks of gestation or has an anterior placenta. There is evidence that the frequency of dry taps decreases as the unit

gains experience with the technique but even in major centres the incidence of dry taps is 1-5%.[102,106,117] In the event of a dry tap the amniocentesis is usually repeated 1-2 weeks later and in almost all cases fluid is obtained on the second attempt.[53]

Ultrasound Diagnosis

It has been found that the risks associated with amniocentesis can be substantially reduced if the placental site is avoided. The placenta may be located using a number of techniques including thermography, radioisotope scanning or ultrasonography.[124,125] Ultrasonography has become the most widely used technique prior to genetic amniocentesis because it has a number of added advantages over the other techniques in that it can also be used to confirm gestational age and to determine a number of fetuses present. In addition, ultrasound will detect certain gross structural abnormalities of the fetus even at this early stage of pregnancy.[126]

Ultrasonic scanning is a simple, safe procedure that has been used for placental localization in the third trimester of pregnancy for the past 10 years.[101] Intermittent or pulsed sound waves of a very high frequency are projected from a crystal under directional control. Serial reflections of these sound waves from tissue interfaces are detected by the crystal and displayed on an oscilloscope to provide a two-dimensional picture. The scan is photographed to give a permanent record and precise measurements of uterine size, fetal size, placental position, etc. can be made. The patient experiences no discomfort from this procedure which takes 15-30 minutes, the only inconvenience is the presence of the oily contact medium on the abdominal skin. Ultra-

sound can be used as early as five weeks gestational age to confirm a pregnancy but by 15 weeks the position of the fetal head and the placenta can be reliably identified prior to amniocentesis.[125,126]

Ultrasonography is usually performed by radiologists and its association with X-rays stimulated much concern about its safety. Despite the superficial similarity between X-rays and ultrasound waves they have several important differences. X-rays operate within the electromagnetic high-energy spectrum and the physical effects of irradiation include ionization which is known to have serious long-term effects. Diagnostic ultrasound on the other hand, depends on the low-power energy in the acoustic spectrum. It is mechanical and non-ionizing and any adverse effects can be expected immediately.[125,127]

Animal studies using cats' brains, frog spawn, rodents and rabbits have shown that the use of ultrasound results in no observable effects on brain function, fertility or chromosomal structure.[125] There has been no increase in the incidence of congenital abnormalities in exposed animals or their progeny. Similarly, in human studies conducted on "at risk" pregnancies or immediately prior to an elective abortion there has been no evidence that diagnostic ultrasound has any detrimental effects on the fetus or the pregnancy.[125] However, in some animal experiments, where animals have been exposed to ultrasound energy far in excess of clinical "dosages", some damage has been reported - stasis of blood in capillaries and hemorrhagic lesions in the nervous system[125,128] - so that although the test can be considered as safe it should probably not be regarded as risk free.

Cell Culture

The detection of chromosome abnormalities in the fetus relies upon the culture and analysis of the cells in the amniotic fluid. The composition of amniotic fluid changes as pregnancy progresses and the mechanisms of its production remain to be fully elucidated[129] but there is experimental evidence that the viable cells originate from the respiratory, gastrointestinal, and urogenital tracts of the fetus and from the amniotic sac which surrounds the fetus.[130] The cells of the amniotic fluid are not easy to culture and because of the scarcity of colony-forming cells in the inoculum, the specimen must be handled with more than the usual care and skill in order to minimize trauma and loss.[131] Each laboratory has its own individual variation of the basic culture method and if the culture is successful, the results of chromosome analysis are available 10 to 21 days after amniocentesis.

Amniotic Cell Culture Methods

The precise techniques for cell culture used by one major Canadian laboratory is described in Appendix B. In brief, the sample of amniotic fluid obtained by amniocentesis is placed in sterile containers of silicon glass for transport to the laboratory. After centrifugation, the amniotic cells are resuspended in a nutrient medium supplemented by fetal-calf-serum, and pipetted into sterile culture dishes. Antibiotics such as streptomycin or penicillin and a fungicide may be added to minimize the risk of bacterial and fungal infection. The cells are then incubated in an atmosphere of 5% carbon dioxide and 95% air at 37°C and left undisturbed for 3 days. There is an initial lag in the establishment of a culture, during which it is assumed that cellular

adaptation to the "in vitro" environment is occurring. Thereafter the cultured cells divide every 16 to 30 hours (in contrast to the generation time of 30 to 90 days in the living organism)[132] and by 10 to 14 days each original cell has divided about 6 times to form a colony of about 64 cells. Every three days the cultures are checked for the presence of actively dividing cells and the medium is changed to provide a continuing supply of nutrients. When sufficient numbers of dividing cells are present, colchicine is added to the cultures in order to arrest the process of cell division at the metaphase stage. The incubation period is continued for a few more hours to allow the colchicine to arrest cell division in as many cells as possible. A solution of hypotonic saline added to the medium at this stage causes the cells to swell and the chromosomes to separate from each other so that they are easier to enumerate and identify. The amniotic cell preparation is then ready for fixing, staining and chromosome analysis procedures which take an additional one to two days, depending on the number and quality of metaphase plates available for analysis.

Once the stained slides of the cells have been prepared a cytogenetics technologist searches the slides for good metaphase spreads. Most laboratories like to perform a chromosome count on 20 to 40 cells[117,132] (if a female karyotype is found, an attempt is made to count cells from several different colonies because of the possibility that some maternal cells have been cultured). A more careful analysis, which includes grouping the chromosomes into the seven alphabetic groups and identifying the sex chromosomes, is done on at least five cells. If a permanent record of the fetal chromosomes is required, photographs are

taken of a few good metaphase plates and the karyotype is prepared in the conventional manner. Searching for enough good metaphase plates can be very time-consuming, it usually requires about half a day but in difficult cases can take much longer. Some experimental work is being done with computer analysis of metaphase plates and while significant advances had been made, it is unlikely to become a practical alternative to manual analysis of amniotic cells in the near future.[133,134]

An additional staining procedure used routinely in some cytogenetics laboratories is "banding". This recently developed procedure allows each chromosome to be identified individually by its characteristic pattern of cross bands. Two techniques are in common usage in Canada:

1) fluorescent banding where the chromosomes are stained with quinicrine mustard or related compounds and examined by fluorescent microscopy &
2) Giemsa banding where the chromosomes are treated with trypsin to partially break down their proteins before they are stained with Giemsa stain. The distinctive bands that appear on each chromosome can then be studied by light microscopy.[24]

"Banding" is of particular value in identifying small translocations and other minor structural abnormalities which may lead to the birth of a seriously defective child. While the procedure is useful as part of a general prenatal diagnostic screen[101] it is <u>not</u> a necessary part of the diagnostic procedure for Down's Syndrome where the extra chromosomal material is usually present as an extranumerary chromosome which can be readily detected by ordinary staining methods. In the vast majority of cases translocation Down's Syndrome can also

be detected by routine staining methods.

Every effort is being made to reduce diagnostic delay to a minimum and several attempts have been made to stimulate cell growth by altering the constituents of the culture medium and by using various hormone preparations. Unfortunately, no specific growth stimulating agent for amniotic cells has been identified thus far. The addition of fetal-calf-serum to the medium supplies essential proteins to the cultured cells and its use results in a higher proportion of successful cultures. However, increasing the amount of calf serum above 30% confers no further advantages and is possibly toxic.[131] A major problem hampering the search for a growth-stimulating agent is the knowledge that even minor alterations in the chemical constituents of the culture medium can result in the spontaneous development of chromosome abnormalities leading to serious diagnostic errors in the analyses.[53]

Success Rates

Success rates for amniotic cell culture (success is defined as the production of a fetal karyotype) have been steadily improving as can be seen from Table 14. It has been suggested that prior to the establishment of a prenatal diagnostic service, the cytogenetics laboratory should be obtaining successful cultures on at least 85% of cases with the first sample of amniotic fluid received.[53] Major laboratories providing such services have success rates of 90-100% with the first sample - the average success rate for the Collaborative series in 1974 was 94%.[135] It is usually possible to detect those samples which are not going to grow adequately by the 10th to 14th day in culture.[53] This allows adequate time for repeat procedures and prenatal diagnosis so that a

TABLE 14

CULTURE SUCCESS RATES

YEAR	AUTHOR	CULTURE SUCCESS RATE %
1966	Steele & Breg	17^{100}
1967	Jacobson & Barter	58^{114}
1968	Nadler	73^{135}
1970	Nadler & Gerbie	97^{102}
1970	Butler & Reiss	95^{112}
1974	Golbus	94^{101}
1974	Collaborative Series	94^{117}

therapeutic abortion can still be offered to the parents if an affected infant is diagnosed. Milunsky, in his large series, found that by recommending repeat amniocenteses in all cases where the cultures were doubtful at 15 days, it was possible to reach a prenatal diagnosis in 100% of cases who had their first amniocentesis on or before the 16th week of gestation.[53]

The Causes of Culture Failure

The proportion of amniotic fluid specimens that fail to provide adequate cell growth for chromosomal analysis varies from laboratory to laboratory but even in well established centres, a sample may fail to grow for unknown reasons. A number of factors are known to contribute to culture failure, however, and these will be discussed in more detail here since this knowledge has implications for the organization of a prenatal diagnostic service.

Delay in initiating the culture of the amniotic fluid specimen is known to be an important factor. In the series of 800 cases reported by Milunsky, 95% (760) of the samples were in culture within 8 hours of amniocentesis and his overall success rate was 90.8%. However, among the 78 failures, 16 specimens (almost 25%) were not cultured for 2-9 days after the amniocentesis; many of these samples were transported to the laboratory by air or regular mail. In an earlier paper, Milunsky reported that of 27 samples transported by air or mail, a prenatal diagnosis could not be made in 10 cases, although results were obtained from one sample which had been in transit for 7 days.[53]

An inadequate volume of amniotic fluid may also result in culture failure. The volume of the specimen is dependent largely on the

stage of pregnancy at which amniocentesis is performed. Most centres find that at 15th to 16th weeks gestational age they can readily obtain a 10 to 20 ml of fluid required for culture.

A closely related factor is a number of viable colony-forming cells in the sample. The use of siliconized glass or plastic has been shown to minimize the loss of viable cells which stick to the surfaces of ordinary glass.[112,131] Once in culture, the greater the attachment of the cells to the dish, the better the chance of successful culture since amniotic fluid cells will not grow in suspension. The attachment can be increased by placing a cover slip over the cells to immobilize them or by leaving the centrifuged cells to attach to the glass culture dishes for a few moments before adding the nutrient medium. In addition, at least one centre advocates turning the patient from her abdomen to her back just prior to amniocentesis so as to disperse the cells evenly through the fluid.[117,136]

In a few cases, cell culture has failed because of an unrecognized intrauterine death. At 16 weeks gestational age it is usually not possible to hear the fetal heart without using an ultrasound device such as the Doptone fetal pulse detector. With the Doptone the fetal heart can be consistently detected after 12 weeks gestational age and it would be a simple matter to check the fetal heart before and after amniocentesis.[48]

Some laboratories have found that the presence of blood in the amniotic fluid specimen results in delay in culture rather than culture failure or that the presence of blood is unrelated to culture success or failure.[96] In most laboratories however, amniotic fluid specimens

which are grossly blood-stained have been found to be difficult to culture, despite the use of techniques which clear the specimen of blood.[53,106] In Milunsky's series of 800 cases, 69.8% of the 53 blood-stained specimens were culture failures. In contrast, only 5.5% of the 747 clear specimens were culture failures. A higher proportion of transported specimens - 15% - were blood-stained so that delay was a confounding factor in this study.[53] Doran, in reporting the experience of the Toronto Antenatal Diagnosis Clinic stated that 50% (4/8) of the grossly bloody taps resulted in culture failure whereas only 1.5% (1/65) of clear specimens resulted in culture failure. This clinic found that avoidance of the placental site at amniocentesis (using ultrasound diagnosis) reduced the frequency of bloody taps from 22% (7/32) to 1 out of 41 specimens and their culture success rate improved from 84 to 100%. They therefore advocated placental localization prior to amniocentesis in the interest of efficiency as well as safety.[106]

In 1973, Robinson et al reported the disturbing finding that culture success rates fell after the use of ultrasound for placental localization.[136] However, in their discussion they state that the significance of this finding is "somewhat dubious" and may be attributable to confounding factors. Later estimates of the proportion of colony forming cells in amniotic fluid before and after ultrasound exposure revealed no significant differences, and their initial findings have not been confirmed in subsequent studies.[136]

Contamination of the cultures by bacteria, fungi, viruses or mycoplasma is a serious problem in culture laboratories. Infected cultures grow poorly and spontaneous chromosomal aberrations may arise

making interpretation of the karyotype difficult, if not impossible.[137]

Amniotic fluid cell cultures have to be handled frequently - at collection, feeding, when checking cell growth and in the final preparation of the chromosomes. The need for strict sterile techniques to be maintained throughout the collection and culture process is emphasized and most centres find it essential to run a separate amniotic culture laboratory in order to minimize the risks of cross-contamination.[138] In a further effort to minimize these risks some laboratories handle amniotic fluid specimens behind plastic shields and under a laminar-flow hoods, devices which decrease the numbers of air-borne organisms which may contaminate the cultures.

The incubator provides a humid, warm atmosphere, an ideal environment for many types of infective organisms. Antibiotics and fungicides to inhibit bacterial and fungal growth can be added either to the media in which the cells grow or to the water baths in the incubator. Despite all these precautions, infection of the cultures can interfere with the successful culture of amniotic cells and in large series infection resulted in culture failure in 0.5% of cases. It has been the experience of culture laboratories that if an organism becomes established in one culture it usually infects all the cultures in the same incubator and because of this problem some laboratories routinely set up several cultures from every patient in each of two separate incubators, preferably in separate locations.[117]

Parallel culture techniques also safeguard the sample from incubator failures. These are uncommon but on occasion the gas mixture or temperature controls may fail or a power failure may result in a

whole incubator-load of cultures being destroyed.[117,138]

The Interpretation of the Karyotype

There are a number of possible pitfalls that must be considered in the interpretation of cytogenetic studies of cultured amniotic cells.

A major problem is the possibility that the cultured cells are maternal rather than fetal in origin. It is difficult to know how often this misinterpretation actually occurs since it is only when a normal female has been predicted and a normal male or a chromosomally abnormal child is born that the error is detected. There has been one report of a normal female being predicted and an abnormal child being born in an American series[53] and several reports of normal males being born after normal females had been predicted including one such case in Canada.[139] In these cases, it is usually found that the cells have grown more rapidly than is usual in amniotic cell culture and it is thought that these cells are maternal white blood cells. Maternal cells do not survive longer than 7 to 10 days in culture and misinterpretation from this source can be avoided by minimizing the chance of maternal blood contamination, delaying analysis until 14 days in culture, analyzing cells from several different colonies and counting the chromosomes in at least 20 metaphase spreads.[53,101,102]

Mislabelling of the specimens is another potential source of error and the American data indicates that this has been responsible for two diagnostic errors. This source of error is, of course, avoidable.

A major problem in diagnostic amniocentesis is the evaluation of twin pregnancies. Prior to the use of ultrasonography, multiple

pregnancies were not recognized at the time of genetic amniocentesis and the results from one fetus study would be applied to the twin.[107] Although ultrasonography is now used to identify twin pregnancies the dilemma still remains since it is technically very difficult to tap both amniotic sacs.[53] Since multiple pregnancies occur in at least one in eighty pregnancies, it seems inevitable that an occasion will eventually arise when one of the twin pair is found to have a major chromosomal abnormality at prenatal diagnosis. The parents will then face the difficult decision of whether to abort both these infants or proceed to term in the hope that one infant will be normal and survive. Statistically if one fetus is diagnosed as having Down's Syndrome there is a 0.83 probability of the other twin being normal and this obviously does not make the decision any easier.[140] Techniques which will permit double amniocenteses are being developed but currently the prenatal diagnosis of multiple pregnancies presents an unresolved problem.

If the karyotype preparation is of good quality there is usually no difficulty in reaching a diagnosis of Down's Syndrome. In the case of Trisomy 21 there is an extra chromosome present to give a total count of 47 chromosomes and when these chromosomes are analyzed by group, the extra chromosome is found to belong to Group G. There is still some controversy as to whether Down's Syndrome is a Trisomy of chromosome 21 or 22 within the G group (22 is a little smaller) but by convention it is regarded as being Trisomy 21.[141] In the few cases of translocation Down's Syndrome the total number of chromosomes is the normal 46 and does the abnormality is not recognized until the chromosomes are analyzed into groups. Usually one member of the D Group is missing and

instead there is one unusually large chromosome which turns out to be a combination of a D group chromosome with an extra G group chromosome. Karyotypes of both these varieties of Down's Syndrome are presented in Figures 6 and 7.

The even rarer cases of mosaic Down's Syndrome have not be identified at amniocentesis to date but the problems associated with the interpretation of mosaicism will be discussed later in this chapter.

In the course of prenatal chromosome analysis for Down's Syndrome it is inevitable that certain other chromosomal disorders such as Trisomies of other autosomes or the sex chromosomes will be detected.

The three best known autosomal anomalies, excluding Down's Syndrome, and the four best known sex chromosome anomalies will be described briefly here.

1) Trisomy E (Trisomy 18 or Edward's Syndrome) is a syndrome of multiple congenital malformations, including mental retardation, which is more severe than Down's Syndrome. The estimated incidence is 1 in 5,000 births and although it is said to occur more frequently among older mothers precise age-specific rates are not available. Most of the affected children die in infancy.
2) Infants affected with Trisomy D (Trisomy 13 or Patau's Syndrome) are also mentally retarded and have multiple congenital abnormalities, few survive infancy. The overall incidence of this defect is estimated to be 1 in 10,000 births.
3) Cri du Chat Syndrome is a partial monosomy where part of chromosome No.5 is missing. This is a very rare disorder whose precise incidence is not known. Life expectancy is not seriously curtailed

although these individuals are microcephalic (small heads), severely mentally retarded and have a variety of other physical stigmata.

4) Turner's Syndrome 45X (a normal female is 46XX) has an incidence of about 1 in 3,000 live births and no maternal age effect has been reported. Turner's Syndrome is a particularly common abnormality among early spontaneous abortions and it has been estimated that only about 2% of all such conceptuses survive to full-term. Of those that do survive, the main abnormalities are sexual infantilism, short stature, an abnormality of the aorta (coarctation) and congenital abnormalities of the urinary tract. The I.Q. is usually within the normal range though many individuals have perceptual problems. Life expectancy is said to be "good", limited only by the presence of coarctation of the aorta. Many patients are mosaics with a mixture of 45X and 46XX cells and the characteristics of the disorder are modified in this case. Most patients are sterile but a few have born normal children.

5) Triple X Syndrome (47XXX) - the incidence of this disorder is about 1 in 800 live births. The females are physically normal but are "more likely to be mentally subnormal" and infertility is frequently a problem. Sometimes four or even five X chromosomes are present and in this case the patient is usually severely retarded.

6) Klinefelter's Syndrome (47XXY) - the incidence of this disorder is 1 in 800 live male births. Subnormal mentality is common and this syndrome accounts for about 2% of institutionalized retarded. Poor sexual development is always present and almost all cases are sterile.

7) 47XYY - this chromosome abnormality, which occurs as a result of paternal non-dysjunction, is present in 1 in 700 live male births. Most XYY individuals are indistinguishable from other members of the general population but they are said to be about six times more likely to be imprisoned than normal XY males and about 3% of males in maximum security prisons are XYY.[24] These individuals are often mildly retarded and although several hormone therapies have been tried, there is no known effective treatment.[142]

Some indication of the extent to which these abnormalities are detected by prenatal amniocentesis in older women is given by the recent report of the Canadian Amniocentesis Registry.[139] Among 256 pregnancies screened on the basis of a maternal age of 40 or more, the abnormal findings were:

8 cases of Down's Syndrome

2 cases of Trisomy 18

1 case of Trisomy 13 and

1 case of XY/XXY mosaic

A number of more minor structural abnormalities of the chromosomes can also be detedted prenatally by routine staining methods and the significance of some of these may be difficult to establish.

It is known that infection in the culture or changes in the pH of the medium can result in spontaneous aberrations in chromosome number or structure[143] so that abnormal findings should always lead to a careful reassessment of the culture method.[53] In addition, careful analysis of cells from parallel cultures allows for verification of any abnormal findings.[117] In a number of cases the unusual chromosome forms

found in a small proportion of amniotic fluid cells has been shown to be artifacts of culture and normal infants have been born.[53]

In one case where a consistently abnormal chromosome 20 was detected in the fetal karyotype, the maternal karyotype had a similar defect. The parents elected to continue the pregnancy and the child was subsequently found to be normal.[53]

In general, when an abnormal chromosomal finding is identified, one should check for

1) consistency in all cells from several different culture dishes,

2) infected cultures,

3) faulty media pH and

4) presence of the abnormality in the parental karyotypes.

The finding of a chromosomal abnormality that has never been described before may lead one to suspect an artifact more readily than if a well known chromosome abnormality is identified. Banding techniques may be useful in clarifying the diagnosis. When the diagnosis is still doubtful after careful analysis of the contributing factors, the parents may wish to have a repeat amniocentesis, but fortunately this is rarely required.

An unresolved problem in the interpretation of cell cultures is that of mosaicism, the presence of two or more distinctly different cell lines in the same culture.[101] As indicated in Chapter 1, the proportions of the two cell lines are usually different in different body tissues and amniotic cells may either exaggerate or minimize the proportion of abnormal cells in such critical tissue as brain tissue. Interpretation of amniotic cell mosaicism is obviously difficult and the decision for

or against therapeutic abortion in this situation may be particularly perplexing for the parents. Fortunately, unexplained mosaicism appears to be quite a rare problem and no cases of a prenatal diagnosis of mosaicism for Trisomy 21 have been reported so far.[53,101]

The final problem to be discussed here is the occurrence of polyploidy (multiples of the normal chromosomal number appearing in each cell). Tetraploidy (92 chromosomes per cell) occurs quite frequently in amniotic cell cultures but it is thought to represent culture of cells derived from the fetal amnion since some of these cells are known to be tetraploid under normal circumstances.[101] Although tetraploidy is found quite frequnntly in human abortuses-only one live born infant with tetraploidy has been described - a child with multiple congenital abnormalities who survived 36 weeks. Accumulated experience with amniotic cell culture suggests that where tetraploidy (or mosaic tetraploidy) is identified from amniotic fluid cell cultures, the infant is very likely to be normal.[53,144]

The prenatal diagnosis of some of these chromosome abnormalities obviously poses some difficult ethical and moral dilemmas. What degree of mosaicism constitutes a significant risk to the unborn child? Should XYY infants be aborted? etc. In some clinics, the policy is to withhold information of doubtful or unknown significance but in many other centres the policy is to inform the parents of the findings and share with them the available information about the condition so that they can reach their own decision.[53]

This outline of the difficulty that can be encountered in the interpretation of fetal karyotypes, may suggest that the procedure is

'more trouble than it is worth". In practice, however, real difficulties in interpretation are uncommon and as more experience in prenatal diagnosis is accumulated, the significance of many of the abnormalities will be clarified. Despite the problems of analysis, wrong diagnoses have been extremely uncommon in recent series.

It should also be emphasized that in a vast majority of cases (95% or more) the results obtained from an amniotic cell culture will serve to reassure prospective parents that their child is chromosomally normal.

Prenatal genetic studies are unique in that there is only a brief opportunity to make a serious diagnosis and the highest possible standards must therefore be demanded. Meticulous attention to cell culture technique and the application of the various measures aimed at anticipating and preventing possible errors are necessary if this procedure is to provide reliable information. Specialized laboratories, highly skilled technologists and the need for expertise in genetic counselling, performance of the amniocentesis and interpretation of unusual karyotypes suggest that this service should be organized on a regional basis..

Reliability of Prenatal Chromosome Analysis

In spite of all the potential sources of error that have been discussed, it is clear that prenatal karyotype analysis of amniotic fluid cells can be an extremely valuable diagnostic test with a sensitivity and a specificity approaching 100%.

The sensitivity of a test is the ability of the test to correctly identify the affected individuals among all the individuals tested for a

particular disorder. In the Canadian series the sensitivity of prenatal chromosome analysis has been 100%.[139] In the American series, among more than 2,000 analyses, there have been two false negatives - one attributable to maternal cell contamination and one where it has been assumed that a sample interchange occurred.[139] Even so, it is clear that the sensitivity of the test, at least for major chromosomal anomalies is very close to 100%.

The specificity of a test is its ability to correctly identify the unaffected individuals among all the individuals tested for a given disorder and in prenatal diagnosis this measure should also be 100%, since unnecessary terminations are unacceptable.

Although there have been some reported difficulties in the interpretation of fetal karyotypes (maternal contamination, polyploidy, etc.) no "unnecessary" therapeutic abortion had been performed in the Canadian series with the possible exception of one case in which one colony of cells was found to have an abnormal translocation. A repeat amniocentesis was requested but the parents refused and asked for a therapeutic abortion. The translocation abnormality was not identified from direct culture of the abortus but bilateral simian creases (an abnormality of the lines of the hand often seen in individuals with genetic abnormalities) were found.[139]

Several thousand genetic amniocenteses have been performed now and the results indicate that genetic amniocentesis and karyotype analysis provides a safe and accurate method of identifying the chromosomal complement of the human fetus. Thus, parents who are concerned about their risks of having a chromosomally abnormal fetus can now choose a

therapeutic abortion if an abnormal fetus is detected prenatally and can thus selectively have only unaffected offspring.

Therapeutic Abortion

Termination of pregnancy during the first twelve weeks is achieved safely using the relatively simple procedures of suction or dilatation and curettage. However, since the results of prenatal chromosome analysis are not available until after the 18th week of pregnancy, any therapeutic abortions indicated on the basis of the analysis must be performed in second trimester when an abortion is technically more difficult and is associated with a higher complication rate. Most second trimester abortions are achieved using the techniques of saline instillation or hysterotomy. Recently, it has been shown that the prostaglandins (substances which occur naturally in the body and which stimulate uterine contractions) are also effective in producing a second trimester abortion and although experience is still limited, this technique may turn out to be considerably simpler and safer than either of the two methods currently used.

Of the three techniques, the most commonly used procedure is the saline abortion, which involves a transabdominal amniocentesis under local anaethesia, the removal of 200 ml of amniotic fluid and the intra-amniotic injection of an approximately equal volume of 20% hypertonic saline. "Labour" usually commences 12 to 24 hours after the injection and is complete by about 36 hours. The process of labour can be shortened by about 12 hours if an infusion of oxytocin is administered but some obstetricians consider that the administration of this drug, simply to expedite delivery, is not warranted since the use of oxytocin can be

associated with serious complications including uterine rupture.[145]

At 18 to 20 weeks of gestation, the placenta is relatively larger and more vascular than it is by the end of pregnancy and so, not unexpectedly the major complications of a saline abortion are hemorrhage, retained placenta and infection. About 2% of the patients lose more than 500 ml of blood and require a blood transfusion and in 10-20% of cases a curettage to remove placental remnants is needed. Evidence of infection (an elevated temperature on two consecutive readings six hours apart) is found in about 1% and although this is rarely serious, it is potentially fatal and must be treated aggressively. Following the completed abortion patients usually remain in hospital for at least 24 hours and the average duration of hospital stay for this procedure is 3 to 4 days.[145]

Maternal deaths resulting from accidental intravascular injection of the hypertonic saline and from widespread infection have been reported. In the large series of second trimester saline abortions analyzed by the Population Council in New York (9,506 cases), two maternal deaths occurred. In one case, the death was unequivocally related to the intravascular injection of saline, (the woman developed hypernatremia, cerebral oedema and convulsions and died 10 days later) but in the other case, (a schizophrenic patient in a psychiatric hospital who committed suicide one month after the abortion), the cause and effect relationship was questionable.[146] It is now recognized that complications following intravascular injection of saline can be avoided by administering the saline as a continuous drip infusion rather than as an injection.[147] Further improvements in technique together with the

careful maintenance of asepsis should reduce the maternal mortality to very low values. For comparison purposes, it should be noted that the maternal mortality rate associated with uninterrupted pregnancies in women 35 or more is 40 per 100,000.[148]

Termination of pregnancy by hysterotomy is regarded as a major surgical procedure and is performed much less frequently. A general anaesthetic is usually given for the hysterotomy which is similar to a cesarean section so that the patient is left with not only an abdominal skin scar but also with a uterine scar which may complicate subsequent pregnancies. Like all surgical procedures, a hysterotomy can be complicated by hemorrhage and infection.[108] Significant complications occur more than twice as often with hysterotomy as with saline abortions and 2 maternal deaths were reported in the New York series of 561 hysterotomies.[146] In both these deaths the presence of pre-existing disease probably contributed to the deaths. One woman, who had rheumatic heart disease (mitral stenosis and incompetence) and was a known heroin addict died on the operating table as a result of a cardiac arrest and the other woman who died of a septicaemia had a long history of severe pelvic infections and multiple abdominal operations.[146]

The risk attributable to the procedure of hysterotomy is difficult to evaluate. In most reported series additional procedures, e.g. sterilization have been performed in a majority of patients. In addition, since the presence of chronic renal or heart disease is a contraindication to saline abortion the hysterotomy group is loaded with high-risk patients. No maternal deaths have occurred among women whose pregnancies have been terminated by hysterotomy for genetic reasons.[53]

Most patients remain in hospital for approximately one week after a hysterotomy.

Despite the disadvantages of hysterotomy it has one important advantage over the saline technique when the abortion is being performed for a chromosomal abnormality - it is often impossible to confirm the prenatal diagnosis by culturing fetal cells following a saline abortion but the diagnosis can readily be confirmed after a hysterotomy.

The use of prostaglandins to terminate second trimester pregnancies seems to be a very promising development. This group of substances which occur naturally in the body have a direct effect on uterine muscle, resulting in contractions which expel the contents of the pregnant uterus in much the same way as a normal labour. Although prostaglandins (usually PGF_2) can be administered by intravenous infusion, amniotic infusion or by vaginal suppositories, the amniotic route seems to be superior on the basis of current studies.[149] Following the infusion of the prostaglandin (less than 1 ml is required) "labour" commences in about 30 minutes and the fetus is delivered about 12 hours later. This is an important advantage over the saline technique since the shorter interval between induction and abortion is much less stressful for the patient and also because it potentially reduces the period of hospitalization required.[149] A further advantage for "genetic" abortions is that chromosomal verification of the diagnosis is possible.[150]

The major side effects of the prostaglandins are gastrointestinal - nausea and vomiting affect almost all patients to some extent and diarrhea is common. The risks of hemorrhage and infection are similar for postaglandins and saline but retained placenta is more common

with a postaglandin induced abortion.[149] No long-term morbidity or mortality has been described so far and if preliminary reports are confirmed, prostaglandins may become the procedure of choice for mid-trimester abortion.

In summary, mid-trimester abortions should not be undertaken lightly since they are associated with appreciable mortality and morbidity. At the present time the risks are probably less than the risks of full-term delivery for older mothers and the widespread use of prostaglandins may make second trimester abortions considerably simpler and safer in the near future.

Legal Considerations

In June 1969, the Canadian Parliament passed a controversial series of amendments to the Criminal Code of Canada which approved abortion where the mother's health was seriously endangered by the pregnancy. In most centres "health" is broadly interpreted as physical and mental well-being and a therapeutic abortion for a disorder such as Down's Syndrome is permitted because of the undesirable effect the birth of a severely handicapped child is likely to have on the "health" of the mother.

Several groups including the Royal Commission on the Status of Women have strongly recommended that abortions be expressly permitted for a broader range of conditions including the situation where "there is a substantial risk that if the child were born it would be greatly handicapped either mentally or physically." A change in the laws to permit a therapeutic abortion in these cases would seem to be in keeping with current social attitudes since a large survey of Toronto wives

conducted almost 8 years ago showed that 76% of the women felt that a therapeutic abortion should be available when there is "a strong chance of a deformed or mentally retarded child".[151]

Some of the most difficult problems raised by a prenatal diagnostic program are of a moral and ethical nature. However, many of these problems are similar to those related to all elective abortions.

If an elective abortion is acceptable for personal or socio-economic reasons, even when it is known that the fetus is normal, a therapeutic abortion performed following the prenatal diagnosis of Down's Syndrome requires no special defence. If a therapeutic abortion is acceptable when the probability of fetal malformation is high, prenatal diagnosis and selective therapeutic abortion can also be justified. However, if it is believed that a therapeutic abortion is never justified or only if the physical life of the mother is in jeopardy a program which would simply provide prenatal information could be seriously questioned.

Individuals will vary widely in their interpretation of what is "right" and "wrong" but fortunately persons who seriously question the morality of abortion in these circumstances are unlikely to present themselves at a Prenatal Diagnosis Clinic and attendance at the Clinic should obviously remain voluntary.

Members of the public may also be concerned about the effect such a program might have on the sex-ratio or the gene pool. While occasional abuse of the program may occur with parent electing to abort a normal fetus who is not the desired sex, most of the parents who attend this type of program are extremely anxious to have normal children

and will probably be unconcerned about the child's sex. If prenatal diagnosis became routine for all pregnancies, there is an increased possibility of abuse but attempts to predict the effect of active choice of a child's sex on the sex ratio indicate that after a brief increase in males the sex ratio would probably return to the previous level.[152]

Broad-spectrum prenatal diagnosis could have an effect on the gene pool by eliminating diseased individuals and proliferating carriers but this is not a major problem with Down's Syndrome since almost all the cases occur as a result of a random chromosome abnormality.

Some of the other diagnoses that are detected as part of a prenatal diagnosis program to prevent Down's Syndrome are less clearly understood and the prognosis for the affected and carrier individuals is less well established.

Parents will, of course, vary widely in the amount of information they want and the risks they are prepared to take. A disorder that is absolutely intolerable to some parents may be acceptable to others. Ideally, the techniques of prenatal diagnosis should be available to all those who can benefit by them and in reaching a decision about the continuation of a particular pregnancy, the parents should have the freedom to make individual and informed choice within broad societal limits.

CHAPTER THREE

ECONOMIC CONSIDERATIONS

The characteristics of Down's Syndrome which were outlined in Chapter One indicated that this serious disorder is clearly of major significance to the affected individual, his family and public. In spite of the efforts of many researchers the precise cause of Down's Syndrome remains elusive and no cure has been identified. Although some progress has been made in the management of individuals with Down's Syndrome, the fact that the natural history of the disorder cannot be radically altered suggests that a means to prevent this disorder should be sought and implemented.

The recent development of a prenatal diagnostic procedure which meets accepted criteria for sensitivity, specificity and safety together with the availability of therapeutic abortion can provide parents with the opportunity to prevent the birth of severely defective infants. If this new technique required few material or labour resources an argument could be made for making it available to the entire pregnant population. However, from the description of the procedures involved in prenatal diagnosis which were outlined in Chapter Two, it is clear that the costs incurred in reaching the prenatal diagnosis of Down's Syndrome are high and estimates of $200-300 are common.

The high cost of a procedure would not, in itself, be a constraining factor if our society had unlimited resources. However,

our resources are obviously limited and it is essential that all programs be subjected to an economic analysis to ensure that the best possible results are obtained from the limited resources available. It is, therefore, important that the prenatal diagnostic program which has been proposed be shown to be economically justifiable in the context of all the other claims on our limited health service resources, before the program is developed or expanded.

Rational decision makers have always tried to weigh the advantages and disadvantages of a proposed activity before embarking on it and frequently such an informal appraisal of a project is adequate. Over the past few decades, however, widespread concern about the rising costs of goods and services, the rapid expansion of the public sector, and the need to choose between competing projects has stimulated the development of a more formalized approach to program evaluation. This approach which is called "Cost-benefit Analysis" was initially applied to water resource programs in the 1930s.[153] It was not until the mid-1960s that cost-benefit studies in the health sector were undertaken in the U.S.A. as part of the Planning-Programming-Budgeting-System (PPBS). The application of PPBS on a government-wide basis in the U.S.A. stimulated further development in the field of cost-benefit analysis since it required that the objectives of all programs in the public sector be defined and that the costs of the program be justified by the benefits resulting from it.[154]

Cost-Benefit Theory

In cost-benefit analysis, the benefits which result from a particular activity are compared with the costs incurred in performing that activity.[155] The technique provides a method of organizing all the

factors which need to be taken into account when a project is under consideration and is intended to facilitate rational decision-making. The methods of cost-benefit analysis can be used to make an economic analysis of a single project, to compare different projects with the same objectives or to make choices between programs with different objectives.

Although all programs should be subject to an economic analysis, cost-benefit analysis is not always the most appropriate technique to use. For example, if two programs have identical outputs or objectives it is only necessary to compare the two programs for the cost incurred in reaching those objectives using the technique of cost-effectiveness analysis. Cost-benefit analysis is the appropriate technique to use when competing projects have dissimilar outputs or in the situation where a unique program results in a complex array of effects and side-effects which need to be logically considered in assessing the program.[156]

The process of performing a cost-benefit analysis can be divided into five stages.

I) Precise identification of the activity which is to be subjected to the analysis and definition of the objectives of the activity.

II) Enumeration of all the costs that are incurred and the benefits that result from the performance of the activity.

III) Evaluation of the costs and benefits associated with the activity for each year of the program - the evaluation is usually made in monetary terms.

IV) Aggregation of the total costs and benefits in such a way that they are directly comparable.

V) Comparison of the total aggregated costs and benefits.

Each of these stages will now be considered in more detail.

I) Identification of the program and definition of the objectives

This step in the analysis usually presents no difficulty. It is advisable to define a program and its objectives precisely and in simple terms so that the costs and benefits associated with the program can be readily identified.

II) Enumeration of costs and benefits

Cost-benefit analysis differs from the usual techniques of financial appraisal which are used in the private sector in that it attempts to allow for all societal gains and losses associated with the program regardless of who is affected whereas a financial appraisal of a program is limited to consideration of the cash flows to and from the sponsoring agency. In addition, cost-benefit analysis is concerned not only with cash flows but also with the evaluation of these items which are not bought or sold and which therefore have no established market price. The cost-benefit analyst tries to establish surrogate prices for these items and includes them in the analysis. Cost benefits are quantified and valued wherever possible but if it proves impossible to express some items in the monetary terms they are still included in the discussion that accompanies the numerical analysis.

Terminology

The terminology used in the classification of costs and benefits is confusing since the various authors employ the same terms for different concepts. In order to minimize further confusion, the terms which are used in this study will be defined in this section.

Most practitioners of cost-benefit analysis use the term "benefits" when referring to the advantageous effects of a program and the term "costs" when referring to the disadvantageous effects of a program. This is the definition which will be used in the economic analysis that follows. However, some analysts have found it useful to think of "benefits" as all the outputs of a program and "costs" as all the inputs of a program regardless of whether they are "good" or "bad" in either category.

The choice of definition in this case is usually not critical to the analysis and is usually made in the interest of clarity. However, it should be recognized that if the benefits and costs are expressed as a benefit-cost ratio the choice of terminology can effect the findings by transferring an item from the numerator to the denominator or vice versa, but in this particular study the numerical benefit-cost ratio is unaffected by the choice of definition. It should be noted that the term "benefits" includes the cost-savings that result from a program: this interpretation is of particular value in the analysis of preventive health programs.[157,158] Thus, in the cost-benefit analysis of the program to prevent Down's Syndrome the major "benefit" is the cost savings that result when the birth of an affected infant is prevented by prenatal diagnosis and therapeutic abortion, i.e. the life-time costs of care are averted. The "costs" of the program are all those costs associated with the diagnostic and preventive procedures, required to identify and abort an affected fetus.

It is useful to classify costs and benefits into several categories since such a classification helps to ensure that all the

important items are included in the analysis.

1) "Direct" costs and benefits are those effects which occur as a direct result of the program meeting its primary objectives.
2) "Indirect" costs and benefits can be thought of as the side-effects of the program. Although such costs and benefits may be included to varying degrees in the analysis, they should always be identified and considered in the final analysis.
3) "Intangible" costs and benefits include those items such as anxiety, happiness, grief, etc. which cannot be quantified and items which can be quantified but not monetized. These items should also be considered in the final deliberations of the decision maker even though they cannot be expressed in monetary terms.

III) The Evaluation of Costs and Benefits

Evaluation involves two steps since it is necessary to quantify a cost or benefit before one can place a value on it. The evaluation of costs and benefits is usually the most time consuming part of a cost-benefit analysis and it is usually at this stage of the analysis that one becomes most acutely aware of the dearth of accurate information.

When placing a value on an item, the market price of the item is used unless one has reason to think that the existing market price does not accurately reflect the "real" cost of the item.[155] The obvious problem that arises if the individual analyst establishes the "real" cost of an item is that the "price" suggested by the analyst may be just as controversial as the market price. Thus, unless it appears that the difference between the "real" cost of the item and the market price of the item is very large, an attempt is not made to correct for the

imperfections of the free market system. In those cases where a market price does not exist, however, the analyst should make an attempt to evaluate the good or service.

For example, in order to perform an economic analysis of the program to prevent Down's Syndrome it was necessary to establish a value for the laboratory component of the diagnostic procedure since a market price for this item was not available.

Similarly, a market price for the value of the health services required by individual with Down's Syndrome was not available and a sub-study was required to quantify and evaluate these services in this analysis.

Adjustment for Inflation

Much of the theory of cost-benefit analysis was developed at the time when inflation rates were low and in most cost-benefit studies adjustments to reflect expected inflationary changes in future prices is not usually made unless the value of some items is expected to change relative to the others.[156]

It is considered acceptable to use either current price levels or anticipated price levels in valuing the costs and benefits of a program but it is essential to evaluate both costs and benefits at the same price level. Current price levels are used in most studies because of the inherent difficulties in predicting future prices but in those instances where anticipated price changes may significantly alter the relationship between the values of benefits and costs, it is necessary to adjust for these anticipated price changes.

In this study, the costs are incurred in the first year of the

project while the benefits appear over many decades. The benefits will thus be affected by inflationary trends while the costs will not be so affected. Therefore, in order to avoid distortion of the benefit-cost ratio in this analysis it is necessary to use projected levels in establishing the value of the costs and benefits. An inflation rate of 9 per cent per annum has been used to predict the value of future costs and benefits in this analysis. This rate reflects inflationary changes that have occurred in the recent past and although it is possible that this value may either underestimate or overestimate future rates, 9% would seem to be a reasonable rate in the present circumstances and in view of existing government policies.

IV) Aggregation of the Costs and Benefits in Comparable Terms

The implementation of a program results in an irregular stream of costs and benefits that occur throughout the whole economic life of the program. Before comparison between the costs and benefits can be made it is obvious that these complex expressions must be simplified. This is accomplished by a process known as discounting as a result of which the streams of costs and benefits are expressed in terms of their equivalent present values.

Discounting

It is a common observation that most individuals prefer to have a sum of money today rather than a promissory note for the same sum of money at some time in the future. In order to persuade an individual to take the promissory note, it is usually necessary to offer him an incentive - usually a sum of money in excess of the original sum. This additional amount is, in effect, an interest payment. In the absence

of inflation, the rate of interest individuals demand is about three per cent so that an individual would find the present value of "a promise of $103 a year from now" to be equivalent to $100 today.

This procedure of establishing the present value of a cost or benefit which is payable or receivable at some time in the future is called discounting and the interest rate which is chosen is called the discount rate.

The general formula for establishing the present value of a stream of costs which are payable in the future is:

$$\text{P.V. Costs} = \sum_{n=1}^{N} \frac{C_n}{(1+r)^n}$$

Where N is the duration of the project in years

C_n is the cost incurred in the n^{th} year and

r is the chosen discount rate.[155-157]

Similarly, the general formula for establishing the present value of a stream of benefits which are receivable in the future is:

$$\text{P.V. Benefits} = \sum_{n=1}^{N} \frac{B_n}{(1+r)^n}$$

Where B_n is the benefit available in the n^{th} year

An example to clarify the procedure is as follows:

Suppose we wish to compare the costs and benefits of a five year project which costs $1,000 in each year and which produces benefits equal to $2,600 in the last two years of the project. Using a discount rate of 3 per cent in the formulae we find:

$$\text{P.V. Costs} = \sum_{n=1}^{5} \frac{\$1,000}{(1 + 0.03)^n}$$

$$= \frac{\$1,000}{1.03} + \frac{1,000}{(1.03)^2} + \frac{1,000}{(1.03)^3} + \frac{1,000}{(1.03)^4} + \frac{1,000}{(1.03)^5}$$

$$= \$970.87 + 942.68 + 915.16 + 888.51 + 862.63$$

$$= \underline{\$4,579.55}$$

$$\text{P.V. Benefits} = \frac{\$2,600}{(1.03)^4} + \frac{2,600}{(1.03)^5}$$

$$= \$2,310.12 + 2,242.84$$

$$= \underline{\$4,552.96}$$

In this example the effect of discounting is to reduce the value of the benefits which are received in future years so as to make their present value less than the present value of the costs, even though the benefits exceed the costs when measured in absolute terms.

Choosing the Discount Rate

The choice of a suitable discount rate is obviously critical to a cost-benefit analysis; the selection of a rate that is too high artificially diminishes the value of future benefits and costs whereas the selection of a rate that is too low artificially inflates the value of future benefits and costs.

All cost-benefit analysts agree that a discount rate should be used but there is no consensus on the choice of a suitable rate. Further, it is by no means clear that costs and benefits should be discounted at the same rate.

The existing rate of interest on government bonds is sometimes used as the discount rate in evaluating projects since this rate supposedly represents the rate of interest that is payable on "risk-free"

investments.[157] However, as many writers have pointed out, current high rates of interest reflect present high inflationary trends and it has therefore been suggested that the current interest rate should be adjusted downwards, to allow for the effect of inflation, before being used as the discount rate in the analysis of a project.[159] The appropriate adjustment that should be made depends on present inflationary trends but no precise guidelines are available. An alternative approach is to adjust for the effect of inflation in the evaluation of costs and benefits and then use unadjusted interest rates for discounting. This method was chosen for this analysis largely in the interest of clarity.

The rate of interest on "risk free" loans is called the private discount rate (PDR) or the private time preference rate (PTPR), since it theoretically represents a private individual's devaluation of future gains. It has been argued that analysts of public projects should use a lower discount rate than that used by private individuals in order to reflect governmental con-ern for the well-being of future generations. Other authors are against a low public rate, arguing that since it is government's main responsibility to serve the existing population, the government discount rate should be similar to private discount rates.[155]

Despite the theoretical arguments for low government discount rates, it is likely that, in practice, government decision-makers implicitly use high discount rates especially for projects where the costs are high and immediate (and therefore attributed to the party in power) and the benefits are delayed (and are attributed to whatever party is in power at that future time).

The choice of an appropriate discount rate is so controversial

that support can be found in the literature for almost any discount rate in the range of 2 to 20 per cent.[160] Each analyst selects the rate that he considers the most appropriate for the study in question. In this analysis a discount rate of 12 per cent has been selected for two main reasons:

1) This rate when used in conjunction with an inflation rate of 9 percent results in a net "real" rate of interest of approximately 3 per cent, which seems to be the implicit discount rate applied by most individuals making investment decisions and
2) 12 per cent is not an unreasonable interest rate to expect on "low risk" investments at the present time.

In the final comparison of costs and benefits the effect of using two other discount rates will be examined. The comparison rates represent "real rates" of interest of 5 per cent and 8 per cent - rates which are required investment returns of 14.4% and 17.7% if inflation continues at 9% per annum. Although it is unlikely that this level of return can be guaranteed on "risk free" investments, rates of 5-8% are commonly used in the literature and some preliminary sensitivity analysis is performed in this analysis to demonstrate the effect of different rates on the benefit-cost ratio.

V) Comparison of Costs and Benefits

There are four recognized ways of making comparisons between the costs and benefits of a program:[157]

1) The net-benefits approach

This comparison simply involves subtracting the present value of the costs from the present value of the

benefits, and any program in which the benefits exceed the costs is then said to have passed the minimum test of economic feasibility. The major disadvantage of this approach is that it does not take into account the size of the initial expenditure. For example, the net-benefit approach would not discriminate between projects A & B below since they both result in the same net benefits.

	Project A	Project B
Present value of Benefits	6,000	11,000
Present value of Costs	5,000	10,000
Net benefits	1,000	1,000

2) Calculation of the benefit-cost ratio

Calculation of the benefit-cost ratio permits ranking of competing projects and provides an estimate of the return on each dollar invested in the program. Using the benefit-cost ratio approach to evaluate projects A and B we find that Project A has the benefit-cost ratio of 1.2 and Project B has a benefit-cost ratio of 1.1; we are therefore able to rank project A ahead of project B.

	Project A	Project B
P.V. Benefits	6,000	11,000
P.V. Costs	5,000	10,000
B/C ratio	6,000/5,000 = 1.2	11,000/10,000 = 1.1

3) Calculation of the internal rate of return

The internal rate of return of a project is a measure of the rate of interest that the project returns to its sponsors.

Symbolically the internal rate of return of a project is calculated by solving the following expression for s, the internal rate of return:

$$\sum_{n=1}^{N} \frac{C_n}{(1+r)^n} = \sum_{n=1}^{N} \frac{B_n}{(1+s)^n}$$

Where N is the duration of the project in years

C_n is the cost in the n^{th} year

B_n is the benefit in the n^{th} year and

r is the chosen discount rate

Using this technique, a project is regarded as acceptable if s r and competing projects can be ranked according to their internal rates of return. Although the internal rate of return approach has some theoretical attractions it is not very useful in practice. The calculation of "s" is tedious and in addition the procedure has been subjected to several other criticisms. The use of the IRR sometimes results in projects being ranked in a different order from that obtained on the basis of their benefit-cost ratios, particularly if projects do not yield their benefits at a uniform rate. Mishan has suggested a "normalization" procedure in which the costs and benefits of a project are compounded forward to a terminal value for comparison.

Mishan then shows that ranking projects in terms of their "normalized" internal rates of return yields the same results as the benefit-cost ratio.[161]

4) The pay-back period approach:

The pay-back period approach calculttes the number of years required before the accumulated present value of the benefits is equal to the present value of the costs. This approach is of limited value and may give absurd results if it is used for ranking projects. In the following example, Project X would be ranked higher than Project Y using this method although the use of any other method would favour Project Y.

	Project X	Project Y
Present value of the cost	$1,000	$1,000
Benefits - Year 1	900	200
- Year 2	200	500
- Year 3	0	1,200
Pay back period	2 years	2½ years
Present value of the benefits (discount rate 3%)	$1,062	$1,764
B/C ratio	1.062	1.764

The Choice of Technique

Of these four approaches, the benefit-cost ratio has proved to be the most useful in the economic evaluation of health programs[158] and it provides the maximum amount of useful information in a format that

is readily understood by non-economists.

While benefit-cost ratio analysis has proved to be of particular value when it is necessary to rank competing projects, it is also a valuable tool in the assessment of unique programs with no competitors.[156] In addition to determining the basic economic feasibility of a program, this approach can also be used to determine the extent to which such a program should be supported, i.e. to determine the scale of the program.

In any diagnostic program one can examine the economic implications of offering the service to groups of individuals who are at successively lower risk in order to establish the groups for whom the tests are economically feasible. For example, in the case of a program to prevent Down's Syndrome one can examine the marginal benefit-cost ratios as the service is offered to successively younger women. Since younger women are known to be at lower risk, the number of women who must be tested in order to detect one affected fetus will increase, the cost associated with case identification will increase and the benefit-cost ratio will decrease. By determining a series of marginal benefit-cost ratios for the various maternal age groups it is possible to determine the youngest maternal age for which the benefit-cost ratio exceeds the chosen "cut-off" figure and to establish an appropriate scale for the project based on economic considerations.

Choosing the "cut-off" benefit-cost ratio is another difficult problem. Theoretically, one should only embark on a program if it has a benefit-cost ratio which is greater than the "next-best" program. Thus if society would gain more from a program to enforce the use of

seat-belts in motor-vehicles than it would from a program to prevent Down's Syndrome, the seat-belt program should receive priority. In practice the allocation of funds is often less logical but despite this it is important to try to determine the social opportunity cost (SOC) of the resources that will be used up by a program, i.e. to establish the present value of the benefits that could be obtained from optimal alternative use of the resources which will otherwise be used in the proposed program.[155,156] A more pragmatic approach that is frequently used is to continue to expand programs as long as the B/C ratio for the marginal case remains greater than 1 since in this situation one is, at least, not losing money.

The Economics of the Prevention of Down's Syndrome - The Literature

In the past few years, as it has become increasingly apparent that prenatal diagnosis and selective therapeutic abortion offers a medically feasible alternative to the birth of severely defective infants, several investigators have made statements about the economic feasibility of routinely providing prenatal diagnosis to various population groups.(Table 15) In most instances, the economic analysis has consisted of a comparison between the estimated life time cost associated with the care of an individual with Down's Syndrome and the costs of amniocentesis and cell culture. Some writers have used this information to make preliminary cost-benefit analyses. Conceptually, relating the costs of case identification and prevention to the benefits or cost-savings achieved as a result of prevention is simple, but in practice, estimation of the various costs, benefits, and risk functions is difficult and estimates have varied widely as

TABLE 15 - EXISTING ECONOMIC ANALYSES OF THE PREVENTION OF DOWN'S SYNDROME

AUTHOR	TECHNIQUE	COSTS	BENEFITS	POPULATION SERVED	ASSUMPTIONS
SWANSON-1970[162]	Compares costs of 20 year program for U.S.A. with "committed" costs for care of the estimated number of children with Down's Syndrome that would otherwise have been born	5.35 billion	18 billion	not stated- ? all pregnant women	- 50 year life expectancy ("conservative") Cost of care = $5000/year ("reasonable estimate") No discounting
MAIDMAN-1972[105]	Compares the cost of the procedure with average life time cost of an individual with Down's Syndrome	$100=$125 for amniocentesis culture and analysis (no source given)	$60,000 (quotes Littlefield) institutional costs only	not stated- favours maternal age of 35+	Institutional-isation: 1/3 in infancy 1/3 by age 10 1/3 by age 30 ? discounted
STEIN-1973[59]	States "the cost of screening mothers over thirty, at the current rates charged in New York City, is certainly less than that of caring for cases of Down's Syndrome among them."	Not Specified	Not Specified	Not Specified	Not Specified

AUTHOR	TECHNIQUE	COSTS	BENEFITS	POPULATION SERVED	ASSUMPTIONS
THOMPSON-1973[24]	Compares the cost of amniocentesis with the daily cost of institutional care for affected infants	$"500,000" ($250 X2450)	$"3.1 million" ($6000 x 20 x 26)	Maternal age 40+	20 year life expectancy (assumed) $6000 per annum (assumed) No discounting
ALLEN ET AL 1974[113]	Compares the cost of amniocentesis with the daily cost of institution-al care for affected infants	$125-$150 for amniocentesis (approximately)	$42 per day (average of 11 institutions in Ontario)	Not Specified	
BUTLER & REISS-1970[112]	Compares the cost of case identification with benefits of case prevention	£30 x 100= £3000	£15,000	Maternal age 40+	18 year life expectancy Institutional-ized at age 4 ? Discounted
CONLEY-1975[158]	Compares case prevention cost with benefits from case prevention to get a B/C ratio of 1.9	$250 for amnio culture analy-sis +$400 for therapeutic abortion. Case prevention cost=$34,000	$65,000 (Institutional care)	The users of a U.S. prenatal clinic with overall risk of 1:121.5	-20 years in institution between years 10-30 -includes 10% capital -costs uses a discount rate of 7% -allows 10% repeat amnio.

can be seen in Table 15.

Much of the variation can be explained by the lack of accurate data on life expectancy, the tendency to equate institutional costs with life-time costs and the extent to which discounting methods are applied.

Similarly, on the cost side most writers make personal estimates of the cost of amniocentesis, culture and chromosome analysis but few include the cost of genetic counselling, obstetric assessment or the cost of the therapeutic abortions that are recommended following prenatal diagnosis.

Despite the difficulties in interpreting these analyses it seems that the provision of a service offering prenatal diagnosis and therapeutic abortion is economically feasible for women aged 40 years and over where the risks of Down's Syndrome are approximately 1 in 100. There is less general agreement about the value of such a program for younger women who are at less risk. However, now that many people feel that prenatal diagnosis should be more widely available, it is important that the economic implications of expanding these programs be examined in more detail.

In the cost-benefit analysis that follows, the classical method of comparing the "costs" associated with case identification and prevention with the "benefits" achieved as a result of case prevention will be used. The changes in life expectancy that have been observed and the effects of the recent trends towards community-based care for the severely retarded will be incorporated into the analysis since it is obviously no longer appropriate to equate institutional costs with the

total cost of care for an individual with Down's Syndrome. The overall effect of the shift to community-based care has been to spread the costs of care more widely and it is necessary to include both the private costs incurred by the family and the public costs of providing special education, employment opportunities, health care and income maintenance, etc. The economic effects of these changes in the patterns of care for the mentally retarded will also be considered in this analysis.

Methods of Analysis

Earlier in this chapter, it was suggested that the procedure of cost-benefit analysis could be conveniently divided into five stages and this sequence will be followed in performing this analysis.

I) Identification of the Program and Definition of the Objectives

The preventive program which is to be analyzed provides prospective parents with a precise prenatal diagnosis of fetal chromosome abnormalities and it also offers parents the option of a selective therapeutic abortion in the event of a defective fetus being identified.

Although the major objective of the program is to prevent the birth of infants with Down's Syndrome, it is recognized that the program may also contribute to the prevention of other chromosomal disorders that are detected as a result of the amniotic chromosome analysis. Most of these disorders are less frequent than Down's Syndrome and in some cases the natural history of the disorder is uncertain; the economic implications of prenatal diagnosis of these disorders is discussed briefly in a later section.

II) Enumeration of the Costs and Benefits

In order to enumerate all the major costs and benefits

associated with the proposed program it is useful to consider the various groups of people who may be affected by the program. The proposed program will have an effect on:

1) the parents who participate in the program
2) the providers of the service - geneticists, obstetricians, nursing staff, technologists, etc.
3) the governmental health budget - public money, and
4) members of the general community

The "direct" costs and benefits of the program are those which result from the program meeting its primary objective, i.e. preventing Down's Syndrome.

On the cost side, this category includes all the costs associated with the performance of the amniocentesis, cell culture and chromosome analysis and all the therapeutic abortions performed as a result of the prenatal diagnosis of Down's Syndrome. It also includes the "intangible" costs of the anxiety generated by the performance of these procedures and the stress of decision making in the case of an abnormality, etc. It does not include the cost of any additional diagnostic tests which may be performed on the amniotic fluid, e.g. biochemical tests, alphafeto-protein assay, nor does it include the cost of those therapeutic abortions that are performed beaause of prenatal diagnosis other than Down's Syndrome - these costs are the "indirect" costs of the program and should be considered separately.

Similarly, the "direct" benefits are equal to the costs-savings which can be attributed to the prevention of a case of Down's Syndrome. The degree of relief which most parents feel when a prenatal

diagnosis reveals no chromosomal abnormality and the potential benefits to medical research are also included as "intangible" benefits in this category.

The "indirect" benefits are those associated with the cost-savings that result when infants with other abnormalities are aborted.

The "indirect" effects of a prenatal diagnostic program whose main objective is to prevent Down's Syndrome, are clearly important, but because accurate data on the severity, incidence and life expectancy for many of these disorders is uncertain, numeric calculations of these benefits and costs are not included in this analysis. The diagnosis of these additional chromosome anomalies can be considered to be a by-product of the program to prevent Down's Syndrome and the benefit-cost comparison that should be made for these indirect effects is therefore

$$\frac{\text{P.V. cost-savings of case prevention}}{\text{P.V. cost of a therapeutic abortion}}$$

This benefit-cost ratio will probably be greater than 1 for all these additional conditions including those conditions where the affected infants die shortly after birth. As the additional information required for a more detailed assessment of the costs of raising children with other chromosome anomalies becomes available it will be possible to include these "indirect" costs and benefits in an economic analysis of prenatal diagnosis.

Preliminary analysis suggests that inclusion of these disorders would show that prenatal diagnosis is economically feasible for younger women than is the case when the prevention of Down's Syndrome alone is considered.

The "intangible" benefits that result from a preventive program may well be the most important benefits. The "savings" attributable to the reduction in family stress, grief and frustration are impossible to measure but are nonetheless very significant. On the other hand, it must be accepted that a few families of severely retarded children feel that these children have brought them much happiness and that the presence of a handicapped child has forced family members to develop skills and inner strengths they might not have discovered in any other way. In the majority of cases, however, it appears that most families prefer not to have a severely retarded child.

This brief review serves to emphasize the extent of the costs and benefits which must be considered in the economic analysis of a program to prevent Down's Syndrome. The various costs and benefits associated with the program are summarized in Table 16.

III) The Evaluation of Costs and Benefits

A. The Evaluation of Cost:

The major quantifiable costs associated with the program are the costs of:

i) genetic counselling

ii) the obstetric assessment

iii) parental chromosome analysis

iv) ultrasound diagnosis to determine placental position and the number of fetuses present

v) the performance of the amniocentesis

vi) amniotic cell culture and chromosome analysis and

vii) selective therapeutic abortion

TABLE 16

THE COSTS AND BENEFITS OF PRENATAL DIAGNOSIS FOR DOWN'S SYNDROME

	COSTS		BENEFITS	
RECIPIENT	MEASUREABLE	INTANGIBLE	MEASUREABLE	INTANGIBLE
CONSUMERS	-Travel Costs -Travel time associated with attending for visits and procedures	-Anxiety and risks of amniocentesis -Stress of decision making -Anxiety and risks of therapeutic abortion -Loss of the happiness a retarded child might have brought	-Absence of parental costs associated with child-raising,* -saving of travel time, time for pregnancy and delivery	-Absence of grief and stress associated with caring for a retarded child -Relief for parents where the prenatal diagnosis is normal -Reproductive freedom
PROVIDERS		-Anxiety associated with the performance of the test, and with the interpertation and confirmation of results		-Advancement of knowledge through research -Development of new technology -Increased job opportunities and job satisfaction

TABLE 16 (continued)

	COSTS		BENEFITS	
RECIPIENT	MEASUREABLE	INTANGIBLE	MEASUREABLE	INTANGIBLE
FINANCIERS	-Cost of case diagnosis* -Cost of case prevention		-Absence of the costs associated with the second half of pregnancy and delivery* -Absence of the public costs associated with raising a retarded child:* -Education -Employment -Health -Residential etc.	
PUBLIC		-Public concern about the mortality and ethics of selective abortion -Concern about long term effects on the gene pool		-Public awareness of the availability of the test and reproductive freedom for "high risk parents" -Value of society of replacement of defective child with a normal child

* Item monetized in analysis

The first five items were valued according to the Ontario Fee Schedule (May 1974) and the costs for these items are as follows:

Genetic counselling (1 hour)	$32.00
Obstetric assessment	$22.00
Parental chromosome analysis (2)	$89.10
Ultrasound diagnosis	$34.00
Amniocentesis	$35.00

Since it is clear that amniocentesis is associated with very low maternal and fetal risks particularly when it is performed in established centres no allowance for maternal or fetal morbidity or mortality was made in this economic analysis.

A policy decision to perform parental karyotypes only in those cases where an abnormal or unusual fetal karyotype is detected would result in a substantial reduction in the cost of item iii. Thus even if we assume that parental analysis is required in as many as 10% of the cases the cost of item iii is only $8.91. However, as indicated earlier the timing of cell culture is uncomfortably tight and if the service is organized on a regional basis the additional delays and costs associated with patient notification and patient travel may outweigh the advantages of this policy. The economic effects of performing parental karyotypes selectively or as a routine will be examined in the analysis.

A surrogate value for the time the parents spend in travelling to and attending the clinic was not obtained for this analysis. The prospective father would spend 1-2 hours at the initial session and the prospective mother would spend an additional 3 hours at the time of amniocentesis. For some parents the initial visit may replace a regular prenatal visit but if prenatal diagnosis is provided only in regional centres, the costs of travel and the additional loss of time from work may be significant. However, even if the average time lost could be quantified the value that should be placed on time spent in voluntarily attending a health clinic is not easy to establish.

At the commencement of this study a fee-schedule price for cell culture and chromosome analysis was not available. In order to obtain an estimate for this service two cytogenetic laboratories were visited (The Hospital for Sick Children in Toronto and the Foothills Hospital in Calgary). The details of the laboratory procedures were discussed with technologists, geneticists and laboratory administrators in order to establish the costs of the service in terms of labour, space, equipment and materials.

At the present time only a limited service is available and both these laboratories had one senior technologist performing all the amniotic fluid cell cultures and analyses. The major component of the cost of chromosome analysis is the cost of labour since both these highly

skilled technologists found that working alone they could only complete 150 analyses per year or 100 per year if "banding" is done routinely. However, they felt that many of the tasks could be deligated to junior technologists and it was considered that the most efficient team would consist of one senior and two junior technologists working in a laboratory approximately 500 sq. ft. in size.

It might be anticipated that the development of still larger units would be more efficient and give rise to "economies of scale" because of better division of labour, optimal use of equipment and less wastage of material. However, the characteristics of the laboratory tasks mitigate against the desirability of larger units for the following reasons:

a) The senior technologists feel that they cannot provide proper supervision for more than 2 junior technologists.
b) The characteristics of the workload make a 1:2, senior: junior ratio desirable.
c) It is thought that the risks of diagnostic error (as a result of culture infection or contamination) would probably increase if larger units were used. This has been the experience in other laboratory areas.
d) The equipment is not grossly underused in a laboratory with three technologists.

The major economy that could be expected if larger units were operated would result from less wastage of

materials, but since materials account for a relatively small proportion of the total cost of the procedure the benefit that might be derived from these larger units is probably outweighed by the additional risks of infection, contamination, etc. Even if it was possible to use more junior technologists this would not result in a very significant cost saving since the differences between the salaries of a senior and junior technologist are not marked.

Laboratory personnel consider that a fully equipped amniotic culture laboratory approximately 500 sq. ft. in size and staffed by three technologists would provide a high quality service at the lowest possible cost. The output of each laboratory should be 450 analyses/year and it is suggested that increased demand for services should result in duplication of the entire unit rather than expansion of the existing one.

The ideal unit characteristics have been used to make the following estimates for the cost of cell culture and chromosome analysis in Table 17, and a more detailed calculation is presented in Appendix C.

The costs associated with a smaller unit where one senior technologist performs 150 amniotic cell cultures per year is presented for comparison in Table 18, and it can be seen that the larger laboratory is more efficient.

The costs associated with chromosome analysis could conceivably be reduced in the future if computer

TABLE 17

THE COST OF AMNIOTIC CELL CULTURE AND KARYOTYPE PREPARATION

Predicted costs for a laboratory with the following characteristics:

- 3 technologists (1 senior, 2 junior)
- 500 sq. ft. laboratory space + 60 sq. ft. darkroom space
- Annual output of 450 analyses
- Karyotypes prepared with regular stain only
  (with "banding" the output would be 300 analyses per annum)
- Toronto culture methods

1. Variable costs (medium, disposable glassware, photographic film, etc.)	$ 15.72	14%
2. Equipment costs (depreciated over 10 years) depending on choice of equipment	$ 6.20-$10.87	~ 7%
3. Laboratory operating costs (CO_2, storage glassware, photographic fluids, etc.)	$ 1.81	2%
4. Labour costs (senior tech @$13,800; junior @$11,500)	$ 81.78	72%
5. Space (serviced)	$ 6.22	5%
Total	$111.73-$116.40	
Average cost	$114	

Note: The estimated cost of a Giemsa banded karyotype is $166

The equivalent Calgary costs were $114 (regular stain) and $170 for a fluorescent banded karyotype.

The similarities existed despite the use of different equipment, culture methods and supply sources.

The variable costs are those costs (item 1) associated with the performance of each test.

The fixed costs (items 2-5) must be met regardless of the output of the laboratory.

TABLE 18

THE COST OF AMNIOTIC CELL CULTURE AND KARYOTYPE PREPARATION

Predicted costs for a laboratory with the following characteristics:

- 1 senior technologist
- 500 sq. ft. laboratory space, 60 sq. ft. darkroom space
- annual output of 150 analyses
- regular staining methods
- Toronto culture methods

Variable costs	$ 15.72
Equipment costs	$ 11.94 - $16.61
Laboratory operating costs	$ 4.10
Labour costs	$ 18.67
Space costs	$ 92.00
	$142.43 -$147.10

technology provides us with an accurate method of scanning cultures for metaphase plates, counting and classifying chromosomes, and preparing karyotypes. There have been some interesting developments in this field in recent years but much work remains to be done before the technology can be applied to amniotic cell cultures. Similarly, the development of a specific factor to speed up cell division would decrease the time taken in the preparation and maintenance of cell cultures and probably decrease the labour costs of chromosome analysis.

The extent to which parents will demand a prenatal diagnostic service is unknown at the present time. It is possible that demand may be so low that it will not be possible to organize laboratories with "ideal" characteristics and the cost of prenatal diagnosis would therefore increase. There are two factors which will tend to suppress the development of small, inefficient laboratories. Firstly, a marked shortage of trained cytogeneticists and skilled technologists can be anticipated and this will tend to encourage the development of larger units which can make the best possible use of trained staff. Secondly, it will be possible for new regional diagnostic centres to be phased in or delayed according to the level of demand for prenatal diagnosis.

The sensitivity and specificity of the laboratory analysis has already been discussed and since it is apparent

that both are approaching 100% - complete accuracy was assumed for the purposes of this analysis.

In summary, the best estimates of the costs associated with each prenatal diagnosis are as follows:

A $326 if all parents are karyotyped prior to amniocentesis ($32 + $22 + $89 + $34 + $35 + $114)

B $246 if 10% of parents are karyotyped as necessary after amniocentesis ($32 + $22 + $9 + $34 + $35 + $114)

An additional $6.00 makes an allowance for a 4% failed amniocentesis rate (dry taps) and for a 4% failed culture rate. The adjusted costs are $332 and $252 under Policy A and Policy B respectively.

The Costs of Therapeutic Abortion

In Chapter Two the techniques used for procuring a second trimester abortion were described. Although prostaglandins may become the procedure of choice in the future, the present techniques are those of saline abortion or hysterotomy. In Toronto, both these methods are used with approximately equal frequency for genetic terminations and the cost applied to this part of the preventive program was therefore calculated as 50% of $90.30 and $180.60 (the 1974 fees for a saline abortion and a hysterotomy respectively, including anaesthetic services). The cost of hospitalization was calculated on the basis of a hospital stay of five days (the experience of the Toronto Antenatal Diagnosis Clinic) at a cost of $100/day. A five-day stay may seem

excessive but since many of these women are over 35 years of age and therefore subject to more complications, this length of stay is probably not unreasonable.

The average cost of a therapeutic abortion calculated in this way is $635.00.

If prostaglandin termination is shown to be safe and effective, it is likely that hysterotomies will become less acceptable and the resultant reduction in hospital stay and procedure cost will decrease the cost of a therapeutic abortion to approximately $400.

The total cost of identifying and preventing the birth of one infant with Down's Syndrome is dependent on at least two factors:

1) the incidence of the disorder in the population being tested and
2) the proportion of parents who decide in favour of a therapeutic abortion when a defective fetus is identified.

The incidence of Down's Syndrome was discussed in Chapter One and using this data it is relatively easy to determine the cost of case identification based on the theoretical estimates of the incidence of Down's Syndrome in the various maternal age groups. (The actual incidence found at a prenatal diagnostic clinic is likely to be a little higher than the theoretical estimates since the theoretical incidence is based on live-birth data and the incidence found at amniocentesis will be inflated by those few affected

fetuses who would have spontaneously aborted in the absence of the program).

The proportion of parents who elect to have a therapeutic abortion following the diagnosis of a fetus with Down's Syndrome is obviously high. A few parents have decided against an abortion in the situation for a variety of reasons - some parents find it impossible to consider abortion after the mother has felt fetal movements - an event which may occur in the interval between the amniocentesis and the culture report; still others may change their minds about the ethics of aborting a defective fetus, etc.

Initially, many clinics required that parents agree to an abortion for a defective fetus before an amniocentesis was performed. Now that the procedure is no longer experimental, few clinics require this commitment and in fact it has proved to be an insignificant problem since almost all parents, faced with the definite diagnosis of a severely retarded and multiply handicapped child, choose to have a therapeutic abortion. In this analysis it is assumed that all parents choose to have a therapeutic abortion after a prenatal diagnosis of Down's Syndrome. In the case of some of the other chromosomal disorders, the parental decision is obviously more complex and only experience with the program will provide information on the acceptability of these disorders to prospective parents.

Another issue which should be considered here is the issue of compliance. It is important to recognize that low compliance rates will only affect the cost of case prevention if demand for the test is so low that culture laboratories are forced to operate at an inefficient level. In all other cases the proportion of Down's Syndrome cases prevented will fall with falling compliance but the cost per case diagnosed will remain constant.

The cost of case prevention (diagnosis and therapeutic abortion) for Down's Syndrome at various incidence rates and under various policies is displayed in Table 19.

B. The Evaluation of the Benefits

The major quantifiable benefits which result from prevention of the birth of an infant with Down's Syndrome are the cost-savings associated with not having to provide the following goods and services for the affected individual:

i) obstetric care during the second half of pregnancy and delivery,

ii) food, clothing, shelter, etc. in the family home or

iii) residential care in a group home or

iv) residential care in an institution,

v) special education in a nursery or special school,

vi) employment opportunities in a sheltered workshop,

vii) health care - acute hospital, physician services, drugs and dentistry,

TABLE 19

THE COST OF CASE PREVENTION BY INCIDENCE OF DOWN'S SYNDROME

INCIDENCE/1000 LB.	POLICY A PARENTAL KARYOTYPES ROUTINELY	POLICY B PARENTAL KARYOTYPES AS REQUIRED
20 (1:50)	$ 17,235	$ 13,235
10 (1:100)	$ 33,835	$ 25,835
6.66 (1:150)	$ 50,435	$ 38,435
5 (1:200)	$ 67,035	$ 51,035
4 (1:250)	$ 83,635	$ 63,636
3.33 (1:300)	$100,235	$ 76,235
2 (1:500)	$166,635	$126,635
1.11 (1:900)	$299,435	$227,435
1 (1:1000)	$332,635	$252,635
.83 (1:1200)	$399,035	$303,035
.66 (1:1500)	$498,635	$378,635
.5 (1:2000)	$664,635	$504,635

NOTE:

-POLICY A - Prenatal Diagnosis = $332/pregnancy

-POLICY B - Prenatal Diagnosis = $252/pregnancy

-BOTH POLICIES ALLOW FOR 4% "DRY TAPS" AND 4% FAILED CULTURE RATES

-COST OF THERAPEUTIC ABORTION FOR THE AFFECTED FETUS = $635.

viii) family allowance (this amount must be subtrated from item (ii) since it is essentially a transfer of payment rather than an additional cost),

ix) family benefits (again this is a transfer payment)

x) child care services provided in the family home (opportunity costs)

Clearly, some of these items are mutually exclusive, e.g.(ii, iii & iv) but evaluation of each of these items enables one to determine the costs that result from changing the mix of services supplied to the individual and to establish the economic effect of changes in the patterns of care available to the severely retarded.

For each of these categories the age-specific costs will be calculated since it is well known that the costs of raising any child vary according to the age of the child.

Several items have not been included either because they are only available to a small proportion of the retarded population (e.g. the recreational camps that are available in some centres) or because they are only in the planning phase (e.g. the proposed life-skills program).

The base-line year for the analysis is 1974 and throughout the evaluation procedure 1974 prices have been used or estimated.

Benefit Categories

i) Obstetric care during the second half of pregnancy and delivery - Prior to the 16th week of gestation most women will have made about three prenatal visits. When a pregnancy ends with a therapeutic

abortion the physician charges for the prenatal visits on a per-visit basis and he would thus claim $52 for these three visits. (The specialist rates have been used since most women presenting for genetic amniocenteses at the present time are "high-risk" patients: the use of general practice rates may be more appropriate if the service was offered to the total pregnant population although the difference in charges is minor). The calculation of the cost-savings achieved by avoidance of obstetric care during the second half of pregnancy and delivery is calculated in Table 20 and it can be seen that the total cost-saving in this category is $648.00. Although $100 per diem may be on the high side for obstetric care which could be provided more economically in a community hospital, the overall figure for cost-savings does not include the costs associated with complications of pregnancy and is probably a conservative estimate.

ii) Food, clothing, shelter, etc. in the family home - Parents today are very aware that the birth of each additional child is associated with a seemingly endless stream of costs. Despite this general awareness relatively few attempts have been made to quantify the size of the investment.

Relative expenditure scales for people of different ages were first developed at the end of 18th Century to estimate food requirements in Britain.[163] This concept was later expanded by Engel who developed a general expenditure scale in the late 19th Century.[164]

Dublin and Lotka estimated the average cost of raising a child to the age of 18 years using the data of the 1935-1936 Federal Study of Consumer Purchases. These authors adjusted their data for childhood

TABLE 20

THE COST OF OBSTETRIC CARE FROM THE 16TH WEEK OF PREGNANCY INCLUDING DELIVERY

A. NORMAL DELIVERY	
Total charges for specialist care & delivery	$200.00
Hospitalization charges (5 days @ $100/day)	500.00
TOTAL	$700.00
B. THERAPEUTIC ABORTION	
In the case of a patient choosing a therapeutic abortion the first three visits are charged at the normal consultation rates	
1st prenatal visit	$22.00
2nd & 3rd prenatal visits ($15.00)	30.00
	$52.00

DIFFERENCE = Cost Savings = $648.00

mortality and determined the average cost of child raising from analysis of a cohort of 100,000 live births.[165]

Later investigators made additional contributions by recognizing that successive children are not equally costly (thus distinguishing between the average and marginal costs of raising children) and by making adjustments for the changes in the standard of living which may occur as family size increases.[163]

Recently, Espenshade reviewed the existing methodology and published his own comprehensive analysis as a monograph, "The Cost of Children in Urban United States".[163] Espenshade's estimates are based on the 1960-1961 Consumer Expenditure Survey conducted in the United States and his estimates were adapted to evaluate the costs of food, clothing, shelter and miscellaneous expenses incurred on behalf of a child with Down's Syndrome maintained in his family home. It was assumed that a child with Down's Syndrome costs the same amount to feed, clothe and shelter as a normal child: this would seem to be a reasonable assumption although the particular items purchased may vary for a child with Down's Syndrome, e.g. more diapers and less sporting equipment. Adjustments were made to Espenshade's figures to reflect 1974 prices (using the Canadian Consumer Price Index)but no adjustment was made for the minor differences in the relative values of the Canadian and American dollar.

Espenshade developed his cost data for three income groups (lower, middle and upper), for three birth orders (first, second and third) and for three age-levels (0-5, 6-11 and 12-17). Since a child with Down's Syndrome is rarely the first-born in a family and since

the disorder is distributed equally through all socio-economic classes, the costs associated with the second child in a middle income family were used.

Espenshade's estimates (1960-1961) together with the 1974 equivalents for the items food, clothing, shelter and other (transportation, recreation, insurance, gifts,and other miscellaneous expenses) are presented in Table 21.

Espenshade does not provide the equivalent estimates for adults and since no other relevant data is available, the cost of food, clothing, shelter, etc. for an adult with Down's Syndrome was assumed to be 90% of the average cost of these items for a teenager. The reduction is intended to reflect the decreased food and clothing required after physical growth has been completed, but is not based on any experimental evidence.

iii) The cost of residential care in a group home - Small residential homes operated under the Homes for Retarded Persons Act by the local Associations for the Mentally Retarded cost $22 per patient day in 1973. The equivalent 1974 price would thus be $23.94 per day or $8,738 per annum.[166] These costs do not include educational costs which will be calculated separately for patients being cared for in a group home.

iv) The cost of long-term residential care in an institution - The per diem costs of provincially operated Mental Retardation Facilities in Ontario was obtained from Mr. E.J. Ball, Accounting and Financial Management Consultant of the Mental Retardation Facilities Division of the Ministry of Community and Social Services. The average per diem

TABLE 21

	0-5	6-11	12-17	C.P.I. MULTIPLIER
FOOD	145 (273.18)	202 (380.57)	511 (962.72)	1.884
CLOTHING	35 (52.47)	68 (101.93)	287 (430.21)	1.499
SHELTER	3 (5.42)	175 (316.22)	366 (661.36)	1.807
OTHER	39 (65,05)	160 (266.88)	536 (894.05)	1.668
TOTAL	(396.12)	(1065.60)	(2948.34)	
VALUES USED IN THIS STUDY	$396	$1066	$2948	

Estimates for the cost of food, clothing, and shelter etc. by age group.

Espenshade's values are given in the table with the equivalent 1974 prices in paraentheses.

cost paid for the institutional care of a retarded person in 1974 was $37.36 or $13,636 per annum and this sum does include some educational costs. Although it is likely that the actual costs of care in an institution are dependent on the age of the patient and on the size of the unit, specific data is not available in Canada. A Scottish investigator has shown that new patients, toddlers and the elderly cost more to care for than active children, adolescents and adults. He also shows that smaller living units are substantially more expensive to operate than larger units.[167] While his analysis is interesting, no attempt has been made to perform age-specific adjustments in this study. The Ministry of Community and Social Services is planning to develop age-specific per diem costs for Ontario[166] and when this data becomes available the cost for institutional care can be adjusted to provide more accurate estimates.

v) Special education - Parents are encouraged to send their retarded children to special Day Centres or Nursery Schools from the age of 2 years. This community service has expanded rapidly in the past few years and at the present time a high proportion of both urban and rural children are transported to regionally organized centres. The average cost per day for a child in these nurseries was $18.50 in 1975 which is equivalent to $16.43 in 1974. (These figures were obtained from Ms. Barbara Cummints, Consultant to the Childrens' Services Bureau of the Ministry of Community and Social Services.) The Day Centres or Nursery Schools operate on a year-round basis (about 220 days per year) and therefore the annual cost of special nursery education in 1974 was estimated as $3,615.00. This amount includes the costs

associated with transportation of the children.

Funds for the operation of Special Schools in Ontario are allocated on a formula basis which allows 1.6 x the allowance for a High School Student plus 6% weighting factor. In 1974 this resulted in $2,095 being allocated for the education of each child in the Special School Program.

vi) Employment opportunities in a sheltered workshop - As indicated in Chapter One adults with Down's Syndrome can be "employed" in Sheltered Workshops. Conley has estimated that the productivity of an individual with Down's Syndrome is about 20% of a normal person's productivity but he makes no adjustment for the additional costs involved in operating a Sheltered Workshop.

A visit to the Sheltered Workshop in Hamilton provided the opportunity to watch clients with Down's Syndrome working at packaging and simple assembly tasks. It was clear that although good work habits were encouraged the major objective of the workshop was <u>not</u> the maximisation of profits. A review of their financial statement for 1974 would have shown an overall deficit of $170,000 if Government grants had not been available. This budget did not include capital costs or volunteer services so that the deficit is underestimated. A simplified budget is presented below:

Annual Operating Costs (1974)	$400,000
Value of Work Produced	$230,000
Government Grants	$170,000
No. of Clients	190

Thus the average annual cost incurred by providing an individual with workshop facilities was approximately $895 in 1974.

vii) Health care costs - The physical abnormalities and susceptibility to infectious disease associated with Down's Syndrome strongly suggest that these patients would make use of health care services to a greater extent than their age and sex-matched counterparts in the general population.

Precise information on the health-care utilization patterns of these patients is not readily available from OHIP records since services are processed according to the primary diagnosis, e.g. appendicitis or otitis media. The presence of a chronic condition such as Down's Syndrome is often not mentioned on the discharge form or visit form submitted to OHIP.

In order to establish the age-specific cost of health care for persons with Down's Syndrome it was necessary to:

a) establish the age-specific costs in the general population for the categories of acute hospital care, physician's services, drugs and dentists, and

b) determine the appropriate factor by which these costs should be adjusted to reflect the approximate age-specific costs for individuals with Down's Syndrome.

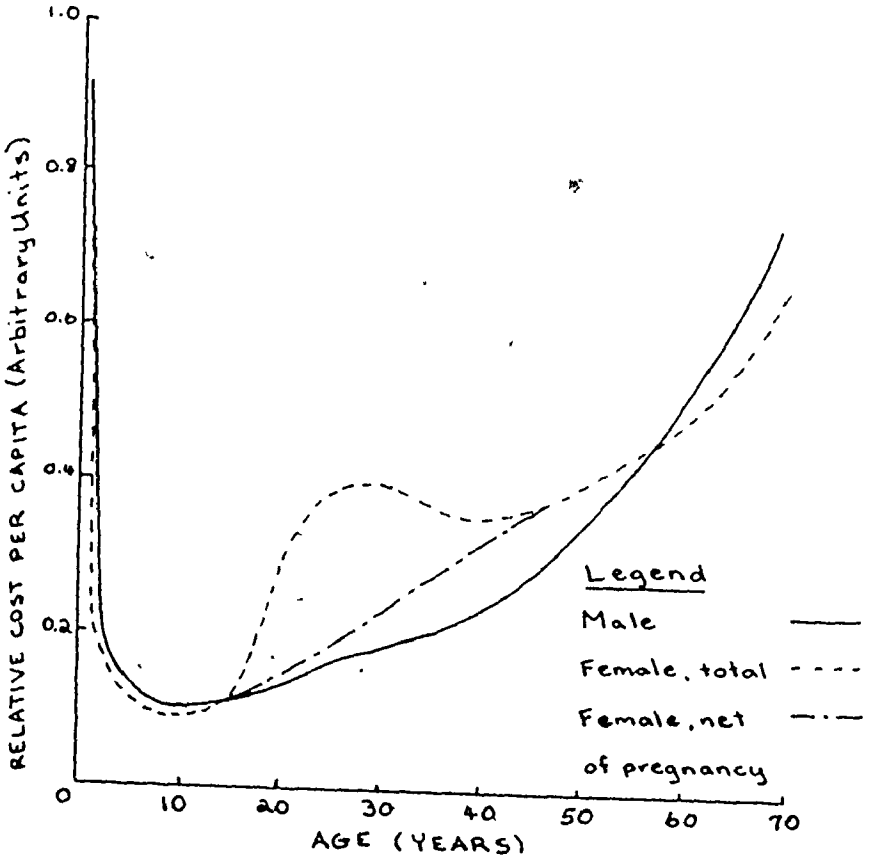
It is widely recognized that the cost of health care is strongly age-dependent but it is only recently that Denton and Spencer[168] developed an age-sex-specific profile of health care costs and demonstrated that these costs are distributed in a U-shaped manner. (See Fig. 13)

FIGURE 13

RELATIVE PER CAPITA COSTS OF HEALTH CARE

FOR MALES AND FEMALES, BY AGE

- after Denton and Spencer[168]



Their findings are based on Ontario data - 1969 hospital statistics (general, allied special, mental and tuberculosis hospitals) and the 1971 expenditure on physician's services for those persons insured under the Ontario Health Insurance Program. The expenditure on drugs was assumed to be distributed in the same way as physician's services.

Using the indices developed by Denton & Spencer in combination with the 1973 Ontario population figures and the total expenditure for health in 1973 (the latest year for which such data is available) on age-sex-specific cost profile can be developed for the general population in 1973 and this data is displayed in Table 22.

Review of the literature suggests that, in contrast to the general population, it is reasonable to assume that the M:F ratio in Down's Syndrome remains at almost 1:1 throughout life[28-32] and since so few females with Down's Syndrome become pregnant an unweighted average of the age-specific indices for males and females-net-of-pregnancy was used to establish a base-line unisex age-specific health care cost profile for use in calculating the health care costs associated with Down's Syndrome (See Column 2, Table 23).

The total health care budget for 1971 was distributed as follows:

53.1% acute care hospitals, T.B. hospitals and government hospitals,

8.6% mental hospitals

24.2% physician's services

14.1% drugs and dentists

TABLE 22

ESTIMATED HEALTH COSTS FOR MALES AND FEMALES - 1973

GENERAL POPULATION

AGE	FEMALES	FEMALES NET OF PREGNANCIES	MALES
0-1	$796	$796	$902
1-4	212	212	233
5-9	106	106	106
10-14	95	95	106
15-19	170	117	117
20-24	361	159	147
25-29	424	212	170
30-34	424	255	212
35-39	382	297	223
40-44	382	350	255
45-49	403	403	318
50-54	435	435	382
55-59	477	477	467
60-64	531	531	562
65-69	605	605	700
70-74	721	721	828
75 +	785	785	902

TABLE .23

ESTIMATED AGE-SPECIFIC UNISEX HEALTH COSTS - 1974 - NET OF PREGNANCY

GENERAL POPULATION

AGE	TOTAL COSTS $	HOSPITAL SERVICES EXCLUDING MENTAL 53.1%	PHYSICIAN SERVICES 24.2%	DRUGS AND DENTISTS 14.1%	MENTAL HOSPITALS 8.6%
0-1	$934	$496	$226	$132	$80
1-4	245	130	59	35	21
5-9	117	62	28	16	11
10-14	111	59	27	16	9
15-19	129	68	31	18	12
20-24	169	90	41	24	14
25-29	210	112	51	30	17
30-34	256	136	62	36	22
35-39	286	152	69	40	25
40-44	332	176	80	47	29
45-49	397	211	96	56	34
50-54	449	238	109	63	42
55-59	519	276	126	73	44
60-64	601	319	145	85	52
65-69	718	381	174	101	62
70-74	853	453	206	120	74

In the absence of more precise age-specific data the costs within each age category were assumed to be distributed in the same way and Table 23 displays the estimated age-specific unisex health care costs in 1974 by each of these four categories (The 1973 prices were inflated by 10% to reflect 1974 prices and the costs were calculated net of pregnancy). This unisex profile of health costs for the general population was used as the base-line for the subsequent analysis of health costs for patients with Down's Syndrome.

The next task in the analysis was to try and establish the appropriate adjustment factor that should be applied to this base-line data to reflect the different utilization patterns of individuals with Down's Syndrome.

The Hospital Medical Records Institute, unlike OHIP offices, collect data relating to all recorded diagnoses and not just the primary diagnosis. With the permission of the director of the institute, Dr. W. Taylor, it was possible to collect hospital utilization data for individuals with Down's Syndrome from this source. (The Medical Records Librarians responsible for coding the HMRI input forms indicated that a careful search of the hospital notes is routinely made for any mention of congenital disorders even if they are not mentioned on the discharge summary form.) The 1973 annual discharge summaries of all the hospitals using the HMRI system were searched and the total number of hospital days attributable to individuals with Down's Syndrome of various ages was obtained.

The analysis was complicated by the fact that only about 50% of Ontario's hospitals were using the HMRI system in 1973. Further,

the various classes of hospital were not represented proportionately and adjustments had to be made to the data to correct for this. The characteristics of the hospitals using the HMRI system are compared with all general hospitals in Ontario in Table 24. The information from this table was then used to calculate the adjustment factor as follows:

	DAYS OF CARE IN HMRI HOSPITALS	TOTAL DAYS OF CARE PREDICTED FOR ALL HOSPITALS
Category A hospitals	664	(664/48) x 100 = 1383
Category B hospitals	1832	(1832/57) x 100 = 3214
Category C hospitals	64	(64/15) x 100 = 427
Total days	2560	5024

$$\text{Adjustment factor} = \frac{5024}{2560} = 1.96$$

This adjustment factor is used in the calculation of the total hospital days attributable to patients with Down's Syndrome (Table 25).

A significant disadvantage of the HMRI data was that the Hospital for Sick Children in Toronto was not using this system in 1973. This hospital obviously plays a major role in the provision of health care for children with multiple congenital abnormalities and access to their data was therefore sought and obtained separately. This data is presented in Table 25.

The final estimates of annual age-specific hospital utilization rates were derived from the HMRI figures (adjusted for the differential representation by hospital category) plus the age-specific hospital days obtained from the Hospital for Sick Children divided by the

TABLE 24

CHARACTERISTICS OF HMRI HOSPITALS - 1973

	NUMBER	% TOTAL
LIVE BIRTHS	66,319	53.6%
ACTIVE BEDS GENERAL	18,610	47.8%
HOSPITALS - CATEGORY A BEDS (EXCL. HSC. PMR. OA AND CHEST)	6,186	48%
HOSPITAL - CATEGORY B BEDS	13,157	57%
HOSPITAL - CATEGORY C BEDS	611	15%
ACTIVE HOSPITAL DAYS	6,220,095	51.3%

NOTE: Among 66,319 live births 51 infants with Down's Syndrome were identified in newborn nurseries. The total expected number from HMRI hospitals was 65 (based on the theoretical estimates of the incidence of Down's Syndrome) but a proportion of these cases would probably not be identified until later childhood.

CATEGORY A - Hospitals are teaching hospitals
CATEGORY B - Hospitals are large community hospitals
CATEGORY C - Hospitals are small community hospitals

HSC - Hospital for Sick Children, Toronto

PMR - Princess Margaret Rose Hospital (Cancer)

OA - Orthopedic & Arthritis Hospital

TABLE 25

ESTIMATED HOSPITAL UTILIZATION FOR CHILDREN WITH DOWN'S SYNDROME

	1-4	5-9	10-14	15-19
HMRI UNADJUSTED HOSPITAL DAYS	1375	299	246	163
HMRI ADJUSTED HOSPITAL DAYS (x 1.96)	2695	586	482	219
HOSPITAL SICK CHILDREN - HOSPITAL DAYS	693	237	71	33
TOTAL HOSPITAL DAYS	3388	823	553	352
ESTIMATED POPULATION OF DOWNS SYNDROME IN ONTARIO	503	587	668	593
AVERAGE HOSPITAL DAYS/ANNUM (DOWN'S SYNDROME)	6.74	1.40	.83	.59
AVERAGE HOSPITAL DAYS/ANNUM (GENERAL POPULATION)*	2.52	.43	.36	.66
MULTIPLE	2.7	3.3	2.3	.9

*SOURCE - Data supplied by Dr. H. D. Walker, Professor, Department of Clinical Epidemcology and Biostatistics McMaster University, Hamilton, Ontario

estimated total number of individuals with Down's Syndrome in each age group.

The estimate of the total population of individuals with Down's Syndrome in each age group was obtained by calculating the survival of appropriate cohorts of Down's Syndrome births using the life table developed for this analysis. The life-table, which is discussed in more detail later in this chapter, reflects current survival patterns and thus over-estimates the survival of patients who are now in the older age groups. Since the analysis to this point is based to such a large extent on estimates and assumptions a further attempt to "correct" for reduced survival in the older age group was rejected. The results of the analysis for the younger age groups are given in Table 25.

This data suggests that children with Down's Syndrome do use hospital services more than their normal counterparts. However, the characteristics of the data sources and the many assumptions, estimates and adjustments that had to be made during this computation demand that the data should be interpreted cautiously and that the figures be regarded as only rough approximations. The errors introduced by the estimates are likely to result in an underestimate of the differences between Down's Syndrome individuals and the general population. The life table used to derive the population estimates for Down's Syndrome by age-group has been based on the recent mortality experience for Down's Syndrome and probably progressively over-estimates the survival of individuals in the older ages. The overestimate of population will result in an underestimate of the average number of hospital days and will tend to minimize the differences between Down's Syndrome individuals and the

general population. In addition, it is probable that in some hospital records the presence of Down's Syndrome was either not mentioned in the notes or not coded on the HMRI form and these errors would also tend to minimize the observed differences.

Although a study based on a consecutive series of admissions to the Montreal Children's Hospital suggested to Scriver et al that children with "genetic" diseases use hospital services about eight times more than expected, the data collected for this analysis suggests that for children with Down's Syndrome a multiple of about 3 might be more appropriate. Accordingly, in this study, hospital costs are calculated as three times the equivalent general population costs until the age of 14 and thereafter the unadjusted average general population costs are used.

For individuals cared for in an institution the situation is somewhat different. Some illnesses, which would require hospitalization if individual lived at home can be managed successfully by the nurses and physicians of a chronic care hospital. The pediatrician who was consulted for estimates of this reduction considered that the hospital care for institutionalized patients is probably about 80% of that required for community-based individuals[170] and this adjustment was therefore used in calculating the acute hospital costs for institutionalized patients in this study.

Since institutional care is being considered as a separate category in this analysis, mental hospital costs were not included in the calculation of the general health costs for patients with Down's Syndrome.

Physician's Services

For individuals being cared for in the family home, physician services were assumed to be distributed in the same way as hospital services, i.e. a multiple of three times the base-line figures was used until the age of 14 and thereafter unadjusted general population costs were used.

For institutionalized patients the cost of physician services was also estimated to follow the distribution of acute hospital costs and thus only 80% of the equivalent costs for the family-based patient were attributed to the institutionalized patient. However, since the government must assume responsibility for the general health supervision of individuals in institutions, a cost of $104 per annum was added to the cost of physician services for these individuals. The $104 represents 26 fortnightly supervisory visits at $4 each. (Fee Schedule, 1974)

Individuals in a group home are being cared for by non-health professionals and the costs of physician services associated with the care of these patients was assumed to be the same as for those patients being cared for in their family homes. However, once again, the government assumes responsibility for the health supervision of these patients and a cost of $104 per annum was added to the cost of physician services for these individuals to represent this service.

Drugs and Dentists

The costs associated with both these services were assumed to be three times the general population costs until age 14 and thereafter no adjustment was made. The multiple of three is considered appropriate for drug charges since the distribution of these charges is

TABLE 26

ESTIMATED AGE-SPECIFIC HEALTH COSTS

FOR DOWN'S SYNDROME 1974 - BOTH SEXES

AGE	HEALTH COSTS IN THE FAMILY HOME	HEALTH COSTS IN A GROUP HOME	HEALTH COSTS IN AN INSTITUTION
0-1	$2562	$2666	$2232
1-4	672	776	663
5-9	318	422	368
10-14	306	410	359
15-19	117	221	201
20-24	155	259	233
25-29	193	297	265
30-34	234	338	299
35-39	261	365	321
40-44	303	407	356
45-49	363	467	406
50-54	410	514	444
55-59	475	579	499
60-64	549	653	560
65-69	656	760	649
70-74	779	883	751

likely to be distributed in the same way as physician services. The multiple of three is also considered appropriate for dentistry because of the serious dental problems that are known to be associated with Down's Syndrome.

In conclusion, the total health costs for persons with Down's Syndrome which have been calculated by summing the age-specific cost components from each of the three categories (hospital, physicians, drugs and dentists), are displayed in Table 26.

viii) Family allowance - The Child Benefit Allowance is currently $20 per child per month but this amount is subject to taxation. For this analysis a taxation rate of 16.66% was used since this was the approximate rate applied to the income of the average married person with three dependents in 1974.[171] The family allowance calculated in this way is equal to $200 per annum but this amount should not be thought of as an additional cost - it is really a transfer payment whose effect is to apply public funds to the private expenses incurred in child rearing. As part of this analysis, the extent of public and private costs associated with the life-time care of an individual with Down's Syndrome will be examined and consideration of the Family Allowance is obviously important in this situation.

ix) Family benefit - The family benefit allowance is payable to adult individuals with Down's Syndrome since they are regarded as permanently unemployable on the basis of their physical and mental disabilities. The monthly allowance of $225 is equivalent to an annual

sum of $2,700. The payment made under the family benefit program should not be considered as an extra cost since it too is a transfer payment and will be considered in the analysis of public and private costs.

x) Child care services - opportunity cost - The evaluation of child care services in the parental home is an unsettled and controversial area: the usual approach has been to value full-time home-makers as full-time domestics even though it is recognized that this method consistently undervalues home-makers.

In order to evaluate child services for this study however, it is necessary to select a value for only those parental services entailed in the care of the child with Down's Syndrome. The parental costs associated with child care are usually ignored in studied of the costs of raising children and no estimates for child care services could be found in the literature. However, since the care of a child with Down's Syndrome requires a great deal of time from one or both parents, it seems desirable to get at least a rough estimate of the time and hence the cost involved. It is recognized that the methods used in obtaining the estimates are far from ideal. The estimates were based on information provided by a very small sample of women and several assumptions, which are not supported by any experimental evidence, were made. Despite these disadvantages such an estimate does provide a "ball-park" estimate of the value of parental services in the care of a child with Down's Syndrome and it is therefore included in the analysis.

The time involved in child care varies according to the age of the child. In this study, age-specific estimates were made of the

annual number of hours spent in each of 12 activities. The estimates were provided by a small group of mothers each of whom had three or more normal children and who thought of the marginal time spent in the various activities for their third normal child as they made the estimates. The average annual estimates in hours for each activity by year of age together with the annual totals are presented in Table 27.

It can be assumed that a child with Down's Syndrome will require more time than a normal child for some activities and less in others. Multiples for each activity were obtained from discussions with the parents of children with Down's Syndrome (a study conducted in 1972), and the age-specific of annual hours of care derived in this way are presented in Table 28.

Having estimated the annual hours involved in the care of these children by year of age the next step is to place a dollar value on each hour spent in this way. Obviously, different individuals will place different values on the time which they might otherwise had been able to spend on hobbies, leisure or productive activities. Various dollar values for parental time were incorporated into the analysis using a cost per hour ranging from $0 to $5 per hour, and the effect of including the value of parental time in the cost of raising a retarded child can be examined.

TABLE 27

ESTIMATED PARENTAL TIME INVOLVED IN THE CARE OF A NORMAL CHILD

ACTIVITY	AGE IN YEARS					
	0-1	1-2	3-5	6-11	12-18	18 +
FOOD AND PREPARATION AND FEEDING	1217	730	274	274	182	182
CHANGING CLOTHING	365	365	182	91	0	0
BATHING	182	182	91	91	0	0
WASHING (CLOTHES & DISHES)	91	91	91	91	91	91
CLEANING	61	182	91	61	0	0
PURCHASING	.36	36	36	72	108	36
PLAYING/COMMUNICATING	365	547	547	182	91	91
TRANSPORTING	0	0	60	52	52	0
WAITING/WATCHING (SPORTS ETC.)	0	0	0	17	17	0
HEALTH VISITS	4	3	2	2	2	0
SCHOOL VISITS	0	0	1	1	1	0
SCHOOL PARTICIPATION	0	0	52	52	0	0
TOTAL HOURS PER YEAR	2321	2237	1427	986	544	400

TABLE 28

ESTIMATED PARENTAL TIME INVOLVED IN THE CARE OF A CHILD WITH DOWN'S SYNDROME

ACTIVITY	AGE IN YEARS					
	0-1	1-2	3-5	6-11	12-18	18 +
FOOD PREPARATION AND FEEDING	1217	1095	411	548	365	365
CHANGING CLOTHING	365	365	365	182	182	182
BATHING	182	182	182	182	182	91
WASHING (CLOTHES & DISHES)	91	91	91	91	91	91
CLEANING	61	182	61	61	61	61
PURCHASING	36	36	36	36	36	36
PLAYING/COMMUNICATING	365	547	547	182	182	182
TRANSPORTATION	0	0	60	52	52	52
WAITING/WATCHING (SPORTS ETC.)	0	0	0	0	0	0
HEALTH VISITS	12	12	6	6	6	4
SCHOOL VISITS	0	0	6	6	6	3
SCHOOL PARTICIPATION	0	0	104	104	0	0
TOTAL HOURS PER YEAR	2329	2510	1899	1450	1163	1067

Life Tables

Before one makes comparisons between costs and benefits of prenatal prevention it is necessary to establish the average life-time cost of raising an individual with Down's Syndrome. From the preceding description of the costs associated with child-raising, it is clear that many of the costs are strongly age-dependent and it is therefore inappropriate to use the simple measure of average life-expectancy in calculating these costs. (The costs of raising two individuals who die at the ages of 1 and 79 years respectively are not equivalent to the costs of raising two individuals who both die at the age of 40 years, particularly when the effect of discounting is included.)

In order to establish the average cost of life-time care for an individual with Down's Syndrome, it is necessary to develop a complete life-table and to establish the proportion of an original cohort who survive to each year of age. The age-specific costs of care can then be applied to the survivors and the average cost of life-time care for an individual in the cohort can be calculated.

The construction and workings of a life table are probably best described using an actual example. Part of the 1970-72 life table for Canadian males is reproduced in Table 29. Column 1 is the age interval under consideration (e.g. 0-11 months, 1 to 1 year 11 months, etc.). Column 2 shows the number of persons alive at the beginning of the interval (l_x). Column 3 is the number of persons dying during the age interval (d_x). Column 4 is the probability of living through the interval (p_x). Column 5 represents the probability of dying during that age interval (q_x), and column 6 is the average number of persons alive

TABLE 29

PART OF THE 1970 - 1972 LIFE-TABLE FOR CANADIAN MALES

AGE	ℓ_x	d_x	p_x	q_x	L_x
0	100000	2002	0.9799784	0.0200216	98210
1	97998	126	0.9987169	0.0012831	97935
2	97872	92	0.9990582	0.0009417	97822
3	97780	83	0.9991561	0.0008438	97738
4	97697	69	0.9992872	0.0007128	97665
5	97628	59	0.9993942	0.0006058	97598
6	97569	51	0.9994794	0.0005206	97543
7	94518	45	0.9995451	0.0004549	97496
8	97473	39	0.9995937	0.0004062	97454
9	97434	38	0.9996158	0.0003841	97415

during the interval (L_x).

The "proportion dying" column forms the basis of the life table and all other columns are derived from it. The data for obtaining q_x comes from national mortality statistics and from the population estimates prepared from census data.

Although no author has reported a complete life table for Down's Syndrome, several investigators have prepared partial life tables for Down's Syndrome or expressed their mortality experience in other ways.[28-33] Since a complete life table is necessary for this analysis, the various mortality estimates from major studies spanning the years 1923 to 1969 were reviewed and compounded to produce a complete life table for Down's Syndrome. The results of recent North American studies using large total Down's Syndrome populations were prefered over older studies relating to institutionalized populations or experience overseas.

In Chapter One the life expectancy of individuals with Down's Syndrome was discussed and mention was made of a detailed study performed by Fabia and Drollette and reported in 1971.[31] For the purposes of this study, the two sex-specific life tables reported by Fabia and Drollette were combined to give a unisex life table for the period from birth to ten years of age. This combined table incorporates the observed male:female sex ratio at birth and the slightly different mortality experience that has been described for males and females during childhood. Although such a combination is not the usual procedure in life table analysis, it is used here in the interest of simplification for the following reasons:

i) There is no evidence that the mortality experience after the age of 10 years is significantly different for males and females with Down's Syndrome.

ii) It is judged that the effects of the underlying disorder of Down's Syndrome are much greater than the differential effects of sex differences.

iii) Health and education costs, employability and productivity are probably not significantly different between males and females with Down's Syndrome so that differentiating between the sexes is not necessary in the cost-benefit analysis.

iv) Some authors do not report the mortality experience of individuals with Down's Syndrome by sex and

v) The use of separate male and female life tables at this stage implies a degree of accuracy which does not exist.

In order to develop the life table beyond the age of 10 years, the probability of dying during a specific interval (q_x) was determined by calculating the average of the male and female probabilities of dying in the same age group in the general population and multiplying this value by a factor to represent the increased mortality associated with Down's Syndrome. The multiples used were derived from review of the literature but since the available information was scanty, variable and largely dependent on institutionalized populations in the older age groups, the actual figures selected reflect the opinions of the author. The resulting life table was discussed with consultant pediatricians and neurologists and it was felt that it was in substantial agreement with the current understanding of survival patterns for Down's

Syndrome. Thus, despite the difficulties encountered in the production of the life table it is probably sufficiently accurate for use in this analysis. The factors used for production of the adult portion of the life table together with the major literature sources consulted are listed in Table 30.

The abridged life table (5 year intervals) was expanded to a full life table by simple extrapolation in order to obtain the average number alive during each single year interval. This figure was calculated by taking the average of the number alive at the beginning and end of each age interval. The calculation rests on the assumption that the death rate is constant throughout the interval and while this is a reasonable assumption after the age of one year it is not appropriate for the first year of life. The average number of infants alive during the first year was calculated using mortality rates for the periods 0-28 days, 1-5 months and 6 months to a year.

The relevant information from the life-table is:

TIME PERIOD	NO. ALIVE AT BEGINNING OF TIME PERIOD	NO. OF DEATHS DURING TIME PERIOD
0-27 days	100,000	7,212
28 days	92,788	9,670
6 months	83,118	6,671
1 year	76,447	

and the calculation of the average number alive during the first year was calculated as follows:

TABLE 30

FACTORS USED FOR CALCULATING THE PROBABILITY OF DYING DURING A SPECIFIED AGE INTERVAL (qx)

AGE GROUP	FACTOR	LITERATURE SOURCES
10-14	20x	Richards and Sylvester,[32] Deaton[33] Forssman and Åkesson[30]
15-19	10x	Richards and Sylvester, Collman and Stoller[29]
20-49	5x	Richards and Sylvester, Öster,[20] Deaton
50-71	6x	Richards and Sylvester, Öster, Deaton

YEAR EQUIVALENTS LIVED BY INFANTS WITH DOWN'S SYNDROME

1st month $92,788 + \frac{7,212}{2}$ = 96,394 month equivalents

1-5 months $(83,118 \times 5) + \frac{9,670 \times 5}{2}$ = 439,765 month equivalents

6-11 year $(76,447 \times 6) + \frac{6,671}{3}$ = 460,906 month equivalents

997,065 month equivalents

= 83,088.75 year equivalents

∴ Average population alive during first year = 83,089

A Life-Table for Down's Syndrome

The partial life table for Down's Syndrome derived for use in this analysis is presented in Table 31 and displayed graphically in Fig. 14. For the Figure it can be seen that more than 50% of individuals with Down's Syndrome can be expected to survive until their 40th year and a few will survive into the 8th decade.

The average life expectancy for an individual with Down's Syndrome can be calculated from the full life-table as follows:

$$\text{Average Life Expectancy} = \sum_{x=0}^{71} \frac{L_x}{l_0}$$

$$= \frac{3,357,308}{100,000}$$

$$= 33.6 \text{ years}$$

Once again, this figure is compatible with present experience of Down's Syndrome and suggests that the life-table developed for this analysis represents a reasonable estimate of present survival patterns in Down's Syndrome.

The construction of the life table was necessary in order to establish the values for L_x (the average number of individuals alive

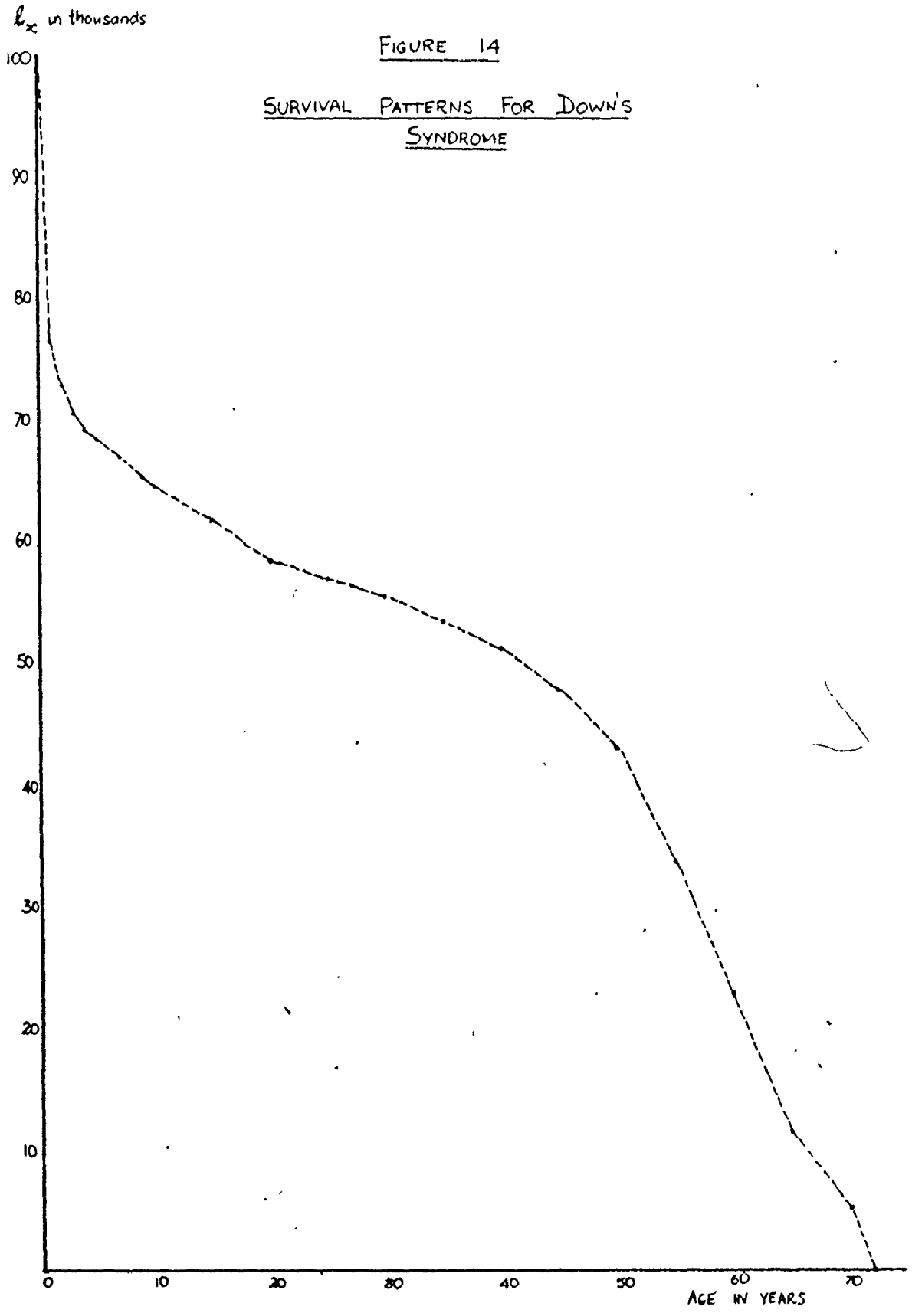
TABLE 31

ABRIDGED - LIFE-TABLE FOR DOWN'S SYNDROME

AGE INTERVALS	ℓx	dx	qx	Lx
0-	100,000	23533	0.23533	83039
1-	76,447	3795	0.0496433	74550
2-	72,652	2108	0.0290150	71598
3-	70,544	1294	0.0183431	69897
4-	69,250	651	0.0094007	68925
5-	68,599	764	0.0113710	68071
6-	67,795	804	0.0118592	67098
7-	66,991	804	0.0120016	66272
8-	66,187	804	0.0121474	65558
9-	65,383	804	0.0122967	64903
10-	64,580	2805	0.0434378	64300
15-	61,775	2996	0.0484999	61476
20-	58,779	1749	0.0297525	58604
25-	57,030	1551	0.0271902	56875
30-	55,479	1750	0.0315393	55304
35-	53,729	2377	0.0442374	53492
40-	51,352	3593	0.0699635	50993
45-	47,759	4948	0.1036007	47264
50-	42,811	8944	0.2089242	41917
55-	33,867	10920	0.3224371	32775
60-	22,947	11349	0.4945728	21812
65-	11,598	8669	0.7474537	10731
70-1	2929	2929	1.0	2197

FIGURE 14

SURVIVAL PATTERNS FOR DOWN'S SYNDROME



in each time period) and these values are found in the last column of Table 31.

This calculation of L_x, the average number of individuals alive in any given year is crucial to the calculation of the average cost of life-time care for an individual with Down's Syndrome. The formula used to calculate the average cost of life-time care (ACLTC) is as follows:

$$ACLTC = \sum_{x=0}^{71} \frac{L_x K_x}{l_o}$$

Where L_x is the average number of individuals alive at age x years.

K_x is the total cost of care for each individual during the period x to (x + 1) years.

l_o is the number in the cohort at age 0 (usually 100,000 in life-tables)

An alternative equivalent expression is:

$$ACLTC = \sum_{x=0}^{71} P_x K_x$$

Where P_x is the proportion of the cohort alive in age interval x to (x + 1) = $\frac{L_x}{l_o}$

The age-specific costs (K_x) associated with the care of individuals with Down's Syndrome in each of three environments (family home, group home, institution) which have been used in the calculation of the life-time costs of care are presented in Table 32.

The age-specific costs of each of the items have been discussed

TABLE 32

AGE-SPECIFIC COSTS OF CARE FOR AN INDIVIDUAL
IN A FAMILY HOME, A GROUP HOME OR AN INSTITUTION

AGE	FAMILY HOME			GROUP HOME	INSTITUTION
	NO. OP. COSTS	OP. COST $2/HR	OP. COSTS $5/HR		
0	2958	7616	14603	11456	15920
1	1068	6088	13618	9566	14351
2	1068	6088	13618	9566	14351
3	4683	8481	14178	13181	14351
4	4683	8481	14178	13181	14351
5	4329	8127	13824	12827	14056
6	3479	6379	10729	11357	14106
7	3479	6379	10729	11357	14106
8	3479	6379	10729	11357	14106
9	3479	6379	10729	11357	14106
10	3467	6367	10717	11345	14097
11	3467	6367	10717	11345	14097
12	5349	7675	11164	11673	14425
13	5349	7675	11164	11673	14425
14	5349	7675	11164	11673	14425
15	5160	7486	10975	11484	14267
16	5160	7486	10975	11484	14267
17	5160	7486	10975	11484	14267
18	3665	5799	9000	10241	14224
19	3665	5799	9000	10241	14224
20-24	3703	5837	9038	10279	14256
25-29	3741	5875	9076	10317	14288
30-34	3782	5916	9117	10358	14322
35-39	3809	5943	9144	10385	14344
40-44	3851	5985	9186	10427	14379
45-49	3911	6045	9246	10487	14429
50-54	3958	6092	9293	10534	14467
55-59	4023	6157	9358	10599	14522
60-64	4097	6231	9432	10673	14583
65-69	3309	5443	8644	9885	14672
70	3432	5566	8767	10008	14774
71	3432	5566	8767	10008	14774

in the text but the cost categories included in each of these calculations are listed in Tables 33-35.

The values of $\sum_{x=0}^{71} PxKx$ which represent the undiscounted and uninflated lifetime cost for caring for an average individual in each of these environments are as follows:

I Family home - no allowance for opportunity costs = $129,031

- $2/hr. opportunity costs = $214,139

- $4/hr. opportunity costs = $299,255

- $5/hr. opportunity costs = $341,813

II Group home = $361,969

III Institutional care = $482,265

(The discounted costs and the costs associated with various mixes of services will be considered in more detail later in this chapter.)

A final benefit category that can be included for consideration at this stage of the analysis is the potential benefit that may result if parents choose to "replace" a defective fetus with a normal child.

Replacement

It is anticipated that the existence of a prenatal diagnostic program will affect the reproductive behaviour of those who use the service. The effect of the birth of a severely retarded child on subsequent family planning was discussed in Chapter One and it was suggested that family limitation in this situation results in a reduction in the number of normal births without significantly reducing the incidence of Down's Syndrome. The effect of a prenatal diagnostic program on subsequent family planning is unknown at the present time but it is likely that at least some parents, who elect to terminate a pregnancy for an

TABLE 33

COMMUNITY-BASED CARE - FAMILY HOME

Cost Categories	Duration
Health	Lifetime
Food, Clothing, Shelter, Etc.	Lifetime
Education	3 - 17 years
Employment (workshop)	18 - 64 years
Child Benefit	0 - 17 years
Family Benefits	18 - 71 years
Opportunity Costs	Lifetime

TABLE 34

COMMUNITY-BASED CARE - GROUP HOME

Cost Categories	Duration
Health	Lifetime
Education	3 - 17 years
Employment (workshop)	18 - 64 years
Residential care	Lifetime
Clothing (provided by family)	Lifetime

TABLE 35

INSTITUTIONAL CARE

Cost Categories	Duration
Health	Lifetime
Residential care (including education and employment)	Lifetime
Clothing (provided by family)	Lifetime

affected fetus, will attempt a further pregnancy to "replace" the aborted fetus, especially when they know that the risk of recurrence can be reduced to zero by prenatal diagnosis.

The anticipated increase in the number of normal births may be attributed to the existence of a prenatal program and this effect should be considered in evaluating the economic effects of such a program. Since a normal child is regarded as a "benefit" in our society, the benefit-cost ratio will be higher when replacement is considered.

In order to include the effects of replacement in the benefit-cost analysis of the program, we need to know:

i) the proportion of parents in the various age groups who will elect to "replace" after a selective therapeutic abortion and

ii) the societal value of a normal infant

If we can obtain values for these unknowns the total societal benefit to be derived from a preventive program can be expressed as:

$B = X + Y (p-q)$ where B is the societal benefit

X is equivalent to the present value of the cost-savings attributable to the prevention of a case of Down's Syndrome,

Y is equal to the present societal value of a normal infant,

p is equal to the proportion of women who "replace" an aborted fetus with a normal pregnancy and

q is the proportion of women who might be expected to "replace" a live-born infant with Down's Syndrome, i.e. in the absence of a prenatal diagnosis program.

Once again, many of these values are unknown and it is necessary to make estimates based on a variety of assumptions in order to get a rough measure of the magnitude of this benefit.

i) The results of Holt's study of family limitation following the birth of a retarded child suggest that, in the absence of a prenatal program, 36% of women over 30 for whom the affected child is a first born will plan another pregnancy and 16% of women over 30 for whom the affected child is a later born child will plan another pregnancy.[90] (The sample size and data reported in this study do not permit a more detailed analysis of replacement by smaller maternal age groupings or more detailed birth order.)

Holt's replacement rates can be applied to the appropriate natality statistics available for Ontario (1973) to obtain "q", the age-specific proportion planning more pregnancies without the program (Table 35, column 3). This value for "q" could be used in the formula developed above.

In order to develop a value for p it is assumed that all parents will try to complete sufficient pregnancies to give them two normal children. Thus, all parents for whom a defective fetus was the product of a first or second pregnancy are assumed to plan a "replacement" pregnancy and all parents for whom the fetus was later born are assumed

to avoid further pregnancies. The results of applying these assumptions to the appropriate natality statistics for Ontario (1973) is also shown in Table 36. The second column in this table represents the age-specific values for "p".

Combining these two estimates allows us to establish the proportion of women in the various age groups who "replace" a pregnancy because of the existence of a prenatal diagnostic program-(p-q), Table 36.

The value of a person's life is another controversial issue and although several economists have attempted to establish the economic worth of a person's life, there is little agreement on the approach that should be used. The most common approach is to base a person's value on their total expected life time earnings discounted to its present value.[171]

Recent analyses have made varying adjustments for the value of unpaid labour (e.g. house work), labour force participation rates and the individual's consumption of goods and services.

This approach has been subjected to numerous criticisms (e.g. does a person's salary or wage really reflect their value to society?) but in the absence of any other practical method the value of a life determined in this way is used by program analysts for decision making.

Rice and Cooper based their extensive analysis on the present value of average life time earnings discounted at 4% and found that the average male and female infant could be valued at approximately $59,000 and $36,000 respectively (in 1964 dollars).[172] If we use a M:F ratio of 1:1 at birth and assume Canadian-American dollar equivalence the equivalent 1974 value is approximately $75,500 per infant.

Conley also derived an estimate for the value of a life based

on life-time earnings, including an imputed value for the home-making services performed by both males and females and he obtained figures of $83,000 and $47,000 for male and female infants respectively in 1972 dollars.[158] If we again make assumptions about the equivalence of the Canadian-American dollar and the sex ratio at birth a 1974 value of approximately $77,500 is obtained - a very close agreement with Rice and Cooper's estimate.

A theoretical estimate of the value of "replacement" normal infants attributable to the prenatal diagnosis program as a "benefit" can thus be calculated as:

.187 x $76,500 = $14,305 for women aged 40-44 years

.253 x $76,500 = $19,355 for women aged 35-39 years

and .385 x $76,500 = $29,453 for women aged 30-34 years

Having developed a theoretical method of estimating the value of the additional benefits attributable to "replacement" it is necessary to qualify the findings by emphasizing that they must be treated cautiously. In fact, because of the controversial nature of the "evaluation of life" and the many assumptions that were used in the estimate of "(p-q)", it can be very reasonably argued that the effect of replacement should be listed as an "intangible" benefit until further data is available.

IV. Aggregation of the Costs and Benefits in Comparable Terms

The costs of case prevention in population groups with various incidence rates of Down's Syndrome have already been presented (in Table 19) and all these costs occur in the year of inception of the program. The "benefits" however accrue slowly over a 71 year period.

TABLE 36

A THEORETICAL ESTIMATE OF "REPLACEMENT" RATES FOR THE ECONOMIC ANALYSIS OF A PRENATAL DIAGNOSIS PROGRAM

MATERNAL AGE GROUP	PROPORTION PLANNING MORE PREGNANCIES WITH THE PROGRAM p	PROPORTION PLANNING MORE PREGNANCIES WITHOUT THE PROGRAM q	DIFFERENCE (ATTRIBUTABLE TO THE PROGRAM) $(p-q)$
30-34	0.501	0.116	0.385
35-39	0.329	0.76	0.253
40-44	0.247	0.60	0.187

In order to express these benefits in terms that are comparable to the costs it is necessary to reduce the stream of benefits to its equivalent present value. This is accomplished by the procedure of discounting that was discussed earlier in this chapter.

The present value of the benefits in this analysis was calculated as follows:

$$\text{P.V. Benefits} = \sum_{n=1}^{71} \frac{(1+g)^n}{(1+i)^n} K_n P_n$$

$$= \sum_{n=1}^{71} \frac{(1.09)^n}{(1.12)^n} K_n P_n$$

$$= \sum_{n=1}^{71} (.9732)^n K_n P_n$$

Where g is the chosen inflation rate.

i is the chosen discount rate.

n is the year in which the benefit occurs.

K_n is the total cost of caring for the individual in the n^{th} year (1974 $).

P_n is the proportion of the cohort alive in the n^{th} year.

The average life-time cost of caring for an individual with Down's Syndrome in each of the three environmental settings under consideration was calculated using this formula and the findings are as follows:

I) Family home - no allowance for opportunity costs = $ 66,371

- $2/hr. opportunity costs = $115,354

- $3/hr. opportunity costs = $139,821

- $4/hr. opportunity costs = $164,338

- $5/hr. opportunity costs = $188,830

II) Group home = $191,997

III) Institutional care = $251,043

These calculations are made on the assumption that an individual with Down's Syndrome remains in one particular environment for life and this is clearly not the usual pattern of care for individuals with Down's Syndrome. Further, the discussion of trends in the patterns of care for severely retarded children in Chapter One would suggest that a mix of these services is seen as desirable. One mix of services that would be compatible with anticipated trends in the patterns of care is as follows:

Age	Life Style
0 - 17 years	Lives in the family home and attends Nursery School/Special School Programs.
18 - 64	Lives in a group home and attends a Sheltered Workshop.
65 - death	Cared for in an institutional setting

This mix of services results in an average life-time cost of $119,127 or $167,030 (including $3/hr. opportunity costs for parental time).

Present patterns of care are difficult to establish. Review of the admission and discharge data from the Regional Centre at Orillia shows that the age of admission to institutions for individuals with Down's Syndrome is increasing - very few infants with Down's Syndrome have been admitted to Orillia in the past decade. There was

no significant difference in the age at admission between the males and females and there was no correlation between the age of the child at admission and the age of the mother when the child was born.(Appendix D)

The age-specific proportion of patients with Down's Syndrome who are in institutions is not known. Two paediatricians who are involved with the management of mentally retarded children were consulted for their opinions on the present patterns of care and the following model is based on their opinions:[170,173]

1%	institutionalized	at birth
6%	"	by 6th birthday
10%	"	" 10th "
70%	"	" 18th "
98%	"	" 40th "
100%	"	" 60th "

It can be assumed that those individuals who are not institutionalized are being cared for in their family homes, since group homes are still in the developmental phase.

The life-time costs associated with caring for a Down's Syndrome individual in this way is: $137,294 (0 opportunity costs). A summary of the discounted values of the "benefits" when different patterns of care are used is presented in Table 37.

V. Comparison of the Costs and Benefits

The major objective of this economic analysis of a prenatal diagnosis program to prevent Down's Syndrome is to establish the incidence rate (and hence the maternal age) at which the monetised costs of case prevention are exactly equal to the monetised benefits attributable

TABLE 37

PRESENT VALUE OF THE COST OF LIFETIME CARE FOR AN INDIVIDUAL WITH DOWN'S SYNDROME - VARIOUS SETTINGS

SETTING	P. V. LIFETIME
Family Home - Life	
0 Opportunity Costs	$ 66,371
$2/hr. Opportunity Costs	115,354
$3/hr. Opportunity Costs	139,821
$4/hr. Opportunity Costs	164,338
$5/hr. Opportunity Costs	188,830
Group Home - Life	191,997
Institution - Life	251,043
Estimated Present Patterns	137,294
"Ideal" Mix of Services	
0 Opportunity Costs	119,127
$3 Opportunity Costs	167,030

to case prevention, i.e. to define the point at which the benefit-cost ratio = 1.

The benefit-cost ratios for various combinations of life-time management and diagnostic policies can be displayed in tabular form as a benefit-cost matrix.(Table 38) However, the number of combinations that are possible and the dependence of the benefit/cost ratio on the incidence of the disorder make a graphical presentation of the data particularly useful.

In Figure 15 the "benefits" are compared with the "costs" in a simple case where there is one diagnostic method and one management model. The point C represents the point at which the benefits and costs are exactly equal and a perpendicular dropped from this point to the X axis identifies the lowest maternal age for which the program can be regarded as economically feasible.

The range of values for the cost of raising an individual with Down's Syndrome that have been developed in this analysis are compared with the cost of case prevention at various incidence rates in Fig. 16.

From this figure it can be seen that the "benefits" are greater than the "costs" for women over 40 years of age, regardless of which policies are chosen. For women in the 35-39 age group the life-time cost of raising an individual with Down's Syndrome in the family home is less than the cost of case prevention. However, since this is an extremely unlikely pattern of care and since the benefits are greater than the costs for all other policies it is reasonable to assume that a program for this age group is also economically justifiable.

If policy B for case diagnosis is compared with the cost of

TABLE 38

A MATRIX OF BENEFIT-COST RATIOS

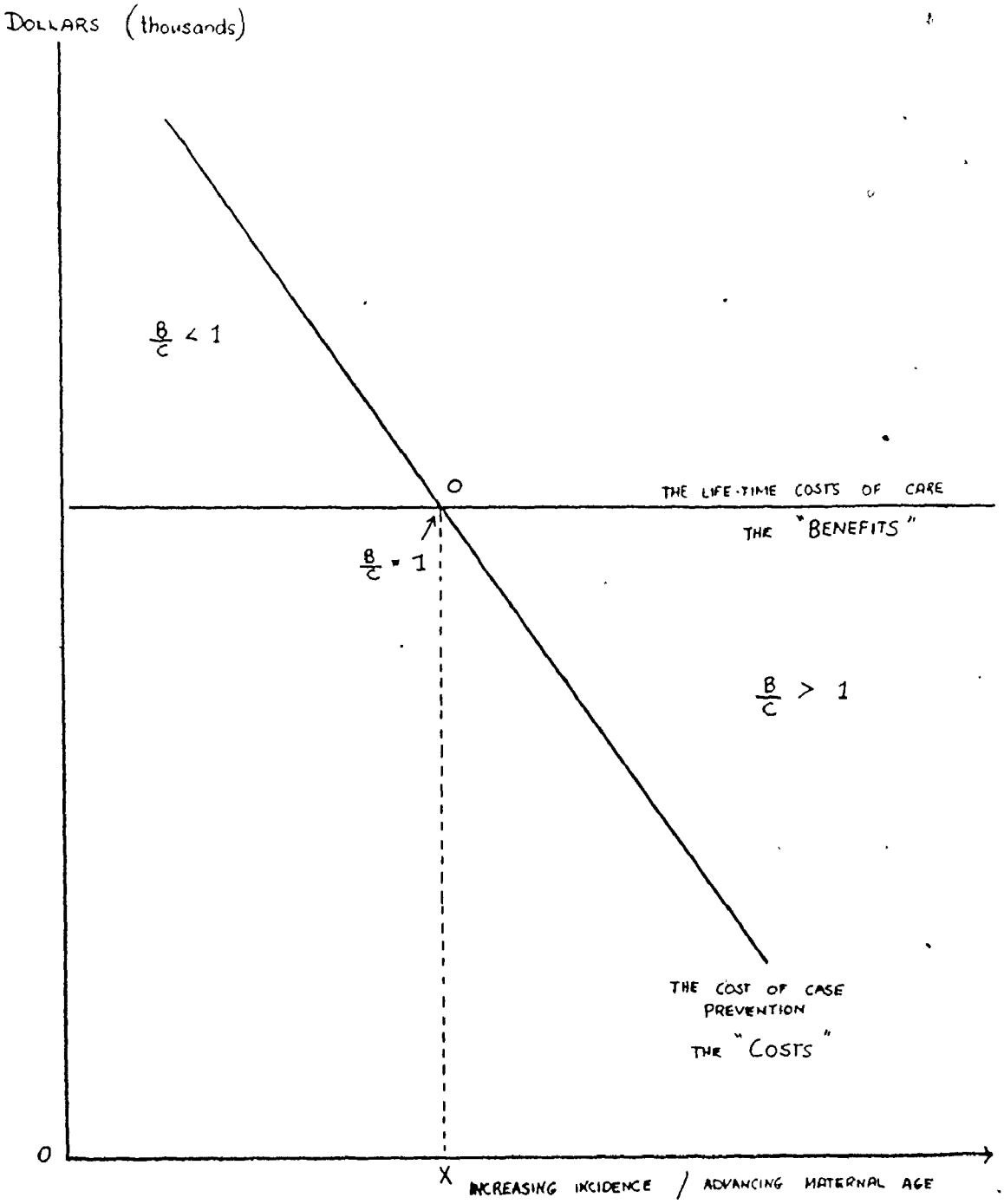
		COSTS					
		Incidence 1:100 Women 40+		Incidence 1:300 Women 35-39		Incidence 1:900 Women 30-34	
		Policy A $33,835	Policy B $25,835	Policy A $100,235	Policy B $76,235	Policy A $299,435	Policy B $227,435
BENEFITS	1. Family Home No Opportunity Costs $66,371	1.96	2.57	0.66	0.87	0.22	0.29
	2. Family Home $2/hr. Opportunity Costs $115,354	3.41	4.47	1.15	1.51	0.39	0.51
	3. Family Home $3/hr Opportunity Costs $139,821	4.13	5.41	1.39	1.83	0.47	0.61
	4. Group Home (Life) $191,997	5.67	7.43	1.92	2.52	0.64	0.84

TABLE 38
(continued)

		COSTS					
		Incidence 1:100 Women 40+		Incidence 1:300 Women 35-39		Incidence 1:900 Women 30-34	
		Policy A $33,835	Policy B $25,835	Policy A $100,235	Policy B $76,235	Policy A $299,435	Policy B $227,435
BENEFITS	5. Institution (life) $251,043	7.42	9.72	2.50	3.29	0.84	1.10
	6. "Present" Patterns $137,294	4.06	5.31	1.37	1.80	0.46	0.60
	7. "Ideal" Pattern No Opportunity Costs $119,127	3.52	4.61	1.19	1.56	0.40	0.52
	8. "Ideal" Pattern $2/hr. Opportunity Costs $167,030	4.94	6.47	1.67	2.19	0.56	0.73

FIGURE 15

COMPARING THE COSTS AND BENEFITS



KEY TO FIGURES 16-18

Management Policy Identification

I Institutional care - whole life

II Group Home care - whole life

III "Ideal" mix of services - see text (includes $2/hr. Opportunity Cost)

IV Family Home - whole life (includes $3/hr. Opportunity Cost)

V Present patterns of care - see text

VI "Ideal" mix of services - see text (No Opportunity Cost)

VII Family Home - whole life (No Opportunity Cost)

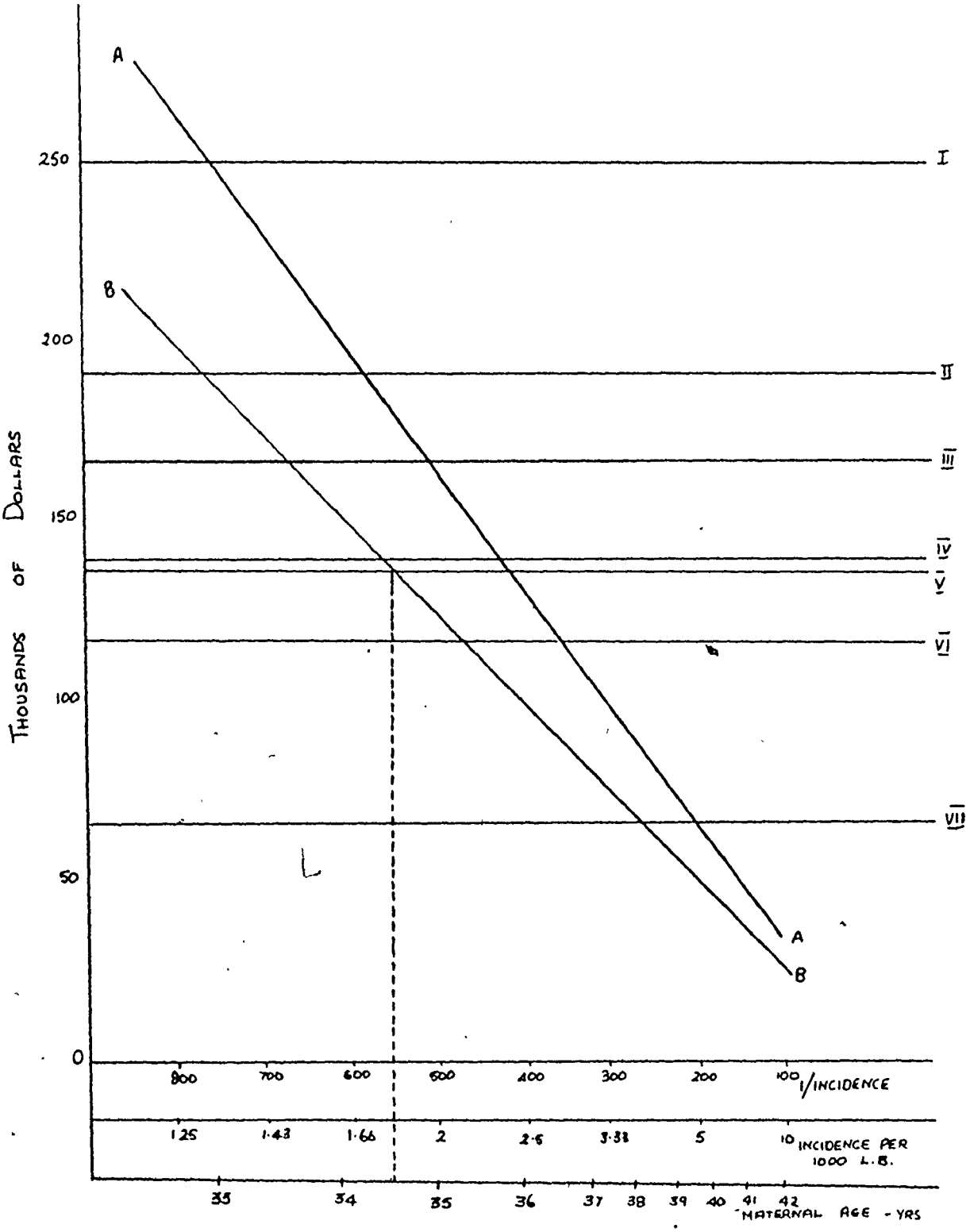
Laboratory Diagnostic Policy Identification

A. All parents karyotyped routinely

B. Parents karyotyped as required (estimate 10%)

FIGURE 16

A COMPARISON OF THE COSTS AND BENEFITS ASSOCIATED WITH A PROGRAM TO PREVENT DOWN'S SYNDROME - CHOSEN DISCOUNT RATE



care under "present patterns", the critical incidence rate is seen to be at approximately 1 in 550 live births (L.B.), which is the theoretical incidence for women of 34.5 years of age.

Thus, from a purely economic viewpoint one may advocate a prenatal screening program for all pregnant women aged 35 years or more.

Although the interpretation of the data is complicated by the existence of the various laboratory and management policies, consideration of the different policies allows individual decision-makers to examine the economic implications of their individual choices, e.g. administrators of the Toronto Antenatal Diagnosis Clinic can easily see the economic implications of routinely performing parental karyotypes. The adoption of this policy means that the "benefit" equal the "costs" at an incidence of approximately 1/400 L.B.

The effect of using higher discount rates to determine the present value of the "benefits" is shown in Figures 17 and 18. Using a discount rate of 5%, the point at which the costs and benefits are equal for "present patterns of care" and Policy B is at an incidence of 1 in 385 L.B., an incidence rate which occurs at a maternal age of approximately 36 years. (Fig. 17)

Alternatively, the choice of a discount rate of 8% results in the costs and benefits being equal at an incidence of 1 in 275 L.B. which is found at a maternal age of 38 years.(Fig.18) It is clear that the determination of the minimum maternal age at which a prenatal diagnosis is economically feasible is fairly sensitive to the choice of discount rate. However, for the reasons outlined earlier in this chapter, it is considered that the choice of a 9% inflation rate and a 12% discounting

FIGURE 17

A COMPARISON OF THE COSTS AND BENEFITS ASSOCIATED WITH A PROGRAM TO PREVENT DOWN'S SYNDROME - 5% DISCOUNT RATE

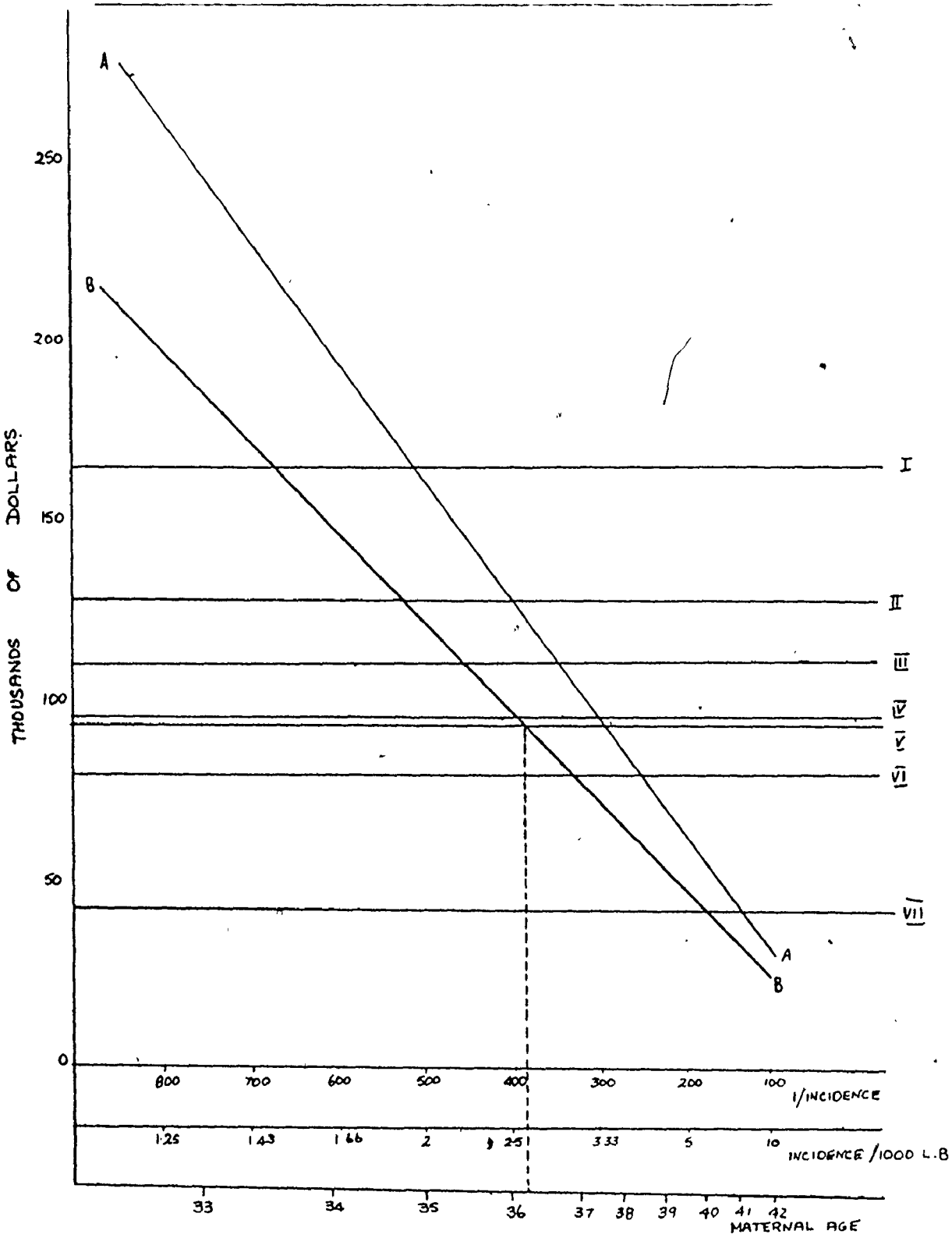
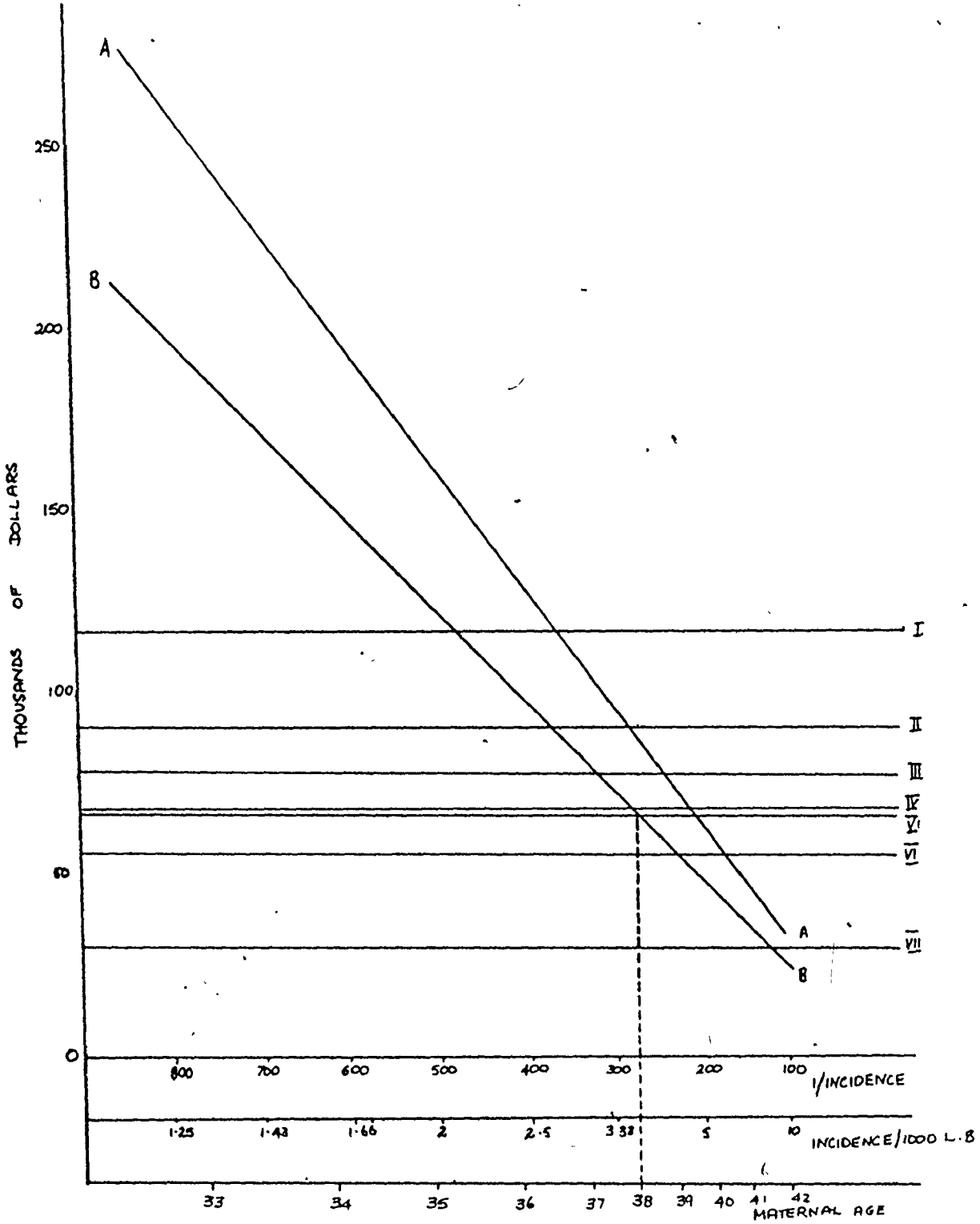


FIGURE 18

A COMPARISON OF THE COSTS AND BENEFITS ASSOCIATED WITH A PROGRAM TO PREVENT DOWN'S SYNDROME - 8% DISCOUNT RATE



rate represent the most appropriate choices for this study and on this basis one can state that a prenatal diagnostic program to prevent Down's Syndrome is economically justifiable for all women over 35 years of age.

It is tempting to expand the benefit-cost matrix in this analysis to develop precise numerical benefit-cost ratios for all the various combinations but review of all the costs and benefits that were enumerated in Table 16 emphasizes the importance of those items which were not monetized in this analysis. In fact, subjective assessment of the "intangible" benefits and costs may make the monetized benefit-cost analysis appear too stringent. As one investigator has said: "The life long care of severely retarded persons is so burdensome in almost every human dimension that no preventive program is likely to outweigh the burden."

If the "intangible" benefits are thought to greatly exceed the "intangible" costs a decision may be made to provide a prenatal diagnosis program for still younger women than that suggested by the monetized B/C ratio. (34-35 years)

The Effect of a Selective Screening Program on the Incidence of Down's Syndrome

Although the incidence of Down's Syndrome is higher among older mothers, the proportion of Down's infants that are prevented by offering the service to "older" women will also be relatively low. The proportion of Down's Syndrome infants born to mothers at different ages is shown below. (1973 data)

Age Group	% All Livebirths	% D.S. Infants	Cumulative %
40 +	1.2	11.8	11.8
35 - 39	4.7	16.5	28.3
30 - 34	14.1	16.4	44.7
25 - 29	34.6	29.1	73.8
20 - 24	33.2	20.8	94.6
19 or less	12.3	5.4	100.0

However, since economic analysis shows that a program to prevent Down's Syndrome is extremely efficient among "older" women and becomes progressively less efficient with younger women, a preventive program should begin with screening this older group even though they produce a relatively small number of affected infants.

A program with the capacity to offer prenatal diagnosis to all pregnant women aged 35 years or more would have cost the province about $2.2 million in 1973 and would have prevented the birth of about 35 infants with Down's Syndrome. Alternatively, a program designed to prevent all 122 Down's Syndrome births in Ontario in 1973 (by screening all pregnancies) would have cost $31-41 million, depending on the laboratory policy chosen.

It should be noted that low compliance rates will affect the total cost of the program and the number of cases prevented but will not affect the cost-per-case identified in each maternal age-group.

Future Trends in Costs and Benefits

Prediction of the changes in"costs"and"benefits"that might occur are obviously both difficult and controversial. Nevertheless, some of the issues are worth exploring, even if only in a superficial

manner.

At the present time, prenatal diagnosis is only available to a very small proportion of women - about 3% of mothers over 40 years of age. If a decision is made to expand the program, a critical shortage of trained cytogenetic-technologists can be anticipated. Trained technologists will be able to demand higher salaries and this will be reflected in higher costs of case prevention, particularly since much of the culture cost is attributable to labour charges. On the other hand, expansion of the program may stimulate the development of new technology (computer methods, culture methods, prostaglandins, etc.) and so reduce the cost of case prevention.

As indicated earlier in this study amniocentesis is currently regarded as an experimental procedure and patients are very carefully assessed and counselled prior to amniocentesis. The procedure itself is generally performed by an obstetrician with a particular interest and expertise in performing amniocenteses. Under these circumstances it is apparent that the test carries a very low risk and is highly sensitive and specific.

It is possible that with expansion of the program it will be impossible to maintain this type of service and some of the activities may be delegated to junior or paramedical professionals. While this can be expected to decrease the cost of prenatal diagnosis, it is impossible to predict what effect such changes might have on the risks, safety and accuracy of the test, and it is important that close surveillance of the programs be continued in order to establish the

optimal pattern of care.

The management of severely retarded children has changed dramatically over the past decade and further changes can be anticipated. The trend seems to be toward increased community participation and a wide variety of support services for the family has been proposed. Introduction of such services will increase the monetisable cost of raising a retarded child but may do much to minimize the intangible costs of family stress.

The calculation of opportunity costs in this analysis was obviously crude however it is clear that these costs represent a major "expense" to the family. If the Government of Ontario decides to provide these families with an extra allowance as is done in Sweden this will result in a further increase in the actual costs of care and in the public contribution towards the cost of raising a retarded child.

The proportions of the age-specific costs that are contributed by the "public purse" in each of the three environments is shown in Table 39. From this table it can be seen that a substantial portion of the total costs are borne by parents who care for their child at home, particularly, in the later years of childhood. If opportunity costs are considered, an even larger proportion of the costs are borne by the family. This situation contrasts with the findings for persons cared for in group homes or institutions where almost all the costs are public costs. It would seem that the major economic effect of the trend away from institutionalization and towards family-based care for severely mentally retarded children has been to shift the costs from the public sector to the private sector.

TABLE 39

PERCENTAGE OF COSTS THAT ARE "PUBLIC" COSTS

AGE	FAMILY HOME			GROUP HOME	INSTITUTION
	0	2	5		
0	93	36	19	100	100
1	82	14	6	99	100
2	82	14	6	99	100
3	96	53	32	100	100
4	96	53	32	100	100
5	95	51	30	100	100
6-11	75	41	24	99	99
12-14	49	34	23	96	97
15-17	47	32	22	96	97
18-71	62-66	52-56	44-45	96	97

Administrative Considerations

The characteristics of the procedures and the shortage of trained personnel suggest that a prenatal diagnosis program should be organized on a regional basis. Should the demand for the test exceed the capacity of the laboratories, a reasonable method of controlling demand might be to select a specific maternal age as an admission criteria in such a way as to match the laboratory's capacity. As the laboratory's capacity expands the minimum maternal age can be progressively reduced until the chosen "cut-off" age is reached. The capacity of a regional laboratory should be planned bearing in mind the trends in age-specific fertility rates and the absolute numbers of births in each maternal age group and the characteristics of an efficient laboratory.

It is of interest that the decline in age-specific fertility rates has been so marked that if laboratories been built and equipped 10 years ago to provide prenatal diagnosis for all women over 40 years of age, the same laboratories would be able to serve all women over 35 years of age now.

Distributional Effects

Since one of the objectives of good government is the attainment of equity, the policy maker is usually concerned about the distributional effects of a proposed program. It would obviously be unacceptable to provide a program which benefits a segment of the population already in a favoured position.

Epidemiological studies have shown that the incidence of Down's Syndrome is independent of socio-economic status, race or geographic location and that the major criterion for entrants into a program to

prevent the syndrome should be advanced maternal age. There is a possibility of maldistribution in such a program if women of lower socio-economic classes have fewer children in the later child-bearing years, if they first seek prenatal care after the 16th week of pregnancy, if their doctors are not aware of the existence of the program or if consumer awareness of the program varies by socio-economic class.

At the present time many doctors responsible for the care of woman during pregnancy are not aware of the availability, safety and sensitivity of prenatal diagnosis by amniocentesis and cell culture. Although the proportion of women aged 40 and over who are being referred for amniocentesis is small (approximately 2.5%) it should be emphasized that the existing programs have a very limited capacity and could not handle amniotic cell culture and analysis for the entire pregnant population over 40.

If facilities are expanded however, it will be important to ensure that all doctors providing prenatal care are made aware of the potential of the program for their patients. In addition, an argument can be made for increasing consumer awareness of both the risks associated with pregnancy at advanced maternal age and of the availability of a program which can enable them to selectively bear chromosomally normal children if their risk of chromosomal disease is unacceptably high.

Equal availability does not necessarily imply equal utilization of the program. It is to be expected that women from differing backgrounds will vary in their personal interpretation of the risks they face and it may well be that the utilization of the service will vary

within population sub-groups. Since individual values are strongly influenced by the climate of social opinion, personal decisions can be expected to change with changing social opinion over time. Despite these external sources of variation, it is important that the service itself be presented in such a way as to be equally available and accessible to all who might benefit from it.

CHAPTER FOUR

SUMMARY AND CONCLUSIONS

The findings of this thesis can be conveniently summarized using the format outlined in the Introductory Chapter, where it was stated that in an evaluation of a program providing prenatal diagnosis and selective therapeutic abortion in order to prevent the birth of infants affected with Down's Syndrome, one should attempt to ensure that:

A) the disorder to be prevented is serious and cannot be treated successfully,

B) the disorder is quantitatively significant in our society,

C) the diagnostic procedure meets acceptable criteria for safety, sensitivity and specificity,

D) the preventive measure is safe and acceptable,

E) the procedures are compatible with existing moral, legal and ethical standards,

F) the service is economically feasible, and

G) the service is administratively feasible in terms of the availability of equipment and personnel.

The findings of the thesis with respect to each of these areas are summarized below.

A) The disorder to be prevented is serious and cannot be treated successfully:-

Review of the literature indicates that Down's Syndrome is a

serious disorder for the individual, the family and society. The most incapacitating feature of the disorder is the severe mental retardation which characterizes all patients with the syndrome. Even with special education programs they remain dependent on others throughout their lives although most individuals can be taught to take care of their basic personal needs and as adults they can usually participate in the programs of sheltered workshops.

In addition to their mental handicaps,many individuals have serious physical handicaps. Congenital abnormalities affecting the heart, gastrointestinal tract, eye, brain, pelvis, teeth and endocrine glands are common. As children, these patients are particularly susceptible to infectious diseases,and degenerative disorders involving the heart and brain often develop prematurely in early adulthood.

Despite the presence of serious physical handicaps, life-expectancy for affected individuals has increased dramatically over the past few decades. Whereas adults with Down's Syndrome used to be uncommon, it is now apparent that the majority of these patients will survive into adulthood and that a substantial proportion can be expected to reach the sixth decade of life.

Priorities in the organization of care for all mentally retarded individuals have undergone major changes in recent years. The emphasis now is on community-based rather than institutional care and parents are encouraged to care for their retarded child in the family home for as long as possible. Special educational and employment facilities are available in most large towns and cities, and small

group-homes providing residential care for retarded adults are also to be developed in the community. The changes in the patterns of care may have done much to improve the quality of life for individuals with Down's Syndrome but unfortunately the underlying disorder remains irreversible.

B) The disorder is quantitatively significant in our society:-

Down's Syndrome is also a quantitatively serious disorder in Ontario. It is the most common diagnostic entity responsible for severe mental retardation and it accounts for 25-35 percent of persons in this category. Approximately 120 infants with Down's Syndrome are born in Ontario each year and crude estimates suggest that there are between 9,000 and 12,000 affected individuals in the province.

Despite a great deal of research, the cause of Down's Syndrome is unknown. The most striking epidemiological finding of this disorder is its strong association with advancing maternal age- the overall incidence of the disorder in Ontario is approximately 1/1,000 live births but the age-specific incidence rises rapidly from 1.15/1,000 live births in women aged 30-34 years to 9.93/1,000 live births in women aged 40-44 years. Although other "high-risk" characteristics have been identified, "advanced" maternal age remains the only useful criterion for predicting the probability of the birth of most infants with Down's Syndrome.

C) The diagnostic procedure meets acceptable criteria for safety, sensitivity and specificity:-

Experience in Canada and the United States suggests that the diagnostic procedures of ultrasound examination and amniocentesis are both safe and reliable when performed by experienced personnel. The

use of ultrasound to localize the placenta prior to amniocentesis appears to increase the safety of the procedure and the efficiency of cell culture.

Successful amniotic cell culture requires meticulous attention to detail and the use of several techniques designed to anticipate and prevent culture failure. Despite the potential difficulties of cell culture, established centres have success rates of over 90%. Chromosome interpretation may also present diagnostic dilemmas but,once again, it is clear that established centres can provide reliable prenatal diagnosis for Down's Syndrome with sensitivity and specificity rates approaching 100%.

D) The preventive measure is safe and acceptable:-

Mid-trimester therapeutic abortions are associated with some maternal morbidity and mortality-complications have been minimized by careful attention to technique and at the present time the risks of a therapeutic abortion are probably less than the risks of a full-term delivery, particularly for mothers over 35 years of age.

E) The procedures are compatible with existing moral, legal and ethical standards:-

The moral, legal and ethical problems raised by prenatal diagnosis and selective therapeutic abortion are possibly the most difficult to deal with. Under Canadian law, a selective therapeutic abortion indicated on the basis of a prenatal diagnosis of Down's Syndrome is permitted if the mother-s health is considered to be seriously endangered by the pregnancy. There is evidence that a large proportion of the population would favour amendments to the law so

that abortions would be expressly permitted for conditions like Down's Syndrome.

Few people would consider abortion to be the ideal method of preventing the birth of severely handicapped children. However, in the absence of any other effective method of prevention many people would consider that a therapeutic abortion is morally preferable to knowingly producing a child with the serious and irreversible handicaps associated with Down's Syndrome.

F) The service is economically feasible:-

The technique used to examine the economic feasibility of the proposed prenatal diagnostic program was cost-benefit analysis. Using this approach, the costs associated with identification and abortion of an affected fetus were compared with the life-time costs that would have been incurred in the absence of a preventive program. This latter amount, the costs foregone, is equal to the "benefits" for the purposes of the analysis.

The costs of offering a diagnostic service to population groups in various "risk" categories were compared with cost of caring for an affected individual in a variety of residential settings.

In order to make the analysis manageable several simplifying assumptions were made. These included:

i) 100% sensitivity and specificity for the procedure of prenatal diagnosis,

ii) No significant maternal or fetal morbidity or mortality associated with amniocentesis,

iii) No maternal morbidity or mortality associated with a mid-trimester abortions in excess of that associated with full-term delivery,

iv) 4% "dry taps" and 4% "failed culture" rates, both requiring repeat amniocentesis,

v) Food, clothing, and shelter costs similar to those of a normal child,

vi) Health care costs three times greater than those for the general population until the age of 15 years,

vii) Productivity similar to that observed at the Sheltered Workshop in Hamilton, Ontario,

viii) Life expectancy similar to that predicted by the life-table developed for this thesis, with an average life expectancy of approximately 34 years,

ix) An inflation rate of 9% and a discounting rate of 12% which give a 'real' discounting rate of 2.75% ('Real' discount rates of 5% and 8% were also included in the analysis for comparison purposes),

x) No specific participation rates were used although it is assumed that the service will be sought by a sufficient number of parents in each centre for the laboratories to operate at the optimal level of 450 analyses/year.

Under these assumptions it was found that the monetisable benefits of the program exceed the monetisable costs of offering prenatal diagnosis to all pregnant women over 35 years of age. Consideration of those effects which cannot be monetised suggests that the

service should be offered to even younger women. In addition, the possibility of downward trends in the costs of chromosome analysis and therapeutic abortion and upward trends in the costs of life-time care may also tend to favour extending the availability of the service to younger women.

G) The service is administratively feasible in terms of the availability of equipment and personnel:-

The characteristics of the diagnostic procedures support the development of regional centres for prenatal diagnosis. If the program is offered to all pregnant women aged 35 years or over a significant shortage of all the personnel involved can be anticipated. The shortage of appropriately trained technologists is likely to be particularly serious. If we assume that:

i) 90% of pregnant women aged 35 years or over will wish to participate in a prenatal diagnostic program and

ii) the total number of births in this age group remains steady at the 1973 level (7,133 live births)

the performance of cell culture and chromosome analysis would require the services of 14 senior, and 28 junior technologists. In Ontario at present there are five small amniocentesis laboratories providing prenatal diagnosis of chromosomal disorders. Thus, a service available to all pregnant women aged 35 years or over is not administratively feasible at the present time - in fact it would be impossible to provide a service to all pregnant women over 40 years of age with the present personnel and facilities.

Since the incidence of Down's Syndrome is so closely related to maternal age, the use of successive maternal ages as admission criteria will allow the service to be phased-in in an orderly manner, in keeping with patient demand and the availability of the necessary personnel.

In summary, prenatal diagnosis for Down's Syndrome represents a major advance in the management of this serious handicapping disorder. The evidence presented in this study supports those who consider that this procedure should now become an established component of routine prenatal care for those "older" women who wish to selectively bear chromosomally normal infants.

The precise definition of "older" will depend on which constraint is being considered. On humanitarian grounds one may consider 30 or even 20 years to be "older", whereas on economic grounds "older" may be defined as 35 years and over. Administrative feasibility is the limiting factor at the present time, and on administrative grounds "older" may be defined as 40 years and over.

The extent to which parents will accept the offer of prenatal diagnosis is not easy to predict at this stage: it is likely that there will be a great deal of individual variation, dependent on the parents' perception of the risks, cultural, religious and educational background, and on the availability, accessibility and social acceptability of prenatal diagnosis and selective therapeutic abortion.

For parents, prenatal diagnosis offers the freedom to reproduce without the fear of producing an infant who is seriously and irreversibly handicapped by a disorder like Down's Syndrome. This freedom is already

available to a few privileged parents. It seems reasonable to offer it to many more.

APPENDIX A

ALERTS TO THE POSSIBILITY OF DOWN'S SYNDROME FROM THE PHYSICAL EXAMINATION

		% frequency Down	Normal
CRANIUM	flat occiput/brachycephaly	75-80	<1
FACE	flattened profile	90	2.5
EYES	epicanthal folds	40-80*	5-10
	upslanted palpebral fissures	80-85	<1
	Brushfield spots	50-70*	5-17
NOSE	small	?	?
	depressed bridge	60-80*	7
MOUTH	high-arched/narrow palate	70	?
	protruding tongue	45	?
EARS	small	75	5-10
	folded/squared-off helix	65	5-10
NECK	short	70	<1
	excess skin-fold in back	75-80*	<1
ABDOMEN-ANUS	umbilical hernia/diastasis recti	?	3
	duodenal atresia	8	.01
UROGENITAL	cryptorchidism (up to 1 year)	25	<1
LIMBS	short (mild)	70	?
JOINTS	hyperflexible	50-80*	5-10
HANDS & FEET	short/broad	60-70	?
	short/incurved 5th finger	50-60	~1
	simian crease	50	4
	wide-space 1st to 2nd toe	45-65	?
	deep plantar furrow	25	?
NERVOUS SYSTEM	hypotonia	20-80*	?
	absent Moro reflex	80-85*	?
CARDIOVASCULAR	congenital defect/murmur	40	<1

*decreases with age. The upper limit of the range refers to the frequency in newborns.

Compiled by: M. Preus, 1976 for the interns and residents of the Montreal Children's Hospital.

APPENDIX A (Cont'd)

THE PROPORTION OF INFANTS WITH DOWN'S SYNDROME MANIFESTING THE 10 BEST CLINICAL SIGNS[16]

Simian Crease	42%
Head Circumference 32 cm.	43%
Tongue Protruding	53%
Gap Between Toe One and Two	67%
Epicanthus	76%
Dysplastic Ears	78%
Flat Face	80%
Hypotonia	82%
Mouth Corners Turned Downward	84%
Abundant Neck Skin	94%

APPENDIX B

CULTIVATION OF CELLS FROM AMNIOTIC FLUID (TORONTO)

Sample Collection

Amniotic fluid is obtained under sterile conditions in the operating room, either by transabdominal amniocentesis or during a hysterotomy.

The fluid is placed in a sterile disposable tube and transported at ambient temperature to the laboratory.

Setting up Cultures

For biochemical testing and karyotyping:

(i) Use one 100 mm tissue culture dish for each 7 ml amniotic fluid (AF).

(ii) Carefully resuspend AF cells in the fluid with a Pasteur pipette.

(iii) Place 7 ml AF in each 100 mm dish, or divide sample in half. Label dishes A and B.

(iv) Add 7 ml tissue culture medium (medium[1] with 15% fetal calf serum v/v, 100 units penicillin per ml, 100 ug streptomycin per ml, and fungizone 2.5 ug per ml).

(v) Incubate undisturbed in CO_2 incubator at 37°C for 48-72 hours.

(vi) Feed on Monday, Wednesday and Friday, until ready for subculture (approx. 14 days for karyotyping and 21 days for biochemical assay).

Feeding

Remove medium from plates with suction. On the first feed, do not suck chamber dry. If AF was bloody, do not disturb the film of blood on the first feed. However, on the subsequent feeds, wash blood off with stream of medium and suck it out.

Add 10 ml of medium into 100 mm plates: 3.5-4 ml medium per single chambered Lab-Tek dish.

APPENDIX E (Cont'd)

Karyotyping of Amniotic Fluid Cells

Karyotyping of amniotic fluid cells is done on cells which are still fastened to the slide of the Lab-Tek dish. When several actively dividing cells are seen, they are ready to harvest. This is usually 24-48 hours after they have been subcultured into the Lab-Tek dish.

(i) .3 ml colcemid is added to a single chambered Lab-Tek dish and allowed to incubate for 1½ to 2 hours.

(ii) Carefully suction off all the medium using a Pasteur pipette and add drop by drop 2 ml of 0.17% sodium chloride in distilled water heated to 37°C. Incubate slides for 26 minutes starting upon the addition of hypotonic.

(iii) Set clock for 15 minutes. Add 1 ml of fresh fixative (methanol 3 parts: glacial acetic acid 1 part) drop by drop from a burette, rotating the slide gently. Remove 2 ml and allow to sit for the remainder of the 15 minute period.

(iv) Add 1½ ml fixative for each of 3 further 15 minute periods, removing 1 ml of solution after each addition of fixative.

(v) When fixation is complete, remove chamber from slide. Wash slide with fresh fixative and give one good blow and rest on a hot plate until dry. Temperature of the hot plate is not calibrated but it will raise the temperature of the water in a beaker to 75°C.

(vi) Hydrolyze in fresh 1 N HCl (198 ml distilled water + 18 ml concentrated HCl) at 60° for 5 minutes. Let slide dry.

(vii) Stain with freshly diluted Giemsa (37.5 ml distilled water + 4.25 ml Giemsa + 1.8 ml of 0.15 normal ammonium hydroxide per Coplin jar) for 4½ minutes. Take slide through 2 changes of acetone, 1 of acetone : xylene (1:1) and 2 changes of xylene, giving the slide 10 dips in each dish. Mount coverslip with Permount.

Analysis

1. Initially 2 slides per patient are made: one from Petri dish A, one from B.

2. 15 cells are counted using both slides. 5 cells are analyzed. Small acrocentrics are recorded in all 15 cells. At least 2 solid stain and 1 banded spread are photographed and karyotyped.

3. If the fetus is a male, the study is complete.

APPENDIX B (Cont'd)

4. If the fetus is a female, a further 15 cells are counted and the small acrocentrics recorded. Further slides are made if necessary.

Additional Components of the Genetic Amniocentesis

A. Mycoplasma Testing: all samples are tested for mycoplasma and T strain on arrival in the laboratory. If cytogenetic mosaicism is found, a further sample is submitted for Electromicroscopy and culture for mycoplasma and T strain.

B. Chromosome studies on parents: all parents have blood drawn for cytogenetic study during their visit to the Antenatal Genetics Clinic. Ideally, 5 cells are counted and 2 analyzed, photographed and karyotyped, one solid stain and one banded, prior to amniocentesis.

C. All amniocenteses are preceded by ultrasonic localization to rule out twin pregnancy and localize placenta.

D. All abnormal lines are frozen down until confirmation of diagnosis has been made. All normal biochemical amniocenteses lines are frozen until term in case a misdiagnosis has been made.

APPENDIX C

THE COST OF AMNIOTIC CELL CULTURE AND KARYOTYPE PREPARATION

450 ANALYSES/YEAR

ITEM 1 VARIABLE COSTS

200 mls. medium cont. calf serum @ $13.00/litre	$ 2.60
20 mls. phosphate buffered saline @ $5.00/litre	0.10
3 mls. trypsin @ $40.00/litre	0.12
50 mls. fixative @ $2.00/litre	0.10
amtibiotics, antimycotics, sterility testing	3.00
2 x 100 mm. falcon tissue culture dishes @ $0.20 each	0.40
4 x Lab Tek slides (single chamber) @ $0.88 each	3.52
2 x pasteur pipettes @ $0.05 each	0.10
1 x sample bottle (siliconized)	0.60
6 x photographic paper (B/W 8" x 10") @ $19.75/100	1.18
35 mm. B/W photographic film	1.00
Miscellaneous - 70% isopropanol, roccal solution (cleaning) hypotonic saline, normal HCl, Giemsa stain, xylene, acetone colcemid, permount, coverslips	$ 3.00
	$15.72

ITEM 2 EQUIPMENT COSTS
(prices from Toronto Laboratory Administrator and Fisher 1975 catalogue)

Laboratory with 3 technologists

2 x incubators @ $1,500 each	$ 3,000
1 x still to give pyrogen free deionized water	350
1 x horizontal laminar flow hood (Biohazard)	4,700
1 x refrigerator	600
1 x centrifuge	800
3 x photomicroscopes @ $5,000-$12,000 each	$15,000-$36,000
1 x inverted microscope	2,500
1 x water bath	500
1 x hot plate	50
Darkroom equipment	
1 x darkroom light (model D with filter)	$ 60
1 x B66 Omega Enlarger with 50 mm. lens	300
1 x dryer	35
Miscellaneous (tongs, gloves, etc.)	20
Total	$27,915-$48,915

APPENDIX C (Cont'd)

THE COST OF AMNIOTIC CELL CULTURE AND KARYOTYPE PREPARATION

450 ANALYSES/YEAR

ITEM 3 ANNUAL LABORATORY OPERATING COSTS

Carbon-dioxide tanks 25 tanks @ $12.00 each		$ 300
Miscellaneous - Paper, coplin jars, 10 ml. pipettes, burettes, storage jars, etc.		400
Photographic fluids		100
Photographic trays 5 every 2 years @ $4.00 each		10
Photographic storage jugs 5 every 5 years @ $4.50 each		5
	Total	$ 815

ITEM 4 LABOUR COSTS

1 x senior technologist @ $12,000 p.a. plus 15% fringe benefits		$13,800
1 x junior technologists @ $10,000 p.a. plus 15% fringe benefits		23,000
	Total	$36,800

ITEM 5 SPACE

500 sq. ft. serviced laboratory space @ $5.00/sq.ft.		$ 2,500
60 sq. ft. serviced darkroom space @ $5.00/sq.ft. (tubs are included in this price)		300
	Total	$ 2,800

APPENDIX D

REVIEW OF THE DATA PROVIDED BY THE
HURONIA REGIONAL CENTRE, ORILLIA - 1974-1975

- Number of patients with a clinical diagnosis of Down's Syndrome - resident at the H.R. Centre = 207

- Number of patients with a clinical diagnosis of Down's Syndrome who have been discharged since 1969 ..... = 118

Patient Category	No. of Cases	Mean Maternal Age at Birth of D.S. Child (S.D.)	Mean Age of Child at Admission (S.D.)	Correlation Coefficient	P Value
Discharges	118	34.79 (6.97)	10.66 (9.98)	0.092	$\sim .3$
Residents	207	33.29 (7.71)	7.5 (5.9)	0.092	$\sim .2$

Conclusion: Since there is not a significant correlation between a mother's age at birth of her D.S. child and the age at which that child is institutionalized - the life-time cost raising a child with Down's Syndrome was assumed to be independent of maternal age.

The Age at Admission by Sex and Time Period

Time Period	Mean Age at Admission Males	Females	P Value (Diff.)
1960-64	6.81	7.50	$>.10$
1965-69*	6.30	8.53	$>.10$
1970-74**	10.19	10.50	$>.10$

*1 female patient admitted at the age of 39 years was excluded from the analysis.

**2 males admitted at the ages of 43 and 45 years were excluded from the analysis.

APPENDIX D (Cont'd)

Conclusion: There is no significant difference between the age at admission for males and females with Down's Syndrome for those patients who are admitted before the age of 30 years.

Note: The increase in the mean age at admission noted for the time period 1970-74 is probably largely attributable to policy changes. No children under 5 years of age have been admitted since 1970.

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