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A study of the three most common chromosome trisomies,21 (Down Syndrome), 18 (Edwards Syndrome) and 13 (Patau Syndrome)

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A STUDY OF THE THREE MOST COMMON CHROMOSOME TRISOMIES, 21(DOWN SYNDROME), 18 (EDWARDS SYNDROME) AND 13 (PATAU SYNDROME).

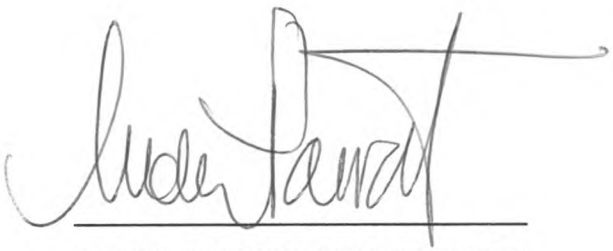
NICOLA MORGAN PARROTT.

A Research Report submitted to the Faculty of Medicine, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the Degree of Master of Science in Medicine.

Johannesburg 1997.

DECLARATION

I declare that this research report is my own, unaided work and I have given full acknowledgement to the sources I have used. It is being submitted for the degree of Master of Science in Medicine at the University of the Witwatersrand Medical School, Johannesburg. It has not been submitted before for any degree or examination in any other university.



NICOLA MORGAN PARROTT

12th day of December 1997.

To my mother and father,

Angela and John Parrott.

For all the love you've shared

and all the support you've given,

THANK YOU.

ABSTRACT

In 1959 Lejeune and his colleagues first demonstrated a chromosome abnormality and showed that "infant mongoliens" had 47 instead of the normal 46 chromosomes in their body cells. Recent studies show that about 1 in 200 infants have recognisable chromosome abnormalities. Trisomy 21 (Down syndrome, DS), trisomy 18 (Edwards syndrome, ES) and trisomy 13 (Patau syndrome, PS) have been found to be the most common trisomies with population incidences of approximately 1 in 650, 1 in 8000 and 1 in 10000, respectively.

Since no detailed study of the three most common trisomies had been carried out in the Johannesburg and Soweto areas, the writer was motivated to investigate the local situation. The aims of the present study were to:
1)determine the incidence, ethnic distribution, annual fluctuation, sex ratio and types of each trisomy; 2)assess the utilisation of the Genetic Counselling Clinics and prenatal diagnostic services by parents of affected children, and 3) gain insight into how a couple copes with an affected infant by interviewing them in their own home.

A thirteen year period from January 1976 to December 1988 was selected, since this time period provided a large sample and the records of these years were well kept and easily accessible to the writer in the Cytogenetics Department at the South African Institute for Medical Research. During these thirteen years, 15359 blood specimens were successfully cultured and karyotyped and results were recorded. These records were studied and the information on DS, ES and PS cases, relative to the aims of the study, was extracted and analysed. At the same time, data from the records on chromosomal studies on amniotic fluid

were collected over a retrospective three year period (January 1986 to December 1988). A total of 3038 amniotic fluid samples were successfully cultured and karyotyped in this period. From the available records the writer extracted the cases with DS, ES and PS and analysed the information. To enrich the purely statistical information, a case study of a Down syndrome child was included in the project. The progress of the infant and the parents was followed for one year and the family was visited and interviewed with a specifically constructed questionnaire on four occasions.

The results of the present study showed that the incidence rate for DS in the total population for the period under review was 1:885. The incidence rates for DS in the White, Black and Coloured and Indian groups (together) were, 1:615, 1:955 and 1:1516, respectively. For ES, the prevalence rate in the total population was 1:10407 and in each population group, White, Black and Coloured and Indian (together), it was 1:9786, 1:9640 and 1:18948, respectively. For PS, the incidence rate in the total population was 1:25274 and in each of the three population groups, it was 1:63609, 1:19279 and 1:37896, respectively. The annual fluctuations in the rates of DS and ES were similar, with highest incidence for both DS and ES, in the total population, being in 1977. The highest incidence of DS occurred in the white population group whereas the highest incidence for PS occurred in the Black population.

When all the population groups were considered together, the incidence, annual fluctuation, and sex ratio in both blood and amniotic chromosomal studies, correlate with those found in both other South African and world wide studies. DS in the Black population, however, may be underdiagnosed and the incidence rate may therefore be too low. The majority of DS, ES and PS cases were of the nondisjunction type and translocations rarely occurred. This finding is also similar to the published

data. However, the high incidence of Mosaic cases found in the DS and PS cases still needs further investigation. There was poor utilisation of the genetic services, particularly by the black population, but this problem could be rectified by increasing the awareness and access for this group especially. The family with a DS child were initially shocked by the diagnosis but through their experience of the different stages of the coping process, they were able to reach psychological homeostasis. The author benefited from the interaction with the family and improved her understanding and the communication skills necessary for practical genetic counselling.

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- My mother, father, husband, two daughters and both brothers for the love, understanding and encouragement they gave me.

LIST OF ABBREVIATIONS

DS	Down syndrome
ES	Edwards syndrome
PS	Patau syndrome
et al (Latin et alii)	And others
ie (Latin id est)	That is
SAIMR	South African Institute for Medical Research
eg (Latin exempli gratia)	For example
Jan	January
Dec	December
AgNOR	Silver staining nucleolar organising region
ASD	Atrial septal defect
VSD	Ventricular septal defect
PDA	Patent ductus arteriosus
RSA	Republic of South Africa
ref.	Referred
Cytogen.	Cytogenetics
Dept. of H & W	Department of Health and Welfare
MR	Mentally retarded
Chrom.	Chromosomal
hosp.	Hospitals
ind.	Individuals
Mat.	Maternal
No.	Number
exam.	Examination
F	Females
M	Males
TMI	Transvaal Memorial Institute
AMA	Advanced maternal age

χ^2	Chi-squared
(O - E)	Observed minus expected
%	Percentage
Incid.	Incidence
C & I	Coloured and Indian
Tot.	Total
DSA	Down syndrome association
"START"	Strive towards achieving results together

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CHAPTER 1

1. INTRODUCTION

1.1 INTRODUCTION AND MOTIVATION FOR THE PRESENT STUDY

Cytogenetic abnormalities have been clinically described since the 17th century (Levine, 1971). In 1857 Virchow first observed human chromosomes in dividing cells (Pei-yu, 1987) but it was not until 1956 that Tjio and Levan improved the techniques of spreading chromosomes enabling them to count the 46 chromosomes of a normal individual, accurately (Levine, 1971). Since then there has been a steady improvement in the ability to identify and analyse the fine structure of the individual chromosomes (Fraser Roberts and Pembrey, 1985). The availability of different banding techniques used in metaphase and prometaphase chromosomes, makes it possible to identify the 23 chromosome pairs of a normal individual or a chromosomal aberration in an 'abnormal' individual (Caspersson et al, 1970). A new era in medical genetics began in 1959 with the demonstration by Lejeune and his colleagues that 'infant mongoliens' (children with mongolism) had 47 chromosomes instead of the usual 46 in their body cells (Lejeune et al, 1959).

In a study done by Jacobs et al in 1974 on an unselected new-born population, more than 1 in 200 infants were found to have recognisable chromosome abnormalities. They also found that chromosomal abnormalities are common in spontaneous abortions and 50% of aborted foetuses are affected. Trisomy 21 (Down syndrome (DS)), trisomy 18 (Edwards syndrome (ES)) and trisomy 13 (Patau syndrome (PS)) have been found to be the most common trisomies (Harper 1993). Down syndrome has a

population incidence ranging from 1 in 650 (Harper, 1993) to 1 in 1200 livebirths (Mikkelsen, 1988), Edwards syndrome ranges in incidence from 1 in 6000 (Fraser Roberts and Pembrey, 1985) to 1 in 8000 (Harper, 1993) and Patau syndrome from 1 in 10000 (Fraser Roberts and Pembrey, 1985) to 1 in 24000 (Borovik et al, 1989) livebirths.

A literature search (discussed in more detail in the literature review), on studies done on chromosomal abnormalities in certain parts of South Africa (Venter and Op't Hof, 1982; Grace et al, 1979; Smart, 1981 and Nelson and Smart, 1982), suggests that the prevalence of DS, ES and PS is generally similar in South Africa to that found in other countries. However, since previous studies had been carried out on small samples in a limited fashion and since no detailed study of the three most common chromosome trisomies (ie. 21, 18 and 13) had been completed in Johannesburg, the writer was motivated to complete the present study.

1.2 SETTING AND SCOPE OF THE PRESENT STUDY

The city of greater Johannesburg and the satellite city of Soweto were chosen as the setting of the present study because of their accessibility and the fact that they were large enough to provide a reasonable-sized sample. These two cities had registered populations of 632,369 and 521,948 persons respectively (National Health and Population Development Department Annual reports, 1988). Together, both cities had a mean annual birth rate of 38,382 livebirths over the 13 year period used in the present study (National Health and Population Development Department Annual reports, 1976 - 1988).

Until 1986, the Cytogenetics Unit at the South African Institute for Medical Research (SAIMR), was the only laboratory in Johannesburg able to process blood and amniocentesis samples for cytogenetic analysis. The samples were sent in from Johannesburg, Soweto and other surrounding areas, as well as from other provinces in South Africa and neighbouring countries. After 1986, a few private laboratories eg. Van Drimmelen P, Grobler P J and Partners, Kempton Park, opened a cytogenetics section and a small percentage of samples were being processed in these laboratories at the time of the present study. Due to the high annual birth-rate in Johannesburg and Soweto, as well as the fact that the cytogenetic unit records were available to the writer, it was appropriate and feasible to obtain information on the three common chromosome trisomies for the present study. The study extended over a 13 year period from January 1976 to December 1988. All the records of the blood samples sent in for chromosome studies during this period were investigated to ascertain those in which a result of Trisomy 21, 18 or 13 was obtained. Within this 13 year time period, three years from January 1986 to December 1988 were selected for special attention and the trisomies detected on amniocentesis during this time, were ascertained.

In order for the writer to get exposure to the human problems associated with a trisomy, a case study of a White Down syndrome infant and his family, was undertaken. This study took place over a one year period.

1.3 AIMS OF THE PRESENT STUDY

The present study was primarily concerned with the collection and analysing of the available data on DS, ES and PS. The aims

of the study were:

1) To determine the incidence, annual fluctuation, ethnic distribution, sex ratio and types (trisomy, translocation or mosaic) of Down, Edwards and Patau syndrome, in blood chromosomal studies over a thirteen year period (Jan 1976 - Dec 1988).
2) To estimate the incidence, annual fluctuation, ethnic distribution and sex ratio of DS, ES and PS in amniotic fluid chromosomal studies over a three year period (Jan 1986 - Dec 1988).
3) To assess the utilisation of the Genetic Counselling Clinics and prenatal diagnostic services, over a three year period (Jan 1986 - Dec 1988), by families who had a child or foetus with DS, ES and PS detected on blood or amniocentesis, respectively.
4) To interview and describe a family with a Down Syndrome infant in order to gain some insight into how they coped with such an infant.

1.4 CONCLUSION

Due to the fact that data on the incidence of DS, ES and PS in blood and amniotic fluid samples were lacking in Johannesburg, the present study was set up to investigate this matter. The source of the material was the Cytogenetics laboratory at the SAIMR and the scope of the study extended over a 13 year period (January 1976 - December 1988). A family with a Down Syndrome child was studied to obtain insight into the psychological coping processes and psychosocial problems associated with having an abnormal child.

CHAPTER 2

2. LITERATURE REVIEW

2.1 INTRODUCTION

The present study involved investigations on the three most common chromosome trisomies which may result in live-born infants, namely, Trisomy 21, 18 and 13. This chapter describes chromosomal abnormalities in general and in order to gain a better understanding of each selected trisomy, a detailed description of all three is included.

Since 1959, when Lejeune et al demonstrated that what Langdon Down (1866) referred to as a mongol child, had 47 chromosomes instead of the normal 46 chromosomes, chromosomal abnormalities have become well defined causes of maldevelopment. Patients with chromosomal abnormalities usually have characteristic phenotypes and often have a similar resemblance to other affected individuals with the same abnormality. The phenotypic abnormalities result from a genetic imbalance, which generally occurs sporadically. The aetiology is usually unknown. The genetic defect, either due to a mutant gene or chromosome aberration, may alter the normal course of development of an individual, but little is known about how any specific imbalance produces its phenotypic consequences (Fraser Roberts and Pembrey, 1985). All autosomal abnormalities, regardless of which chromosome is involved and whether the chromosomal material is deleted or present in excess, are characterised by the following four factors, which in combination with one another may be defined as a 'syndrome' (Schinzel, 1984):

1. Intrauterine and postnatal growth retardation

2. A pattern of dysmorphic signs
3. Malformations (usually multiple) and
4. Impaired mental development.

Although it is not obligatory for all the above four factors to occur together in an individual with a syndrome, mental deficiency is the most consistently found feature (Schinzel, 1984).

A pattern of dysmorphic findings is the most useful parameter for clinical recognition of an individual case. Dysmorphic features are considered to be variants of normal shape and size and there is often no clear cut borderline between dysmorphic and normal. Dysmorphisms, in contrast to malformations, usually do not adversely affect the function of an organ, but play an aesthetic role. However it is sometimes difficult to differentiate between a dysmorphic feature and a malformation; an uvula bifida would be defined as a dysmorphic feature while a cleft of the soft palate would be a malformation (Schinzel, 1984).

Deviations from the normal chromosome complement can be grouped into those involving an abnormal number of normal chromosomes and those involving a structural change in one or more chromosomes (Thompson and Thompson, 1982). Either of these two types of deviations may on occasion lead to the same phenotypic results. Down syndrome, for example, may be caused by an extra chromosome occurring free in each body cell or by a Robertsonian translocation where an extra chromosome 21 is translocated onto another chromosome (Sutton, 1980), usually chromosome 14 or otherwise another chromosome 21 (Harper, 1993).

2.2 NUMERICAL CHROMOSOME ABNORMALITIES

An aberration of chromosome number may arise through the process of nondisjunction, which is the failure of paired chromosomes or sister chromatids to migrate properly during anaphase. Nondisjunction may occur either during the first or second meiotic division or mitosis (Thompson and Thompson, 1982). There are a number of causative factors that have been suggested for the nondisjunction event. These factors include the following : genes predisposing to nondisjunction (Penrose, 1961, Alfi et al, 1980), interchromosomal effects (Nielsen et al, 1974), parental mosaicism (Hsu et al, 1971), alpha-1-antitrypsin deficiency (Fineman et al, 1976), environmental agents, eg. viruses and irradiation (Stoller and Collman, 1965; Uchida et al, 1968), accelerated ageing in young mothers (Emanuel et al, 1972), maternal thyroid antibodies (Fialkow et al, 1971), seasonally and preovulatory overripeness (Jongbloet, 1971), delayed fertilisation (German, 1968) and physiological changes in the female reproductive tract (Ford, 1973). These postulated factors affecting the ovum after meiosis I - eg. changes in the female reproductive tract and delayed fertilisation - are generally discounted by the data indicating that errors are primarily in meiosis I (Dewald, 1987; Magenis, 1988). The error may, however, be due to one of the following phenomena:

a) asynapsis - failure of normal pairing of homologous chromosomes (Warren et al, 1987) and/or lack of chiasma formation (Magenis, 1988),

b) desynapsis - premature separation following normal pairing (Warren et al, 1987) in meiosis I,

c) actual nondisjunction where the homologous pair or the double stranded chromosome may fail to separate into chromosomes or chromatids (Fraser and Nora, 1975)

perhaps due to nucleolar persistence (Magenis, 1988),

d) anaphase lag - where one of the chromosomes may be late in reaching the pole of the spindle and be excluded from the newly formed nucleus (Sutton, 1980), in meiosis I or II or at mitosis.

2.2.1 First Meiotic Nondisjunction

A numerical chromosome abnormality may occur at the first meiotic division as the result of one of the following mechanisms:

a) **Asynapsis:**

In the very early stages of meiosis, a chromosome may fail to associate with its homologue. If the chromosome pair fail to associate, they will then lie free and segregate from each other at random during anaphase I of the first meiotic division. Should one pass to each pole of the spindle, normal gametes will be formed. Should both pass to one pole, four abnormal gametes will be produced; two gametes both with each chromosome of a given pair and two gametes with neither (Sutton, 1980).

b) **Desynapsis:**

If homologous chromosomes are correctly associated with one another, but fail to segregate properly at anaphase I or the first meiotic division, these same four abnormal gametes will be produced. Figure 2.I (page 9) shows how these four abnormal gametes are produced as well as the normal gametes from normal disjunction.

Actual nondisjunction or anaphase lag may also occur at the first meiotic division resulting in the same four abnormal gametes (Sutton, 1980).

2.2.2. Second Meiotic Nondisjunction

In the case of nondisjunction at the second meiotic division, the sister chromatids will fail to segregate properly at anaphase II and only two abnormal gametes will result: one having an extra chromatid, the other being nullisomy for the same chromatid (Fraser Roberts and Pembrey, 1985). Figure 2.2 (page 10) depicts how the two abnormal and two normal gametes are formed because of nondisjunction at meiosis II.

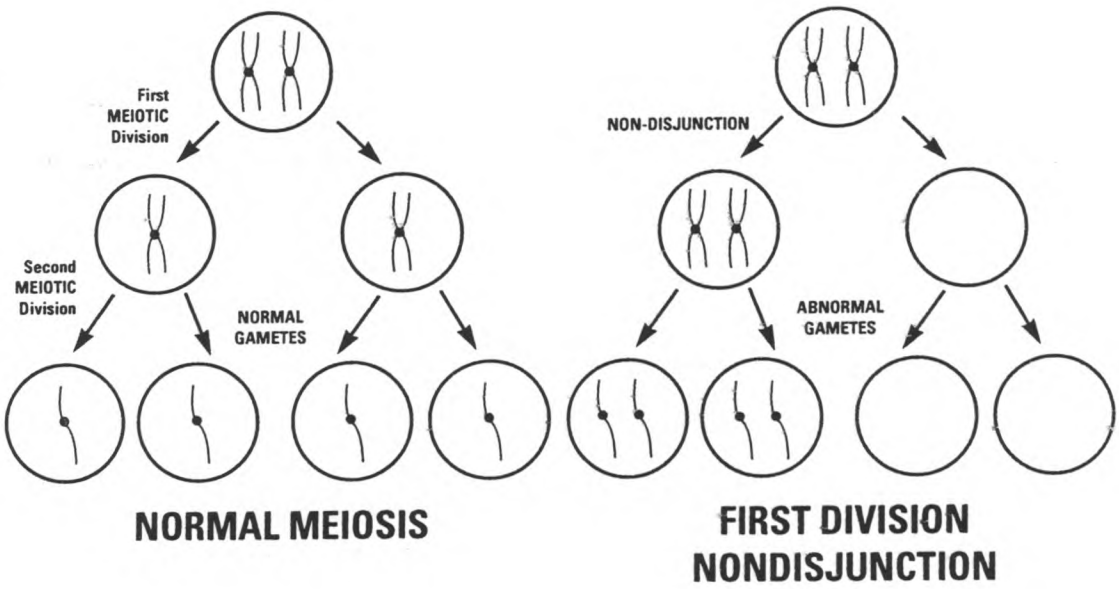


FIGURE 2.1 Nondisjunction at meiosis I resulting in four abnormal gametes (after Sutton, 1980).

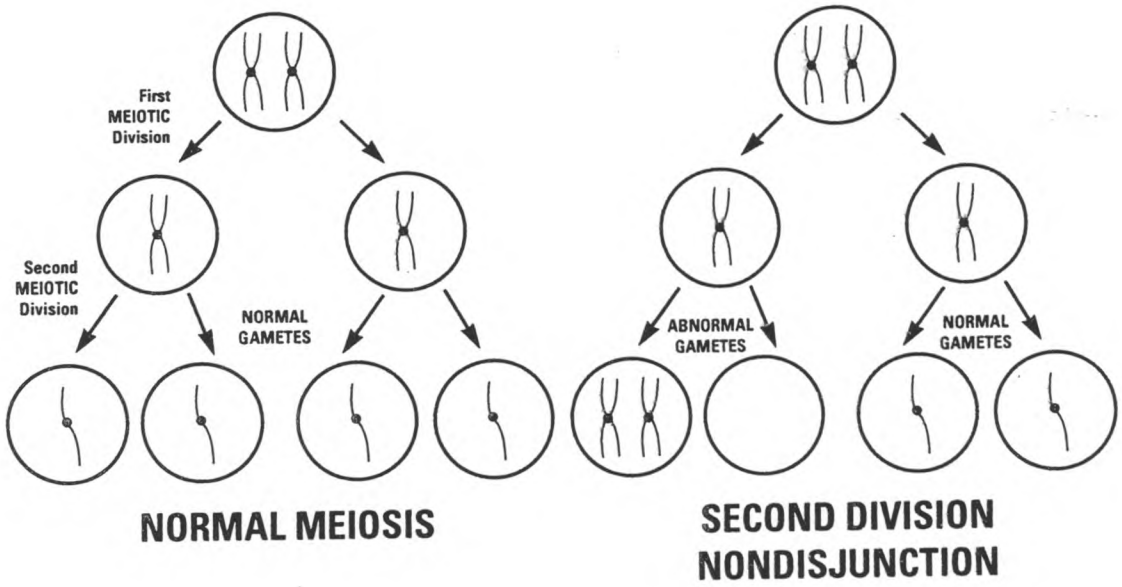


FIGURE 2.2 Nondisjunction at meiosis II resulting in two abnormal gametes (after Sutton, 1980).

2.2.3 Nondisjunction at Mitosis

Nondisjunction may occur at the first and second cleavage division of the cycle, i.e. during mitosis. If nondisjunction occurs at the first cleavage division, two abnormal gametes will result; one being a viable cell line having an extra chromatid, the other being nullisomy for the same chromatid, therefore nonviable. If nondisjunction occurs at the second or subsequent cleavage divisions, two or more cell lines with different chromosome totals may result (Fraser and Nora, 1975). Such an individual with more than one cell line is termed a 'mosaic' (Fraser Roberts and Pembrey, 1985).

Chromosomal mosaics usually have only two karyotypically distinct cell lines and usually whole chromosomes are involved (Clarke et al, 1989). The alterations in karyotype may either be numerical or structural. However, mosaicism involving an autosomal structural rearrangement is rare (Clarke et al, 1989).

Mosaic individuals may have any or all of the abnormalities associated with a particular syndrome or virtually no abnormalities at all, depending on the proportion of normal to abnormal cells and in which tissues the abnormal chromosome occurs (Sutton, 1980).

2.3 STRUCTURAL CHROMOSOME ABNORMALITIES

Structural aberrations result from chromosome breakage, followed by reconstitution in an abnormal combination. Chromosome breaks normally occur at a low frequency but may be induced by a wide variety of breaking agents (clastogens) such as ionising radiation, many chemicals (Vogel and Motulsky, 1986) and viral infections (Thompson and Thompson, 1982). Stable types of aberrations: deletions, duplications, inversions, translocations and insertions, resulting from breakage, are capable of passing through cell division unaltered. Unstable types such as dicentrics, acentrics and rings fail to undergo regular cell division (Thompson and Thompson, 1982) and are usually lost (Sutton, 1980). The only chromosomal anomalies that are likely to be transmitted from parent to child are structural rearrangements of the inversion, small deletion, translocation or isochromosome types (Thompson and Thompson, 1982).

2.3.1 Robertsonian Translocations

Centric fusions or Robertsonian translocations are the most

frequent rearrangements in humans (Schinzel, 1984). These translocations are named after W.R.B. Robertson, an American geneticist, born in 1881 (Stedman's Medical Dictionary). They occur when two acrocentric chromosomes break at or close to the centromeres on the long arm of one and the short arm of another and then fuse (Pei-yu, 1987). One translocation chromosome results, either a metacentric or dicentric as evidenced by C-banding (Pei-yu, 1987), formed by the long arms of two different or homologous acrocentrics (Schinzel, 1984). A smaller translocation product, containing the two acrocentric short arms, is found exceptionally in mosaics, but is usually lost. A rearrangement between the long arms of two acrocentric homologues evidently results from isochromosome formation and rarely from a translocation (Schinzel, 1984).

2.3.2 Isochromosome Formation

By definition, an isochromosome is a chromosome containing a mirror duplication of one chromosome arm or of a chromosome segment containing a centromere (Schinzel, 1984) i.e. the two arms of the chromosome are identical (Sutton, 1980). Isochromosome formation occurs during the first or second meiotic division or mitosis where the centromere of a chromosome divides in the wrong plane yielding two daughter chromosomes, each of which carries the information of one arm only but present twice. This will result in the formation of a disomic gamete and therefore a trisomic zygote (Thompson and Thompson, 1982 ; Schinzel, 1984). The presence of a Robertsonian translocation or isochromosome in an individual may be the result of either:

1) segregation in the offspring of a balanced carrier or
2) a newly arisen mutation (Vogul and Motulsky, 1986).

It may be concluded that either one of the proposed mechanisms of nondisjunction, translocation or isochromosome formation may result in a numerical or structural chromosome abnormality.

2.4 TRISOMY 21 (DOWN SYNDROME)

Since the present study involved a detailed investigation of trisomy 21, 18 and 13, which all result from some of the chromosomal aberrations described above, these three trisomies and the proposed mechanisms of how they arise will now be described in detail.

2.4.1 Historical Background of DS

According to Pei-yu (1987), E. Seguin coined the term 'furfuraceous idiocy' in 1846 which supposedly referred to Down syndrome. However, most people accept that the first report on Down syndrome was that of Langdon Down in 1866 (Thompson and Thompson, 1982). In Down's report in 1866, he set out the classic clinical description of the disease and recognised its common occurrence in populations of mentally retarded patients (Nyan and Sekati, 1987). Down stated that a 'large number of congenital idiots are typical mongols' and considered his patients to resemble members of the Mongolian race. He interpreted the condition as 'an atavism toward a more primitive mongoloid type of individual', hence the term mongolism or mongoloid. It was not until 1961 that G. Allen urged that

this term be dropped since it implied racial connotations which were misleading and unpleasant. Since then the term Down syndrome has become more widely used. It was suggested by Waardenburg in 1932 and Penrose in 1939 (Hamerton, 1971) that the condition might be caused by a chromosome abnormality, but it was not until 1959 that Lejeune et al were able to demonstrate that children with Down syndrome have 47 chromosomes instead of the normal 46, the extra chromosome being a small acrocentric, which has since been designated chromosome 21.

2.4.2 Phenotypic Features of DS

Down syndrome can usually be diagnosed at birth or shortly thereafter, by its characteristic phenotypic features, the most common of which, according to Nyan and Sekati (1987), include the following :

* hypotonia (found in 80% of cases)
* a poor Moro reflex (found in 85% of cases)
* hyperflexibility of the joints (found in 80% of cases)
* excess skin on the back of the neck (found in 80% of cases)
* flat facial profile (found in 90% of cases)
* slanted palpebral fissures (found in 80% of cases)
* anomalous auricles (found in 60% of cases)
* dysplasia of the pelvis (found in 70% of cases)
* dysplasia of the midphalanx of the fifth finger (found in 60% of cases)
* Simian crease (found in 45% of cases)

Hall (1966) showed that at least four of these abnormalities occurred in all the 48 affected new-borns in their sample,

while six or more occurred in 89% of their cases. Other abnormal features which are also common to Down syndrome include the following : a tendency to keep the mouth open and protrude the tongue, small stature with an awkward gait, brachycephaly, a small nose with a low nasal bridge, epicanthic folds, speckling of the iris (Brushfield spots), peripheral hypoplasia of the iris, hypoplasia and irregular placement of the teeth, a short neck, short and broad hands with clinodactyly, a wide gap between the first and second toes, fine, silky hair, and soft skin (Smith, 1982). Congenital heart malformations occur in about 40% of patients (Nyan and Sekati, 1987). Septal defects are the most common, including ventricular septal defect, atrial septal defect and atrioventricularis communis, i.e. endocardial cushion defects.

Mental deficiency is common to all patients, and the IQ ranges from 25 to 50 (Smith, 1982; Nyan and Sekati, 1987) with rare instances as high as 70 to 80 (Nyan and Sekati, 1987). Generally, social performance is beyond that expected for mental age, averaging three and a half years above mental age for the older individuals (Nyan and Sekati, 1987). None of the above features is always present in a Down syndrome individual and each may be present in an occasional normal individual. But it is the unusual concentration of features (see Figure 2.3) in an individual that is characteristic of Down syndrome (Sutton, 1980).

It is of relevance to the present study to note that according to Christianson et al (1995) the craniofacial features of the black South African DS neonates can be quite similar to

those of the unaffected black neonate which may explain reasons why DS may be less easily diagnosed in black than in white infants. Often the clinical diagnosis in white infants presents no particular difficulty, but karyotyping is nevertheless indicated for confirmation. The type of Down syndrome, whether it is the typical nondisjunction type, a translocation or a mosaic type, must be determined (Thompson and Thompson 1982).



FIGURE 2.3 A group of Black Down syndrome children with characteristic features.

2.4.3 Natural History of DS

Down syndrome individuals are thought to be "good babies" i.e. they are very quiet, sleep a lot and are happy. They tend towards mimicry, may be friendly, have a good sense of rhythm and enjoy music. Mischieviousness and obstinance

may also be characteristic and 13% of cases have severe emotional problems (Smith, 1982).

Hypotonia, or general floppiness, is highly characteristic of patients with Down syndrome, especially in infancy, but muscle tone tends to improve with age and they do learn to walk (Nyan and Sekati, 1987). Patients with Down syndrome often have a low birth weight for their gestational age, although the weight can be normal. Postnatal growth is usually relatively slow and during the first eight years, secondary centres of ossification are often late in development. However, during later childhood, the osseous maturation is more 'normal' and final height is usually attained around 15 years of age (Smith, 1982). Mental retardation is usually quite severe and therefore the developmental milestones are delayed. Individuals with Down syndrome do talk, usually with a raucous voice, but they may learn only a few words and short sentences. Attention span is short and co-ordination may be poor. Most patients are considered trainable but not educable and although development tends to be encouraging as the patient slowly achieves the developmental milestones, the rate of progress tends to slow down with age (Nyan and Sekati, 1987). Early developmental enrichment programs for Down syndrome children have resulted in improved rate of progress during the first four to five years of life (Smith, 1982). Whether such training programs will appreciably alter their ultimate level of performance remains to be determined.

Congenital heart defects are the major cause of early

mortality and 44% of those with cardiac anomalies die in infancy. Acute leukaemia has an approximate incidence of 1% in Down syndrome patients (Nyan and Sekati, 1987) and lower respiratory tract infections may pose a serious problem (Smith, 1982). They are also highly susceptible to infection, may die of pneumonia in infancy and age prematurely (Nyan and Sekati, 1987).

Adolescent sexual development is usually somewhat less complete than normal. Males may have undescended testicles and a relatively small penis. They are generally infertile, have very low levels of testosterone and pubic hair tends to be straight (Nyan and Sekati, 1987). Females have late puberty and early menopause but they may be fertile and a number have had children (Nyan and Sekati, 1987).

In later years, the skin becomes wrinkled but premature ageing may be more appreciable in the blood vessels. Alzheimer's disease has been increasingly recognised (Nyan and Sekati, 1987). According to Baird and Sadovnick (1988) the long-term survival of Down syndrome individuals is significantly poorer than that for the general population. However, over half the affected individuals can be expected to survive into their fifties and 13.5% will still be alive at age 68.

2.4.4 The General Population Incidence of DS

Down syndrome is the most common trisomy, with a general population incidence ranging from 1: 578 (Leisti et al, 1985) to 1:1149 (Mikkelsen, 1988). It is well documented that there is a relationship between the age of the mother at

conception, and the incidence of nondisjunction type DS (Hassold and Jacobs, 1984), and there is a linear increase in the incidence of DS with increasing maternal age (Fraser Roberts and Pembrey, 1985).

2.4.5 The Ethnic Distribution of DS

There are few studies in which the ethnic distribution of DS has been documented. Krivchenia et al (1993) compared observed incidences for each population group (White and other) in Ohio with Atlanta, Georgia. They observed an incidence of 1:868 and 1:1022 for liveborn DS individuals in the White population and 1:1136 and 1:1017 in all other population groups in Ohio and Atlanta, respectively. These results showed no statistical significance between the different population groups. Adeyokunnu (1982) reported an incidence of 1:865 livebirths in a Nigerian hospital which showed that DS occurs as commonly in Negroes as in other races. Kromberg and Zwane (1993) reported an incidence of DS of 1:600 in the local Black population which is higher than the normal population incidence and was associated with the high number of older women having pregnancies. In Smart's study (1981), a high incidence of 1:185 DS cases was noted in the White mentally retarded population, the reasons for which were not determined. He also documented incidences of 1:830 and 1:1170 for the Coloured and Black populations, respectively, which are similar to the general population incidence.

2.4.6 The Sex Ratio of DS

According to a number of published studies, there is no difference between the number of females born with DS and

the number of males born with DS (Nelson and Smart, 1982; Leisti et al, 1985; Mikkelsen, 1988). The only study where a preponderance of males was unexpectedly noted, was a study carried out by Speed et al (1976) in Scotland and no apparent explanation was given for this result.

2.4.7 The Genetics of DS

There are three types of Down syndrome, namely, nondisjunction, translocation and mosaic. These three types are discussed below.

2.4.7.1 Nondisjunction Type DS

The most common type of Down syndrome is the nondisjunction type where the extra chromosome 21 is lying free in the cytoplasm, i.e. it is not translocated to another chromosome. In a Scandinavian study, this type occurred in about 90% of Down syndrome cases detected (Mikkelsen, 1988). In a study done in Cape Town, South Africa, 91% of Down syndrome cases were of the nondisjunction type (Nelson and Smart, 1982). The error may occur in the first or second meiotic division in the mother or father (Dewald, 1987), or in the mitotic division of the very early embryo (Fraser and Nora, 1975).

a) **The Mechanism of Nondisjunction**

In two different reviews it was suggested that in about 86% of cases, the extra chromosome 21 in nondisjunction cases of Down syndrome was maternal in origin, in about 9% of cases, it was

paternal in origin (Petersen et al, 1992; Yoon et al, 1996) and in less than 5% of cases, the error was mitotic (Yoon et al, 1996). When the origin of the extra chromosome 21 was maternal, the nondisjunction event occurred during the first meiotic division in approximately 75% of cases and during the second meiotic division in 25%. When the origin of the extra chromosome was paternal, the nondisjunction event was said to occur during the first meiotic division in approximately 50% of cases and during the second division in 50% (Yoon et al, 1996).

The apparent higher incidence of meiotic I than meiotic II nondisjunction events has been attributed to many biological factors, including ageing processes, double silver staining nucleolar organising regions (AgNOR's), abnormal synaptonemal complexes, smoking, alcohol consumption, thyroid autoimmunity, hepatitis, oral contraceptives and fertility drugs (Dewald, 1987). Whatever the theory may be as to why the nondisjunction event occurs, the most important factor that is considered is increased maternal age, since it is the only factor that has been unequivocally associated with the conception of trisomies (Hassold and Jacobs, 1984).

b) **Nondisjunction, Maternal Age and the Corresponding Incidences**

It is well known that there is a correlation between

the incidence of the nondisjunction type Down syndrome and advancing maternal age (Hassold and Jacobs, 1984). Whether the maternal age effect is associated with increased production of abnormal eggs or decreased destruction of abnormal embryos is still to be determined. The obvious hypothesis for the age effect is the 'older egg model' - that is, most errors involving the numerical assortment of chromosome 21 occur in oocytes, with the error rate increasing as women age (Stewart et al, 1988). However, the results of other cytogenetic studies indicate that 70-75% of nondisjunctional events involving chromosome 21 occur in maternal meiosis I, regardless of maternal age (Stewart et al, 1988). This contradiction led in part to the 'relaxed selection' hypothesis, which suggests that the age related increase in frequency of Down syndrome may ensue from an inability of older mothers to reject trisomy 21 conceptuses (Stein et al, 1986). This implies that younger mothers have an ability, diminishing with increasing maternal age, to discriminate against chromosomally abnormal conceptuses. Indeed, maternal genotype can affect in utero survival of aneusomic murine conceptuses (Vekemans and Trasler, 1985). However, there is also evidence against this model : Down syndrome resulting from an unbalanced translocation does not show significant maternal age dependence as would be predicted on the basis of the hypothesis (Hook, 1983). Further, the relaxed selection model

depends entirely on analysis of chromosomal heteromorphisms, which have limitations (Stewart et al, 1988). Because of this evidence, the intuitively appealing hypothesis that advanced maternal age is associated with increased nondisjunction rather than with decreased selection remains viable. The definitive study to resolve this issue will require complete ascertainment of the parental source of the extra chromosome in a large number of Down syndrome subjects (Stewart et al, 1988).

There is a gradual linear increase in the rate of DS with increasing maternal age up to thirty years and a rapid logarithmic type of increase after the age of thirty-three years (Fraser Roberts and Pembrey, 1985). Using three large studies done in Sweden (Hook and Lindsjo, 1978), Australia (Sutherland et al, 1979) and South Glamorgan (Young et al, 1980), Harper calculated approximate risk figures (see Table 2.1) as follows: in mothers twenty to thirty years of age, the risk increases from less than 1:1000 livebirths to 1:909; at thirty-five years, it rises to 1:384; and by forty years to 1:112. Thereafter the rise is progressively steeper, the risk to mothers aged forty-five and over being 1:25 (Harper, 1993).

TABLE 2.1 Risk of Down syndrome in relation to maternal age (live birth figures calculated for individual years)(after Harper, 1993)

Maternal Age at Delivery	Risk
30	1 in 909
34	1 in 474
35	1 in 384
36	1 in 307
37	1 in 242
38	1 in 189
39	1 in 146
40	1 in 112
41	1 in 85
42	1 in 65
43	1 in 49
44	1 in 37

In a study done in 1988, Mikkelsen observed the changing percentage of Down syndrome cases born to women over the age of 35 years. In Denmark in the 1950's, 50% of Down syndrome cases were born to mothers over the age of thirty-five years. The percentage went down to 25% in the 1970's and was reduced to 8% in the 1980's. This decrease may be attributed to the advent of prenatal diagnosis (Mikkelsen, 1988).

Using Mikkelsen's study (1988), the absolute number of Down babies born to young mothers (<30 years) is 64% because even though the risk is lower at younger maternal ages, there are so

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many more births (Mikkelsen, 1988).

c) **Nondisjunction and Paternal Age**

Paternal age is also thought to play a role in the nondisjunction event occurring. This possible paternal age effect has been disputed for a long time (Mikkelsen, 1988). Stene et al (1977) proposed a paternal age effect for the age group over fifty-five years on data obtained in Copenhagen. A few studies confirmed a weak paternal age effect (Matsunaga et al 1978; Stene and Mikkelsen, 1984), but most studies could not demonstrate a paternal age effect (Hook and Cross, 1982; Ferguson Smith and Yates, 1984). To elucidate the question further, a European collaborative effort was organised to compare maternal and paternal meiotic failures and age distributions of the parents (Aymè et al, 1986). In the paternal failures, a maternal age effect was observed as also previously shown by Mattei et al (1980). This finding is unexplained so far, but possibly related to relaxed selection in the pre-recognition phase of pregnancy in elderly women carrying a trisomic foetus (Stein et al, 1986).

When paternal cases were matched for maternal age, a weak paternal age effect could be shown for first meiotic division errors in fathers. Second division failure in the fathers was negatively associated with paternal age (Aymè et al, 1986).

d) **Recurrence Risks and Familial Nondisjunction**

The risk of another affected child being born to a couple who have had one Down syndrome child (of the nondisjunction type) is increased over the normal risk, but the increase does not show a simple relation to maternal age (Harper, 1993). According to Stene et al (1984) parents (under the age of 35) of a child with trisomy 21 have approximately a 1% risk of recurrence for each subsequent pregnancy. Mikkelsen (1979) states that from 35 years and upwards, the recurrence risk is twice the normal age specific risk.

In 1985 Cavalli et al reported nondisjunction type Down syndrome in three first cousins (2 males and 1 female). When the parents' chromosomes were studied, they were found to be normal. This hypothesis suggests that nondisjunction is not always a random phenomenon, i.e. it may be familial, and that it may be controlled by some kind of genetic predisposition (Cavalli et al, 1985). In 1988, Nielsen et al studied a family where there was also multiple recurrence of trisomy 21. Down syndrome with free trisomy 21 in two or more siblings of healthy and phenotypically normal young parents is rare and has at least two possible explanations. Firstly, cryptic or low percentage mosaicism may be considered. The other possibility is the genetic predisposition to nondisjunction which may be caused by

autosomal recessive genes (Alfi et al, 1980), although there is no definite evidence for the latter in man (Yokoyama et al, 1981). No estimates have been made for the rate of multiple recurrence of nondisjunction Down syndrome in man (Nielsen et al, 1988).

2.4.7.2 **Translocation Type Down Syndrome**

Though Down syndrome always involves trisomy for chromosome 21, in between 3% (Nyan and Sekati, 1987) and 5% (Harper, 1993) of cases, the extra chromosomal material is present not as a separate chromosome, but as a translocation of chromosome 21 onto another acrocentric chromosome, i.e. a Robertsonian translocation. The most frequent such translocations to occur are the t(14;21) and the t(21;21) translocation or isochromosome 21 (Harper, 1993). Approximately 55% of the translocations in Down syndrome involve a translocation of 21 (a G group chromosome) to chromosomes in the D group (13 - 15) and 41% involve a translocation with another G group chromosome (Sutton, 1980). About 60% of the D-G translocations involve chromosome 14, the remaining 40% are equally divided between 13 and 15. Most of the G-G translocations (83%) are with another 21 chromosome, the remainder with chromosome 22 (Sutton, 1980). In the study conducted by Mikkelsen et al (1976) in Copenhagen, 63.6% of translocation Down syndrome were found to be due to a t(14;21) translocation, 27.3% due to a t(21;21) translocation and the remaining 9.1% were due to a t(21;22)

translocation.

Other chromosomes that have been shown to be involved in translocations are chromosomes 13 (Clarke et al, 1989) and 15 (Harper, 1993). The presence of a Robertsonian translocation in an individual may be the result of either :

1) segregation in the offspring of a balanced carrier or
2) a new mutation, i.e. a de novo event.

Of the t(14;21) translocation Down syndrome cases, about 50% will arise de novo while the other 50% will be inherited (Nyan and Sekati, 1987). Figure 2.4 shows a schematic representation of how the t(14;21) translocation may have arisen, the gametes produced, and the possible resulting zygotes.

Theoretically, if either one of the parents carries a t(14;21) balanced translocation, six types of gametes could be produced:

1) a normal gamete,
2) a gamete that would lack the 21 chromosome and upon fertilisation would produce a zygote that is monosomic for 21,

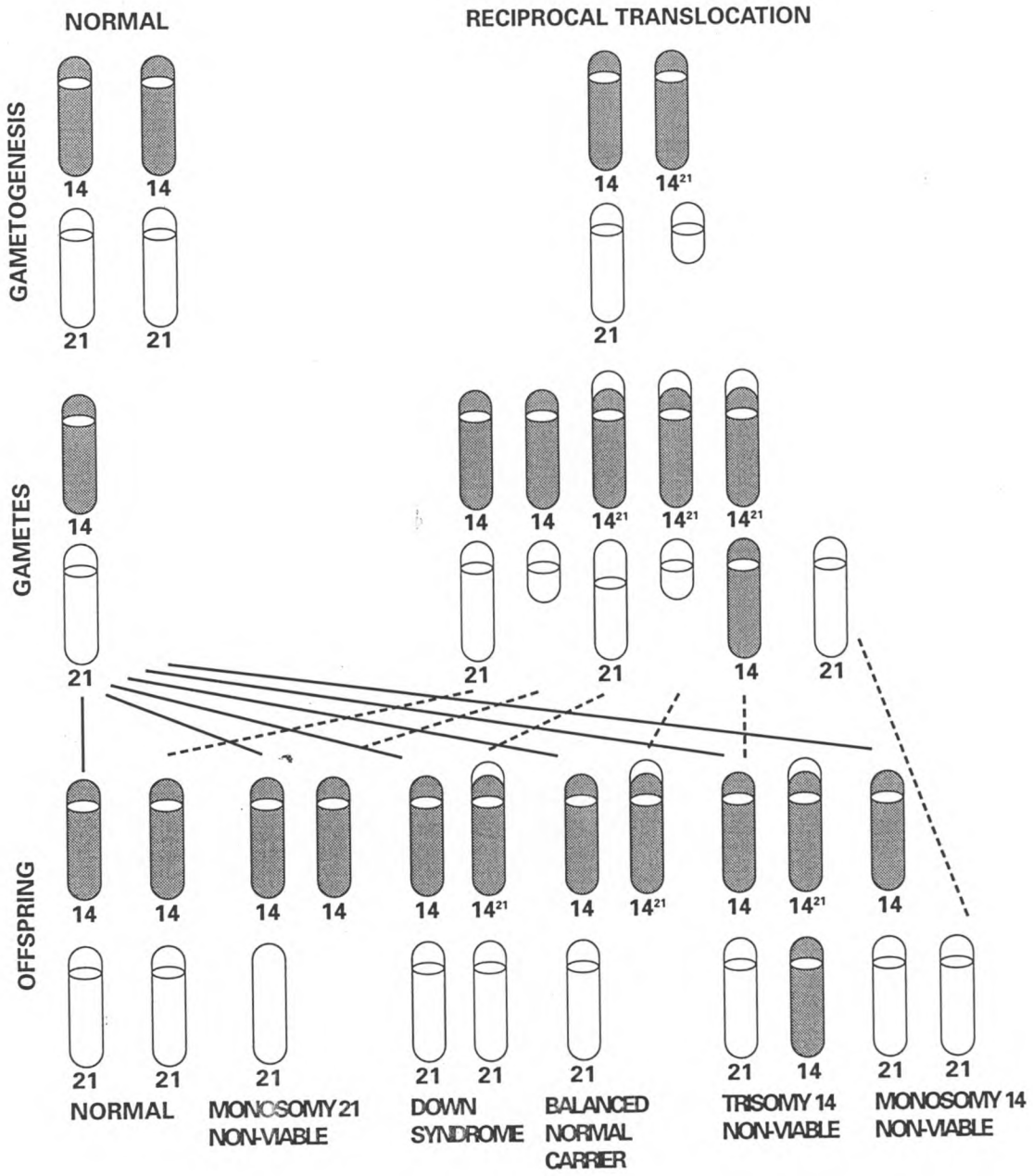


FIGURE 2.4 Diagram illustrating the observed consequences of a centric fusion between chromosomes 14 and 21, in a mating of a normal to a carrier of the balanced translocation (after Fraser Roberts and Pembrey, 1985).

3) a gamete that would lack the 21 and a free G chromosome but have a large 14/21 translocation chromosome ; fertilisation would produce an individual with a balanced translocation like the parent,
4) a gamete that would have a 21 chromosome as well as the 14/21 translocation and upon fertilisation would lead to an offspring with Down syndrome (Nyhan and Sekati, 1987)
5) a gamete that would have a 14 chromosome as well as the 14/21 translocation chromosome and upon fertilisation would result in an offspring with trisomy 14 and
6) a gamete that would lack the 14 chromosome and upon fertilisation produce a zygote monosomic for 14 (Thompson and Thompson, 1982).

Two of these gametes result in zygotes that lack large amounts of chromosomal material and are therefore nonviable. The third gamete which leads to a trisomy 14 zygote is also nonviable (Thompson and Thompson, 1982). Thus, only three of the gametes will result in viable offspring and the theoretical risk is therefore 1 in 3 (Nyan and Sekati, 1987). However the observed risk of having a Down syndrome child if one of the parents is a balanced translocation carrier has been shown to be lower than the theoretical risk (Harper, 1993). Harper (1993) states that mothers carrying the balanced translocation have a 10% risk to their offspring, while fathers carrying a balanced

translocation will have a 2.5% risk to their offspring.

These lower than expected risks if the mother or father are carriers, may be explained by the fact that all gametes may not occur with equal frequency. Studies of chromosomal anomalies in other organisms indicate that various gametic combinations are not equally probable (Sutton, 1980).

In patients with Down syndrome who have a t(21;21) translocation, 94% of cases are sporadic (Nikolis and Kekié, 1986). Thus, in the remaining 6% of cases (Nyan and Sekati, 1987) one of the parents is a balanced t(21;21) translocation carrier and there will be a 100% risk to their offspring (Harper, 1993).

The two possible gametes formed in this situation are:

1) one lacking a 21 chromosome which when fertilised, is assumed to lead to a lethal monosomy and
2) one with the translocation 21/21 chromosome which when fertilised would lead to a child with Down syndrome (Nyan and Sekati, 1987).

Data concerning the rarer 21/22 translocation are much less extensive than for either the t(14;21) or t(21;21) but risks are similar to those available for the 14/21 translocation. The incidence of Down syndrome in her offspring is about 9% when the mother has a 21/22 translocation and approximately 4% when the father is a carrier (Nyan and Sekati, 1987).

2.4.7.3 **Mosaic Type Down Syndrome**

About 1 - 2% of the cases of Down syndrome are

mosaic in their karyotype (Clarke et al, 1989). A chromosomal mosaic has at least two cell lines with different karyotypes derived from a single zygote. There is usually a normal cell line and an abnormal cell line which contains the extra chromosome 21 material (Nyan and Sekati, 1987).

Most patients reveal mosaicism for an additional chromosome 21 (Schinzel, 1984) the resulting karyotype being 46,XX/47,XX, +21 or 46,XY/47,XY, +21, while mosaicism involving an autosomal structural rearrangement will result in the karyotype 46,XX/46,XX, der(14;21)(q10;q10) which is uncommon and only a few cases have been documented (Clarke et al, 1989).

Patients with trisomy 21 mosaicism may have the classical appearance of Down syndrome or may look essentially normal depending on the preponderance of the abnormal cell line. The greater the proportion of cells with a normal complement of chromosomes, the more likely it is that the child will appear normal (Clarke et al, 1989). Exceptionally, mental development in a mosaic individual may even be normal despite the clinical features of Down syndrome (Clarke et al, 1989). It is possible that many persons are mosaic for trisomy 21 without expressing any significant clinical signs (Sutton, 1980). Such persons might have only a small proportion of their cells trisomic. If this small proportion included gonadal tissue, the risk of producing a trisomic offspring could be high (Sutton,

1980). There are no accurate risk figures for offspring of a mosaic individual, but amniocentesis is indicated (Harper, 1993).

2.5 TRISOMY 18 (EDWARDS SYNDROME)

In addition to trisomy 21, trisomy of other autosomal chromosomes also occurs. The most common is trisomy 18 or Edwards syndrome.

2.5.1 Historical Background of ES

Edwards syndrome or trisomy 18 was first described in 1960 by an English investigator, Edwards, and his colleagues, in a female child. The condition was originally referred to as E-trisomy because until chromosome banding came into use, the specific chromosome concerned could not be positively identified, except as being in the E group (Thompson and Thompson, 1982). Edwards designated the extra chromosome as chromosome 17. At the same time, the Americans Patau et al (1960) and Smith et al (1960) provided a further clinical description of two patients with the E-trisomy but identified the extra chromosome as chromosome 18. By autoradiographic methods, Gianelli and Howlett (1966) were able to confirm that the extra chromosome was number 18.

2.5.2 Phenotypic Features of ES

Children with Edwards syndrome have a broad spectrum of anomalies (130 have been identified). The most common and important abnormal features associated with Edwards syndrome are the following : growth deficiency,

microcephaly with a characteristic facies (triangular in shape, with a disproportionately small lower segment and a relatively broad and high forehead, narrow palpebral fissures, small nose, small mouth, micrognathia and small low set ears), a short sternum, a small pelvis with limited hip abduction, cryptorchidism in males, hypoplasia of the labia majora with a prominent clitoris in females, hands and feet flexed deformities, clenched hand with overlapping of the index finger over the third finger and the fifth finger over the fourth, low arch dermal ridges on finger tips, hypoplasia of the nails, rocker bottom and/or club feet with syndactyly and cleft lip and palate (see Figure 2.5). Most patients also have brain, heart, kidney and gut malformations. All Edwards syndrome individuals have mental retardation (Smith, 1982; Urban and Bersu, 1987). At birth there is usually severe asphyxia and failure to thrive. About 80% - 90% of patients die within the first week, mostly from apnoeic spells, cardiac failure and respiratory insufficiency (Schinzel, 1984). Young et al (1986) and Carter et al (1985) estimated medians of survival of infants with Edwards syndrome to be 2.5 and 5.3 days respectively and in 1988 Goldstein and Nielsen reported the median survival of affected individuals to be 6.0 days. Cases of long survival in individuals with trisomy 18 are rare and only a few cases have been reported, e.g. a twenty-one year old female, who was not a mosaic, was reported by Smith et al in 1989.

2.5.3 Natural History of ES

Babies with trisomy 18 are usually feeble, with low birth weights for gestational age. They have a limited capacity for survival. Resuscitation is often performed at birth and

they may have apnoeic episodes in the neonatal period (Smith, 1982). They have feeding difficulties, a poor sucking reflex and a high-pitched cry (Nyan and Sekati, 1987). Once the diagnosis has been established, limitation of all medical means for prolongation of life has been recommended (Smith, 1982).



FIGURE 2.5. Prominent clinical features of a liveborn infant with Edwards syndrome.

2.5.4 **The General Population Incidence of ES**

Edwards syndrome is the second most common multiple malformation syndrome with a general population incidence ranging from 1:3500 (de Grouchy and Turleau, 1983) to 1:8000 livebirths (Nora and Fraser, 1974). In a study done

by Goldstein and Nielsen (1988), the prevalence at birth (liveborn and stillborn) was reported to be approximately 1:7000. As is the case in Down syndrome, there is a relationship between maternal age and the incidence of Edwards syndrome. The risk of having a baby with this syndrome increases with advancing maternal age (Harper, 1993). At the maternal age of thirty-five years, the risk of having a trisomy 18 baby is 1 in 2000, and at the age of 43 the risk has been estimated to be 1 in 350 (cases picked up on amniocentesis, Ferguson-Smith, 1983). In a study done by Goldstein and Nielsen (1988) in Denmark, the incidence of Edwards syndrome in the liveborn population from mothers of thirty to thirty-five years was found to be 1 in 3799 and from mothers of forty to forty-four years was 1 in 298.

2.5.5 The Sex Ratio of ES

A most striking feature of Edwards syndrome is the disturbed sex ratio observed among affected livebirths. The sex ratio has been shown to be three affected females to one affected male (Weber, 1967; Anneren, 1986). This 3:1 ratio does not apply among foetal deaths, where there is a preponderance of males, therefore suggesting preferential survival of females (Taylor, 1968).

2.5.6 The Genetics of ES

Karyotyping of Edwards syndrome individuals by chromosome analysis is important to confirm the diagnosis as well as to determine whether the patient has either the nondisjunction type, translocation type or mosaic type of trisomy 18. Almost all cases are found to result from a

nondisjunction event occurring in maternal meiosis (Kondoh et al 1988). This event is strongly associated with maternal age (Thompson and Thompson, 1982).

Very few cases of translocation Edwards syndrome have been described in the literature. From the available literature it appears that only a few affected subjects have been reported, some of which had presumptive translocations which resulted in a duplication of the larger part of an E chromosome; the others had a secondary trisomic event with a presumptive isochromosome. With the single exception of the subject reported by Brodie and Dellaire (1962) in which the mother was a balanced heterozygote, all remaining subjects had sporadic translocations (Hamerton, 1971).

About 10% of all Edwards syndrome cases are mosaic (Thompson and Thompson, 1982). In these mosaics, two or more cell lines are present, one of which is normal and the other has an extra chromosome 18, resulting in the karyotype 46,XX/47,XX, + 18 or 46,XY/47,XY, + 18 (Hook and Yunis, 1965). In the case of a mosaic Edwards syndrome, there is partial clinical expression of the pattern of trisomy 18, with longer survival and any degree of variation between nearly normal and the full pattern of expression (Smith, 1982).

2.5.7 Recurrence Risks of ES

Recurrence of Edwards Syndrome of the nondisjunction type is uncommon but insufficient data have been collected to give accurate risks (Harper, 1993). The recurrence risk is estimated at 1%, similar to that given for Down syndrome

(Harper, 1993). Maternal age is also a factor. Using, Ferguson-Smith's study (1983), Harper calculated the age specific risks for trisomy 18 at amniocentesis (see Table 2.2). The recurrence risk of Edwards syndrome to a mother over the age of thirty-five years, is about twice the overall population risk for that age group (Harper, 1993).

TABLE 2.2 Maternal age and specific risks for Trisomy 18 found at amniocentesis. (after Ferguson-Smith, 1983 and Harper, 1993)

AGE (IN YEARS)	RISK FOR TRISOMY 18 (rate per 1000 amniocenteses)
35	0.5
36	0.7
37	1.0
38	1.4
39	2.0
40	2.8
41	3.9
42	5.5
43	7.6

2.6 TRISOMY 13 (PATAU SYNDROME)

The third most common viable trisomy is Trisomy 13 or Patau Syndrome.

2.6.1 Historical Background of PS

Patau syndrome was apparently first described clinically by Bartholin in 1957 (Warburg and Mikkelsen, 1963). But it was only in 1960 that Patau et al discovered its trisomic aetiology using autoradiographic techniques (Thompson and Thompson, 1982). Because the three pairs of D-group chromosomes were originally indistinguishable, Patau syndrome or Trisomy 13 was first termed D1 - trisomy (Thompson and Thompson, 1982). Subsequent autoradiographic and fluorescence studies have provided evidence that the extra chromosome in this syndrome is homologous with pair 13 (Gianelli and Howlett, 1966; Yunis and Hook, 1966).

2.6.2 Phenotypic Features of PS

Many abnormalities have been found to be associated with Patau syndrome (see Figure 2.6). The most important and common of these are described by several different authors (Smith, 1964; Warkany et al 1966; Taylor, 1968; Hodes et al, 1978; Pettersen et al. 1973), as the following: growth deficiency, a holoprosencephaly type defect with varying degrees of incomplete development of the forebrain and olfactory and optic nerves, microcephaly, typical facies characterised by a v-shaped hemangioma over the nasal bridge, deep set eyes with microphthalmia and/or colobomata of the iris, cleft lip and palate, absence of the philtrum and malformed low set ears, polydactyly of the

hands and feet, flexion of the fingers with or without overlapping, palmar axial triradii are often distally and/or radially placed, transverse palmar creases, cryptorchidism in males, bicornuate uterus in females and cardiac eg. atrial septal defect (ASD), ventricular septal defect (VSD) and patent ductus arteriosus (PDA), renal eg. polycystic kidneys, and abdominal malformations eg. omphalocele. Severe mental retardation is associated with all cases of Patau syndrome (Schinzel, 1984).



FIGURE 2.6. Prominent clinical features of an aborted foetus with Patau Syndrome

2.6.3 Natural History of PS

Early postnatal lethality is high and an infant with Patau syndrome will rarely survive more than one year. There have been several reports on the survival of children with trisomy 13. Magenis et al, (1968) presented data on highly selected material comprising 172 regular trisomy 13 patients. They found that 28% had died by one week, 44% by one month, 73% by four months and 86% by one year. Redheedran et al (1981) reported a mean survival for trisomy 13 of 24 days (range 1-82 days) and Goldstein and Nielsen (1988) of Denmark found a median survival of 2.5 days for trisomy 13.

2.6.4 The General Population Incidence of PS

Patau syndrome is the third most common viable, multiple malformation syndrome after Down and Edwards syndrome, with a general population incidence ranging from 1 in 5000 (Smith, 1964) to 1 in 12000 (Hook, 1980). The risk of having an affected baby increases with maternal age (Smith, 1964). According to data from Ferguson-Smith's (1983) study of cases detected at amniocentesis, mothers aged 35 years have a risk of 1 in 5000 of having a Patau syndrome baby. This risk increases to 1 in 900 at the age of 40 years.

2.6.5 The Sex Ratio of PS

Goldstein and Nielsen (1988) reported a sex ratio of 1: 1.4 ratio of males to females in the liveborn population and a ratio of 1:1.7, females to males in the prenatally diagnosed cases. When these cases are added, there is no difference

between the number of male and female cases with PS.

2.6.6 The Genetics of PS

Karyotyping for an infant suspected of having Patau syndrome is important to confirm the diagnosis. The type of Patau syndrome, such as nondisjunction, translocation or mosaic has to be established. About 80% of all Patau syndrome cases are 'free trisomies' (Schinzel, 1984), a result of the nondisjunction event occurring at maternal meiosis I (Hassold et al, 1987) and there is an association with advanced maternal age (Schinzel, 1984). The remainder of cases, about 20% are due to rearrangements, predominantly Robertsonian translocations, and a few mosaic cases. In a study of 41 abortuses with trisomy 13, from a Honolulu hospital, Hassold et al (1987) found that 77% were simple trisomies of the nondisjunction type, 20.5% were due to a translocation and 2.5% were mosaic. The most common Robertsonian translocation occurring is the t(13:14), 60% of which are the result of a de novo event. Of the remaining cases about 25% are maternally inherited and 15% are paternally inherited (Hook, 1981). The theoretical risk to offspring if one of the parents is a balanced translocation carrier will be 1 in 3, but the observed risk is said to be less than 5% (Schinzel, 1984). Less common is the t(13:13) translocation which almost always occurs as a de novo event (Parslow et al, 1973). The small percentage (±2.5%) of mosaic cases clinically show less distinct dysmorphic features, fewer malformations, longer survival and mostly severe mental retardation,(but not as profound as in the full Patau syndrome case (Schinzel and Schmid, 1974). Most cases

are mosaic for an additional chromosome 13, with karyotype 46,XX/47,XX,+13 or 46,XY/47,XY,+13 (Taylor, 1968). The recurrence risk for parents who have had one affected child is 1%, as is the case in Down and Edwards syndromes (Harper, 1993).

2.7 PREVIOUS STUDIES ON DS, ES AND PS

Since Down, Edwards and Patau syndromes are the most common trisomies occurring (Harper, 1993), a large number of studies have been carried out in various countries throughout the world. Because of the large number of studies reported, only some of the largest and most quoted, as well as most of the South African studies, have been selected for review. The specific studies were chosen for their relevance to the aims of the present study. Details from some South African studies are presented in Table 2.3. All of the South African studies, except for Smart(1981) and Kromberg and Zwane (1993), involved the determination of all chromosome abnormalities, with no specific aim to determine numbers of DS, ES and PS. The studies of Smart(1981) and Kromberg and Zwane (1993) specifically looked at only DS cases, in order to determine a specific incidence of DS in that particular sample. No specific studies have been carried out in South Africa to determine the incidence of ES and PS. The only South African figures available for ES and PS, are those mentioned in passing by Kromberg et al (1989), who recorded four ES cases and one PS cases, detected by amniocentesis, between 1976 and 1985. This study also reported on 39 cases of DS.

Table 2.4 records data on specific DS studies from other countries. The incidence of DS is reported in all studies and the

types of DS are also recorded, with the exception of the study carried out by Mikkelsen in 1988.

Table 2.5 presents details on DS, ES and PS from other countries. All studies, except for that done by Borovik et al, specifically looked at ES and/or PS and/or DS. The incidence of each trisomy was recorded and in some cases the sex ratio was documented. The sex ratio is denoted as females to males in all the tables and all percentages appearing in brackets are percentages of the total sample.

TABLE 2.3 Previous South African studies on DS, ES and PS.

AUTHORS	Grace et al	Smart	Venter & Op't Hof	Nelson and Smart	Kromberg & Zwane
DATE OF REPORT	1979	1981	1982	1982	1993
DATES OF STUDY	6/'75 - 12/'77	1977-1978	1972-1982	1972-1978	1991
LOCATION OF STUDY	Umgeni Institution	Cape Peninsula	All over RSA (cases ref. to Dept. of H &W)	Alexandra Centre	Johannesburg (Cytogen. unit)
SAMPLE SIZE	512 (MR subjects+ chrom.study)	57756 (livebirths)	2533 (chrom.study)	725 (MR subjects + chrom. study)	24 000 (livebirths)
No. OF DS CASES	42(8.2%)	77(0,13%)	397(15,7%)	116(16,0%)	40
Nondisjunction	39(93,0%)	-	372(93,7%)	105(90,6%)	-
Translocation	3(7,0%)	-	14(3,5%)	4(3,4%)	-
Mosaic	0(0,0%)	-	11(2,8%)	7(6,0%)	-
INCIDENCE OF DS	-	1:750	-	-	1:600
SEX RATIO IN DS	-	-	-	1:1.1	-
No. OF ES CASES	-	-	-	-	-
No. OF PS CASES	-	-	-	-	-

TABLE 2.4 Previous Studies conducted elsewhere in the World on Down Syndrome.

AUTHORS	Mikkelsen et al	Speed et al	Leisti et al	Iselius & Lindstein	Krivchenia et al
DATE OF PUBLICATION	1976	1976	1985	1986	1993
DATES OF STUDY	1960-1971	1966-1971	1965-1979	1968-1982	1970-1989
LOCATION OF STUDY	Copenhagen	N.E. Scotland	Northern Finland	Sweden	Ohio & Atlanta,USA
SAMPLE SIZE	204771 (livebirths)	2770 (MR ind. + chrom. study)	152235 (livebirths)	1548403 (livebirths)	905532 (livebirths)
No. OF DS CASES	235(0,1%)	250(9,0%)	263(0,17%)	1986(0,1%)	1296
Nondisjunction	162(68.9%)	235(94,0%)	211(80,2%)	1543(77,7%)	-
Translocation	11(4.6%)	5(2,0%)	11(4,2%)	96(4,8%)	-
Mosaic	4(1.7%)	10(4,0%)	4(1,5%)	33(1,6%)	-
Not Karyotyped*	58(24.7%)	-	37(14,0%)	314(15,8%)	-
INCIDENCE OF DS	1:871	-	1:578	1:780	1:955
SEX RATIO IN DS	-	1:1.6	1:1,1	1:1,27	-

*Only a clinical diagnosis of DS was made and/or the individual died before being karyotyped.

TABLE 2.5 Previous Studies done on DS, ES and PS in four other countries.

AUTHORS	Annerén	Farag et al	Goldstein & Nielsen	Borovik et al
DATE OF PUBLICATION	1986	1988	1988	1989
DATES OF STUDY	1981-1982	1986	1977-1986	1/82-12/85
LOCATION	Sweden	Kuwait	Denmark	Brazil
SAMPLE SIZE	186800 (All births)	32237 (Births in 3 hosp.)	95 (cytogen. exam.)	73192 (Births in 8 mat. hosp.)
No. OF DS CASES	-	25	-	99
INCIDENCE OF DS	-	1:1290	-	1:737
No. OF ES CASES	37	4	76	13
INCIDENCE OF ES	1:8500	1:8059	1:7343	1:5630
SEX RATIO IN ES	3F:1M	-	2.3F:1M	-
No. OF PS CASES	-	-	19	3
INCIDENCE OF PS	-	-	1:29373	1:24397

2.8 GENETIC COUNSELLING AND AMNIOCENTESIS

Since the introduction of mid-trimester amniocentesis in the 1950's coupled with the successful development of amniotic cell culture in the 1960's (Cramer and Hirschhorn, 1985) many thousands of procedures have been performed. This process allows the detection of various chromosomal abnormalities in the foetus including the trisomies 21,18 and 13. Genetic counselling is an integral part of this service. An investigation of the use of prenatal diagnosis and genetic counselling by families with a history of a trisomy, is one of the aims of this study and therefore these two procedures are briefly described below.

The scientific advances in the field of medical genetics and bioengineering have had an incalculable impact on the development of prenatal diagnosis.

Within the past quarter-century, a dramatic advance in the nature of genetic counselling has been witnessed, changing it from a recitation of statistical probability, to the ability to confirm (with the use of prenatal diagnostic techniques) the presence or absence of an abnormality for which the foetus is at risk. This assurance is still limited to only a small proportion of hereditary abnormalities. Nonetheless, the element of gambling with the well-being of future offspring has been eliminated for many families at risk for a genetic problem (Cramer and Hirschhorn, 1985).

Foremost among prenatal diagnostic techniques is amniocentesis (Cramer and Hirschhorn, 1985), the most common and well used method in South Africa (Kromberg et al, 1989). Technological advances and the use of ultrasonography have made amniocentesis a safe and accurate procedure (Cramer and Hirschhorn, 1985), although there is an associated risk of spontaneous abortion which in

Johannesburg is about 1 in 140 (Kromberg et al, 1989).

The term amniocentesis is used for the procedure by which a sample of the amniotic fluid which surrounds the baby is removed, transabdominally, by syringe at 15 - 18 weeks gestation (Thompson and Thompson, 1982). The cells of the foetus, present in the amniotic fluid, are cultured and then analysed cytogenetically, and also biochemically when necessary. Should a chromosomal disorder be detected and depending on the nature of the defect, the parents are given the option of terminating the pregnancy.

Amniocentesis is carried out for the following reasons:

1) Advanced maternal age (35 years or more)
2) A previous child with a chromosomal disorder
3) A family history of a chromosomal disorder
4) Foetal sexing for X-linked disorders
5) Parental anxiety
6) Abnormal maternal serum screening results: ie. high alpha (α)-fetoprotein (AFP) levels suggesting a neural tube or other defects in the foetus; low AFP and unconjugated oestriol levels as well as high human chorionic gonadotrophin levels, suggesting a DS foetus (Wald and Cuckle, 1988).
7) Biochemical or molecular analysis for genetic disorders such as organic acidemias, mucopolysaccharidoses, Tay Sachs disease and cystic fibrosis (Harper, 1993).
8) To identify chromosome breakages resulting from exposure to radiation.

The majority of analyses are performed because of an increased risk of a cytogenetic abnormality, especially with advanced maternal age,

where there is a high risk of carrying a trisomic foetus eg. trisomy 21,18 and 13, to term (Schreinemachers et al, 1982).

Genetic counselling undertaken either by genetic counsellors, general practitioners, gynaecologists or any other knowledgeable specialists, provides the necessary information needed by those who are considering amniocentesis. The genetic counselling process involves attempts to help an individual or family to: comprehend the medical facts, diagnosis, prognosis and management of an individual with a genetic disorder; appreciate the genetics of the disorder and risk of recurrence in relations; understand the options for dealing with the recurrence risk; choose an appropriate course of action in view of the risks and family goals and act in accordance with this decision; and make the best possible adjustment to the disorder (Fraser, 1974).

In conclusion, prenatal diagnosis, by amniocentesis together with appropriate genetic counselling, is of great importance when decisions concerning an unborn child with a high risk of having a genetic abnormality have to be made.

2.9 PSYCHOSOCIAL EFFECTS OF HAVING A HANDICAPPED CHILD

The presence of a child in the family who is severely mentally retarded is potentially detrimental to the self-esteem of the family as a whole, and is also an increased burden on the family resources, both material and emotional. The impact is felt by parents, brothers and sisters in all social classes.

DS is the most common condition in which parents realise soon after birth that their child has little chance of fulfilling most modest aspirations. The parents initial reaction closely resembles grief,

followed by a number of coping stages through which the parents must pass before the grief is resolved and emotional equilibrium is once more established (Gath, 1985).

The first stage of the coping process is shock. Some parents are so stunned at first that they are unable to comprehend that such an event has happened to them. The second stage is denial, where parents can appear to be oblivious to the abnormality and to have failed to understand the implications of what has been said to them. This stage may last a long time, even years. Sadness or depression and anger are the characteristic emotions expressed at the following stage. Anger may be extreme and may be directed at different persons involved eg the doctor who broke the news or a family member, and continued support is invaluable at such a time. Adaptation follows the first emotional reactions to trauma (Gath, 1985) where parents attempt to re-establish psychological homeostasis (Emery and Pullen, 1984).

Coping is seen as behaviours, cognitions or perceptions directed at the resolution or mitigation of potentially stressful life events. Resources are managed by the family to control and direct change within the family system and thus decrease vulnerability to stress. Potential resources include the health and energy of individual family members, their problem solving skills, their perceptions and definitions of their situation, relationships within the family, and the family's social and support networks (Byrne and Cunningham, 1985). How people cope will be determined in part by their previous experiences, and parents will use their personal resources in the same way they have found them to be effective in past crises. Some will want to talk about their feelings, while others, more practical, will seek more concrete solutions. Some parents will look for others who

have dealt with similar difficulties, but others may cope just as adequately in private. Eventually, many families are able to function in a healthy way and a significant few have found their lives enhanced by what they had thought was going to be an intolerable burden (Gath,1985).

2.10 SUMMARY AND CONCLUSION

The three most viable common chromosome trisomies, namely Trisomy 21, 18 and 13, were described in some detail in this chapter. Each trisomy presents as a specific "syndrome" having characteristic malformations, patterns of dysmorphic signs, impaired mental development and intrauterine and postnatal growth retardation. The majority of these trisomies arise as a result of an abnormal number of normal chromosomes due to nondisjunction. Structural change , the most common being Robertsonian translocations, and mosaics, having at least two cell lines, one of which is abnormal, may also result in trisomic individuals.

Previous prevalence studies of DS, ES and PS in various countries show that the prevalence rates are approximately 1:800, 1:8000 and 1:24000, respectively, and annual fluctuations in the incidence of DS were noted by Iselius and Lindstein (1986) in Sweden. Studies on ethnic distribution are presently only available for DS and in all the reports there is no significant difference in the incidence of DS between the different population groups. No difference in the sex ratio has been reported for both DS and PS but Anneren's(1986) study in Sweden, as well as other studies, have reported a distortion in the sex ratio of liveborn ES cases.

Mid-trimester amniocentesis was first introduced in the 1950's and coupled with prenatal diagnosis and genetic counselling, it forms an

important option for at risk parents who need to make a decision concerning their unborn child, with a high risk of having a genetic abnormality.

CHAPTER 3

3. MATERIALS AND METHODS

3.1 INTRODUCTION

In this chapter the writer details how she set about collecting the information necessary to carry out the retrospective study on the occurrence of DS, ES and PS in blood and amniotic fluid samples in the Johannesburg and Soweto area. The methods used in the prospective study on the parents of a Down Syndrome child are also specified. In addition the setting and scope of the study, the identification and selection of subjects, and the methods of data collection and analysis are described below.

3.2 SETTING OF THE PRESENT STUDY

The setting of the study was the greater city of Johannesburg including Soweto. Johannesburg is the largest city in Gauteng, having a population of about 632369 (374915 of whom were Whites, 114088 Coloureds, 47197 Asians and 96169 Blacks - National Health and Population Development Department Annual Reports, 1988) at the time of this study. Soweto, on the other hand, had a population of about 521948 (434 of whom were Whites, 2627 Coloureds, 219 Asians and the majority, 518679, Blacks - National Health and Population Development Department Annual Reports, 1988) at the time of this study. Soweto was included in this study since a large proportion of the trisomy 21, 18 and 13 cases detected on either blood or amniotic fluid samples, were from Black individuals living in Soweto.

The combined population of Johannesburg and Soweto had a total mean birth rate of about 38383 live births per annum calculated for the 13 year period, January 1976 to December 1988, from the

figures provided by the Central Statistics Department Pretoria (1990). This large base population could provide a sample of affected births, sufficient for the purposes of this study.

The blood and amniotic fluid samples included in this study were those sent in for chromosome studies to the Cytogenetics unit, located at the South African Institute for Medical Research (SAIMR). The Cytogenetic unit was incorporated into the newly established Department of Human Genetics, under Professor T. Jenkins, in 1975 (Malan, 1988). At the time of this study, there was a staff of 15 who participated in different fields of cytogenetic service and research. The Cytogenetics unit was the primary setting of the study since most of the information needed for the study was contained in registers, reports, patient files and computers within the laboratory. Also, the laboratory and the information in the registers, reports and files were easily accessible to the writer and the size of the sample that could be obtained from the records was large enough to carry out the proposed aims of the study.

The two major genetic counselling clinics established in Johannesburg and Soweto provided the setting for the part of the study on the utilisation of these resources. Whether or not the parents of a DS, ES or PS child used these services to obtain genetic counselling or support, before or after the diagnosis and/or termination of an affected child, was investigated.

The Transvaal Memorial Institute (TMI) genetic counselling clinic in Johannesburg, which was established in 1972 by Professors T. Jenkins and J. Hansen (Malan 1988) catered for many White, Coloured, Indian as well as some Black patients, while the genetic counselling clinic at Baragwanath Hospital (established in 1987) was

attended by mostly Black patients because of its proximity to Soweto. Using records from these two genetic counselling clinics, the attendance by the families who had an affected DS, ES or PS child, could be determined.

3.3 SCOPE OF THE PRESENT STUDY

Specimens of blood and amniotic fluid are sent to the SAIMR Laboratories by general practitioners, medical specialists, medical staff at hospitals, health clinics and genetic counselling clinics, and genetic nurses. The mean annual number of blood specimens was approximately 1200 (calculated from January 1976 to December 1988) and the mean annual number of amniotic fluid specimens was approximately 1000 (calculated from January 1986 to December 1988). These samples were sent in for chromosomal studies mostly from the greater Johannesburg area but also from all over South Africa, as well as Namibia, Botswana and Zimbabwe. However, only the cases that originated from Johannesburg and Soweto were included in this study.

The thirteen year period from January 1976 to December 1988 was selected, since this time period provided a sample large enough for the purpose of this study. Also the records for these years were well kept and easily accessible to the writer. Another important fact was that this laboratory was providing the only cytogenetic service to the whole geographical area, except for a few samples in the latter years, which allowed for both nominators and denominators to be calculated most accurately. During this time period a total of 15359 blood specimens were successfully cultured and karyotyped and the results recorded. These files were studied and the details of the cases of DS, ES or PS were noted.

The data for chromosomal studies on amniotic fluid were collected over a three year period, January 1986 to December 1988. This time period was chosen to complement a previous study carried out by Professor. J G R Kromberg and colleagues (Kromberg et al, 1989) which covered a decade from January 1976 to December 1985. A total of 3038 amniotic fluid samples were successfully cultured in the selected three year period. The karyotypes were obtained and the details were recorded. From these records, the writer extracted the cases with DS, ES or PS and analysed the information to provide the material needed to fulfil the aims of this study.

A case study of a White infant with Down Syndrome and his parents was included in the present study. The infant was followed for a one year period, during which time the parents were visited and interviewed on four occasions.

3.4 IDENTIFICATION AND SELECTION OF SUBJECTS

The subjects for this study were selected from the records of the 15359 blood specimens and 3038 amniotic fluid specimens received by the Cytogenetics Unit during the thirteen and three year period under review, respectively.

Altogether, 1531 cases of DS, ES and PS were identified and of these, 672 cases were born in Johannesburg and Soweto. A total of 25 DS, ES or PS cases were extracted from the records of the amniotic fluid specimens. The details on the year of birth, ethnic distribution, sex ratio, type of trisomy and whether the parents of either an affected child or foetus used the Genetic Counselling clinic or not , were collected on all the DS, PS and ES cases from both

blood and amniotic fluid chromosomal studies and were noted by the writer and analysed. The ethnic groups that were used for the purpose of the present study were White, Black and 'Coloured and Indian'. The Coloured and Indian populations were grouped together since the samples from each group were too small to consider separately.

The subject for the prospective study of a family with a Down syndrome child was sought by the writer from among the DS children attending a stimulation group at the Transvaal Memorial Institute (TMI). A physiotherapist assisting the group and a genetic nurse from the TMI, both suggested that one particular family was very approachable and would be happy to participate in the case study. The parents were approached by the writer at the group (held once a month at the TMI), which the couple attended together with their DS child. The parents agreed that the writer could make home visits, and each parent would participate by being interviewed and completing a questionnaire.

3.5 METHODS OF DATA COLLECTION

The sources of information for this study, the methods of collecting the necessary data from the records, as well as the techniques used to collect the data for the case study, are discussed below.

3.5.1 Sources of Information for Retrospective Study

The sources of information available from the cytogenetic unit, SAIMR, were:

a) **Registers:** In the registers, details were recorded for each sample received in the laboratory. These details included age, ethnic group, sex of the patient and

indication for chromosome studies (e.g. possible DS) and the results for these studies. The registers were used to determine the total number of: blood samples for each year between 1976 and 1988; amniotic fluid samples for each year between 1986 and 1988; whether the samples were from Black, White, Coloured or Indian patients; amniocentesis cases referred for advanced maternal age (AMA), and the number of AMA cases in which either DS, ES or PS was diagnosed.

b) **Reports:** The reports (kept separately from those in the patients' files and filed according to years), for the time period, January 1976 to December 1988 on the results of blood chromosome studies, and from January 1986 to December 1988 on amniotic fluid chromosome studies, were used to determine the number of DS, ES and PS cases detected in these years. At the same time, the names of the affected individuals were noted, so that the patients' individual file could be consulted. The reports were utilised in order to determine the accuracy of the diagnosis. Then the numbers of affected individuals were cross-checked with the numbers of affected individuals obtained from the registers.

c) **Patient files:** Information on when and where the infant was born, the ethnic group, sex of the infant, the type of trisomy or translocation, and whether or not the parents used the genetic counselling clinic, was collected from the patient's personal file. These personal files were conveniently classified: 10A-i containing the trisomy 21 cases; 10A-ii the Mosaic trisomy 21, 10A-iii the

translocation type DS; 11A Patau syndrome and 12A, Edwards syndrome. The files for affected individuals during the period January 1976 to December 1988 were located and the necessary information was extracted for each patient. The files for patients who had amniocentesis were also classified: 20A denoting AMA; 20B, a previous child or relative with DS; 20C a previous child with another chromosomal abnormality; and 20D, a translocation carrier parent or mosaicism in the patient. The files for patients who had had DS, ES and PS prenatally diagnosed on amniocentesis in the period January 1986 to December 1988 were examined to determine the ethnic group, the sex of the foetus, whether or not the pregnancy was terminated and whether the parents attended a genetic counselling clinic before and/or after the termination.

d) **Computer files:** As from January 1987, all information included in the files was computerised. Thus the necessary information was obtained from computer print out and the patient files were used to cross-check that the information was correct. All information prior to computerisation, i.e. January 1976 to December 1986, was obtained only from consulting the patient files.

The annual reports on Regional Birth Statistics published by the Department of National Health and Population Development were also consulted. These reports were available at the Johannesburg City Health Department library in the Civic Centre and they were used to obtain information on the number of livebirths in Johannesburg and Soweto for every consecutive

year from 1976 to 1988. The number of livebirths was collected so that a denominator would be available for calculating prevalence rates of the three trisomies under investigation.

3.5.2 **Collection of Data from the Records on Blood Chromosomal Studies**

Data were collected from the records on blood chromosomal studies as follows :

a) The cases of DS, ES and PS were identified from the registers, reports, patient files and computer files, in which details on incoming samples and their results were recorded.

b) The residential address for each case, or the hospital from which the specimen was sent, was then noted and only those from Johannesburg and Soweto were selected for further analysis.

c) In order to estimate the prevalence of DS, ES and PS, the number of cases of each trisomy referred from this region were compared with the number of livebirths in Johannesburg and Soweto (obtained from the Department of National Health and Population Development). Annual estimates were calculated for each year from 1976 to 1988.

d) Data were collected and recorded on ethnic group, age or date of birth, sex of the affected infant and type of chromosome abnormality (trisomy, translocation or

mosaic). Once the age or date of birth for each trisomic individual was determined, these individuals were included in the sample representing their year of birth, so that accurate annual incidence rates could be calculated. The utilisation of the genetic counselling clinic by the parents with a child with either DS, ES or PS, was also noted.

3.5.3 **Collection of Data from the Records on Amniotic Fluid Chromosomal Studies**

Data were collected on amniotic fluid chromosomal studies, as follows:

a) DS, ES and PS cases were extracted from the recorded results for all the cases in which amniotic fluid chromosomal samples had been analysed.

b) The incidence rates for DS, ES and PS found in amniotic fluid specimens were determined by comparing the total number of cases with each trisomy with the total number of livebirths (obtained from the Department of National Health and Population Development). Annual rates were then obtained for each consecutive year from 1986 to 1988. In order to calculate a more complete incidence rate for the three trisomies for a three year period, the incidence rates found prenatally were added to the incidence rates determined postnatally using the blood specimen results, from 1986 to 1988.

c) For each individual case of DS, ES and PS the date of the amniocentesis, the ethnic group of the parents, the sex of the foetus, whether or not there was a termination of the

pregnancy, and the parents' utilisation of the genetic counselling clinic, was noted.

3.5.4 The Case Study

In order to gain insight into how the selected parents coped with having a Down Syndrome infant, a questionnaire was constructed allowing for the mother and father to complete the relevant questions together or separately, depending on the type of questions. The first section on the biographical and diagnostic information was completed together, while the last section of questions relating to emotional issues was completed separately by each parent.

3.5.4.1 Construction of a Questionnaire

A questionnaire refers to a device for securing answers to questions using a form which the respondent fills in himself (Goode and Hatt, 1952). It is a highly structured data collection technique whereby each respondent is asked more or less the same set of questions (de Vaus, 1986). A questionnaire is generally sent through the mail (Young 1974).

Questions should be asked so that the resulting data are directly related to the stated purpose of the research (Berdie and Anderson 1974) which in the present study was to gain an insight into how parents cope with a DS infant.

A structured questionnaire (as described by Young, 1974) was constructed, and both definite and concrete and preordained questions were included. Probing questions were used only when the need arose to clarify vague or

inadequate replies by respondents, or when more details were needed than those supplied by them.

Another aspect of questionnaire construction is the fitting of items together in such a way as to make the entire questionnaire a unit. That is, there should be logical progression such that the respondents are:

a) drawn into the interview by awakening their interest
b) easily carried along from questions which are simple to answer, to those which are complex
c) not affronted by an early and sudden request for personal information
d) never asked to give an answer which is embarrassing
e) brought as smoothly as possible from one frame of reference to another, rather than made to jump back and forth (Goode and Hatt, 1952)

The form of the particular questions may require responses which are either closed or open ended. The writer made use of both types of responses. Closed form questions are used when data which can be categorized are required. Types of closed form questions are :

a) A multiple choice type question where a respondent will choose from a set of planned responses (Young, 1974)

   eg. What type of DS does your child have?

   a) Trisomy 21
   b) Translocation
   c) Mosaic
   d) Don't know

b) Dichotomous questions, that is, where the question requires a 'yes' or 'no' answer (Berdie and Anderson, 1974). These questions are subject to the least bias (Young, 1974) and the majority of questions in the present study were of this type.
eg. Is this your first child?
YES..... NO.....
(The probe question that followed was then: If not, how many other children do you have?)

c) Likert style format, i.e. rating scale (deVaus,1986) questions were also used eg. How do you see your DS child's mental capabilities?

1	2	3	4	5
Very Slow	Slow	Average	A little above average	Much above average

d) Ranking format, where the respondent is asked to rank a whole set of items (de Vaus 1986 ; Berdie and Anderson, 1974) eg. Question 46 in which the respondents were asked to rank the emotions they felt during the coping process in order, according to when the given emotion was experienced (See Appendix A).

Open end responses are free and spontaneous expressions on the part of the respondents who are not limited to make their replies relevant to a particular

question posed (Young, 1974) and may formulate their own answers (de Vaus, 1986). Open end responses are used chiefly for intensive studies of a limited number of cases or preliminary exploration of new problems and situations. At times the respondent is asked to write a descriptive essay and express his viewpoints, describe his relationships, attitudes, indicate his problems and report on details and events without restrictions (Young, 1974). An example from the questionnaire for the present study is "What feelings do you have towards your DS child?" (See Appendix A)

In the case of the closed questions, the respondent was asked to tick the appropriate box or encircle the number next to the response. With the open ended questions sufficient space was left for answers to avoid the respondent cramming in the response, but not too much space so as to discourage the respondent from completing the questionnaire because of the time it would apparently take (de Vaus, 1986).

The following factors were considered by Berdie and Anderson(1974), Young(1974), and de Vaus(1986), when wording the questions :

a) simple language should be used, and jargon and technical terms should be avoided.
b) short questions which were not confusing.
c) no double barrelled questions.
d) no leading questions, i.e. respondents are to give an answer without feeling that they are giving the wrong answer or a disapproved-of response.

e) avoid questions which use 'not' which can be difficult to understand.

f) respondents should have the necessary knowledge to answer a question

g) words used should have the same meaning to all subjects.

h) no prestige bias should occur in the questions

i) avoid ambiguity

j) avoid blunt direct questions in a sensitive area of questioning

k) the frame of reference must be clear
eg. a time frame - last year, last month

l) the questions shouldn't artificially create opinions

m) use of personal or impersonal wording

n) the questions should not be unnecessarily detailed or objectionable.

The questionnaire for the present case study consisted of 68 questions. All questions were constructed by the writer using the abovementioned guidelines. In questions 1 - 35, general information on the mothers pregnancy, as well as the history and health of the DS child from birth onwards was requested. Questions 36 - 68 were more complex and dealt with the psychosocial effects of having a DS child and how each of the parents coped in such a situation (See Appendix A).

3.5.4.2 **Home Visits and Completion of the Questionnaire**

By telephonic arrangement, visits were organised to the home of the family when it suited them, and the writer. The family was visited by the writer four times over a period of one year; first

when the child was eight months old, then when the child was 14 months, again at 19 months, and lastly at 20 months of age.

On the first two visits to the home, the writer became familiar with the family by taking down a family history in the form of a pedigree, as well as talking with the parents about their infant. This allowed the family and writer to feel at ease with one another.

On the third visit, the writer explained the questionnaire to the parents, and gave it to them to read, allowing them to query any questions they did not understand. The parents were given three weeks to complete the questionnaire. Each parent was expected to complete the questions separately, on the same questionnaire, or give a single response where indicated. On the last visit, the writer went through the completed questionnaire with the parents again, clarifying the vague answers received to the questions asked.

All the information collected from the family was recorded and the findings are summarised in the fifth chapter of this study.

3.6 STATISTICAL ANALYSIS OF THE RESULTS

The Chi-square test was chosen to test the significance of the results observed in the present study. The Chi-square test applies to nominal data and is concerned with the question of whether or not the differences between an observed set of frequencies and a theoretically expected set of frequencies are significant (Nel et al, 1988).

The measure of deviation of ratios is χ^2 which is given by the equation:

$$\chi^2 = \Sigma\frac{(O-E)^2}{E}$$ (Bishop, 1983)

The initial step in significance testing is to identify the null hypothesis (Nel et al, 1988). In the present study the null hypothesis was: "There is no significant difference between the two samples tested". This null hypothesis was either rejected or accepted after: χ^2 had been calculated, the critical value for the χ^2 statistic was obtained from the χ^2 distribution table and a comparison was made between the calculated χ^2 and the critical values to determine whether the calculated χ^2 value was greater or less than the critical value (Nel et al, 1988). In order for the critical value to be obtained the number of degrees of freedom (n-1) was determined. In general if there are n categories, there will be (n-1) degrees of freedom (Bishop, 1983).

The hypothesis was tested at the 0,05 significance level ($p \leq 0,05$) i.e. there was a 95% or greater chance that there was a significant difference between the two samples (Bishop, 1983).

The χ^2 significance test was selected since it is the most appropriate test that could be used for testing the significance between the sets of data obtained in the present study.

3.7 SUMMARY AND CONCLUSION

In this chapter, the setting (the greater metropolitan region of Johannesburg and Soweto) and the scope of the study are described. The time period under investigation was thirteen years, from January 1976 to December 1988. The subjects with DS, ES and PS required for the study were identified from the records held at

the Cytogenetic Unit of the SAIMR. The methods of data collection included a record search and patient file inspection to obtain the details required on DS, ES and PS, for the incidence, annual fluctuation, ethnic distribution, sex ratio and types of trisomy. For statistical analysis and to assess the significance of the results, the χ^2 test was used. A questionnaire was constructed to collect data for the case study part of the project and a suitable family were selected and interviewed using this questionnaire. The information obtained from these methods of data collection was analysed and the results are presented in the following chapter.

CHAPTER 4

4. RESULTS

4.1 INTRODUCTION

Data were collected, from the results of blood and amniotic fluid chromosomal studies, on the three common viable chromosome trisomies, 21, 18 and 13, and the findings are reported in this chapter.

The chapter is divided into three sections and describes :

- the results from an analysis of the records on the blood chromosomal studies (Section 1).
- the results from the analysis of amniotic fluid chromosomal studies, as well as the results on incidence rates for the three trisomies for the selected three year period for both blood and amniotic specimens, combined (Section 2).
- the results on whether the parents of affected infants used the genetic counselling clinic and prenatal diagnostic service (Section 3).

The results from the case study on parents with a Down syndrome child are reported in the following chapter (chapter 5).

4.2 THE OCCURRENCE OF THE THREE TRISOMIES IN BLOOD CHROMOSOMAL STUDIES

A total number of 16 562 blood samples were cultured in the Cytogenetic laboratory over the period of thirteen years (Jan 1976 - Dec 1988). Altogether, 15 359 (92,74%) of these samples were successfully analysed and the chromosome results were obtained. Out of the 15 359 samples studied, 1 531 (9,98%) cases were found to have either Down syndrome (DS), Edwards syndrome (ES) or Patau syndrome (PS). Table 4.1 shows the results obtained.

TABLE 4.1 Cases with Down, Edwards and Patau syndrome detected in 15 359 blood samples (Jan 1976 - Dec 1988).

Syndrome	Cases With A Trisomy		% Of Total Blood Samples	
	No.	%	No.	%
Down	1377	90.0	----	8.97
Edwards	104	6.7	----	0.68
Patau	50	3.3	----	0.33
TOTAL	**1531**	**100.0**	**15359**	**9.98**

Of the 1531 trisomy cases, 672 (44%) were born in Johannesburg or Soweto. This group comprised 600 subjects with Down syndrome, 51 with Edwards syndrome and 21 with Patau syndrome.

As expected Down syndrome was found to be the most frequently occurring condition, followed by Edwards syndrome and then Patau syndrome. The ratio of DS to ES to PS cases was 11.76 : 1 : 0,41. Therefore Down syndrome occurred about ten times more often than Edwards syndrome and about thirty times more often than Patau syndrome in this sample. Edwards syndrome occurred about twice as frequently as Patau syndrome.

4.2.1 The Incidence of the Three Common Chromosome Trisomies.

According to Taber's cyclopedic medical dictionary the term incidence is defined as the frequency of occurrence of any event or condition over a period of time and in relation to the population in which it occurrs. The incidence of DS, ES and PS in the general population of greater Johannesburg and Soweto (all ethnic groups included) was estimated for the thirteen year period under attention, using numbers detected for each trisomy and the birth rate statistics for the geographical area.

In order to estimate an annual incidence rate and assess annual fluctuation, the number of affected individuals was compared with the number of live births in Johannesburg and Soweto, for each consecutive year (collected from the National Health and Population Development Department Annual Reports, 1976-1988). The relevant figures and incidence for each trisomy in each year is recorded in Table 4.2.

TABLE 4.2 The incidence by year for DS, ES and PS in the total population of Johannesburg (1976 - 1988)

Year	Total No. of Births	Ds		Es		Ps	
		No.	Incid.	No.	Incid.	No.	Incid.
1976	31 785	28	1:1135	4	1:7496	2	1:15893
1977	29 514	45	1:656	5	1:5903	0	----
1978	30 012	29	1:1035	4	1:7503	0	----
1979	30 403	37	1:822	3	1:10134	1	1:30403
1980	40 810	53	1:770	3	1:13603	2	1:21624
1981	43 248	40	1:1081	4	1:10812	0	----
1982	45 851	42	1:1092	2	1:22925	2	1:22925
1983	46 226	46	1:1005	5	1:9245	1	1:46226
1984	46 573	92	1:506	3	1:15524	2	1:23287
1985	46 086	51	1:904	4	1:11522	3	1:15362
1986	44 189	35	1:1263	5	1:8837	5	1:8838
1987	46 866	43	1:1090	2	1:23433	1	1:46866
1988	49 194	59	1:834	7	1:7028	2	1:24597
TOTAL	**530 757**	**600**	**1:885**	**51**	**1:10407**	**21**	**1:25274**

4.2.1.1 **Incidence and Annual Fluctuation of Down Syndrome**

The mean incidence rate for Down syndrome was found to be 1:885 over the 13 year period and there was much annual fluctuation (see Figure 4.1). The highest incidence of DS was found to be in the years 1984 (1:506) and 1977 (1:656) and the lowest incidence in 1986 (1:1263).

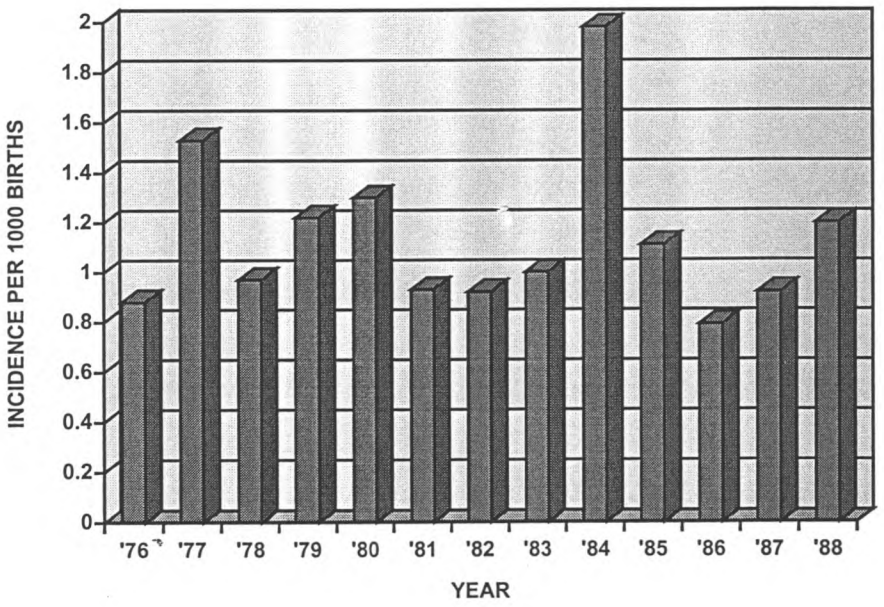


FIGURE 4.1. Annual Incidence Rates of DS (1976-1988)

The results of chi-squared tests on the data showed that there were significant differences between the consecutive years 1976 and 1977 (χ^2=5,39; p<0,05) and between 1983 and 1984 (χ^2=15,36; p<0,001). When the years 1976 to 1981 and 1982 to 1988 were grouped, no significant difference was observed between the two groups (χ^2=0,07; p>0,9), showing that there had been no significant increase or decline in the incidence between the first six year period and the subsequent seven year

period.

4.2.1.2 **Incidence and Annual Fluctuation of Edwards Syndrome**

The fluctuating annual rates for ES are shown in Figure 4.2. These rates followed a similar pattern to those for DS, with the highest rate (1:5903) being in 1977 and the lowest (1:23433) being in 1987. Again there was no real decline in incidence of ES over time.

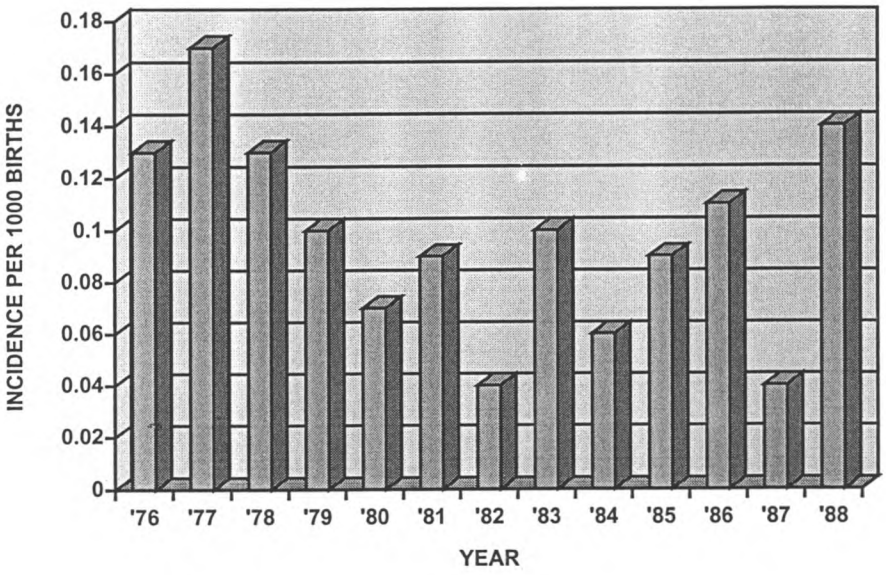


FIGURE 4.2 Annual Incidence Rates of ES (1976 - 1988)

Chi-squared testing for significance between incidence figures for each year was not carried out because the samples of ES cases were so small for each year. As an alternative, the years 1976 to 1981 and 1982 to 1988 were grouped together, but as was the case with the DS incidence rates, no significant difference was found between the two periods (χ^2=0,846; p>0,5).

4.2.1.3 **Incidence and Annual Fluctuation of Patau Syndrome**

Figure 4.3 shows the highest rate of PS (1:8838) was observed in 1986 while in the years 1977, 1978 and 1981 there were no PS cases.

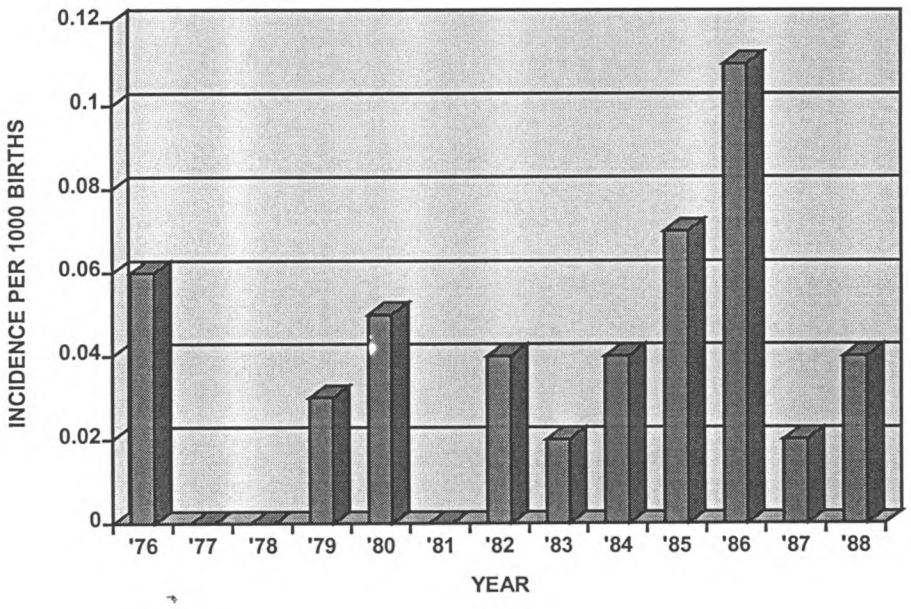


FIGURE 4.3 Annual Incidence Rates for PS (1976 - 1988)

Since the sample of PS was so small (21 Cases), the data were not compared with those available for DS and ES. The number of PS cases for the years 1976 - 1981 and 1982 - 1988 were grouped, but no significant difference was found between the two groups using chi-squared testing ($\chi^2 = 2.064$; $p>0.1$).

4.2.2 **Ethnic Distribution**

The sample was divided into three ethnic groups as follows: a) White; b) Black; and c) Coloured and Indian (C & I). The

number of cases of the three trisomies in each ethnic group appears in Table 4.3.

TABLE 4.3 Ethnic Distribution of Cases of DS, ES and PS in Johannesburg (1976 - 1988)

Ethnic Group	Cases Detected With A Trisomy							
	DS		ES		PS		TOTAL	
	No.	%	No.	%	No.	%	No.	%
White	207	34.5	13	25.5	2	9.5	222	33.0
Black	343	57.2	34	66.7	17	81.0	394	58.6
Coloured & Indian	50	8.3	4	7.8	2	9.5	56	8.4
TOTAL	**600**	**100**	**51**	**100**	**21**	**100**	**672**	**100**

As expected, most cases of DS, ES and PS were in the Black population, which is the largest population group in this geographical area with the highest birth rate. The ratio of DS:ES:PS in each population group was as follows:

The White population group: 15.9:1:0.2
The Black population group: 10.1:1:0.5
The Coloured and Indian population group: 12.5:1:0.5

From these figures, DS appears to be sixteen and thirteen times more common than ES in the White and C & I populations respectively while only ten times more common in the Black population. This finding suggests that there is either

an excessive number of ES cases in the Black population or an underdiagnosis of DS cases in this population. At the same time, DS is about eighty times more common than PS in the White population, while in the Black population, DS is only twenty times more common than PS. These figures suggest that PS occurs more frequently in the Black population than in any other group, or again, that DS is not being adequately detected in the Black population group.

In Table 4.4 data on the ethnic distribution of the total number of bloods studied are presented.

TABLE 4.4 Trisomy Results on cases presenting for Chromosome Studies by ethnic group.

Ethnic Group	No. of cases studied	Cases detected with a trisomy							
		DS		ES		PS		TOTAL	
		No	%	No.	%	No.	%	No.	%
White	9235	207	2.2	13	.14	2	.02	222	2.4
Black	5173	343	6.7	34	.66	17	.33	394	7.6
Coloured & Indian	951	50	5.3	4	.42	2	.21	56	5.9
TOTAL	**15359**	**600**	**3.9**	**51**	**.33**	**21**	**.14**	**672**	**4.4**

From the table it can be seen that more blood samples were received from white subjects than from Black subjects. However, the Black population group has a higher pick - up rate

(7.6%) for all the trisomy cases together, when compared with the pick - up rate (2.4%) in the White population. The difference between the two groups was significant (χ^2=220.63; p<0,001). The pick-up rate for all three trisomies was also significantly higher in the Coloured and Indian group (5.9%) than in the White population (χ^2=39.24; P<0,001).

In order to estimate the incidence of DS, ES and PS in each population group, the total number of affected individuals is compared with the total number of births over the thirteen year period for each population group. The data appear in Table 4.5.

Table 4.5 Incidence of DS, ES and PS in each population group (1976 -1988)

Ethnic Group	Total no. of births	Cases detected with a trisomy					
		DS	Incid.	ES	Incid.	PS	Incid.
White	127217	207	1:615	13	1:9786	2	1:63609
Black	327748	343	1:915	34	1:9640	17	1:19279
C & I	75792	50	1:1516	4	1:18948	2	1:37896
TOTAL	**530757**	**600**	**1:885**	**51**	**1:10407**	**21**	**1:25274**

The data presented in this table suggest that DS occurs more frequently in the White than in the Black population, and less frequently in the Coloured and Indian populations. The many possible reasons for these findings will be discussed in the Discussion Chapter. The incidence of ES appears to be similar in the White and Black population groups, while the rate in the Coloured and Indian groups is much lower. The findings also suggest that the incidence of PS is much higher in the Black

population group, than in both the White and Coloured and Indian groups.

4.2.3 Sex Ratio

The number of males and females with either DS, ES or PS is reported in Table 4.6

TABLE 4.6 Cases of DS, ES and PS by sex (1976-1988)

Sex	DS		ES		PS		TOTAL	
	No.	%	No.	%	No.	%	No.	%
Male	322	53.7	13	25.5	11	52.4	346	51.4
Female	278	46.3	38	74.5	10	47.6	326	48.5
Total	**600**	**100**	**51**	**100**	**21**	**100**	**672**	**100**

In the total number of trisomy cases there were 1.1 males to 1 female. The sex ratio for DS cases was 1.2 males to 1 female. For ES cases it was 1 male to 2,9 females and for PS cases it was 1.1 to 1 respectively. Statistical testing using the χ^2 test (Bishop, 1983) indicates that there was no significant difference between the number of male and female cases detected with either DS (χ^2=3.23; p>0,05) or PS (χ^2=0.05; p>0,05). However, in the group of ES cases there were significantly more females than males (χ^2=12.25; p<0,001).

4.2.4 Types of Down, Edwards and Patau Syndrome

The data on the different types of DS, ES and PS appear in Table 4.7. The translocation category includes all the different types of translocations found in this series of cases.

TABLE 4.7 Types of DS, ES and PS found in 672 affected cases in Johannesburg and Soweto.

Type of Chromosome abnormality	Number of cases for each trisomy					
	DS		ES		PS	
	No.	%	No.	%	No.	%
Trisomy	559	93.2	50	98.0	16	76.2
Mosaic	21	3.5	1	2.0	3	14.3
Translocation	20	3.3	0	0.0	2	9.5
Total	**600**	**100.0**	**51**	**100.0**	**21**	**100.0**

As expected the nondisjunction (or ordinary trisomy) type of DS, ES and PS occurred more frequently than either the translocation or mosaic type cases. Among the DS cases there was little difference in the number of those with the mosaic (21) or translocation (20) type. In the cases with ES however, no translocation cases were observed. Among the PS cases only 76% were nondisjunction and the proportion of mosaic and translocation cases was much higher than in the DS and ES groups.

4.2.5 **Unbalanced Robertsonian Translocation.**

Table 4.8 presents the data on the different unbalanced Robertsonian translocations observed in the cases of DS and PS. No translocations were detected in the ES cases.

TABLE 4.8 Unbalanced Robertsonian Translocations Resulting in DS and PS.

DS			PS		
Translocation type	**No.**	**%**	**Translocation type**	**No.**	**%**
t(14q;21q)	11	55.0	t(13q;14q)	1	50.0
t(21q;21q)	5	25.0	t(13q;13q)	1	50.0
t(13q;21q)	2	10.0			
t(21q;22q)	1	5.0			
t(5q;21q)	1	5.0			
TOTAL	**20**	**100**	**TOTAL**	**2**	**100**

In the 20 cases of translocation type DS, five different Robertsonian translocations were observed, t(14q;21q) was the most frequently occurring translocation followed by t(21q;21q). In each of two cases the DS was caused by a rare translocation, namely t(21q;22q) and t(5q;21q).

4.3 AMNIOTIC FLUID CHROMOSOMAL STUDIES

This section of the study includes chromosome results obtained on amniotic fluid samples over a three year period from January 1986 to December 1988. Altogether 3038 samples were successfully processed during this period.

4.3.1 **Incidence and Annual Fluctuation of DS, ES and PS Detected in Amniotic Fluid Samples.**

In the three year period of this part of the study, 25 cases (0.82%) of women who had foetuses in utero with either DS, ES or PS were identified. In Table 4.9 the number of each trisomy detected by year is presented.

TABLE 4.9 The Incidence of DS, ES and PS Cases in Amniotic Fluid Samples (1986 - 1988)

Year	Total No. of cases*	DS		ES		PS	
		No.	Incid.	No.	Incid.	No.	Incid.
1986	1016	4	1:254	0	0	0	0
1987	1011	4	1:253	2	1:506	1	1:1011
1988	1011	12	1: 84	2	1:506	0	0
Total	**3038**	**20**	**1:152**	**4**	**1:760**	**1**	**1:3038**

*These numbers include only those amniotic fluid samples on which a result was obtained (Approximately 97% of the total received).

The number of cases of Down syndrome occurring by year was similar in the first two years of the study but increased three fold in the third year. There were significantly more cases in the year 1988 as compared with 1987 ($\chi^2=4$; $P<0,05$). These 25 trisomy cases represented affected infants who if they had been born would have been included in the blood sample study reported above. Therefore they should be added to the incidence figures presented above to obtain a more accurate incidence rate for the three trisomies.

4.3.2 Incidence Rate of DS, ES and PS Detected in Amniotic Fluid and Blood Samples (1986 - 1988)

The total incidence rate, from blood and amniotic fluid sample results, was calculated for the years 1986 to 1988 for which the data were available. The livebirth figures from the greater Johannesburg area and Soweto during this three year period were used as the denominator in order to calculate the combined incidence rates for the three trisomies. The results appear in Table 4.10. They provide a more accurate incidence figure since there is a more complete ascertainment of affected individuals in this period than is available through either blood or amniocentesis samples alone.

Table 4.10 Incidence of DS, ES and PS in Blood and Amniotic Fluid Samples (1986 -1988) for N = 140249 Livebirths.

SAMPLE	DS	ES	PS
Blood	137	14	8
Amniotic fluid	20	4	1
TOTAL	**157**	**18**	**9**
Combined Incid.	1:913	1:7960	1:15920
Blood Incid.	1:1023	1:10018	1:17531

When adding the trisomies detected in amniotic fluid samples to the trisomies detected in the blood samples as expected, there is an increase in incidence rates for all three trisomies and a more realistic actual rate is obtained.

4.3.3 Ethnic Distribution

The data available on the ethnic group of the mothers in the sample who had DS, ES and PS detected in their foetuses on amniocentesis appears in Table 4.11.

Out of the total number of 3038 amniocenteses, the vast majority (94%) of samples studied were from White subjects, followed by "Coloured and Indian" and then Black subjects. Appropriately, therefore, the largest number of DS, ES and PS cases were detected in samples from the White population. No cases of DS, ES and PS were detected on amniocentesis in the 'Coloured and Indian' population over this three year period.

Table 4.11. Ethnic Distribution of Cases of DS, ES and PS Detected on Amniocentesis (1986 - 1988).

Ethnic group	Cases detected on amniocentesis							
	DS		ES		PS		Total No. of Amnios	
	No.	%	No.	%	No.	%	No.	%
White	19	95.0	3	75.0	1	100.0	2859	94.1
Black	1	5.0	1	25.0	0	0.0	83	2.7
Coloured & Indian	0	0.0	0	0.0	0	0.0	96	3.2
Total	**20**	**100.0**	**4**	**100.0**	**1**	**100.0**	**3038**	**100.0**

4.3.4 **Sex Ratio**

The number of males and females affected by each syndrome, as detected on an amniotic fluid sample is reported in Table 4.12. Using the figures presented in Table 4.12 the sex ratio could be calculated and for DS cases it was 1.1 males to 1 female. Although there were more males than females affected

by DS, the sample was too small to show a significant difference (χ^2=0,2; p>0,5). For ES cases the sex ratio was 1 male to 3 females. No male PS cases were detected. This result was similar to that found in the blood chromosome study reported above.

TABLE 4.12 Sex Ratio in DS, ES and PS Cases Detected on Amniocentesis (1986 - 1988)

Sex	DS		ES		PS		Total	
	No.	%	No.	%	No.	%	No.	%
Male	11	55.0	1	25.0	0	0.0	12	48.0
Female	9	45.0	3	75.0	1	100.0	13	52.0
TOTAL	**20**	**100.0**	**4**	**100.0**	**1**	**100.0**	**25**	**100.0**

4.4 UTILISATION OF GENETIC COUNSELLING CLINICS AND PRENATAL DIAGNOSTIC SERVICES IN JOHANNESBURG

The utilisation of genetic counselling clinics and prenatal diagnostic services by the parents, after a trisomy had been diagnosed on blood or amniocentesis in their child, was assessed over a period of three years (Jan 1986 - Dec 1988).

This section is divided into two parts :

Section 1: includes the parents' use of the genetic counselling clinic after a trisomy was diagnosed on a blood sample from their child

Section 2: describes the utilisation of prenatal diagnostic services and genetic counselling clinics after either DS, ES or PS was detected on an amniotic fluid sample.

4.4.1 **Utilisation of Genetic Counselling Clinics After the Birth of an Infant with Either DS, ES or PS.**

For parents who had an infant clinically diagnosed as having either DS, ES or PS, the opportunity was available for an appointment at a Genetic Counselling Clinic in Johannesburg. At this Clinic, genetic counselling, information on the condition and an explanation of the cytogenetic diagnosis was provided. The few couples with an affected infant who used this resource is recorded in Table 4.13.

TABLE 4.13 Utilisation of the Genetic Counselling Clinic After the Birth of a Child with Either DS, ES or PS (1986-1988) by Population Group.

Ethnic group	DS		ES		PS		Total	
	No.	%	No.	%	No.	%	No.	%
White	14	35.9	2	33.3	1	33.3	17	35.4
Black	23	59.0	4	66.7	2	66.7	29	60.4
Coloured & Indian	2	5.1	0	0.0	0	0.0	2	4.2
Total	**39**	**100.0**	**6**	**100.0**	**3**	**100.0**	**48**	**100.0**

According to the files of trisomy cases studied, out of the total number of 1531 trisomy cases, obtained from results of blood chromosome analysis of patients from Johannesburg and Soweto (See Table 4.1), only 48 (3.1%) attended a Johannesburg Genetic counselling clinic during the years 1976 to 1988.

4.4.2 **Utilisation of Prenatal Diagnostic Services and Genetic Counselling Clinics After Either DS, ES or PS had Been Detected on Amniocentesis.**

Over a three year period (January 1986 - December 1988) a total of 3125 amniocenteses were performed, 3038 of which were successfully cultured and results were obtained. On investigation of these 3125 files, the majority of patients referred for counselling and amniocentesis (2378 out of 3125, 76.1%) were of the advanced maternal age category, i.e. the mother was 35 years or older. Since the incidence of DS, ES and PS is known to increase with advanced maternal age, the files for these women were investigated in more detail to establish how many had affected infants. The results are presented in Table 4.14.

TABLE 4.14 AMA Cases in which DS, ES or PS was Diagnosed in the Foetus (1986-1988).

Year	Total No. AMA cases	No. of AMA'S							
		DS		ES		PS		Tot.	
		No.	%	No.	%	No.	%	No.	%
1986	808	3	0.37	0	0.00	0	0.00	3	0.37
1987	798	4	0.50	2	0.25	1	0.13	7	0.88
1988	772	11	1.42	2	0.26	0	0.00	12	1.68
Tot.	**2378**	**18**	**0.76**	**4**	**0.17**	**1**	**0.04**	**23**	**0.97**

Altogether there were 23 cases of women with trisomic

foetuses out of 2378 amniocenteses performed in which the mother was aged 35 years or older. In this group of women, therefore, the risk of having a trisomic infant was 1%. There were a further two cases in which a trisomy was diagnosed in younger women (<35 years). One of these cases was referred because the mother had a previous infant with DS and the other had had a child affected with hydrocephalus.

Once either DS, ES or PS had been detected on amniocentesis, the parents could attend the Genetic counselling clinic to discuss the condition which had been diagnosed. They then had two options, either to request a legal termination or to continue with the pregnancy. The number of parents, including both mothers from older and younger age groups, who attended the Genetic counselling clinic for counselling regarding a prenatally diagnosed trisomy and those who decided to terminate is reported in Table 4.15.

TABLE 4.15 Rate of Termination for a Trisomic Foetus and Utilisation of the Genetic Counselling Clinic (either Before and/or After the Termination)(1986 -1988).

Year	No. of cases of trisomy	Terminated		Counselled	
		No.	%	No.	%
1986	4	4	100.0	2	50.0
1987	7	7	100.0	0	0.00
1988	14	12	85.7	4	28.3
Total	**25**	**23**	**92.0**	**6**	**24.0**

Only a quarter of the parents with affected foetuses attended a Johannesburg Genetic counselling clinic. Most (92%) of those who were given the diagnosis of a trisomy in the foetus in utero, requested termination of the pregnancy. In the two cases in which a termination did not apparently take place, one foetus miscarried before a termination was performed and in the other case, the patient was lost to follow up.

4.5 SUMMARY AND CONCLUSION

Nearly one tenth of all the samples received in the Cytogenetics laboratory in the thirteen year period under review, resulted in either DS, ES or PS, indicating that these trisomies are a common chromosome finding. Out of the 15 359 blood chromosomal samples successfully cultured, one of the viable common trisomies (DS, ES or PS) was found in 672 Johannesburg and Soweto cases.

The figures for each trisomy were compared with the birth rate in Johannesburg and Soweto for the thirteen year period and the corresponding incidence rates were calculated. The mean incidence rate for DS was found to be 1:885, for ES, 1:10413 and for PS, 1:25288. As expected, most cases of DS, ES and PS were found in the Black population, mostly because they provided the largest sample in this study. However, other reasons might include their lower use of prenatal diagnostic services and of family planning clinics so that black mothers may continue child-bearing over the age of 35 years, more often than other groups do.

The sex ratio of males to females in the DS and PS cases was more or less even but for ES cases there was an excess of females (3:1). Among all the trisomy cases the nondisjunction type was found to be

most common, although in PS cases it occurred in 76% of cases compared with 93% and 98% for DS and ES, respectively. A large proportion of the remaining PS cases were mosaic (14.3%), a larger proportion than in the DS and ES cases. The most frequently occurring DS translocation type was t(14q; 21q).

Over a 3 year period (January 1986 - December 1988) the prevalence of DS, ES and PS in amniotic fluid samples was 1:152, 1:760 and 1:3038 respectively. When this period, was investigated and the results on both blood and amniotic fluid samples were combined, the incidence figure in comparison with the thirteen year rates was lower for DS (1: 913), ES (1:7690) and PS (1:15920). The largest number of DS, ES and PS cases were detected in the White population, since White patients provided the largest sample of amniotic fluid samples received. In the advanced maternal age group (2378 cases) in this study, the risk of having a DS, ES or PS foetus was 1%. Out of the total number of 1531 families having a child with a trisomy diagnosed in a blood sample, only 48 (3.1%) attended a Johannesburg Genetic Counselling Clinic after the diagnosis had been made. Out of 25 cases where either DS, ES or PS was diagnosed on amniocentesis, 23 were referred for amniocentesis because of their advanced maternal age. Most (92%) of the pregnancies in which an affected foetus was found were terminated at the parents' request. The results found here will be discussed and compared with those from other international and local studies in Chapter 6.

CHAPTER 5

5. CASE PRESENTATION

5.1 INTRODUCTION

Since Down syndrome is the most common viable trisomy, there are a large number of families in South Africa who have an affected child. The writer, therefore decided to include an in depth investigation of a family with a Down syndrome infant in the present study. The aim was to gain insight into how the parents coped with the infant, as well as to obtain some understanding of the psycho-social effects of having such an infant on the parents.

The parents were interviewed at their home on four occasions using a questionnaire on the third visit. In this chapter, findings from the information collected over the four interviews (including the completed questionnaire) on the family background, the family pedigree, the history of the pregnancy, the affected child, and the parents' attitudes and feelings are reported.

5.2 THE E FAMILY.

Mr E. E. and Mrs J. E. are parents of Eugene, a male infant with Down syndrome. At the time of his birth, Mrs E was 37 years of age and Mr E was 30 years of age.

5.2.1 Family Background

Mr and Mrs E were a middle class white couple who lived in a flat in Kempton Park. Mr E was an accountant and Mrs E worked as an operations assistant for a shipping company before the birth of Eugene.

Both Mr and Mrs E are bilingual, although Mr E came from an

Afrikaans background and Mrs E had English ancestry. The family pedigree is shown in Figure 5.1. The information was obtained from Mr (III_1) and Mrs (III_2) and has not been verified from any other source.

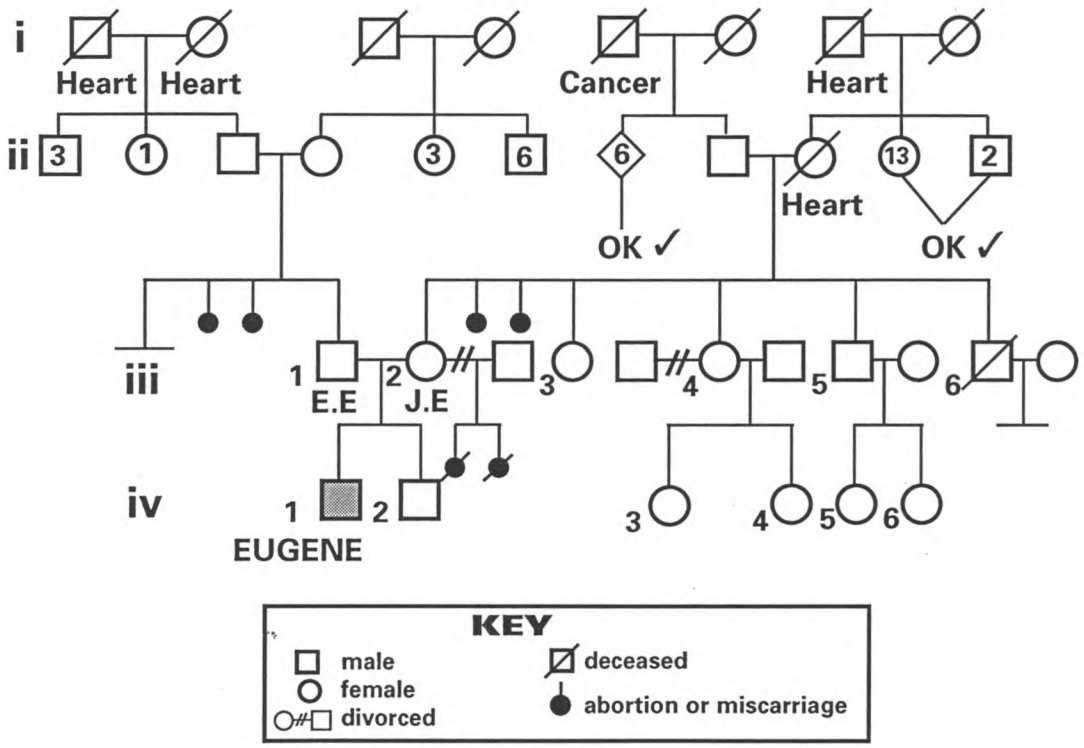


FIGURE 5.1: Pedigree of the E Family

There was no family history of Down syndrome or any other genetic disorder. However, Mrs E's sister was a diabetic. Mrs E was married previously and had had two elective abortions in the early stages of pregnancy (first trimester) during her first marriage. She stated that these terminations were done for psychological reasons pertaining to herself, and her previous husband, but she did not elaborate on this subject.

5.2.2 **History of the Pregnancy with Eugene**

Mrs E's pregnancy (which resulted in the birth of the Down syndrome infant) was the first from her second marriage and she was 37 years old at the time. At this age, she had a risk of 1 in 250 for Down syndrome and 1 in 123 (Hook, 1981) for any chromosomal abnormality, but the couple were not referred for Genetic counselling.

The pregnancy progressed well, with the only infection being vaginal thrush. Mrs E did not require any medication during the pregnancy and neither she nor her husband were exposed to radiation before or during the pregnancy. The pregnancy did not reach full-term and Eugene was delivered at 38 weeks gestation. However, the delivery was normal and the baby boy weighed 2,44kg. Mrs E became pregnant again a year later and after an amniocentesis and prenatal diagnosis with a normal result, she had a normal boy.

5.2.3 **General History of Eugene E**

The paediatrician informed Mrs E about seven hours after Eugene's birth, that he thought the infant had Down syndrome. The diagnosis was confirmed on chromosomal analysis and the results showed that Eugene had Down syndrome of the nondisjunction type (47,XY,+21).

Mrs E had little knowledge of Down syndrome before the birth of Eugene and she did not notice anything abnormal about him at first. Only after information had been given to her by the staff of the District Health Clinic, the Sunshine Centre (a pre-school centre for mentally handicapped children) staff, a paediatrician and the Down syndrome Association, did Mrs E's knowledge of the syndrome increase and she was able to

recognise Eugene's specific Down syndrome characteristics, i.e. his up-slanted eyes, webbed neck, palmar crease, cleft between his toes, short stubby fingers, curl of the little finger (clinodactyly), flattened bridge of his nose and low-set ears.

Eugene was born with an endocardial cushion defect, which was surgically corrected by "inserting a patch over the hole", according to Mrs E. He improved physically after the operation. He was very susceptible to infections and had a history of chest, ear, throat, urinary tract and penis infections during his first year of life.

Eugene's milestones, according to his parents, were as follows: he smiled at an early age, rolled over at six months, sat between ten to twelve months, started to crawl at eighteen months, walked along tables and sofas at eighteen and a half months. However, he stopped walking because of his heart operation, and then started again at about two years. He started talking at about one year, using single words such as mama, baba, dada, aya (hello) and um (come). Although Eugene did not show a failure to thrive at any time, he had varied eating and sleeping habits, sometimes eating and sleeping poorly. However, at the time of his heart operation, he was bigger than expected and did not suffer any setback after it. Eugene's mental capabilities were seen by his parents as being reduced, at the time of the interviews. They also expected him to have decreased intellectual functioning in the future.

Mr and Mrs E made contact with the local Down syndrome Association (DSA) which organises parent meetings. At these

meetings parents may discuss the problems and joys they encounter as a result of having a Down syndrome child. The Association also offers assistance and advice regarding coping with an affected child. Mr and Mrs E, however, preferred to handle Eugene in their own manner and did not attend the meetings. They felt that being in contact with the DSA did not benefit them in any way. Mr and Mrs E, however, retained contact with the Sunshine Centre and Eugene followed their home education programme. This programme is called "START" which stands for "Strive towards achieving results together". The START programme involves physical and mental stimulation of the child at home and the activities are divided into the following categories: gross motor, fine motor, activities of daily living, receptive language and cognitive skills. Mrs E felt that Eugene benefited tremendously from this programme and she eagerly awaited each new section of the home education course. Eugene received therapy, once a month, each from an occupational therapist, a speech therapist and a physiotherapist, which also helped him progress. Mr and Mrs E both noticed a physical and mental improvement in Eugene after he started these therapy sessions.

When asked how they saw Eugene's future, Mr and Mrs E felt that he would be "acceptable" in society and be able to master something to earn a small income, perhaps in sheltered employment or in a government department, e.g. helping with admissions in a small hospital.

5.2.4 Psychosocial Effects on the Nuclear Family

During the interview on the psychosocial effects of having a Down syndrome child, both parents were present but each had

a chance to answer each question separately.

After hearing the diagnosis that Eugene had Down syndrome, both Mr and Mrs E were very disappointed. Mrs E, however, felt that she had had a premonition that something was wrong with her baby. At first, before leaving the hospital, Mrs E had wished that her baby would die. However, at the time of these interviews, she was relieved that there was assistance available to help her child and she stated that she "loved him to bits and would ensure that he stayed alive with as much all round quality as possible". Mr E was initially warned about Eugene's progress, but during the interviews he said that he "would not exchange him for anything" and "loves him a lot".

Both Mrs and Mr E felt that they had accepted the birth of their Down syndrome child even before Mrs E was discharged from hospital. Mrs E felt that having a Down syndrome child had affected her mental and physical health, since she experienced a lot of stress and frustration with trying to do too much for Eugene and felt that she was not as energetic as before. Mr E, however, felt that his health had not altered since Eugene was born.

Both Mr and Mrs E felt that their social life had changed. Before Eugene's birth they had had a very full social life but afterwards they felt that they could not leave Eugene and therefore stayed at home a lot more than they used to do. Mr and Mrs E both felt that they could cope with Eugene's condition. They received support from each other, the immediate family and friends, and some comfort from literature sources such as books and leaflets.

While learning to manage their child, Mr and Mrs E experienced different emotions. Mrs E stated that she was initially shocked for about three days after the birth of her child and then she became anxious as to how she would deal with the problem. This anxiety lasted about a month. She also experienced feelings of guilt and blamed herself for her child's condition. She overcame this feeling once the family appeared to have accepted that Eugene had Down syndrome. Mrs E stated that she never denied her child's diagnosis, nor did she feel any anger towards anyone because of Eugene's problem. She added that she had not been depressed due to the situation.

Mr E, on the other hand, felt he experienced many more emotions than his wife. He stated that at first he was shocked and then tried to deny his child's condition for about three months. After this period he came to accept the problem but then felt anxious as to how he would deal with it. Mr E also said he experienced feelings of anger towards his child, himself, his wife and his family, as well as feeling depressed and guilty for a short period. Although Mr and Mrs E experienced these different emotions at different times during their coping process, they felt that the birth of Eugene did not strain their marriage in any way. They agreed that they were still as happily married after the birth, as they were before.

The relationship between all the family members was good before Eugene's birth and was still good at the time of the interviews. The extended family were notified immediately, by both parents, of the baby's condition. According to Mrs E, her father was initially shocked and felt pity towards his daughter

and her brothers and sisters were distressed about the news. Her family eventually accepted Eugene although Mrs E felt that her father was not aware of the associated complications. Both, Mr and Mrs E reported that the family felt that Eugene was "not too far behind" and they were all relieved to see that the parents were coping well. According to Mr E, his parents were initially disappointed, because Eugene was their first grandchild, but have since accepted him with love.

Before the birth of Eugene, Mr and Mrs E planned to have two children. This decision was not altered after his birth and Mrs E had her second child almost two years later. The couple were informed about the Genetic Counselling Clinic soon after they received Eugene's diagnosis and they attended for genetic counselling. They felt that this session benefited them since it "made us realise that no one was truly to blame". Prior to Eugene's birth, both parents stated that they knew of the increased risk of having a Down syndrome child associated with advancing maternal age and were also aware of the possibility of prenatal diagnosis. Although they mentioned this risk to the Gynaecologist, he felt prenatal diagnosis was not necessary and they therefore went ahead with the pregnancy. Mrs E, however, had an amniocentesis in her subsequent pregnancy. Both Mr and Mrs E stated at the time of the interviews with the writer, that they would terminate a pregnancy if an affected foetus was diagnosed. They felt that after their deaths, their children would not receive as high a standard of care as they were able to give them.

A special message from Mr and Mrs E to others with the same

plight is: **"Count your blessings. Down syndrome is the least affected of handicapped persons, as you will notice in time".**

5.3 SUMMARY AND CONCLUSION

The writer interviewed a couple with a Down syndrome infant four times and collected general information on the family background, history of the mothers' pregnancy and the infant's first year of life. Both parents were initially very disappointed about the diagnosis of Down syndrome in their son, but with the support of family and friends, they were eventually able to accept him, having experienced the normal emotions of shock, denial, anxiety, guilt, anger and depression. By making contact with the Sunshine Centre (for pre-school children with an intellectual disability), the parents learned more about DS and were able to put their son on a stimulation programme, which produced pleasing results. Both parents have learned to cope well with having a DS infant but in a subsequent pregnancy they chose to have amniocentesis as they felt that they would request termination if an affected infant, was diagnosed.

This case history shows how the parents, after the initial shock of the diagnosis can adapt, cope with the affected child and constructively assist him to reach his potential. They are also able to plan their future children using the genetic counselling and prenatal diagnosis facilities and by choosing the best available option, to meet their needs, they can improve their quality of life.

CHAPTER 6

6. DISCUSSION AND CONCLUSION

6.1 INTRODUCTION

The findings of this study, presented in Chapter 4, showed that in a thirteen year sample from Johannesburg and Soweto, Down, Edwards and Patau syndromes, occurred in all ethnic groups. There was marked annual fluctuation over the period, in the incidence rates for the three trisomies and the sex ratios were similar for DS and PS but not for ES. Several different karyotypes were associated with each condition but non-disjunction trisomies accounted for over 90% of DS and ES cases but only for 76% of PS cases.

In this chapter, these findings from the present study, will be compared with those from other South African and international studies. The incidence rates, annual fluctuation, ethnic distribution, sex ratio and types found, in both blood and amniotic samples, for each trisomy will be discussed. Also, interesting psychological aspects from the case study will be compared with the reported psychological reactions to stress situations and to the presence of a Down syndrome child in the family. Finally, the limitations of the present study will be discussed and some suggestions for further research and recommendations for future action will be outlined.

6.2 BLOOD CHROMOSOMAL STUDIES

6.2.1 Incidence in the Total Sample

According to the findings of the present study, which was based on samples received in the cytogenetics laboratory at the SAIMR, the estimated incidence of Down syndrome in all population groups together, in the thirteen year period

investigated (Jan 1976 - Dec 1988) was 1:885 (600 in 531057 live births). This rate is similar to that reported in other laboratory based studies, for example: Mikkelsen et al (1976) observed an incidence of 1: 871 in Denmark; Iselius and Lindstein (1986) recorded an incidence of 1:780 in Sweden. In Smart's South African study in the Cape Province (1981), an incidence of 1:750 was documented in the population studied.

Although the incidence of DS in the present laboratory based study is similar to that found in other such studies, it may represent an underestimate and the true incidence may be somewhat higher due to the fact that some DS infants born, especially those born to Black women, may not be diagnosed neonatally. This could be ascribed to the fact that after delivery of their infants, black women often remain for a short period only (± 24 hours), in the hospitals. Also, normal black infants may have some features in common with some DS infants, such as flat facies and a broad nasal bridge, and therefore some affected infants may remain unrecognised initially (Kromberg and Zwane, 1993; Christianson et al, 1995) until their slow development or learning problems are observed.

The mean incidence rate for ES in the present study was 1:10413 (51 in 531037 live births). These results were compared with three separate studies, one conducted by Anneren (1986), with a sample size of 186800 births, another by Farag et al (1988), with a sample size of 32237 births and the last by Goldstein and Nielsen (1988) where 76 cases of ES were identified. Anneren found an incidence of 1:8500 for ES in Sweden, Farag et al documented an incidence of 1:8059 for ES in Kuwait and Goldstein and Nielsen reported an incidence of

1:7343 for ES in Denmark.. These figures were slightly higher than those found in the present study again possibly due to underdiagnosis in the developing black community in which health services are also developing and are not always accessible.

PS was found to have a mean incidence rate of 1:25288 (21 in 531037 live births) in the present study. In comparison, Borovik et al (1989) documented a similar incidence rate of 1:24397 for PS in Brazil.

These incidence rates represent a minimum incidence for livebirths, the actual incidence rates at conception are much higher since a percentage of the trisomy foetuses do not reach term, either being miscarried at an early stage or are now more frequently being picked up on amniocentesis or chorionic villus sampling in women over the age of 35 years.

6.2.2 Annual Incidence

The annual incidence rates of ES followed a similar fluctuating pattern to that of DS with the highest incidence for ES and the second highest incidence for DS, in the thirteen year period investigated, being in 1977. This increased incidence in 1977 occurred in the total population studied which included all population groups. Whether the increase occurred in a particular population group, in that particular year, for example, the Black population, requires further investigation. The increased incidence in 1977 may have been due to a large number of older women (>35 years, at high risk for producing infants with a trisomy) than usual, by chance, giving birth that year, and/or such women may not have attended a genetic

counselling clinic or opted for amniocentesis, again by chance.

Alternatively, it might have been due to the natural cyclical fluctuation which occurs in the incidence of trisomies as reported by Iselius and Lindstein (1986). Possible environmental factors which have an effect on increasing the nondisjunction rate of the chromosomal material, or increasing the predisposition of mothers to nondisjunction resulting in a trisomy, may have been prevalent in 1977. However, such factors have not yet been identified in the present study, although it is possible that high levels of radiation e.g. diagnostic X-rays or exposure to chemicals e.g. pesticides may be one of them (Uchida et al, 1968).

6.2.3 Ethnic Distribution

As expected from the numerical size of the population groups in South Africa, the majority of cases of DS,ES and PS (394 cases) were observed in the Black population, which is the largest group.

Amongst all the population groups, the highest incidence of DS occurred in the White population (1:615). This figure is possibly the most accurate since it is the White population group who are probably more informed about the genetic risks and who have access to and use the best genetic diagnostic services. Even though these prenatal diagnostic services are available, the incidence rate is still higher than in some other countries. A possible explanation for this high incidence rate is the fact that the population in the geographical region studied, are presently dwelling over previous gold mining areas where radiation rates

may have been or may still be at high levels (Prof McGregor, Department of Geology, University of the Witwatersrand - Personal communication) thus causing certain problems to arise in the genetic material which may result in nondisjunction.

This DS incidence rate is higher than that reported by Iselius and Lindstein (1986), who found an inciednce rate for DS, of 1:780 in Sweden. This lower Swedish rate may be a result of the more extensive use of the prenatal diagnostic services by the at- risk women in Sweden in comparison with their counterparts in South Africa. Another factor that may be considered is that there may be fewer older women in Sweden reproducing than there are in South Africa. However, the figure (1:650) for the overall world population rate presented by Harper (1993) is similar to that reported in this study.

In the present study an incidence of 1:955 was reported for DS in the Black population group. This rate is similar to the results of Smart's study where an incidence rate of 1:1170 was reported for the Black population and 1:830 for Coloured , Indian and Asian groups, and to Adeyokunnu's (1982) study where he reported an incidence of 1:865 in a Nigerian hospital. Although the incidence rate of 1:955 for DS in the Black population is similar to some other studies there is a marked difference from that of 1:600 documented for this group by Kromberg and Zwane (1993). This difference may be explained partly by the fact that Kromberg and Zwane's study (1993) was conducted over a one year period, while a thirteen period was used in this study. At the same time, the Kromberg and Zwane study was a hospital and clinic based study, while in the

present study the figures were obtained from a laboratory to which samples are referred. The figures for such laboratory based studies are likely to be lower than those obtained from hospitals where infants are clinically examined. In 1974, Axton and Levy estimated the incidence to be 1:600 in Southern Rhodesia (now Zimbabwe), a higher incidence in comparison to the results of the present study, but similar to those obtained by Kromberg and Zwane (1993). Although the incidence rates in the Black population group in the present study may differ from those found in other reports, the incidence of DS in the Black population (1:955) is much lower than the rate reported for White individuals (1:615). Since there is thought to be a large proportion of Black women over the age of 35 years who are child-bearing and are therefore at a high risk for a chromosomal abnormality, this incidence for DS in the Black population may be assumed to be an underestimate, probably also due to both underdiagnosis and possibly a higher mortality rate because of poorer primary health care facilities.

An increased number of PS cases (1:19279) was noted in the Black population in comparison with the White, and the Coloured and Indian population groups, in which the incidence rate was 1:63609 and 1:37896, respectively, as well as the total group of all subjects in which the rate was 1:25274. The rate in the Black population was therefore more than three times higher than the rate in the White population. Although there is no obvious reason for the increased incidence of PS in the Black population, the following hypotheses may be considered:- black women may have an increased ability over other women to carry the affected foetus to term; or perhaps a reduced likelihood of spontaneously aborting such a foetus; or they may

be more susceptible to the environmental factors causing nondisjunction of chromosome 13. However, there were only 17 cases in the Black population and two cases in both the White, and the Coloured and Indian group, so although the denominators were large, the sample could be too small to draw any reliable conclusions. This finding should therefore be regarded only as a trend that requires further investigation.

6.2.4 Sex Ratio

The sex ratio of male to female infants with DS, in the total sample, were observed to be 1.2:1. This ratio is similar to that reported in another South African study where Nelson and Smart (1982) found a 1.1:1 ratio of Down syndrome males to females in the Cape.

The ratio of males to females for the ES cases in the present study, however, was 1 : 2.9. Anneren (1986), Goldstein and Nielsen (1988) and Baty et al (1994), also found a preponderance of ES females with a sex ratio of 3 females to 1 male. This phenomenon has been ascribed to the preferential survival of female foetuses with ES compared with affected male foetuses (Taylor,1968).

Goldstein and Nielsen (1988) reported a ratio of 1.1 PS males:1 PS female in their ten year study in Denmark. This is exactly the same as the PS male to female ratio of 1.1:1 reported in this study. In another study, however, Baty et al (1994) reported that there were more girls than boys presenting with PS in Utah. The sample in both the present study (21 cases of PS) and the Danish study (19 cases of PS) may be too small to draw firm conclusions with regards to the sex ratio although it seems likely

that males and females are equally at risk for having PS.

6.2.5 Types of DS, ES and PS

a) **Non-disjunction type**

As expected, in the present study, most (93.2%) of DS cases were of the nondisjunction type. In the four other South African studies carried out on DS in the Transvaal, Natal, Cape Province and the whole of South Africa (Venter and Op't Hof, 1982; Grace et al, 1979, Nelson, 1982, and Retief et al, 1983, respectively), the nondisjunction form also occurred most frequently. Mikkelsen et al (1976) and Speed et al (1976) confirm this predominance of nondisjunction type DS with percentages of 90% and 94%, respectively, of all DS cases karyotyped.

Similarly, 98% of ES cases in this study were of the nondisjunction type. This finding corresponds with that of Kondoh et al (1988) who stated that almost all ES cases are of the non-disjunction type.

In the present study, however, only 76% of PS cases occurred as a result of nondisjunction. According to Schinzel (1984), 80% of all PS cases are a result of non-disjunction, therefore the results of the present study are in accordance with his findings, and nondisjunction is responsible for fewer cases of this trisomy than is the case for DS and ES. Increased rates of nondisjunction of chromosomes 21,18 and 13 are associated with increased maternal age (Harper, 1993). It can therefore be surmised

that a large percentage of these nondisjunction type DS, ES and PS cases were born to mothers over the age of 35 years, although paternal age may also play a role (Mikkelsen,1976).

b) **Translocation type**

In the present study, various types of translocation DS cases were observed. The majority of the Robertsonian translocations reported for DS were those involving chromosomes 21 and 14 (55% of all DS translocations) followed by t(21;21) (25% of all DS translocations) and the remaining 20% were translocations between chromosome numbers, 21 and 13; 21 and 22 and 21 and 5 (not reported elsewhere). These figures support those reported in Mikkelsen's study (1976) in Denmark in which 63.6% of translocations were reported to be due to a t(14;21) translocation and 27.3% due to a t(21;21) translocation. An interesting investigation for further studies would be to determine which translocation was more prevalent in each population group and the possible reasons why the difference in types of translocation occurred, if any.

No translocation ES cases were found in the 51 cases of ES in the present study. According to the literature, it appears that only a few cases of translocation ES have been described in the published articles reviewed, all of which were translocations between chromosome 18 and another D group chromosome (Hamerton, 1971). It can therefore be surmised that translocation cases of ES are very rare.

The most commonly occurring Robertsonian translocation for PS cases is the t(13;14) (Hook,1981) followed by t(13;13) (Parslow et al,1973). In the present study only two out of 21 PS cases in total, were translocation PS and one was of the most common type reported in the literature i.e. t(13;14) and the other was t(13;13).

c) **Mosaicism**

Mosaicism, arising from two cell lines with different karyotypes, was observed in all three groups of trisomies. Of all the Down syndrome cases, 3.5%, were reported to be mosaic in the present study. This figure was lower than the 5.7% reported by Retief et al in 1983 but marginally higher than the 1% that was documented by Clarke et al in 1989, but it is difficult to propose a possible explanation. According to Thompson and Thompson (1982), mosaicism in ES occurs in 10% of cases. The present study's figure of 2% is much lower than the expected number of mosaics reported. A possible reason for this is the small sample number of ES cases (51 cases) which may produce insignificant data.

Of the 21 PS cases, 14.3% were reported to be mosaic in the present study. This figure is substantially higher than the figure of 2.5% reported by Hassold et al (1987) in Honolulu in 41 cases of PS.

The reason for this apparent increase in mosaicism in Down and Patau syndrome in the present study is not known. However, it is possible that local environmental

factors, different to those found elsewhere in the world, could have played a role in causing some of the cell lines to undergo nondisjunction during the zygotic stage. At the same time, different environmental factors may have resulted in abortion of normal trisomic foetuses, but allowed mosaic cases to reach term thus resulting in a higher incidence of mosaics. It is possible that full trisomies are more likely to spontaneously abort, whereas the mosaic foetus may come to term, especially where antenatal care and prenatal diagnosis and genetic counselling services for the majority of the population are less than satisfactory.

An area for further investigation is the ethnic distribution of mosaic cases of DS, ES and PS which may lead to an answer as to why there is a difference locally in the number of mosaic cases for each trisomy in comparison with other studies. It may be hypothesised that the genetic and/or socioeconomic differences in each population group may have a role to play in the probability of the mother carrying the mosaic foetus to term. Alternatively there may be geographical or environmental factors such as increased radiation, due to the gold mining and other minerals occurring in the area, leading to a higher rate of mosaicism.

6.3 AMNIOTIC FLUID CHROMOSOMAL STUDIES

6.3.1 Incidence and Annual Fluctuation

The number of amniocenteses performed each year is on the increase. This can be demonstrated by the fact that in the

decade from 1976 to 1985, only 4554 cases of amniocentesis were performed in Johannesburg (Kromberg et al, 1989), while 3038 cases were performed in the three year period from 1986 till 1988.

Out of these 3038 cases included in the present study, 20 cases of DS were detected (i.e. 1 in 152 pregnancies). These results are lower than those of Kromberg et al (1989) who reported finding an average of one DS case in every 117 amniocenteses over a period of ten years (1976 - 1985).In order to achieve a better perspective of the prevalence of the trisomies detected on amniocentesis, the data from Kromberg et al's study was combined with the present study's three year data to provide the following statistics: 1:128 for DS, 1:949 for ES and 1:3796 for PS. The slightly lower DS rate in the present study may be attributed to the fact that as amniocentesis and prenatal diagnosis become more popular, more low risk women start to request the procedures, leading to a lower pickup rate for DS. Another factor is the shorter time period (3 years vs. 10 years) and smaller sample studied in the present research project. The majority of these DS cases were detected in 1988 (12 cases),although the number of amniocentesis performed that year was little different to any other year (in 1986 and 1987 there were 1016 amniocenteses performed and in 1988, 1011 were done). This high rate of DS in 1988, may be explained by either, normal annual fluctuations which are evidenced in the present study and have been reported elsewhere (Iselius and Lindstein in Denmark ,1986), and/or possible environmental factors which may have had an effect on increasing the occurrence of non-disjunction of chromosomal material in either the ova at meiosis I or II, or the sperm; or an increase in the

number of mothers, over the age of 35 years, that gave birth in 1988.

The sample of ES(N=4) and PS(N=1) cases detected by amniocentesis was too small for consideration.

6.3.2 Ethnic Distribution

The majority (94.1%) of amniotic fluid samples included in the present study, originated in the white population, although the majority of pregnant women are black (Kromberg et al, 1989). It appears that there is a lack of awareness and therefore reduced utilisation of the genetic services available in the Black, Coloured and Indian populations. It is important that these population groups are made familiar with the risks associated with pregnancies in older women, with the amniocentesis procedure and its usefulness, and with the genetic counselling facilities that are available to them. By increasing the level of awareness in these groups, the number of amniocenteses performed should be increased and if the options of prenatal diagnosis and selective abortion are taken up, the number of DS, ES and PS births will be decreased.

6.3.3 Sex Ratio

There was no real difference noted in the male to female ratios of the DS(1.1:1) cases from amniotic fluid samples and this ratio was similar to that found in this study on liveborn DS infants (1.2:1). Iselius and Lindstein from Sweden (1986) noted a male to female ratio in DS abortuses of 1.2 to 1 which was the same as they found for liveborn DS infants.

The small sample of ES cases (N=4) detected on

amniocentesis, however, showed a preponderance of females to males (3:1) which differs from the 1:1 ratio of ES males to ES females detected by prenatal diagnosis, in a study of 46 cases reported by Goldstein and Nielsen(1988). The sample size in the present study (N=4) was too small to draw conclusions. In the liveborn cases studied here, however, the sex ratio was distorted (female to male ratio of 2.9:1) and the results from the amniotic fluid samples support this skewed ratio.

Since only one PS case (a female) was detected by amniocentesis, no conclusions can be drawn with regards to the sex ratio in PS.

6.3.4. Incidence Rates of the Trisomies from Blood and Amniotic Fluid Results Combined

More accurate figures for the incidence rates of DS, ES and PS can be obtained by combining the results from the blood and amniotic fluid samples. This was done over the three year period under investigation and the following incidence rates were obtained for DS, ES and PS, respectively: 1 in 861, 1 in 9655 and 1 in 24138. These revised incidence rates are more in line with the international figures which were found to be higher than those reported here in most cases.

6.4 UTILISATION OF THE GENETIC COUNSELLING CLINICS AND PRENATAL DIAGNOSTIC SERVICES

Genetic counselling clinics provide an important service to the public, and particularly to the people who are concerned about their risks for having an abnormal child. Utilisation of these services by families after the birth of a child with DS, ES or PS was shown to be poor,

with only 48 out of 1531(3.1%) families with a child with one of these trisomies presenting for counselling. Once either DS, ES or PS had been detected on amniocentesis, utilisation of the genetic counselling service was better, but still only six out of 25 families (24%) attended a genetic counselling clinic.

A large percentage of the persons who did not attend a genetic counselling clinic could well have lived at distances too far away from the clinic, since the laboratory on which this study was based is a referral centre for a large geographical area. Alternatively, they may have been counselled by their own medical practitioner or specialist. Also, many couples who had a trisomy diagnosed were probably in the older age group and not intending to have more children, and therefore they may not have recognised the relevance of genetic counselling nor requested referral for counselling.

However, many people are neither aware of the availability of genetic services nor aware of what they can offer. It would therefore be of benefit to educate the affected families, especially in the Black population, about the value of these services so that they may obtain the detailed and relevant information they require from the highly qualified genetic counsellors available at genetic counselling clinics. The media could also be used more extensively for this purpose.

On investigation of the indications for referral for prenatal diagnosis in the present study, the majority of patients (76.1%) attended for advanced maternal age. This was also demonstrated by Kromberg et al in 1989, who reported that 73.5% of cases were referred for this reason.

Out of the total of 3125 amniocentesis performed, 25 trisomies were

detected, and in these cases, the majority (23 couples, 92%), opted for termination of the pregnancy. This clearly shows the non-acceptance of the abnormal infant with a trisomy. It also indicates a reluctance of people in this community to take on the burden and responsibility of a mentally handicapped child and/or child with a limited life expectancy (as is the case in ES and PS) when they have the choice in advance.

6.5 LIMITATIONS OF THE STUDY

There are a number of limitations that may have resulted in some inaccuracy of the results obtained in the present study. These limitations include the following:

1) A small number of blood and amniotic fluid samples were sent for chromosomal analysis to other laboratories during the latter years of this study. This could have resulted in cases being missed and the incidence figures reported here being too low. This problem could also have caused differences in the annual fluctuation, and differences in the ethnic distribution if the use of the private laboratories increased over the years or if there was biased use of these services by specific population groups. For the same reason the study could not be extended to beyond 1988 since the numbers of samples sent to private laboratories increased rapidly after that date.
2) Not all the information available from the cytogenetics department at the SAIMR was computerised. The results of the present study therefore relied on manual retrieval of information with regard to the numbers , ethnic distribution, sex, and types of DS, ES and PS in the study sample. Numerical errors therefore may have occurred, resulting in some inaccurate figures being reported.
3) The number of DS cases detected in the Black population and

maybe in the other population groups as well, may give an underestimate of the incidence due to the fact that some cases remain undiagnosed, or may only be diagnosed when the child is older. Similarly the incidence rates for ES and PS may be too low.

4) The total number of livebirths in the Johannesburg and Soweto area may be inadequately recorded by the Department of Central Statistics. This may be due to some infants, particularly those from the black population, not being registered. Such inaccurate denominators may result in the incidence of DS, ES and PS being calculated as too high in the present study.

5) Another limitation of this study is the lack of published data, particularly on the Black population from South Africa and other African countries, with which to compare the results. Without such comparisons, it is difficult to assess whether the results of the present study are as might be expected, or whether the results are unusual and isolated findings.

6.6 SUGGESTIONS FOR FURTHER RESEARCH

With data being readily available in the files at the cytogenetics unit of the SAIMR and possibly at the private laboratories with cytogenetic units, and since information is now becoming more easily accessible due to computerisation, ongoing statistics could be continually added to the findings obtained from the present study. Thus the sample size could be increased and data collected over a longer time period which would result in more reliable and accurate incidence rates and better information on annual fluctuation, sex ratios and types of DS, ES and PS.

Another project might be designed to investigate, the ethnic distribution of DS, ES and PS (particularly PS, since this study

suggests an increased rate occurs in the black population). This could be determined by establishing the birth rate for each separate population group and reporting the numbers of DS, ES and PS for each year. By reporting these figures, the difference in annual incidence for each population group, and whether or not a particular population group is responsible for an increased or decreased incidence in a particular year could be investigated.

Another area for future research, is to determine the ethnic distribution of the types of DS, ES and PS. This may allow for an explanation for the difference in incidence rates of the different types, especially for mosaic cases, compared to other international studies.

Maternal age is related to the increased risk of having any one of the viable common trisomies. It would therefore be of interest to determine the age of the women who gave birth to either a DS, ES and PS case, which were detected on blood chromosomal samples and the age distribution of all pregnant women. This would enable us to determine the age specific risks for women in South Africa. This age analysis was not performed in this study but if it was done in the future, it could also provide some information on the number of older women not using the prenatal diagnosis services. To assess the type of women in this category, data should be collected on socio-economic status and education levels too. Other factors such as, paternal and environmental factors (Mikkelsen et al, 1976) which may have resulted in an increase in the number of common trisomies born in a particular year should also be investigated more thoroughly. Identifying these factors could lead to planning a prevention programme and to a possible decrease in the births of these common trisomies.

6.7 IMPLICATIONS AND RECOMMENDATIONS OF THE STUDY FOR FUTURE ACTION

One of the limitations of this study was the possible inaccuracy of the data retrieved regarding the Black population resulting from both the relatively limited number of the blood and amniotic fluid samples referred for chromosomal analysis. This suggests that there is a lack of knowledge regarding genetic abnormalities and indications for amniocentesis and prenatal diagnosis. The fact that many samples were received with a poor clinical description of the patient and were subsequently found to have normal chromosomes also supports the possible need for increasing the knowledge of the medical personnel submitting samples of both the common trisomies and the congenital abnormalities associated with them. This problem may be overcome by further education of the clinicians working in the hospitals in which Black infants are delivered, so that DS cases are picked up neonatally. Earlier diagnosis of DS in a child would hopefully allow the parents to be referred for appropriate counselling, so that they understand the condition and the options they have with regard to caring for their child and their future family planning (these options were successfully used by the family with a DS child studied in this project).

Another issue which arose from the findings of the present study was the underutilization of the Genetic Services available to the community, especially by the black population. It would be of great benefit to all concerned to educate both the medical community and the general public, regarding the availability of these genetic services and the information that can be gained by attending a genetic counselling clinic. All pregnant women over the age of 35 years should consider having genetic counselling and discussion of their risks, so that they can choose whether or not to have an

amniocentesis for prenatal diagnosis followed by selective abortion. Relevant counselling would allow for the consideration of all the given facts and for appropriate decision making, in terms of the needs and desires of each individual couple. Kromberg and Zwane (1993) have already shown that 95% of Black mothers would have accepted prenatal diagnosis if they had been offered it, and 55% would have acted on the information provided and would have requested termination of the pregnancy for an affected foetus. Therefore these services would not be inappropriate in this community.

6.8 DISCUSSION AND CONCLUSION REGARDING THE FAMILY STUDY

According to Emery and Pullen (1984), the essence of genetic counselling is the counsellor's ability to transmit genetic information about an inherited disorder of concern to the counselees so that it will be incorporated into decision making. The counsellor should recognise the various stages of the counselee's coping process, as they relate to the comprehension of new genetic information, as well as its incorporation at the emotional levels (Falek, 1977). The coping response of individuals under stress are considered as phenotypic expressions of psychological mechanisms attempting to re-establish the dynamic steady state. The sequence of responses commonly observed in individuals under stress is 1)shock and denial, 2)anxiety, 3)anger and/or guilt and 4)depression, as stages that individuals experience in the process of achieving 5)psychological homeostasis. These stages are essential elements of the coping response to a stressful event. The new information must be received and incorporated on both cognitive and emotional levels before any behavioural adjustments can take place (Emery and Pullen,1984).

By conducting the case study, over a one year period, the author was able to gain a better understanding of the psychological aspects and problems of having a Down syndrome child. It allowed for the stages of the coping process to be assessed in the parents, providing a basis for insight into how they coped with the affected child. This increased insight should lead to improvement in the author's communication during practical genetic counselling of families with intellectually disabled children.

During interviews with the parents of the Down syndrome child, the author could identify the course of the stages of the coping process. The mother stated that initially she was shocked, although she never denied her child's diagnosis. Thereafter she became anxious as to how to deal with the problem of having a child with Down syndrome. At the same time, feelings of guilt were experienced by the mother, who blamed herself for her child's condition. No feelings of depression were reported and the mother eventually, through the support of her family, was able to accept her child's condition and achieve psychological homeostasis.

When the father of the Down syndrome child was interviewed he reported that he felt that he experienced more emotions than his wife. At first he was shocked and then he denied his child's condition. Once this stage was over he became anxious as to how he was going to deal with the situation. The father also experienced feelings of anger towards himself, his wife, his family as well as his affected child. This was followed by guilt and depression, another two stages of the coping process. As with the mother, the father eventually came to accept the situation and through support from his wife and his family, he reached a steady psychological state.

It was not only the immediate family who were affected by the birth of the Down syndrome child. The parents reported that once the extended family were notified of the baby's condition, they too experienced different emotional states, eventually reaching acceptance.

Byrne and Cunningham (1985) and Gath (1985) all describe parental reactions and adaptation and attachment to a DS child. These authors discuss the different stages of the coping process through which a person will move in order to finally accept their DS child. Both parents in the present study went through typical stages of the coping process and in doing so, together with the added support from their family, they were able to accept their DS child and make the necessary arrangements to stimulate his mental development to its maximum potential. Gath (1985) also describes the effects that having a DS child may have on the parents' social activities and the possible strains that may occur in the marital relationship. Both parents felt that both these two aspects had been adversely affected after the birth of their DS child, but they were able to work through it with the help of close family members.

By experiencing and working through each psychological stage, the parents learned to accept the Down syndrome child and make an informed decision when it came to having another child. Since the parents made the decision to have prenatal diagnosis during the mother's second pregnancy, it can be assumed that the genetic counsellor imparted the necessary information which allowed the parents to make an informed decision regarding this pregnancy.

Another facet of the psychological impact of a child with Down syndrome on the nuclear family was the stress experienced by the

mother. According to the mother, her mental and physical health was affected by having a Down syndrome infant. She ascribed this to the stress and frustration associated with trying to do too much for her child. This phenomenon was also reported by Kromberg and Zwane (1993) in a study on Down syndrome and maternal stress in the black population in South Africa. According to their results, mothers of Down syndrome children reported significantly more stress indicators than controls. Nearly half the group described their poor general health and the increase in their health problems since the child's birth.

This study provided an example of a couple with a Down syndrome child who experienced the different stages of the coping process and eventually reached psychological homeostasis. It is important for genetic counsellors to take cognisance and be sensitive to each emotional stage of the coping process and to provide information appropriately on both cognitive and emotional levels. This will lead to improved insight and informed decision making being achieved by the counselee.

6.9 SUMMARY AND CONCLUSIONS RELATING TO THE AIMS OF THE STUDY

When relating the findings of the present study to the initial aims, the following conclusions can be drawn:-

1) The first aim of the study was to determine the incidence, annual fluctuation, ethnic distribution, sex ratio and types of DS, ES and PS in blood chromosomal studies over a thirteen year period (Jan 1976 - Dec 1988). The results showed that the incidence of DS (1:855), ES(1:10413) and PS (1:25288) were somewhat similar to those reported in other International and local South African studies. The incidence of DS was, however,

slightly lower than expected, probably due to the laboratory based nature of this study and to the underdiagnosis of this condition, especially in the Black population.

The annual fluctuation of both DS and ES, peaked in 1977. The reasons for this peak are not clear. The results on the ethnic distribution showed a higher incidence rate of DS in the White population than the Black population, probably due to a better pick-up rate in the former group who have better access to diagnostic and prenatal diagnostic services. A higher incidence of PS was noted in the Black population (1:19279) than the White population (1:63609), which may be a genuinely increased rate but requires confirmation on a larger sample.

The sex ratio for both DS and PS was found to be more or less even, but was highly distorted in the ES sample, showing a preponderance of females to males (2.9:1, respectively), confirming the findings in other countries (Anneren, 1986, in Sweden and Goldstein and Nielsen, 1988 in Denmark).

The proportion of nondisjunction and translocation types of DS, PS and ES correlate to the published data. However, there was an excess of mosaics in DS and PS cases, which has not been reported elsewhere. The reasons for this finding are; possible environmental factors eg excess radiation due to the occurrence of minerals in the area studied for this project, and/or the survival of mosaic foetuses in comparison with a high mortality rate of trisomy foetuses in a population which has poor ante-natal care.

2) The second aim was to estimate the incidence, annual fluctuation, ethnic distribution and sex ratio of DS,ES and PS in amniotic fluid chromosomal studies over a three year period

(Jan 1986 - Dec 198). The results showed that the incidence of DS in amniotic fluid samples, increased in 1988 in comparison with 1986 and 1987 showing the annual fluctuation again. The majority of the amniocenteses resulting in DS cases were from the White population indicating that this group used the prenatal diagnostic services more frequently than other population groups. The sex ratio for DS, ES and PS found in amniotic fluid samples correlated with the findings in liveborn infants.

3) The third aim was to assess the utilisation of the Genetic Counselling Clinics and pre-natal diagnostic services, over a three year period (Jan 1986 - Dec 1988), by families who had a child or foetus with DS, ES and PS detected on blood or amniocentesis, respectively. Utilisation of Genetic counselling services, after the birth of a child with a trisomy was poor. This problem could be rectified by actively encouraging and motivating the parents of a newly diagnosed case of DS, ES or PS to attend for genetic counselling and by increasing the education and awareness of the general public about the services offered.

4) The fourth aim was to interview and describe a family with a DS child in order to gain some insight into how they coped with such an infant. Insight was gained into the parents' coping patterns with regard to their child with Down syndrome in the first two years after the birth. The psychological aspects of the coping process were noted especially. The stages in the coping process were different for each parent but similar to those documented in the literature. As a result of the interviews with the parents, the author gained a better understanding of the coping process and improved her communication skills which will be useful in practical genetic counselling situations in the

future.

6.10 SUMMARY AND CONCLUSION

The results of the present study demonstrated that when all population groups are considered as a single group, the incidence, annual fluctuation, ethnic distribution and sex ratio, in both blood and amniotic chromosomal studies, correlate with those found both in studies in other countries and in other studies conducted in South Africa. However, the results were not exactly as expected. The incidence of Down syndrome in the Black population was too low, probably due to underdiagnosis and missed cases, and the incidence in the White population was too high for a community using prenatal diagnosis.

The common types of DS, ES and PS, nondisjunction and translocation, also correlate with the published data, but the excess of mosaic karyotypes found in the DS and PS cases still needs further investigation.

The findings from this study provide new information, which was not available previously, on the occurrence and the estimated prevalence rates of the three common viable trisomies, as well as their karyotypes, in the local Black population. The findings on the trisomies in the White population basically support those found in other studies.

The present study, as expected, also provided evidence that the prenatal diagnostic service is used mainly the white population. However, there was poor utilisation of the genetic services after the birth of a child with a trisomy by all population

groups. These problems could be rectified by increasing the education and awareness, in all groups but especially in the black population.

The family case study provided the author with an insight into how parents cope with a DS child. The findings showed that parents react and cope differently and the coping process should be considered from this viewpoint. The authors communication skills were improved by the interaction with the parents during the study and together with a more thorough knowledge of the three common trisomies, this should lead to her improved performance in the genetic counselling situation, especially when families with a DS, ES or PS present.

APPENDIX A

QUESTIONNAIRE FOR CASE STUDY INTERVIEW

GENERAL QUESTIONS

1. Name of your Down syndrome child .....

2. Date of birth .....

3. Weight of baby at birth .....

4. Was this your first child? YES..... NO.....
   If not, how many other children do you have?.....

5. Did your pregnancy with this child go well? YES..... NO....
   If not, why not?.....

6. Did you have any infection/s during this pregnancy? YES..... NO.....
   If yes, what infections did you have?.....

7. Did you take any drugs during this pregnancy? YES.... NO.....
   If yes, what drugs did you take?.....

8. Were you or your partner exposed to any large doses of radiation before this pregnancy?
   YES..... NO.....

9. Were you exposed to any large doses of radiation during this pregnancy? YES..... NO.....

10. Was this pregnancy full term? YES..... NO.....
    If not, how many weeks was this pregnancy?.....

11. Was it a normal delivery? YES..... NO.....
    If not, why not?.....

12. How soon after the birth were you informed that your child had Down syndrome?.....

13. Who informed you that your child had Down syndrome?.....

14. Was a chromosomal diagnosis made on your child? YES.....
    NO.....

15. What type of Down syndrome does your child have?
    Trisomy 21 .....
    Translocation .....
    Mosaic .....
    Don't know ..... (tick the correct answer)

16. Did you have any knowledge of Down syndrome before the birth of your Down syndrome child?
    YES..... NO.....
    If yes, what did you know about Down syndrome?.....

17. Did your knowledge of Down syndrome increase after the birth of your Down syndrome child?
    YES..... NO.....
    If yes, what knowledge have you gained?.....

18. If additional information was gained, what source did you use?.....

19. What features, that are different from normal, did you notice about your Down syndrome child when he/she was first born?
    .....

20. Once you had gained more knowledge about Down syndrome, what other features did you notice about your Down syndrome child?
    .....

21. Was your baby born with any congenital defects? YES..... NO.....
    If yes, what are they?.....

22. Were you in contact with the Down syndrome Association?
    YES..... NO.....
    If not, why not?.....
    If yes, do you think it benefited you in any way? YES..... NO.....
    If yes, how did it benefit you?.....

23 Did you follow a Home Education Program? YES..... NO.....
    If yes, which one?.....
    How did the Home Education Program benefit your Down syndrome child?.....

24. Does your Down syndrome child receive any therapy?
    YES..... NO.....
    If yes, what type of therapy?.....
    How often did your Down syndrome child receive therapy?.....
    If not, why not?.....

PSYCHOSOCIAL QUESTIONS

25. After being notified that you had a Down syndrome baby, what was your initial reaction?
    Mother.....
    Father.....
    If yes, how did your initial reaction change?.....

26 .Did your initial reaction to your Down syndrome child change over time?
    Mother YES..... NO.....
    Father YES..... NO.....
    If yes, how did your initial reaction change?.....

27. What feelings did you experience towards your Down syndrome child a) at first b) later?
    Mother a).....
    b).....
    Father a).....
    b).....

28. Did you ever accept the birth of your Down syndrome child?
    Mother YES..... NO.....
    If yes, when did you start accepting the birth of your Down syndrome child?.....
    If not, why not?.....
    Father YES..... NO.....
    If yes, when did you start accepting the birth of your Down syndrome child?.....
    If not, why not?.....

29. Was there any change in your mental health since the birth of your Down syndrome child?
    Mother YES..... NO.....
    If yes, specify.....
    Father YES..... NO.....
    If yes, specify.....

30. Was there any change in your physical health since the birth of your Down syndrome child?
    Mother YES..... NO.....
    If yes, specify.....
    Father YES..... NO.....

If yes, specify.....

31. Did your social life change in any way since the birth of your Down syndrome child?
    Mother YES..... NO.....
    If yes, specify.....
    Father YES..... NO.....
    If yes, specify.....

32. Did you learn to cope with your Down syndrome child?
    Mother YES..... NO.....
    If not, why not?.....
    Father YES..... NO.....
    If not, why not?.....

33. If you did cope with your Down syndrome child, did you receive any support during your coping process from:
    Mother a)your partner YES..... NO.....
    If not, why not?.....
    b)your family YES..... NO.....
    If not, why not?.....
    c)other sources
    1)friends/professionals YES..... NO.....
    If yes, who?.....
    2)literature YES..... NO.....
    If yes, which literature?

    Father a)your partner YES..... NO.....
    If not, why not?.....
    b)your family YES..... NO.....
    If not, why not?.....
    c)other sources
    1)friends/professionals YES..... NO.....
    If yes, who?.....
    2)literature YES..... NO.....
    If yes, which literature?

34. During your coping process did you experience any of the following emotions?
In which order did you experience them and for how long?

Mother:		**ORDER**	**HOW LONG?**
a)Shock at the birth of your DS child	YES..... NO.....	123456789	.....
b)Denial of your DS child's condition	YES..... NO.....	123456789	.....
c)Anxiety towards how you would deal with your DS child	YES..... NO.....	123456789	.....
d)Anger towards your DS child	YES..... NO.....	123456789	.....
e)Anger towards yourself	YES..... NO.....	123456789	.....
f)Anger towards your partner	YES..... NO.....	123456789	.....
g)Anger towards your family	YES..... NO.....	123456789	.....
h)Depression	YES..... NO.....	123456789	.....
i)Guilty because of your DS child	YES..... NO.....	123456789	.....

Father:		**ORDER**	**HOW LONG?**
a)Shock at the birth of your DS child	YES..... NO.....	123456789	.....
b)Denial of your DS child's condition	YES..... NO.....	123456789	.....
c)Anxiety towards how you would deal with your DS child	YES..... NO.....	123456789	.....
d)Anger towards your DS child	YES..... NO.....	123456789	.....
e)Anger towards yourself	YES..... NO.....	123456789	.....
f)Anger towards your partner	YES..... NO.....	123456789	.....
g)Anger towards your family	YES..... NO.....	123456789	.....
h)Depression	YES..... NO.....	123456789	.....
i)Guilty because of your DS child	YES..... NO.....	123456789	.....

35. Do you blame yourself or your partner for your Down syndrome child's condition?
    Mother YES..... NO.....
    Father YES..... NO.....
    If yes, why? Mother.....
    Father.....
    If not, did you ever blame yourself or your partner?
    Mother YES..... NO.....
    Father YES..... NO.....
    If yes, how did you overcome it?
    Mother.....
    Father.....

36. What were family relationships like before the birth of your Down syndrome child?
    Mother's side GOOD..... FAIR..... POOR.....
    Father's side GOOD..... FAIR..... POOR.....
    (tick the correct answer)

37. What were family relationships like after the birth of your Down syndrome child?
    Mother's side GOOD..... FAIR..... POOR.....
    Father's side GOOD..... FAIR..... POOR.....
    (tick the correct answer)

38. How long after the birth of your Down syndrome child were your a)parents and b)sibs told about your child's condition?
    Mother a)..... b).....
    Father a)..... b).....

39. Who told your a)parents and b)your sibs about the birth of your Down syndrome child?
    Mother a)..... b).....
    Father a)..... b).....

40. What was your a)parents and b) your sibs initial reaction to the birth of your Down syndrome child?
    Mother a)..... b).....
    Father a)..... b).....

41. Did your a)parents and b)your sibs initial reaction towards the birth of your Down syndrome child change in any way?

Mother's side	a)parents	YES.... NO.....
		If yes, how has their initial reaction changed?.....
	b)sibs	YES.... NO.....
		If yes, how has their initial reaction changed?.....
Father's side	a)parents	YES.... NO.....
		If yes, how has their initial reaction changed?.....
	b)sibs	YES.... NO.....
		If yes, how has their initial reaction changed?.....

42. Did your a)parents and b)your sibs accept the birth of your Down syndrome child?

Mother's side	a)parents	YES.... NO.....
		If yes, when did they start accepting?.....
		If not, why not?.....
	b)sibs	YES.... NO.....
		If yes, when did they start accepting?.....
		If not, why not?.....
Father's side	a)parents	YES.... NO.....
		If yes, when did they start accepting?.....
		If not, why not?.....
	b)sibs	YES.... NO.....
		If yes, when did they start accepting?.....
		If not, why not?.....

43. Were you and your husband happily married before the birth of your Down syndrome child?
(circle the correct answer)

1	2	3	4
Definitely not happy	Maybe sometimes	Happy	Very happy

44. Did the birth of your Down syndrome child strain your marital relationship in any way at any time?
YES..... NO..... DON'T KNOW.....
If yes, has the problem been solved? YES..... NO.....
If not, why not?.....

45. How many children did you plan to have before the birth of your Down syndrome child?.....

46. Did your decision to have a certain number of children change after the birth of your Down syndrome child?
YES..... NO.....
If yes, has your certain number increased or decreased?.....

47. Are you aware of the Genetic counselling clinic at the Transvaal Memorial Institute?
YES..... NO.....

48. Did you attend the Genetic counselling clinic after the birth of your Down syndrome child?
YES..... NO.....
If yes, did it benefit you in any way? YES..... NO.....
How did it benefit you?.....
If not, why not?.....
Will you attend Genetic Counselling before your next pregnancy?
YES.... NO.....
If not, why not?.....

49. Do you know the risk for future offspring? YES..... NO.....
If yes what is the risk?.....
Do you perceive this risk to be high? YES..... NO.....

50. Are you aware of prenatal diagnosis? YES..... NO.....

51. Were you aware of prenatal diagnosis before the birth of your Down syndrome child?
YES..... NO.....
If yes, why did you not have prenatal diagnosis?.....
If not, would you have liked to have known about prenatal diagnosis?
YES.... NO..... Why?.....

52. If you have another pregnancy, will you have prenatal diagnosis?
YES..... NO.....
If yes, why?.....
If not, why not?.....

53. If prenatal diagnosis revealed another Down syndrome foetus, would you terminate the pregnancy?
YES..... NO.....
If yes, why?.....

If not, why not?.....

54. What message would you as parents of a Down syndrome child like to convey to others who have a Down syndrome child?
.....

***** THANKYOU FOR YOUR KIND CO-OPERATION IN ANSWERING THIS QUESTIONNAIRE*****

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