CYSTIC FIBROSIS GENETIC COUNSELLING:

AN AUDIT OF COUNSELLEES AND THEIR AT-RISK RELATIVES

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Science in Medicine in Genetic Counselling

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DECLARATION

I, Shelley Macaulay, declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine in the branch of Genetic Counselling, in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

……...….

…….…...day of…….…, 2008.

DEDICATION

To my family and friends who have always supported, encouraged and guided me throughout my eight years of studying.

ABSTRACT

Cystic fibrosis (CF) is an autosomal recessive disorder that occurs in all ethnic groups. Mutations in the cystic fibrosis transmembrane regulator (*CFTR*) gene are responsible for pulmonary obstruction, chronic lung infections, pancreatic insufficiency, meconium ileus, failure to thrive and infertility.

Genetic testing for CF at the DNA level is available. A diagnosis of CF in an individual has implications for other family members and so genetic counselling should form part of CF management. Genetic counselling has been offered by the Clinical Unit of the Division of Human Genetics, National Health Laboratory Service and the University of the Witwatersrand, Johannesburg, for many years. At the beginning of 2006, genetic services were introduced into the CF Clinics of Johannesburg Hospital by way of specialist Genetic Counselling Clinics. The study aimed to determine who utilises the CF genetic counselling services and why, to estimate the number of at-risk relatives per family, and how many of them had mutation testing and genetic counselling. Finally, the study explored what impact the specialist Genetic Counselling Clinics had on the overall service of genetic counselling.

The files of 153 families seen for CF genetic counselling from 1990 to 2006 were analysed. The majority of counsellees (93%) were white. Most counsellees were parents of CF probands (35%). Relatives with carrier risks of 67% (siblings) and 50% formed only 7% and 6% of all counsellees respectively. Most individuals attended genetic counselling in order to gather information. On average, 5.9 ± 3.45 families were seen for CF genetic counselling per year from 1990 to 2005, whereas in 2006, 58 families were seen. Paediatrician, physician and nurse referrals increased notably during 2006 compared to prior years. In 140 unrelated CF-affected families, 1991 at-risk relatives, with carrier risks above 25%, were identified. Only 11% of these relatives had mutation testing and only 8% attended genetic counselling.

Uptake of genetic counselling is greater when the service is integrated into CF treatment clinics than when it is offered externally. The low uptake of mutation testing and genetic counselling by at-risk relatives suggests that new methods of educating individuals for cascade screening and testing are required.

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LIST OF ABBREVIATIONS

1st	First
%	Percentage
CBAVD	Congenital bilateral absence of the vas deferens
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane regulator protein
CFTR	*Cystic fibrosis transmembrane regulator* gene
CHB	Chris Hani Baragwanath Hospital
DGMC	Donald Gordon Medical Centre
DNA	Deoxyribose nucleic acid
GP	General Practitioner
JHB	Johannesburg Hospital
mmol/L	Millimoles per litre
MRC	Medical Research Council
n	Absolute number
NHLS	National Health Laboratory Service
NSGC	National Society of Genetic Counselors
Obs/gynae	Obstetrician/gynaecologist
PGD	Preimplantation genetic diagnosis
RNA	Ribonucleic acid
SAIMR	South African Institute for Medical Research
TMI	Transvaal Memorial Institute, now known as The Memorial Institute
vs.	Versus
WHO	World Health Organization

CFTR Mutations

3120+1G→A	A substitution mutation. At position 3120+1 in intron 16 of *CFTR*, a guanine base is substituted by an adenine base.
ΔF508	A deletion mutation. The deletion of three base pairs causes the loss of the amino acid phenylalanine at position 508 in the CFTR protein.
IVS8-5T	The 5-thymidine allele in intron 8 of *CFTR*. The 5T allele is a variant of the polythymidine tract and has the lowest splicing efficiency.

CHAPTER 1: INTRODUCTION

Cystic fibrosis (CF) is one of the most common autosomal recessive disorders in the white population (Turcios, 2005). In families affected with CF, numerous individuals are at risk of being carriers for the condition. Genetic counselling serves an important role in educating such individuals about the condition, their genetic risks and the testing options available to them as well as providing psychosocial support (Weil, 2000). In order to gain a better understanding of the utilisation of CF genetic counselling, the following study focussed on various aspects of the families of individuals with CF who presented for CF genetic counselling offered by the Division of Human Genetics, National Health Laboratory Service (NHLS) and the University of the Witwatersrand, Johannesburg from 1990 until the end of 2006. The study also aimed to assess what impact the newly established specialist Genetic Counselling Clinics, within the CF Clinics of Johannesburg Hospital, have had on the Division of Human Genetics, NHLS and the University of the Witwatersrand's genetic counselling service.

This chapter reviews the clinical and genetic aspects of CF and discusses the principles and practices of genetic counselling. Particular reference is made to genetic counselling for CF-affected families focussing on the benefits of the service. The motivation behind the study, as well as the study's aims and objectives, are discussed at the end of chapter one.

1.1 CYSTIC FIBROSIS

Cystic fibrosis affects a number of systems in the body; the respiratory tract, pancreas, gastrointestinal system, exocrine sweat glands and genital tract (Boat, 2004). Initial presentation of the disease may occur from before birth to adulthood (Minasian, McCullagh & Bush, 2005).

1.1.1 Disease Frequency

Despite being more common amongst individuals of northwest European decent, CF has been described in almost every ethnic group (Minasian et al., 2005). The disease has been reported to be present at varying frequencies amongst Hispanics, African Americans, Ashkenazi Jews and Asian Americans (National Institutes of Health website, 1997) as well as South African blacks (Padoa, Goldman, Jenkins et al., 1999).

Studies in the South African population have indicated that the calculated incidence of CF is 1 in 2000 and 1 in 12000 among the white and coloured groups respectively (Hill, MacDonald, Bowie et al., 1988). For several years it was thought that CF was exceptionally rare in black South Africans, however, a study carried out by Padoa et al. (1999) predicted a CF incidence of between 1 in 784 and 1 in 13924 births in South Africa's black population. An adjusted incidence of 1 in 4624 births was calculated from the given range (Padoa et al., 1999).

There is therefore a relatively high carrier rate amongst the different populations in South Africa. Carrier frequencies for CF in South Africa have been estimated as 1 in 20 for whites and 1 in 55 for coloureds (Hill et al., 1988) and an adjusted carrier frequency of 1 in 34 (range of 1 in 14 to 1 in 59) for the black population (Padoa et al., 1999). One must, however, take into consideration that the study carried out by Padoa et al. (1999) was performed on a relatively small sample (1360 black individuals) and so the estimated carrier frequency of 1 in 34 in the South African black population may not be entirely accurate.

1.1.2 Clinical Features

In its classic form, clinical manifestations of CF involve the respiratory and gastrointestinal tracts. The disease was initially recognised as a distinct illness by a pathologist called Andersen in 1938 (Andersen, 1938). The disease was later termed "mucoviscidosis" (Farber, 1944), a term appropriate for a disease responsible for the accumulation of thick mucous secretions, that result in blocked airways and secondary infection. Obstruction of exocrine

glands by mucous secretions is the underlying cause of illness in CF patients (Rowe, Miller & Sorscher, 2005). Table 1.1 lists some of the common clinical findings of the disease.

Table 1.1 The common clinical manifestations of cystic fibrosis (Boat, 2004).

Presenting Features of Cystic Fibrosis
- Acute or persistent respiratory symptoms - Failure to thrive, malnutrition - Abnormal stools - Meconium ileus, intestinal obstruction - Electrolyte, acid-base abnormality - Nasal polyps, sinus disease - Rectal prolapse - Hepatobiliary disease - Other (e.g. azoospermia and meconium plug syndrome)

Chronic pulmonary disease accounts for the majority of CF morbidity. Thick mucous secretions in the lungs cause airway obstruction and provide ideal conditions for bacterial pathogens to colonise. *Pseudomonas aeruginosa* and *Staphylococcus aureus* become well established within the lungs of CF individuals causing severe pulmonary infections and destruction of lung tissue (Turcios, 2005). Right-sided cardiac failure is often secondary to chronic pulmonary disease caused by fibrotic alterations in the lungs as a result of recurrent infections. In such an instance the best treatment for a patient is a lung transplant (Boat, 2004) and in some cases, a heart-lung transplant (Turcios, 2005).

Approximately 90% of patients with CF have pancreatic insufficiency resulting in reduced pancreatic secretions. With CF, digestive proenzymes tend to remain in the pancreatic ducts thus causing destruction of pancreatic tissue. Failure to thrive, malabsorption and stools with high fat content result from impaired pancreatic functioning. Affected individuals therefore require pancreatic enzyme replacement therapy and are advised to consume high calorie diets. Another clinical feature of CF is that in about 15-20% of affected newborn infants, the ileum

is completely obstructed with meconium. This obstruction is known as meconium ileus. The failure to pass meconium appears within the first one to two days of life in CF-affected newborns (Boat, 2004).

The reproductive tract is another organ involved in CF. Approximately 98% of male patients with CF are infertile. In these males spermatogenesis is normal and the infertility is due to azoospermia resulting from congenital bilateral absence of the vas deferens (CBAVD) (Ratjen & Doring, 2003; Boat, 2004). It has also been documented that a large proportion of men diagnosed with CF-associated CBAVD do not present with the lung and pancreatic symptoms of CF (Daudin, Bieth, Bujan et al., 2000). Fertility rates amongst females with CF are also thought to be reduced due to the accumulation of thick cervical mucus (Boat, 2004).

1.1.3 Prognosis

In the United States of America 70% of patients are diagnosed with classic CF by one year of age and 90% by eight years of age (Turcios, 2005). The predicted age of survival for persons affected with CF has greatly improved over the years due to intensive medical treatment and management. The CF Foundation Patient Registry indicated that in 1985 the median age of survival was 25 years whereas in 1997 the median age of survival was 30 years. In 2005 the predicted survival reached 36.5 years (Cystic Fibrosis Foundation, 2006). It has been predicted that the median age of survival for babies born in the 1990s or later is 40 years (Minasian et al., 2005).

1.1.4 Mode of Inheritance

Cystic fibrosis is a single gene disorder. It is inherited in an autosomal recessive manner. Both parents have to be carriers of a mutation in the gene responsible for CF in order to have an affected child. Affected individuals will therefore have two mutations whereas carriers will have one. An affected individual can be either homozygous for a specific mutation (they have two copies of the same mutation), or they can be compound heterozygotes and have two

different mutations. During each pregnancy between two carriers there is a 1 in 4 (25%) risk of having an affected child, a 2 in 4 (50%) risk of having a child who is a carrier and a 1 in 4 (25%) chance of having a child who is neither a carrier nor affected.

1.1.5 The Genetics of Cystic Fibrosis

The gene responsible for CF is the *cystic fibrosis transmembrane regulator* (*CFTR*) gene which was cloned in 1989. This gene is located at position 7q31.2 and consists of 27 exons (Riordan, Rommens, Kerem et al., 1989).

The CFTR protein acts as a chloride channel and is expressed in the apical membranes of epithelial cells lining the respiratory tracts, intestines, vas deferens and pancreatic, sweat and bile ducts. The overall effect of these chloride channels is to decrease the level of sodium chloride within the cell and make secretions more liquid (Boat, 2004; Turcios, 2005). It has been hypothesised that defective CFTR protein results in the inability of epithelial cells to secrete salt and water due to excessive reabsorption of salt and water. As a result, secretions are dehydrated and adhesive, making them more difficult to remove by mucociliary actions and other mechanisms (Boat, 2004).

The absence of CFTR protein influences the expression of a number of other gene products. Such gene products include proteins that are necessary for inflammatory responses, maturational processing, cell signalling and ion conductance. These additional proteins act as modifiers of the CF phenotype and are likely to account for the significant differences in clinical severity among patients with the same mutations in *CFTR* (Rowe et al., 2005).

1.1.5.1 CFTR Mutations

There are currently 1546 *CFTR* mutations reported which include missense, frameshift, splice-site, nonsense, promoter, insertion and deletion mutations as well as non-pathogenic sequence variations (Cystic Fibrosis Genetic Analysis Consortium website, 2007). Studies have

indicated that there is, to a certain degree, a genotype-phenotype correlation in individuals with *CFTR* mutations; different classes of mutations are responsible for mild to severe forms of CF (Ratjen & Doring, 2003). The various *CFTR* mutations are grouped into six classes (Turcios, 2005; Strausbaugh & Davis, 2007) based on how they affect the CFTR protein. Classes I, II and III are referred to as severe mutations whereas classes IV, V and VI are mild mutations. Table 1.2 lists the various classes of mutations, the type of defect they cause and the typically expected phenotype.

Table 1.2 The six different classes of *CFTR* mutations (Strausbaugh & Davis, 2007).

Mutation Class	Nature of Defect	Expected Phenotype
Class I	Defective protein production and premature termination of CFTR production	Severe pulmonary disease & pancreatic insufficiency
Class II	Defective trafficking of CFTR- it does not reach the apical membrane	Severe pulmonary disease & pancreatic insufficiency
Class III	Defective regulation of CFTR	Severe pulmonary disease & pancreatic insufficiency
Class IV	Altered chloride conductance	Pulmonary disease & pancreatic sufficiency
Class V	Reduced synthesis of functional CFTR	Pulmonary disease & pancreatic sufficiency
Class VI	Accelerated turnover of CFTR from cell surface	Pulmonary disease & pancreatic sufficiency

In general, the combination of a class IV, V or VI mutation with a class I, II or III mutation results in a less severe phenotype in which pancreatic function is sustained. A combination of two severe mutations, from classes I, II or III, results in the classic CF phenotype with pancreatic insufficiency (Daudin et al., 2000; Richards & Haddow, 2003; Minasian et al., 2005).

In men with CBAVD, the genotype usually includes at least one mild mutation not typical of CF patients. The RNA splice site variant, IVS8-5T, is frequently associated with CBAVD and is sometimes combined with a severe mutation. However, the penetrance of such a genotype is incomplete thus resulting in a mild phenotype which is often isolated CBAVD (Daudin et al., 2000). Although the relationship between genotype and pancreatic status and CBAVD is relatively well understood, the relationship between pulmonary disease and genotype is less clear (Minasian et al., 2005).

Several *CFTR* mutations are population specific. In white individuals worldwide the most common mutation is ΔF508 which is a class II mutation that results in *CFTR* lacking a phenylanine (F) residue at position 508 (Rowe et al., 2005). A study carried out by Goldman, Graf, Ramsay et al. (2003) showed that in South Africa, the ΔF508 mutation occurred at a frequency of 76% and 50% amongst white and coloured CF patients respectively. However, this mutation was not detected in the South African black CF patients. A splice-site mutation, namely 3120+1G→A, was identified as being most common amongst black CF patients as it occurred at a frequency of 46%. This mutation was also shown to occur at a frequency of 17% amongst coloured CF patients (Goldman et al., 2003)

Mutation detection rates in individuals are therefore highly dependent upon the ethnicity of the patients and different tests are therefore required for different populations. Currently, the Molecular Laboratory of the Division of Human Genetics, NHLS and the University of the Witwatersrand, Johannesburg, test for 30 CF-causing mutations. Only one of those 30 mutations, the 3120+1G→A mutation, is tested for in black South Africans whereas all 30 mutations are tested for in individuals of other ethnic groups.

1.1.6 Diagnosis

Clinical, molecular and familial criteria are required for a diagnosis of CF in a patient. Table 1.3 lists the diagnostic criteria.

Table 1.3 Diagnostic criteria for cystic fibrosis (Boat, 2004).

Diagnostic Criteria
Presence of typical features (respiratory, gastrointestinal or genitourinary)
OR
A history of CF in a sibling
OR
A positive newborn screening test
PLUS
Laboratory evidence for CFTR dysfunction:
Two elevated sweat chloride concentrations obtained on separate days
OR
Identification of two CF mutations
OR
An abnormal nasal potential difference measurement

- *Sweat Test*

The most widely used diagnostic test for the classic form of CF is the sweat test, which measures the sodium and chloride levels in the sweat of individuals. Cystic fibrosis patients have elevated sweat sodium and chloride levels. In children, sweat chloride levels in excess of 60 mmol/L are diagnostic of CF. Despite being the most common diagnostic test for CF, the sweat test is technically challenging and positive results need to be confirmed. Diagnostic criteria for CF therefore require two positive sweat chloride tests (Brown & Schwind, 1999).

- *Molecular Testing*

Since the cloning of the *CFTR* gene, direct mutation testing can be performed to confirm a diagnosis of CF. The presence of two *CFTR* mutations confirms a CF diagnosis. However, identification of only one mutation, or failure to find any mutations, cannot exclude a diagnosis as it is possible that an individual has one or two unknown mutations. In such instances further clinical tests are required (Ratjen & Doring, 2003).

In situations where CF has been confirmed by other clinical methods, and where direct mutation analysis cannot be performed, a technique known as linkage analysis can be utilised for indirect testing in a family. Linkage analysis, however, cannot be used for primary diagnosis of CF. The essence of the technique is to identify which parentally derived chromosomes 7 are present in the CF affected individual. This is done by using DNA markers that are situated at positions (loci) close to the disease gene. The technique therefore requires a clinically diagnosed CF individual's DNA as well as that of the parent or healthy sibling. Depending on which markers are present in the CF affected individual, one can identify which chromosomes carry disease-causing mutations and which carry normal gene copies. By testing other family members for the specific markers one can determine whether or not they have inherited one or both chromosomes that are present in the affected individual, thus inferring their genetic status for CF (Hulsebus & Williams, 1992). In order for linkage analysis to be feasible in a family, the selected linked markers need to differ on the two maternally-inherited and two paternally-inherited chromosomes thus making the family fully informative for the chosen markers (GeneReviews website, 2007).

Direct testing can be used for both primary and secondary diagnosis of CF as well as for carrier detection. Once a diagnosis of CF has been made in a family, indirect testing can be performed for diagnostic purposes as well as for carrier testing. If the familial mutations are known, a potential carrier or affected individual can be tested for those specific mutations. If one or both mutations are unknown, linkage analysis can be used to track the disease-causing allele.

1.2 GENETIC COUNSELLING

The genetic counselling process is one that incorporates information giving and addresses psychosocial aspects that may arise. The National Society of Genetic Counselors (NSGC) of America defines genetic counselling as being "the process of helping people understand and adapt to the medical, psychological, and familial implications of the genetic contributions to disease" (Resta, Biesecker, Bennett et al., 2006). Furthermore, as discussed in Resta et al. (2006), the NSGC states that the process incorporates:

- Assessing the possibility of the disease occurring or recurring based on one's family and medical histories.
- Educating and informing individuals about the mode of inheritance of a disease, the testing options available, the management choices, disease prevention, as well as what resources are available and what research is being conducted.
- Counselling to encourage informed decisions to be made and for individuals to adapt to the risk or condition.

The role of the genetic counsellor is therefore to inform patients about specific disorders and the associated risk and to also ensure that the patients benefit from the information and receive assistance in any decision making process. The counsellor should provide assistance in a non-directive and non-judgemental manner (Weil, 2000; Harper, 2004).

Carl Rogers' client-centred theory is at the core of the genetic counselling process. The theory focuses on the counsellor being genuine, empathic and having unconditional positive regard (Eunpu, 1997; Weil, 2000). Unconditional positive regard involves recognising the counsellee as a whole individual with his or her strong points, limitations and emotions. Empathy involves feeling for and understanding the counsellee's experiences. Genuineness involves the counsellor being open to his or her own feelings whilst interacting with the counsellee, and being able to express them in an adapted but truthful manner during the session (Weil, 2000).

Genetic diagnosis of one family member lends insight into the genetic risk of other family members. When individuals attend a genetic counselling session a genetic counsellor is able to identify which family members are at risk of being carriers (with X-linked and autosomal recessive conditions), or affected (with dominant conditions), through the drawn pedigree. Informed decisions regarding reproduction can be made once these relatives have been educated about their risks (Koch & Svendsen, 2005).

1.2.1 Pedigree Analysis

The construction and analysis of an accurate family pedigree is an essential component of the genetic counselling process. A comprehensive pedigree should be drawn using standardised pedigree symbols. It should consist of at least three generations and include important medical information of family members, as well as record ethnicity (Bennett, Steinhaus, Uhrich et al., 1995; Wolpert & Speer, 2005).

Family history provides a framework upon which a genetic counsellor can establish the mode of inheritance of a particular condition and identify other at-risk individuals within the family. Relatives identified from a pedigree as being "at-risk" should be offered genetic counselling, medical screening and when possible, genetic testing. The purpose of educating and offering such services to these relatives is to increase awareness, provide informed choice, and ultimately lead to prevention, in order to reduce the morbidity and mortality related to the disease (Wolpert & Speer, 2005).

The pedigree also provides insight into social and biological relationships within a family. Matters such as adoption, pregnancy termination, pregnancies conceived by assisted reproductive technologies and deaths are all included when taking a family history (Bennett et al., 1995). Furthermore, obtaining a family history can often provide opportunities for the genetic counsellor to address psychosocial issues (Eunpu, 1997). Discussion about one's family's medical history may invoke painful memories about loss, illness and difficult situations. A genetic counsellor should address and respond to such issues in an empathic manner. Obtaining a family history therefore allows a genetic counsellor to gather both

medical and psychosocial information and therefore gain a better understanding of family health and dynamics (Weil, 2000). The family pedigree is therefore a powerful, reliable, non-invasive and inexpensive technique that provides significant information in genetic counselling (Wolpert & Speer, 2005).

1.2.2 Genetic Risk Assessment

"Genetic risk refers to the probability of carrying a specific disease-associated mutation, or of being affected with a specific genetic disorder" (Ogino & Wilson, 2004). Calculating and presenting risk figures are key components of genetic counselling. The risks discussed with counsellees will depend upon the nature of the genetic counselling session, the disorder, and its pattern of inheritance.

Where Mendelian disorders are concerned, analysis of family pedigrees will allow one to determine the genetic risks for other family members. One can determine an individual's probability of being a carrier for a specific genetic disorder by his or her relationship to an affected relative or an obligate carrier (Ogino & Wilson, 2004). Genetic risks can be presented in percentages (e.g. 50%) or in proportions (e.g. 1/2) (Fransen, Meertens & Schrander-Stumpel, 2006). Where recessive disorders are concerned, carrier risks decreases by half at each step down a pedigree. Therefore, if an individual has a 50% (1/2) probability of being a carrier, his or her offspring will have a 25% (1/4) probability of being a carrier (Ogino & Wilson, 2004). Several factors influence an individual's genetic risk. These factors include ethnicity, family history and genetic testing results (Ogino & Wilson, 2004).

Bayesian analysis may be utilised to refine an individual's risk for a genetic disorder. "Bayesian analysis allows calculation of the probability of a particular hypothesis, either disease or carrier status, based on family information and/or genetic test results" (Ogino & Wilson, 2004). Mutation detection rate is an important factor when calculating genetic risks for recessive disorders. This is because it is virtually impossible to reach 100% test sensitivity due to mutations being diverse and population specific, such as in the case of CF. Bayesian analysis takes into account the fact that the failure to detect any disease-causing mutations in

an individual does not necessarily eliminate the likelihood that the individual carries any mutations. Instead, it considers the possibility that the person could be carrying an unknown mutation that has not been tested for, and so their risk can be greatly reduced but it can never be zero (Ogino & Wilson, 2004).

Most individuals tend to under- or overestimate their risk for familial disorders, and so accurate understanding of risks can often have a positive psychosocial effect upon a person seeking genetic counselling (Lafayette, Abuelo, Passero et al., 1999; Wolpert & Speer, 2005; Fransen et al., 2006).

1.3 CYSTIC FIBROSIS GENETIC COUNSELLING

Genetic counselling plays an important role where a diagnosis of CF has been made. Not only does a diagnosis of CF directly affect the patient and his or her parents as they are at further risk of having more affected children, but it indirectly affects extended family members as they are at risk of being carriers and of having affected children (Chapman & Bilton, 2004). Veach, Truesdell, LeRoy et al. (1999) assessed reasons why individuals seek genetic counselling. Twenty-seven counsellees provided 34 reasons for attending genetic counselling. The most frequently reported reason, was "to gather information" (44.1% *n*=15 responses). The flow of genetic information and psychosocial support available through CF genetic counselling has numerous advantages to families in several situations, some of which are discussed below.

- *A Diagnosis of CF*

For parents, coming to terms with a new diagnosis of CF in their child can be an exceptionally difficult and emotional time. In many cases individuals have never heard about CF until they have an affected child. One particular study highlighted how parents who received genetic counselling for CF described the process as being a very positive experience. Some of these parents also stated that the explanation about and understanding of the genetics behind CF

alleviated feelings of guilt and blame (Collins, Halliday, Kahler et al., 2001). In a study conducted by Henley and Hill (1990) on a South African cohort of 60 families, including 18 CF patients, 29 of their siblings and 60 mothers and 54 fathers, genetic knowledge of CF was assessed. The investigators found that CF patients and their siblings were inadequately informed about the inheritance of CF. Fifty percent of CF patients and 33% of siblings were unaware that both parents had to be carriers of a CF-causing mutation in order to have a child with CF. Furthermore, the study indicated a lack of parental knowledge regarding recurrence risks for CF in future pregnancies. Approximately 40% of mothers and 31% of fathers incorrectly gave themselves a 25% chance of not having an affected child in future pregnancies.

It is also important that CF probands themselves receive genetic counselling at some stage in their lives so that they too can understand the medical information, inheritance risks and testing options available to them. A genetic counsellor can also address the emotional aspects of living with CF.

- *Carrier Detection*

Once a diagnosis of CF has been made in a family member, genetic counselling should ideally be extended to relatives as well as their partners, so that they can understand the implications the diagnosis has for them and their offspring (Roberts, Schwarz, Kerr-Liddell et al., 2003). Should a relative of a CF proband be found to be a carrier, carrier testing in his or her partner would be important. Many individuals are introduced to CF by association with families of CF-affected individuals, usually through marriage or relationships with relatives of such families. Genetic counselling therefore not only offers blood relatives of CF probands information, options and support, but extends to their partners who would otherwise be external to the situation.

With particular reference to CF, many individuals can benefit from learning whether they carry a disease-causing mutation or not. Lafayette et al. (1999) reported that 60% of relatives of individuals with CF underestimated their risk of being carriers. Despite this, 63%

overestimated their chance of having a child with CF. It was also reported that 53% underestimated the carrier frequency in the general population. These figures highlight that many potential carriers are unaware of their genetic risks. The results also indicate a lack of knowledge about the overall disease prevalence and inheritance pattern. Studies such as these emphasise the usefulness of genetic counselling for educating CF families about the disease and the testing options that are available to them.

- *Prenatal Testing*

Before the introduction of prenatal diagnosis for CF in the 1980s, the majority of parents of a child with CF chose to either decrease the number of children they had planned or not have any more children (Brown & Schwind, 1999). Currently, couples who have previously had a child affected with CF can have prenatal diagnosis by chorionic villus sampling or amniocentesis in further pregnancies. Direct DNA mutation analysis is used when the CF mutations in a family are known. In cases where the CF-causing mutation in a particular family cannot be identified, linkage analysis is performed on the fetal DNA (Hulsebus & Williams, 1992) (see section 1.1.5). A more recent advancement is a technique referred to as preimplantation genetic diagnosis (PGD). Preimplantation genetic diagnosis involves *in vitro* fertilisation and testing of one to two cells from an embryo for a genetic condition. Selective implantation of unaffected embryos then follows. Cystic fibrosis is one of several disorders for which PGD is available (Keymolen, Goossens, De Rycke et al., 2007). Preimplantation genetic diagnosis is not yet available in South Africa and so couples wishing to pursue PGD would need to go overseas.

Super, Hambleton, Elles et al.(1986) looked at eight urgent enquiries for prenatal diagnosis for CF in already-pregnant couples and reported the unfavourable factors that accompany the situation. Firstly, in a state of urgency, feelings of anxiety and fear are raised and so counsellees are less likely to make calm, clear judgements. Secondly, the extent to which the detailed genetic information is understood may also be inhibited by the individual's emotional state. Thirdly, in situations where pregnancy is involved, time pressure forces individuals to make hasty decisions regarding testing.

- *Male Infertility*

Genetic counselling should also be considered for men presenting with isolated CBAVD who are found to have one or two *CFTR* mutations. Although they may not present with typical symptoms of CF, it is important for such individuals to fully understand the spectrum of CF and the implications to other family members who consequently have increased genetic risks (Fitzpatrick, Hutton, Babul et al., 1996).

1.3.1 Genetic Counselling Clinics in Johannesburg, South Africa

In certain countries such as Australia (Collins et al., 2001) and America (Ciske, Haavisto, Laxova et al., 2001), newborn screening is available for CF. Although this service is available to a limited degree in the private sector in South Africa (P. Cole (Lancet Laboratories) 2007, pers. comm., 23 August 2007), it is not yet readily available to the state sector. Therefore, CF testing and genetic counselling is almost solely dependent upon opportunistic referrals from medical professionals or family members.

Since 1975 the genetic counsellors and medical geneticists of what is now the Division of Human Genetics, NHLS and the University of the Witwatersrand, Johannesburg, have been providing genetic counselling for CF patients and their families. The clinics were highly dependent on referrals by doctors treating CF patients in and around Johannesburg. However, at the beginning of 2006, specialist Genetic Counselling Clinics were implemented within the paediatric and adult CF Clinics of Johannesburg Hospital. All CF families treated in the clinics were systematically approached and offered genetic counselling. The genetic counselling clinics run once a week in each clinic. The intention of this newly implemented service was to increase awareness about the genetics of CF in patients and their relatives, and therefore encourage family members of affected individuals to utilise genetic counselling and testing in order to improve understanding of their risks.

1.3.2 Cascade Genetic Screening for Cystic Fibrosis

Cascade screening identifies which close relatives of an individual affected with a specific condition are potentially carriers of the condition and offers them tests for family-specific mutations (Morris, Law & Wald, 2004). Considering that the carrier risk of close relatives of affected or carrier individuals is generally higher than the population risk, cascade screening is considered by some to be a far more feasible method of identifying carriers than population screening, which is expensive and raises many ethical concerns (Krawczak, Cooper & Schmidtke, 2001). Table 1.4 lists the CF carrier risks for relatives of a CF proband.

Table 1.4 Probabilities of being a carrier for a CF-causing mutation (adapted from Roberts et al., 2003).

Relationship to Person with CF	Chance of Being a Carrier
Biological parents	100%
Child of a person with CF	100%
Grandparent	1 in 2 (50%)
Healthy brother or sister	2 in 3 (67%)
Niece or nephew	1 in 3 (33%)
Aunt or uncle	1 in 2 (50%)
First cousin	1 in 4 (25%)
Second cousin	1 in 8 (12.5%)
Non-blood relative	Population carrier frequency

Fanos and Johnson (1995) investigated the barriers to carrier testing amongst adult siblings of CF-affected individuals. Twenty-six brothers and 28 sisters, 54 siblings in total, were interviewed in order to determine levels of understanding about carrier status and to asses how and by whom information about CF carrier testing was transmitted through the families. Only 26% of siblings reported their mother as the primary source of information and a further 13% reported being informed about CF carrier testing by their father. The CF-affected individual was the source of information for only 7% of the siblings and 9% of the siblings reported

being educated about CF carrier testing by another unaffected sibling. Forty-five percent of the siblings were told about carrier testing by a medical professional. Some of these siblings also reported that they found it difficult to pass on information regarding CF to extended family members, such as cousins. One of the major problems noted by the investigators was that CF was often seen as being situated within the nuclear family as opposed to the extended family.

Previous studies have assessed family histories of CF patients and identified how many relatives were at high risk of being carriers. In one study performed by Lafayette et al. (1999), 38 families were assessed and among those families 238 relatives were classified as being high risk. High risk was defined as 50% or greater and included adult siblings and half siblings (over 17 years of age), as well as aunts and uncles of the proband. A proportion of these identified relatives were approached by medical professionals and counselled on all aspects of CF including the clinical features, the inheritance pattern and testing options. It was recorded that 93% of these relatives chose to have carrier testing after their discussions with the medical professionals.

Studies such as the ones performed by Lafayette et al. (1999) and Fanos and Johnson (1995) indicate that relatives are generally not receiving adequate information from the probands or their parents to make informed choices. Counsellors and doctors therefore need to be more proactive in creating an awareness of the disease and its prevalence and encouraging members of CF families to attend genetic counselling.

The ideal approach to contacting at-risk relatives for genetic counselling and cascade screening has been extensively debated. On the one hand individuals have “the right not to know” their genetic status (Koch & Svendsen, 2005) and concerns over altered self-concept and stigmatisation after carrier knowledge have been raised (McConkie-Rosell & DeVellis, 2000; Roberts et al., 2003). On the other hand one of the main aims of cascade genetic screening is to allow people to make informed reproductive decisions with regard to the risk of passing the mutation on to their children (Hulsebus & Williams, 1992). In order for this to be achieved it is essential that these at-risk relatives be informed about their own risks (Callanan, Bloom, Sorenson et al., 1995).

1.4 MOTIVATION FOR RESEARCH

Until this study, the profiles of individuals presenting for CF genetic counselling at the clinics of the Division of Human Genetics, NHLS and the University of the Witwatersrand, Johannesburg, had not been described. In addition, studies have not looked at the reasons why these individuals attend genetic counselling clinics and how many at-risk relatives are present in their families. There is also a lack of literature on South African cystic fibrosis patients and their families. A better understanding of these counsellees will assist genetic professionals in assessing who utilises the service and when and why they request it. It will also highlight certain aspects of the service that could be improved upon as well as add insight into genetic counselling for CF in South Africa.

In addition, assessing the number of at-risk relatives who present for counselling could indicate whether more active outreach educational programmes about CF carrier risks are warranted. An estimation of the number of potential carriers within the CF families will also lend some insight into how many individuals should ideally be attending genetic counselling. The information gained from this study could assist in improved planning of CF genetic counselling services by highlighting whether the current protocol in the CF Clinics of Johannesburg Hospital is effective and sufficient, or whether other health care professionals need to be approached in order to increase the awareness of CF genetic counselling. If the data indicate that only a small proportion of those at-risk of being carriers are actively seeking information on the disease, their risks and their genetic status, it may suggest the need to provide greater public awareness of the disease and the genetic counselling service.

1.5 AIMS

A main aim of this study was to establish who utilises the CF genetic counselling service in Johannesburg and to identify areas that require improvement. The study also aimed to establish an estimate of how many at-risk relatives each family has, and whether or not these relatives have themselves pursued genetic counselling and testing. Finally, the research proposed to evaluate what impact the introduction of the specialist Genetic Counselling Clinics at the CF Clinics of Johannesburg Hospital has had on the utilisation of and referral to genetic counselling.

1.6 OBJECTIVES

1) To gather information on the CF counsellees including independent variables such as age, sex, employment status, ethnicity and relationship to the proband (if not the proband themselves).
2) To determine if mutation analysis was performed in each family and on whom testing had been performed.
3) To assess who refers counsellees for genetic counselling.
4) To determine the reasons why individuals come for genetic counselling.
5) To assess the drawn family pedigrees and establish a minimal estimate of how many relatives have risks of 25% or more of being carriers.
6) To determine how many of the at-risk relatives had genetic counselling through the Division of Human Genetics, NHLS and the University of the Witwatersrand.
7) To determine how many of these at-risk relatives have sought carrier testing.
8) To assess what impact the introduction of the specialist Genetic Counselling Clinics at the CF Clinics of Johannesburg Hospital has had on the uptake of and referrals to genetic counselling.

CHAPTER 2: SUBJECTS AND METHODS

The study was descriptive, retrospective and file-based, and it incorporated quantitative analysis. Ethics approval was granted by the Human Research Ethics Committee (Medical), Faculty of Health Sciences, the University of the Witwatersrand, reference number: M060943 (Appendix B). The following chapter describes the subjects of the study and how they were recruited, followed by the methods employed. This chapter also lists the terminology used to describe certain individuals or aspects pertaining to the study. Finally, a description follows of how the collected information was analysed.

2.1 SUBJECTS

Subjects for this study were all CF families counselled at the genetic counselling clinics of the Division of Human Genetics, NHLS and the University of the Witwatersrand, Johannesburg, from the first year that direct CF mutation analysis was implemented in the Division (1990) until the end of 2006. These families had one or more individuals confirmed to be affected by CF or, in instances where there was no CF proband, one or more family members confirmed to be CF carriers.

All counselling files in the Division of Human Genetics should contain standard information on the counsellee(s), the referring individual and a three-generation pedigree representing all family members at the time of consultation. Medical and genetic counselling documentation should also be present.

2.1.1 File Collection

In the Genetic Counselling Unit of the Division of Human Genetics, NHLS and the University of the Witwatersrand, a card system is used to keep records of all individuals attending genetic counselling for various conditions. Each condition is listed on separate cards and filed alphabetically. A list of all individuals who attended genetic counselling with a diagnosis of

CF from 1990 until 2006 was compiled from the cards listed under "Cystic Fibrosis". In total, 170 entries existed under "Cystic Fibrosis" for the period spanning 1990 to 2006. Of those 170 files, five were excluded due to a diagnosis of CF in a suspected proband being later ruled out (based on information in the counselling files). A further 12 files could not be located and so the total number of files analysed was 153.

In order to maintain anonymity on the data collection sheets, a unique "CF File Code" was assigned per data collection sheet. Each one of the 153 files represented one family. Twenty-three of the 153 files were linked as the families were related.

2.2 METHODS

2.2.1 Data Capture

By means of a data collection sheet drawn up for this study (Appendix A), information was gathered from the 153 files. The data collection sheet was divided into three main sections: the particulars of the counsellee(s), the counselling session and pedigree and relative analysis.

Particulars of the counsellee(s) that were gathered included the number and description of counsellees present, their ages, employment status and ethnic grouping. The information gathered on the counselling session included the venue of genetic counselling, the reason(s) for attendance, the referring individual and whether there were any follow-up consultations. Pedigree analysis included assessing whether consanguinity was present within the family and determining how many at-risk relatives each family had. Carrier risks were assigned to these individuals. All individuals within the families who had mutation analysis were noted along with their test results.

Some of the data were divided into pre- 2006 (1990-2005) and 2006. This was in order to compare ethnicity and some genetic counselling aspects (genetic counselling venues, referring

individuals and reasons for attending genetic counselling), before and after the introduction of the specialist Genetic Counselling Clinics at the CF Clinics of Johannesburg Hospital.

The following considerations were taken into account when data were obtained from the files (refer to Appendix A):

- ***Terminology***
  - The term "proband" referred to an individual affected with CF.
  - A "relative" referred to a family member that was related by blood. It therefore excluded individuals related to a proband through marriage or adoption.
  - A "counsellee" referred to the individual attending genetic counselling who was 12 years of age or older. Szybowska, Hewson, Antle et al. (2007) assessed the informational needs of adolescents with genetic conditions and classified adolescents as being between 12 and 19 years of age and so 12 years of age was used as a minimal counsellee age for this study. Adolescents generally have the ability to involve themselves at the adult cognitive and verbal level in which genetic counselling is carried out (Weil, 2000).
  - "First genetic counselling session" referred to the initial counselling session attended by a family during the years 1990-2006. Any prior genetic counselling sessions (<1990) were not included in this study. Occasionally further consultations occurred and these were referred to as "follow-up sessions."
  - "Counsellees" were described based on their relationships to the CF proband in their families. Where there was more than one nuclear family with a CF proband, the nuclear family that was more closely related to the counsellee(s) was considered the reference proband.
  - Ethnicity of counsellees was determined from patient-reported information recorded in the counselling file by the genetic counsellor during a genetic counselling session. In addition, molecular testing requests information, including

patient ethnicity, from the referring doctor. Therefore, the stated information was used.

- The referring individual was classified as a "general practitioner (GP)", "specialist", "relative", "self-referral" or "other". Counsellees who were referred by members of their families were grouped under "relative" referrals. This group differed from the "self-referral" group in that "self-referral" pertained to those individuals who sought genetic counselling on their own behalf and were not informed about the service by any of their relatives or medical staff.

- "At-risk relatives" were exclusively blood relatives who each had a minimum carrier risk of 25%. Individuals with smaller risks were not considered at-risk relatives for the purpose of this study.

- ***Pedigree analysis and at-risk relatives***

- Assessing the number of at-risk relatives in a family involved drawing a pedigree from the one present in each file. In cases where families had further genetic counselling consultations, the most recent pedigree was used.

- Although biological parents of probands are obligate carriers for CF mutations, they too were considered at-risk relatives. There may have been scenarios where the proband (their child) may have received genetic counselling but the parents had not. Their lack of knowledge and understanding would make them at-risk of having further affected children.

- Although grandparents are also at-risk of being CF carriers, they were not included as at-risk relatives in this study in an attempt to focus on the generations where carrier status would have implications for reproduction.

- At-risk relatives were therefore categorised as having carrier risks of 100% (1/1), 67% (2/3), 50% (1/2), 33% (1/3) or 25% (1/4) (see Table 1.4).

Data were entered into an Excel spreadsheet. For the 23 files that were linked, information pertaining to the number of at-risk relatives and family members who had mutation testing and genetic counselling was only entered once per family.

Figure 2.1 illustrates a hypothetical CF family pedigree containing all possible first, second and third degree relatives regarded as "at-risk relatives" for this study. All individuals drawn in blue are at-risk relatives with carrier risks of 25% or greater. Siblings to the probands are assumed to be healthy. Each person's relationship to the CF proband is noted as well as his or her probability of being a carrier.

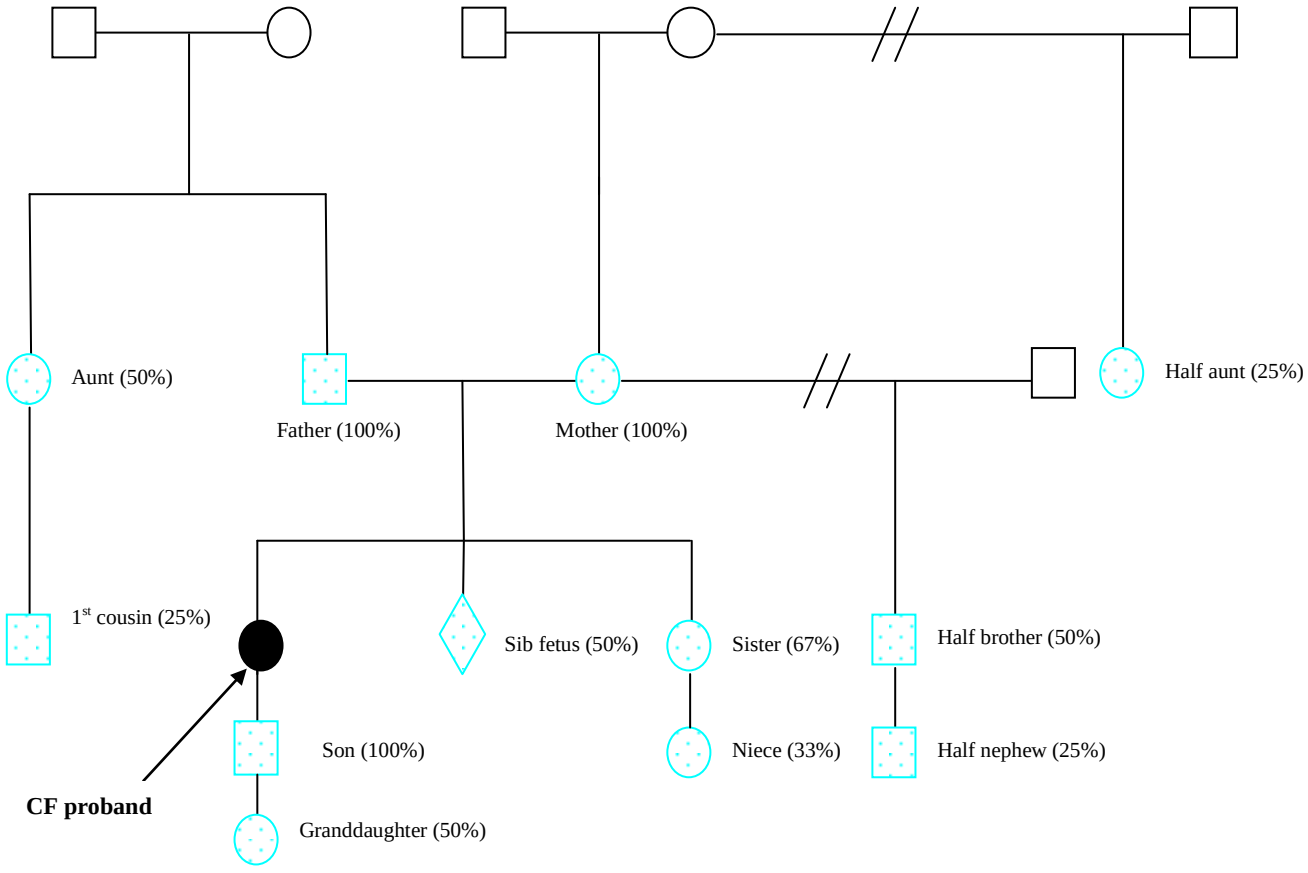

Figure 2.1 A hypothetical cystic fibrosis family pedigree illustrating all possible at-risk family members.

2.2.2 Data Analysis

Since this study was descriptive, most of the data generated were expressed as frequencies. The subjects (families or individuals) used for the various analyses differed at times and thus the denominators per calculation varied. Figure 2.2 represents a comprehensive layout of which subjects were used for each analysis.

Percentages were rounded off to the nearest whole percent and other figures were rounded off to one decimal place, except in the case of standard deviations, where such figures were rounded off to one decimal place more than the mean. Means and standard deviations were calculated using Excel's Statistical Analysis application. A statistician from the Medical Research Council (MRC) and the University of the Witwatersrand was consulted to validate the analyses.

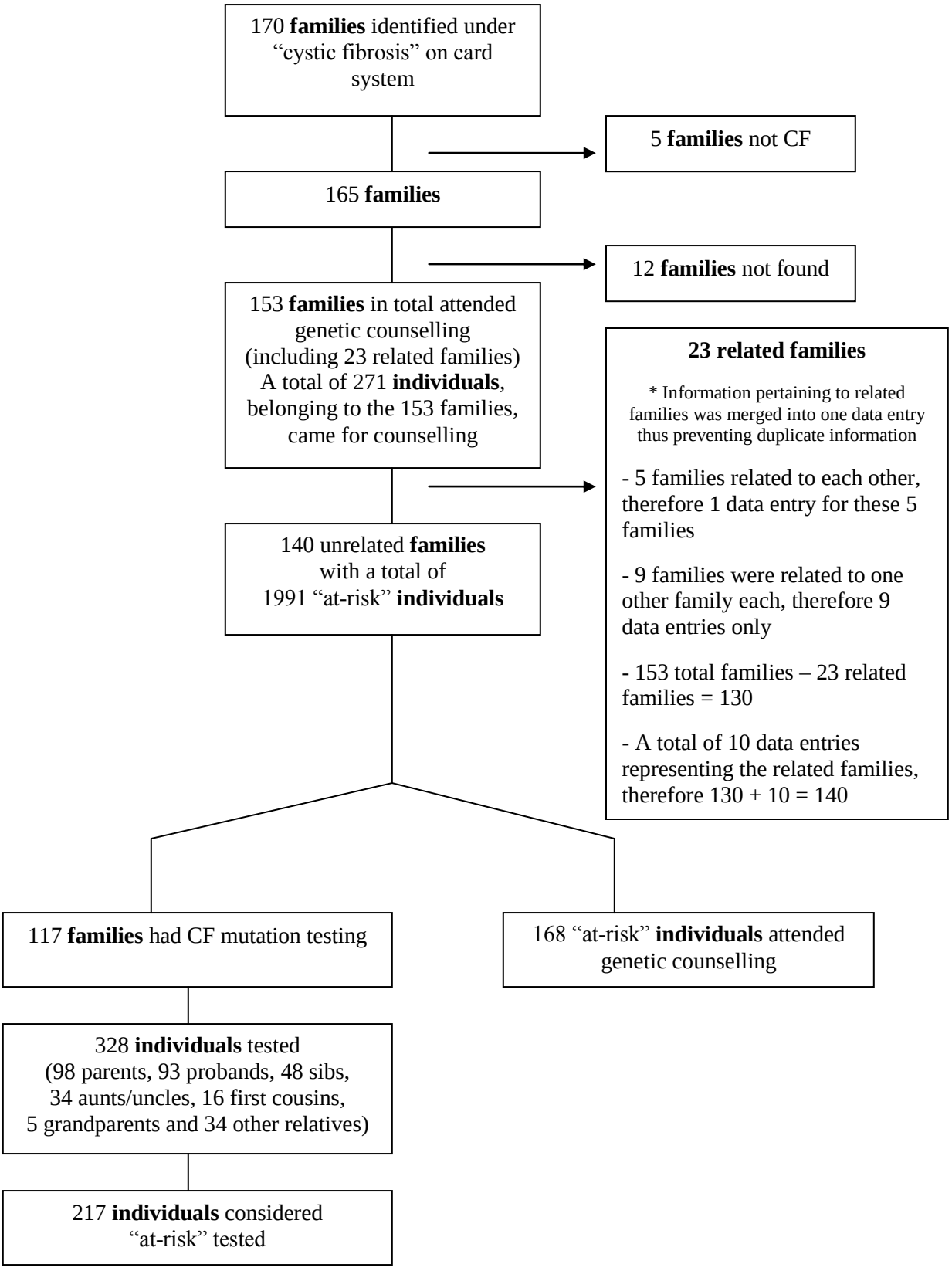

Figure 2.2 A breakdown of subjects used for each analysis.

CHAPTER 3: RESULTS

Results were generated from the 153 CF family files (unless otherwise stated) for the various queries listed on the data collection sheet (Appendix A). Some of the data were analysed in pre-2006 and 2006 groups. Although it is not ideal to compare data collected over 16 years to those collected over one year, these two time periods were used in order to assess what the impact was of the introduction of the specialist Genetic Counselling Clinics at Johannesburg Hospital's CF Clinics, in 2006. Comparative data included the locations where genetic counselling took place, the ethnicity of counsellees, their reasons for attending an initial genetic counselling consultation and who referred them.

3.1 DEMOGRAPHICS

One hundred and fifty-three families were seen for CF genetic counselling over a 17 year period (from 1990-2006) (refer to Figure 2.2). The age of counsellees ranged from 12 to 66 years with a mean age of 30.1 ± 9.19 years. It was noted that one counsellee was present at 26% (40/153) of the counselling sessions whilst 71% (109/153) of the time two counsellees attended a session. More than two counsellees were present at 3% (4/153) of the sessions. The majority of counsellees, 71% (193/271) were employed. Five out of the 153 families (3%) were consanguineous (marriage or relationship between blood relatives). Three of the consanguineous families involved relationships between first cousins, one relationship involved second cousins and the third relationship involved first-cousins-once-removed.

3.2 GENETIC COUNSELLING VENUES

Over the years the CF genetic counselling venues have changed together with changes in location of all genetic counselling clinics. Until 1998, the majority of cases were seen at the then Transvaal Memorial Institute (TMI). During 1999 and 2000, most genetic counselling sessions took place at the South African Institute of Medical Research (SAIMR) which has since been renamed the National Health Laboratory Service (NHLS) in Braamfontein,

Johannesburg. From 2001, private patients received genetic counselling at the Kenridge Hospital, now known as the Donald Gordon Medical Centre (DGMC). Currently, almost all private patients attend DGMC for genetic counselling. "Other" places of counselling included home visits and outreach clinics. Figures 3.1a and 3.1b illustrate how the distribution of CF genetic counselling at the various locations has changed over the years and how the majority of cases in 2006 were seen at Johannesburg Hospital, when Genetic Counselling Clinics were introduced at CF Clinics.

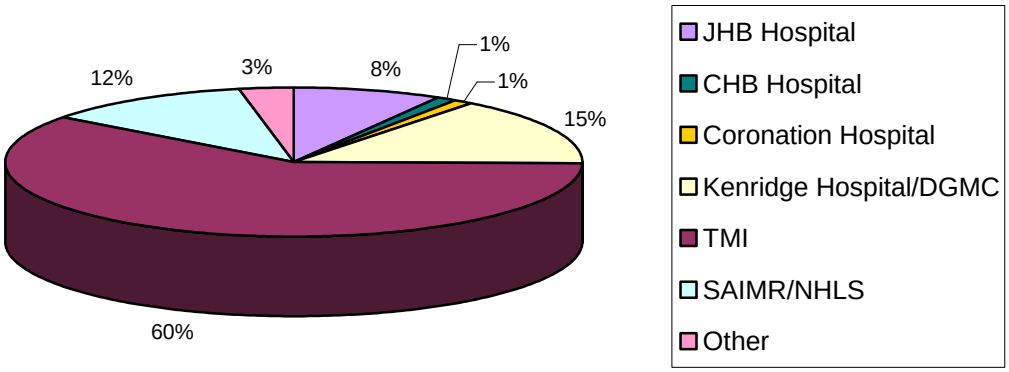

Figure 3.1a Location of CF genetic counselling sessions from 1990-2005.

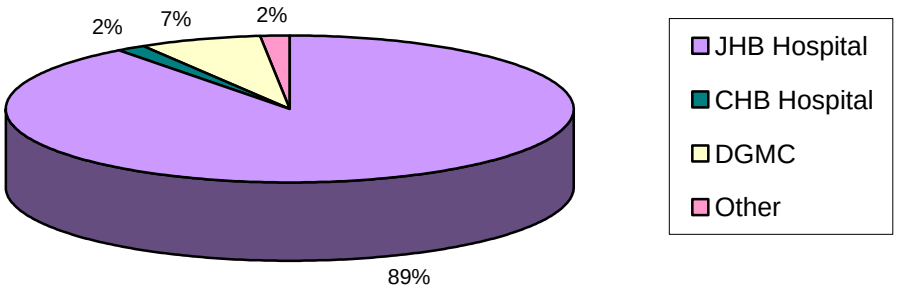

Figure 3.1b Location of CF genetic counselling sessions during 2006.

3.3 COUNSELLEE NUMBERS

The number of families attending CF genetic counselling has fluctuated slightly over the years between 1990 and 2005 but generally, fewer than 10 families were seen per year. Ninety-five families received CF genetic counselling from 1990-2005 and a further 58 families received CF genetic counselling during 2006 (Figure 3.2).

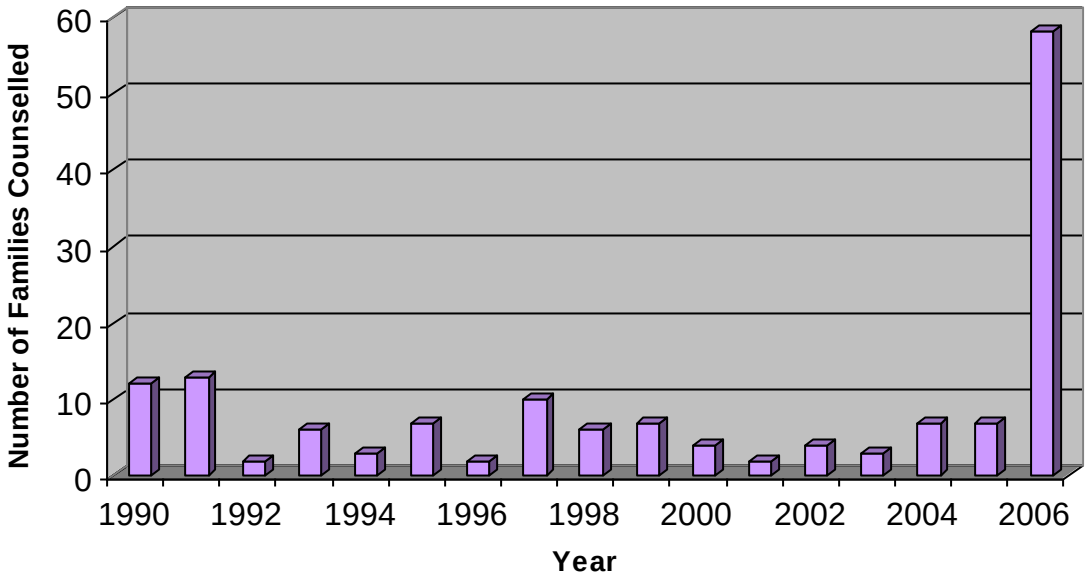

Figure 3.2 The number of families who attended CF genetic counselling from 1990 until the end of 2006.

A total of 271 individuals, belonging to the 153 families, attended initial genetic counselling sessions over the 17 year period (refer to Figure 2.2). Of the 271 counsellees, 114 (42%) were male and 157 (58%) were female. Thirty-five percent of the total counsellees were counselled during 2006. From 1990-2005 a mean of 5.9 ± 3.45 families and 11 ± 6.6 individuals were seen per year. Therefore, a mean of 1.9 ± 0.39 individuals per family attended genetic counselling over the time period of 1990-2005. In 2006, 95 individuals, belonging to the 58 families, were counselled that year. A mean of 1.6 ± 0.64 individuals per family attended genetic counselling during 2006.

3.4 ETHNICITY OF COUNSELLEES

The ethnicity of those individuals counselled pre-2006 and those counselled during 2006 was compared. Table 3.1 lists the absolute numbers (*n*) of individuals per ethnic group that attended genetic counselling from 1990-2005 and during 2006. The table also lists the mean number of individuals per ethnic group seen per year from 1990-2005.

Table 3.1 The ethnicities of the individuals who attended an initial CF genetic counselling session from 1990-2005 compared to those who attended in 2006.

Ethnicity	**Number and Percentages of Counsellees**				
	1990 - 2005		**2006**	**Total**	
	n	**mean number of individuals seen per year ± SD**	***n***	***n***	**% of total counsellees seen over 17 years**
White	170	5.7 ± 3.24	83	253	93%
Black	2	0.1 ± 0.34	5	7	3%
Coloured	2	0.1 ± 0.25	6	8	3%
Indian	2	0.1 ± 0.25	1	3	1%
Total	**176**		**95**	**271**	**100%**

As expected, the majority of counsellees were white. When compared to the mean number of black, coloured and Indian individuals seen per year prior to 2006, the absolute numbers of individuals belonging to these ethnic groups increased during 2006.

3.5 RELATIONSHIPS OF COUNSELLEES TO PROBANDS

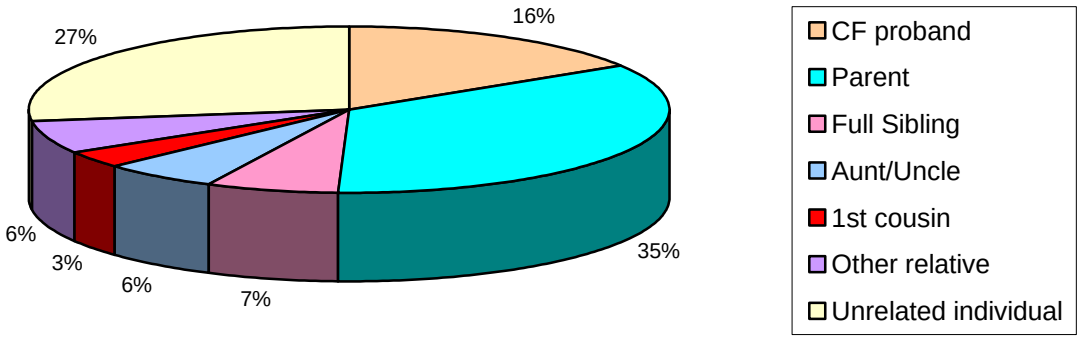

Figure 3.3 Proportions of the counsellees with varying relationships to CF probands.

Figure 3.3 represents the relationship categories for the 271 counsellees who attended initial CF genetic counselling sessions. The majority of counsellees (93/271) were parents of CF probands. The second largest group of counsellees consisted of individuals who were not related to a CF proband (74/271). In almost all cases an "unrelated individual" was a partner of a person who was a blood relative of a proband. The third largest group, comprising 16% of all counsellees, consisted of CF probands (44/271). Twenty-one of the CF probands were female and the other 23 were male. Siblings of CF probands made up the fourth largest group of counsellees (18/271) followed by aunts/uncles (16/271) and "other relatives" (17/271) who equally each comprised the fifth largest group of counsellees. "Other relatives", who comprised 6% of all counsellees, included nieces, nephews, grandparents, first-cousins-once-removed and children of CF probands. Only 3% (9/271) of counsellees were first cousins of CF probands.

3.6 REFERRING INDIVIDUALS

In order to compare the number of referrals from various groups of individuals before and after the introduction of the specialist Genetic Counselling Clinics at the CF Clinics of Johannesburg Hospital, the mean number of referrals made by each group of referring individuals per year for the period of 1990-2005 was calculated. These means were then compared to the absolute number of referrals made by each group of referring individuals during 2006. Figure 3.4 illustrates the results of the comparison.

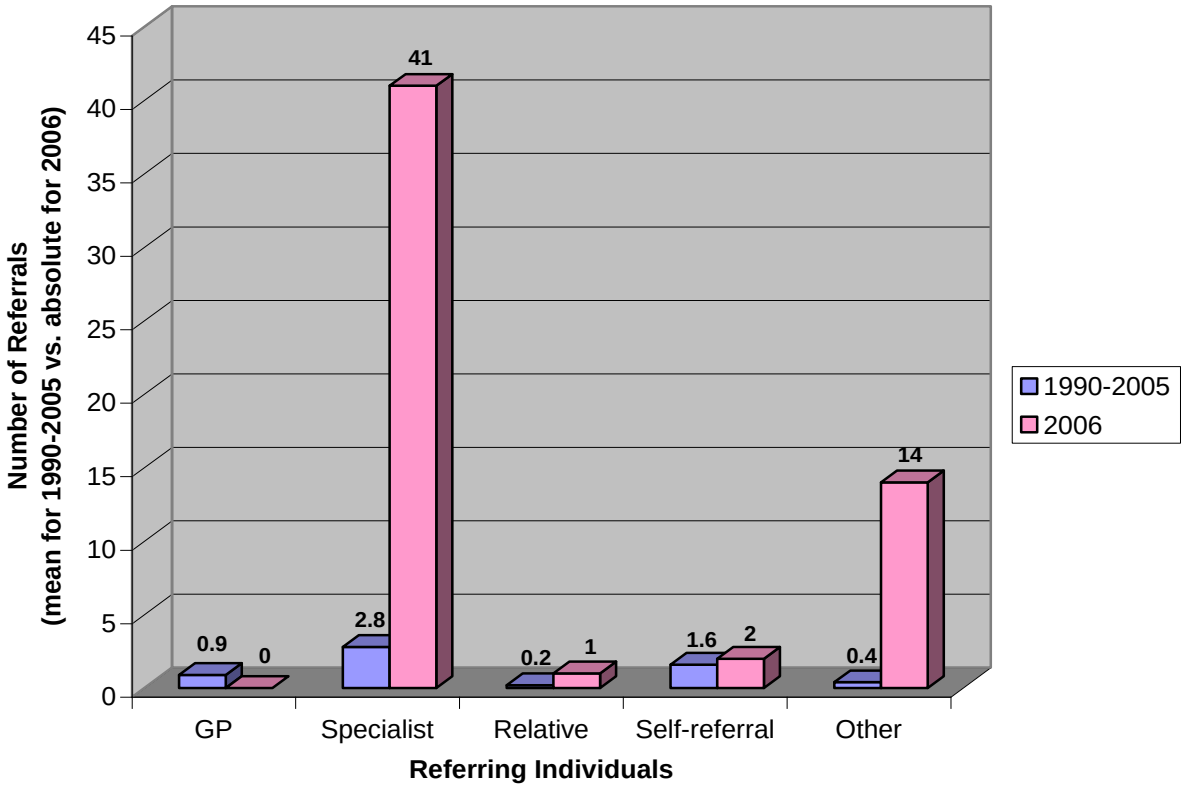

Figure 3.4 The mean number of referrals made by groups of referring individuals per year for 1990-2005, versus the absolute number of referrals from groups of referring individuals during 2006.

Overall, the majority of referrals have been from medical specialists. However, as depicted by Figure 3.4, specialist referrals increased considerably during 2006 compared to the prior 16

years. Referrals by "other" individuals also appeared to increase notably during 2006. Twenty-four percent (14/58) of all referrals during 2006 came from "other" individuals all of whom were nurses within the CF Clinics of Johannesburg Hospital. General practitioner, relative and self-referrals appeared to remain the same over the 17 year period.

3.6.1 Referring Specialists

As mentioned in section 3.6, most referrals for CF genetic counselling over the 17 year period were from medical specialists. Figure 3.5 illustrates the mean number of referrals made by the various groups of referring specialists during the years 1990-2005 compared to the absolute number of referrals made by each group of specialists during 2006. There was an increase in paediatrician and physician referrals during 2006 (Figure 3.5).

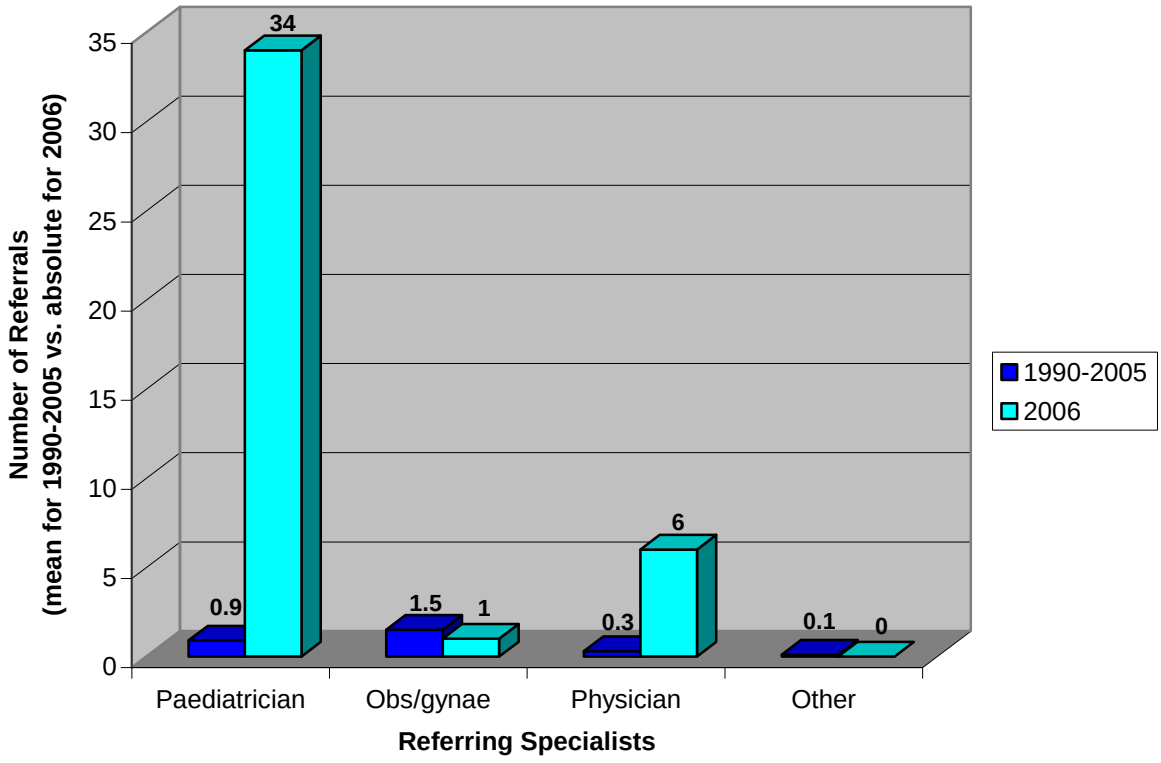

Figure 3.5 The mean number of referrals made by groups of specialists per year for 1990-2005, versus the absolute number of referrals made by groups of specialists during 2006.

3.7 REASONS FOR ATTENDING GENETIC COUNSELLING

The reasons why counsellees chose to attend an initial genetic counselling session were grouped into four categories (Table 3.2).

Table 3.2 Reasons why counsellees attended an initial genetic counselling session.

Reason	Number of families		
	1990 - 2005		2006
	n	**mean number of families seen per year ± SD**	***n***
Information gathering	45	2.8 ± 1.87	56
Result giving session	1	0.1 ± 0.25	0
Planning a family	14	0.9 ± 0.96	0
Prenatal counselling	35	2.2 ± 2.34	2
Total	**95**		**58**

"Information gathering" was the main reason why individuals attended CF genetic counselling over the 17 year period. During 2006, the number of families that attended for this reason increased compared to the average 2.8 families that attended for that reason per year during 1990-2005.

Attending an initial genetic counselling session for result giving is very unusual. However, in the one case noted in Table 3.2, the family had had CF carrier testing performed by a private laboratory and had not received genetic counselling beforehand. The family presented themselves for genetic counselling in order to have their results explained to them.

The small numbers of families attending CF genetic counselling per year for the reasons of "planning a family" and for "prenatal counselling" have remained constant over the 17 years.

3.8 FOLLOW-UP CONSULTATIONS

Twenty-seven out of the 153 families (18%) had follow-up genetic counselling consultations. Sixty-seven percent of families who came for follow-up consultations had one additional session (18/27), 15% of families had two additional sessions (4/27) and 19% of these families had three additional sessions (5/27). A total of 41 follow-up sessions took place of which 29 (71%) occurred during 2006. Twelve counsellees at these follow-up sessions had not been present at the initial genetic counselling sessions. They included two female CF probands, two grandmothers, two uncles, two fathers, one mother and two aunts of CF probands as well as one unrelated male individual who was a partner to a relative of a CF proband. These 12 counsellees accompanied individuals who had been present at initial genetic counselling sessions. The reasons why families came for follow-up consultations are listed in Table 3.3.

Table 3.3 Reasons why counsellees attended follow-up CF genetic counselling sessions.

Reason	**Families Attending Follow-up Sessions (1990-2006)**	
	n	**%**
Information gathering	6	15%
Result giving session	20	49%
Planning a family	1	2%
Prenatal counselling	14	34%
Total	**41**	**100%**

Most of the families returned for genetic counselling in order to receive test results. This was followed by families returning for prenatal counselling. Follow-up sessions that involved information giving were based on the previous genetic counselling sessions and were the third most common follow-up sessions held. Seven of the 12 counsellees (58%) who had not been present at an initial genetic counselling session, attended an “information gathering” follow-up

session. The remaining five new counsellees (42%) accompanied individuals for follow-up prenatal counselling. “Planning a family” was the least common reason for follow-up sessions.

3.9 FAMILY MEMBERS WHO HAD MUTATION TESTING

Although 153 CF files were assessed, the total number of unrelated families was 140 (refer to Figure 2.2). Twenty-three of these families did not have mutation analysis and so the total number of family members who had direct mutation testing was derived from 117 unrelated families (refer to Figure 2.2). Not all of these tested individuals attended genetic counselling. They may have been tested either in the Molecular Genetics Laboratory at the NHLS in Braamfontein, Johannesburg, or elsewhere.

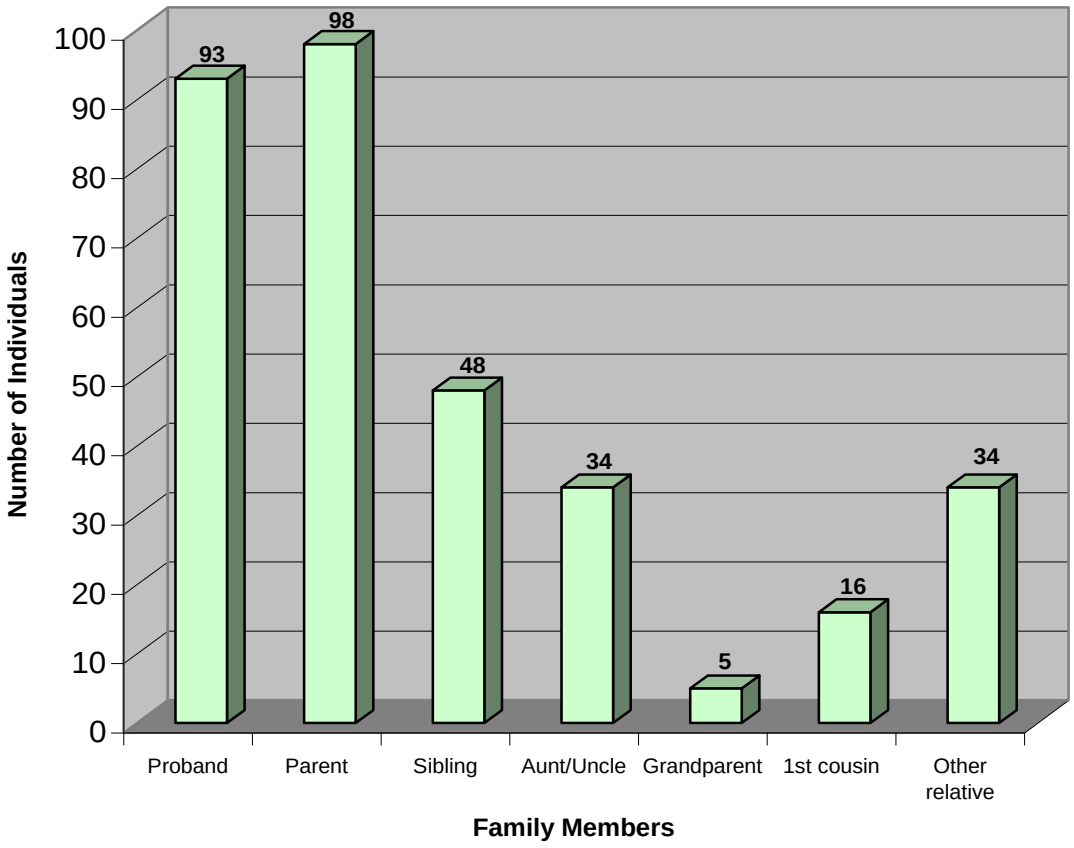

Figure 3.6 Numbers and descriptions of family members who pursued CF mutation analysis from 1990-2006.

In total 328 family members belonging to the 117 families had mutation testing (refer to Figure 2.2). The number of individuals tested per family ranged from 1 to 14 with a mean of 2.8 ± 2.26 individuals per family having mutation testing. The graph in Figure 3.6 shows which family members had mutation testing. Of the 328 family members who had mutation analysis, 217 (66%) individuals were classified as "at-risk" according to this study (refer to section 2.2). Probands were not included in the "at-risk relative" count.

Thirty percent of all testing (98/328) was performed on parents of CF probands. This was followed by 28% of tested individuals being CF probands (93/328), 15% of tested individuals being siblings (48/328) and 10% of those tested were aunts and uncles (34/328). "Other" relatives also made up 10% (34/328) of all individuals tested. "Other" relatives who had testing included children, half siblings, nephews, a half nephew, a great aunt, first-cousins-once-removed, sibling fetuses of CF probands, as well as parents and siblings of confirmed carriers. The carrier risks of these "other" relatives ranged from 12.5% to 100%. First cousins comprised 5% (16/328) of all relatives who had mutation analysis and grandparents comprised 2% (5/328) of such individuals (Figure 3.6).

In six of the 117 tested families (5%) only one CF-causing mutation was identified and in nine of the 117 tested families (8%) no CF-causing mutations were identified.

3.10 AT-RISK RELATIVES: NUMBERS AND MUTATION ANALYSIS

The number of at-risk relatives was calculated in the 140 unrelated families. In total, 1991 family members were identified as being "at-risk" (refer to section 2.2. including Figures 2.1 & 2.2). The mean number of at-risk individuals per family was calculated as being 14.3 ± 9.20 (range 3-59). Only 11% (217/1991) of all the at-risk relatives had mutation analysis (refer to Figure 2.2). Figure 3.7 graphically represents the proportions of the 217 tested individuals belonging to the different carrier risk categories. Most mutation analysis was performed on those at highest risk, and those at 33% risk were least tested.

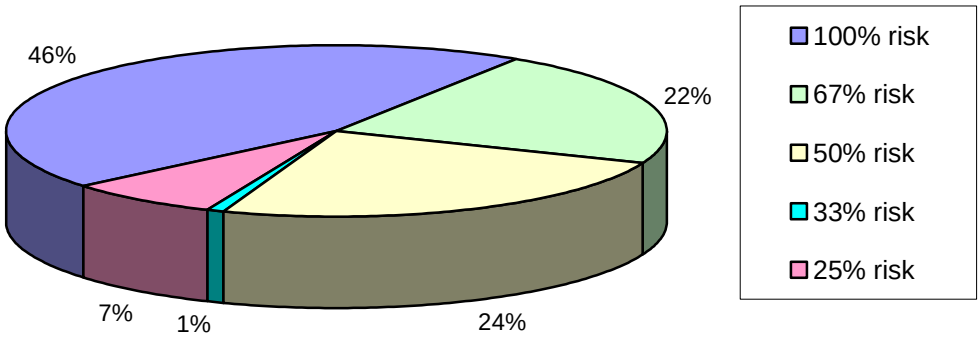

Figure 3.7 The proportions, by risk category, of at-risk relatives who had CF mutation testing.

Table 3.4 lists the numbers of at-risk individuals in each risk category, how many of those individuals had testing and of those who had testing, how many were proven to be carriers or affected. Of the four who were tested and were diagnosed as being affected, three were sibling fetuses to probands and were diagnosed prenatally, and one individual was a supposedly healthy sibling of a proband.

Table 3.4 Total number of at-risk individuals calculated in the 140 unrelated families including those who were tested and the overall test results.

Carrier Risk	Total Number of At-Risk Individuals	At-Risk Individuals Tested		Tested Individuals Proven to be Carriers		Tested Individuals Proven to be Affected	
	n	***n***	**%**	***n***	**%**	***n***	**%**
100%	271	99	37%	86	87%	0	0%
67%	123	48	39%	35	73%	1	2%
50%	662	53	8%	29	55%	3*	6%
33%	53	2	4%	1	50%	0	0%
25%	882	15	2%	8	53%	0	0%
Total	**1991**	**217**		**159**		**4**	

*Fetuses diagnosed by prenatal testing

From Table 3.4 it is evident that 37% (99/271) of all identified obligate carriers had mutation testing. Thirty-nine percent (48/123) of siblings (at 67% risk) had testing. Only 8% (53/662) of all at-risk relatives at 50% risk and 4% (2/53) of those at 33% risk chose to have mutation analysis. A minimal 2% (15/882) of all individuals at 25% risk pursued mutation testing.

Seventy-three percent (159/217) of all individuals tested were proven to be carriers. Only 87% (86/99) of the individuals at 100% risk who were tested were proven to be carriers by mutation analysis. Exclusion of the 271 obligate carriers (100% risk) resulted in a total of 1720 potential non-obligate carriers amongst the 140 families. Of these individuals, 118 (7%) had mutation testing. Seventy-three of the 118 individuals (62%) who were tested were proven to be carriers. A high proportion of siblings (73% of those tested) had positive carrier statuses and at least half of the tested individuals in the other risk categories were proven to be carriers.

3.11 GENETIC COUNSELLING OF AT-RISK RELATIVES

The final analysis performed on all at-risk relatives was to determine how many of them had ever attended genetic counselling within the Genetic Counselling Clinics of the NHLS and the University of the Witwatersrand, Johannesburg. Based on counselling records, only 168 at-risk relatives came for genetic counselling (refer to Figure 2.2). Therefore, approximately 8% (168/1991) of all at-risk relatives attended CF genetic counselling within our service.

CHAPTER 4: DISCUSSION

The results of the study have given an indication of who utilises the service of CF genetic counselling, offered by the Division of Human Genetics, NHLS and the University of the Witwatersrand, Johannesburg. They have also illustrated what impact the new specialist Genetic Counselling Clinics have had on the overall service of genetic counselling to CF families. Areas of the current genetic counselling service requiring improvement have been identified and new methods for educating and attracting at-risk relatives are suggested.

4.1 WHO ATTENDS CF GENETIC COUNSELLING AND WHY?

4.1.1 Attendees

The data obtained from this study show that the majority of individuals who attend CF genetic counselling are parents of CF probands (Figure 3.3). This would be expected as parents of affected children are the most likely individuals to access medical information and resources.

According to this study, the majority of CF counsellees are in their thirties, are employed and belong to the white population. In addition, counsellees usually attend a genetic counselling session as a couple. The majority of couples were parents of CF probands. Considering that most known CF-affected individuals are from the white population (Hill et al., 1988), it would be expected that the majority of counsellees were white. However, considering the estimated carrier frequency of 1 in 34 amongst the black South African population (Padoa et al., 1999), one would expect a substantial number of CF-affected black individuals, and consequently, a considerable number of black CF counsellees. However, the statistics from this study show that only 3% of all counsellees were black. It is likely that CF is still not being adequately diagnosed in black individuals (see section 4.2.3 for further discussion).

After parents of CF probands, the group of "unrelated individuals" was the next major group of counsellees (Figure 3.3). These individuals were almost always partners to relatives of CF

probands. In many cases partners of relatives of CF probands only learn about CF once they have met their partner or his/her family (Callanan et al., 1995) and so it is encouraging to see a large proportion of these individuals attending genetic counselling because their risks, as a couple, are not insignificant.

Cystic fibrosis probands themselves were the third most common group of counsellees (Figure 3.3). The proportions of male versus female CF probands were very similar as would be expected considering CF affects males and females in equal proportions. When a genetic diagnosis is made, usually in childhood, the parents of the affected child are typically the recipients of the genetic information. It is likely that when such information is received soon after a genetic diagnosis has been made, parents may feel emotionally overwhelmed and may not grasp the genetic information fully. Consequently, the information they discuss with their children may be limited and sometimes inaccurate. Also, parents might not necessarily feel comfortable to discuss information that CF probands wish to know as young adults. It is therefore of utmost importance for probands to receive genetic counselling at an appropriate time in their lives. Since the introduction of the specialist Genetic Counselling Clinics at the CF Clinics of Johannesburg Hospital, the number of probands attending genetic counselling has increased. This is an encouraging finding as Henley and Hill (1990) showed that half of South African CF probands were unaware of the inheritance pattern of the disease. The fact that CF probands themselves are the third major group of individuals counsellees, suggests that the current service is effective in educating CF probands about their condition when they are old enough to receive the information. It also indicates that CF probands are living through to adolescence as a result of improved medical treatment.

A concerning finding is the small proportion of siblings and extended family members, who are at significant risk, attending genetic counselling. With respect to healthy siblings who are at 67% risk of being carriers, one would expect more to be attending genetic counselling in order to discuss their risks and options. However, only 7% of all counsellees were siblings (Figure 3.3). This echoes a lack of knowledge amongst siblings of CF probands regarding the disease and its inheritance as found by Henley and Hill (1990). Such inadequate knowledge can cause siblings to have misconceptions about their carrier status and the condition itself.

Genetic counselling should therefore be viewed as being essential for siblings of CF probands. From the current results, siblings in general, are not presenting to find out more about their genetic status. A possible solution to this problem is discussed in section 4.1.2.

The low uptake of genetic counselling by non-nuclear family members, such as aunts, uncles and cousins of CF probands, has been reported in other studies. This may be due to the fact CF is often viewed as a nuclear family problem which does not encompass extended family members (Fanos & Johnson, 1995). Extended family members may not believe they are at risk of being carriers as they are not within the nuclear family. Also, communication between family members about the disorder may be insufficient and so the poor attendance of such individuals for genetic counselling is directly related to their unawareness of their risks (Lafayette et al., 1999). Denial can be another factor inhibiting relatives of CF probands from attending genetic counselling (Weil, 2000). Perhaps those who are actually informed about their risks through family members fail to believe the possibility that they may be carriers and therefore do not seek genetic counselling thus denying themselves clarity on the situation.

4.1.2 Reasons for Attending

The results from this study support the finding of Veach et al. (1999) as "information gathering" was the most common reason why individuals attended genetic counselling over the 17 year period (Table 3.2). This result suggests there is a need for CF genetic counselling as individuals require basic genetic information. Even in cases where a diagnosis of CF has been known for many years, families have a specific need to understand the genetic component of the condition. This should be provided by medical geneticists or genetic counsellors.

It is encouraging to see that only a small number of individuals first attended CF genetic counselling while a pregnancy was ongoing (Table 3.2). Prenatal genetic counselling for CF is usually urgent and not ideal for the reasons highlighted by Super et al. (1986) (see section 1.3). Combined with the high proportion of "information gathering" sessions, the low number of prenatal sessions is a positive finding. These figures suggest that individuals have been

educated about their risks before future pregnancies, and can make careful informed reproductive decisions. However, it is possible that the small number of prenatal genetic counselling sessions is due to the fact that individuals are unaware of the availability of prenatal diagnosis for CF.

According to Collins et al. (2001), the main reason why people do not present for genetic counselling is because they are not aware of its existence. The low number of siblings and extended family members attending CF genetic counselling is likely to be due to a lack of knowledge that they are at-risk, combined with the lack of awareness of the service. The use of an information pamphlet or a cascade letter discussing CF could be an effective way of informing siblings and other relatives about CF and their associated risks, and inviting them to attend genetic counselling. At Royal Manchester Children's Hospital in England, parents of affected children are encouraged to pass on a cascade booklet specially written for the extended family, giving details of how to make contact with the genetic counselling service and to organise genetic testing. This cascade booklet has been effective and well accepted amongst medical professionals and families of CF probands (Roberts et al., 2003). This is something that should be put into practice when individuals attend CF genetic counselling at our clinics. Not only would such a booklet, pamphlet or letter reduce the burden parents of probands might feel in having to educate and inform family members about the condition, but it would increase awareness of risks amongst relatives and empower them to come forward to find out more information. However, one of the pitfalls of such a method is that its success is still dependent upon the parents of the CF proband passing the cascade booklet on to other relatives.

It would be useful to follow-up new CF diagnoses made within the Molecular Genetics Laboratory of the Division of Human Genetics, NHLS and the University of the Witwatersrand, more aggressively. When a new diagnosis of CF is made, the parents of the affected individual should receive a cascade booklet, letter or pamphlet in order to make them aware of the genetic counselling service. Alternatively, a genetic counsellor should discuss referral of the tested patient for genetic counselling with the referring clinician.

4.2 THE IMPACT OF THE SPECIALIST GENETIC COUNSELLING CLINICS

Based on the results of the current study, the introduction of the specialist Genetic Counselling Clinics at the CF Clinics of Johannesburg Hospital has been positive in that the number of referrals, counsellees, and follow-up consultations increased considerably during 2006 compared to prior years.

4.2.1 Counselling Venues

Over the years the venues where individuals have received genetic counselling for CF in Johannesburg through the Division of Human Genetics, NHLS and the University of the Witwatersrand have changed. Since the introduction of the Genetic Counselling Clinics at the CF Clinics of Johannesburg Hospital in 2006, almost all cases have been seen there (Figure 3.1b).

Small proportions of families were seen at the Kenridge Hospital/DGMC over the 17 year period (Figures 3.1a & b). This is indicative of the small number of private patients seen for CF genetic counselling. Although it is possible that some of the private patients were treated at the specialised CF Clinics at Johannesburg Hospital and therefore attended genetic counselling there during 2006, the results mainly highlight the lack of referrals to genetic counselling from doctors in private practice.

The numbers of cases seen at Chris Hani Baragwanath Hospital (CHB) and Coronation Hospital over the 17 year period were exceptionally low (Figures 3.1a & b). Patients suspected or diagnosed as having CF are likely to be transferred to Johannesburg Hospital's CF Clinic as it is specialised. In such cases, these patients would therefore be seen for genetic counselling at Johannesburg Hospital. However, considering that the patients of CHB are predominantly black and those at Coronation Hospital are predominantly coloured, another possibility for the small numbers of counsellees seen at these two hospitals could be due to missed diagnoses of CF in patients of the black and coloured ethnic groups. Low referral rates of CF patients to

genetic counselling by doctors at these two hospitals could be another reason for the small number of black and coloured counsellees.

4.2.2 Counsellee Numbers

Ninety-five families received CF genetic counselling over a 16 year period (1990-2005) whereas 58 families received CF genetic counselling during 2006 alone (Figure 3.2). The small number of individuals attending CF genetic counselling before 2006 is indicative of poor referral of all patients and their families.

The Victorian Clinical Genetics Service in Australia ensures that the majority of parents of CF children participate in genetic counselling "as a matter of course" by incorporating genetic counselling as a whole component into the clinical care programme for CF. Through the integration of the service into the care programme, uptake is more likely to be favourable (Collins et al., 2001). The results of the current study are in agreement with this as there was a substantial increase in families counselled during 2006. Therefore, when genetic counselling is available within the clinic where a child is being treated, the utilisation of the service is far greater than when the service is offered externally and requires efforts from clinical staff, in terms of referral and administration, and from patients attending an additional clinic. Convenience, low costs and familiarity with the clinic, especially for hospital patients, are positive factors associated with the incorporation of the genetic counselling service into treatment clinics.

There is, however, a catch up effect, and it would be expected that counsellee numbers for first referrals will decrease somewhat once the majority of patients and their families at the CF Clinics of Johannesburg Hospital have been seen for genetic counselling. From the beginning of January 2007 until the end of August 2007, 23 families had received CF genetic counselling at the CF Clinics, and of those 23, only five had been seen previously. Bearing in mind that this figure is not representative of the entire year, 18 new families seen for genetic counselling in the first eight months of the year is very encouraging and suggests that the specialist Genetic Counselling Clinics at the CF Clinics of Johannesburg Hospital are still effective and

new patients are being referred. Hopefully follow-up sessions will continue as well and an increase in extended family referrals will be seen within time.

4.2.3 Ethnicity of Counsellees

Prior to 2006, a mean of 0.1 black, coloured and Indian counsellees were being seen per year. During 2006, although few black and coloured individuals were counselled, the numbers were greater than those seen over the previous 16 years (Table 3.1). This increase in black and coloured counsellees could suggest that more CF patients are being diagnosed amongst these two population groups. It could also simply represent that black and coloured patients are being concentrated at the CF Clinics of Johannesburg Hospital or that there is improved referral of patients for genetic counselling. Improved accessibility to genetic counselling at the CF Clinics is also a likely explanation for the increase in black and coloured counsellees.

One of the main problems with identification of black, coloured and Indian CF probands is the low mutation detection rate amongst these population groups. Although not essential, the presence of two CF causing mutations in an individual confirms a diagnosis of CF especially when there is large phenotypic variation amongst affected individuals. However, it is difficult to confirm a diagnosis of CF at the molecular level. This is because in South Africa, only 46% of mutations are detected amongst black CF patients and 74% of mutations are detected amongst coloured CF patients, compared to the 90% mutation detection rate in white CF patients (Goldman et al., 2003). The carrier frequency and the mutation detection rate in the South African Indian population remains unknown. This may account in part for the lower number of black, coloured and Indian counsellees seen. Due to the difficulty in confirming a diagnosis of CF at the molecular level, the sweat test should remain the standard diagnostic investigation.

4.2.4 Referring Individuals

Over the years the majority of referrals for CF genetic counselling have been from specialists (Figure 3.4) but referrals from such individuals, in particular from paediatricians and physicians, increased notably during 2006 (Figure 3.5). In addition, referrals during 2006 from "other individuals," all of whom were nurses within the CF Clinics, increased (Figure 3.4). The increases in paediatrician, physician and nurse referrals are likely to be the direct result of the introduction of the specialist Genetic Counselling Clinics at the paediatric and adult CF Clinics of Johannesburg Hospital. The doctors and nurses practicing in those clinics were referring patients and their families for on-site genetic counselling as they saw them for their regular follow-up appointments. With particular reference to CF, Hulsebus and Williams (1992) describe nurses as being an essential component of the health care delivery system as they can act as educators, counsellors, and promoters to ensure ethical management of patients' genetic information. Considering the close interaction most nurses have with patients on a day-to-day basis, it would be worth training more nurses who have contact with CF patients about the availability and importance of genetic counselling and testing for CF patients and their families in order to optimise referrals. Educating doctors about the need for genetic counselling, even in specialist clinics, should also be advocated.

Relative and self-referrals have remained low over the 17 years (Figure 3.4). Communication may be very poor amongst family members, and carrier perceptions may not be high amongst relatives. A study conducted by Sorenson, Cheuvront, Bruning et al. (1996) in America involved an active recruitment process to identify relatives of CF probands who were at risk of being carriers. The investigators made use of proband and/or parent assistance in providing the contact details of at-risk relatives. Only 54% of families approached assisted the investigators by providing them with the required information on their relatives. The results indicated reluctance amongst some probands and their parents to discuss the condition with their families and identify relatives at risk of being carriers. This reluctance to communicate with family members about the disorder could explain the poor number of relative referrals seen in the current study. Therefore, in a genetic counselling session, the genetic counsellor should

actively discuss the importance of communication between family members as well as make use of an information booklet, pamphlet or letter as discussed in section 4.1.2.

Ideally one would hope that at-risk individuals are taking the initiative and referring themselves for genetic counselling in order to find out more information about the disorder and their risks. However, if relatives are not aware of, or concerned about, their risks they are not likely to refer themselves for genetic counselling, hence the small number of self-referrals.

According to the World Health Organization (WHO) "it is the individual's ethical duty to tell blood relatives that their relatives may be at genetic risk." The World Health Organization does not recommend that genetic professionals make direct contact with relatives but that they rather act as mediators by instilling a feeling of duty and responsibility towards relatives in the counsellees (WHO, 1998). Based on the small number of relative and self-referrals, family members are not being informed about their genetic risk and so another approach needs to be taken. The use of the previously mentioned cascade letter, pamphlet or booklet addressed to the at-risk relatives inviting them to genetic counselling would be a favourable option in order to increase awareness amongst family members without genetic professionals making direct contact with them.

4.2.5 Follow-up Consultations

The majority of the follow-up consultations (71%) took place during 2006 and most follow-up sessions were in order for counsellees to receive their mutation testing results (Table 3.3). The large numbers of follow-up sessions occurring in 2006 reflect the usefulness of having the service of genetic counselling at the CF Clinics. Cystic fibrosis patients tend to return to the CF Clinics for regular treatment which therefore makes it convenient for them to return to the Genetic Counselling Clinics for their test results at the same time. Returning to the genetic counselling clinic for test results is the ideal situation. In instances of positive carrier results the genetic counsellor is "breaking bad news" and so it is important to give results in person (Weil, 2000). In addition, negative carrier tests require interpretation. A negative carrier test does not necessarily always reduce the tested individual's risk of being a carrier to zero.

Prenatal counselling was the second most common reason why families returned for additional consultations. A very small proportion of counsellees returned when they were planning to start families (Table 3.3). There are several reasons for this latter finding. Firstly, it may be that the information gathering sessions were sufficient and individuals did not need to return for more information when they were planning to have children. Secondly, some families may have chosen not to have children. Thirdly, families could have sought information from other sources, such as their obstetricians and gynaecologists, and not have returned to the genetic clinics. These reasons were not available to this study.

4.3 OVERALL UPTAKE OF MUTATION TESTING

Mutation analysis was not a standard procedure performed on patients at the CF Clinics of Johannesburg Hospital before 2006. With the introduction of the specialist Genetic Counselling Clinics at the CF Clinics of Johannesburg Hospital, the importance and usefulness of mutation analysis has been emphasised. Individuals are offered testing by the genetic counsellor. By identifying which side of the family a specific mutation arises from, mutation analysis for other relatives is made far easier. Testing the CF proband for the disease-causing mutations and then testing the parents to determine which parent carries which mutation is the ideal scenario. Furthermore, future treatment is likely to be dependent upon the types of mutations an individual has. A drug known as PTC-124 has been shown in clinical trials to be effective in overriding CF nonsense mutations that generate stop codons, thus allowing full-length proteins to be produced (Hamed, 2006). Similarly, the aminoglycoside antibiotic, gentamicin, has been shown to be effective in suppressing stop codon mutations (Sermet-Gaudelus, Renouil, Fajac et al., 2007). Future drug design and administration is therefore likely to be dependent upon one's genotype and so it would be important to determine what mutations an affected individual has.

On average, 2.8 individuals per family had CF mutation testing. The difference between the number of parents of CF probands who had mutation testing and the number of CF probands tested was negligible. If one considers that there are two parents for every CF proband, one would expect almost twice as many parents as probands to have had CF mutation testing. The

results therefore indicate that there is under-testing of parents. This is possibly due to parents of CF probands being assumed to be carriers and therefore not confirming their carrier status through mutation analysis.

Siblings of CF probands were the third most commonly tested group of individuals. A small proportion of aunts, uncles, grandparents as well as first cousins chose to have mutation testing (Figure 3.6). Sorenson, Cheuvront, DeVellis et al., (1997) reported how relatives who have completed their families, those who are in the process of completing their families, and those who have not yet considered having children, have varying interests in CF testing. This might explain the varying uptake of mutation analysis amongst these different individuals.

With respect to grandparents, on the whole they are past their reproductive years and so carrier testing does not have immediate implications for them. Grandparents beyond reproductive age are usually discouraged from testing because discovering one is a carrier can often cause feelings of guilt from passing on the defective gene (Roberts et al., 2003). However, for the sake of effective cascade testing, identifying which grandparent carries a CF-causing mutation could be useful in tracing which side of a family is at risk of having carriers of that mutation. Therefore, during a genetic counselling session emphasis should be put on the value of knowing a family's mutations and from which side they originated. Family pedigrees are very useful in identifying which individuals mutation analysis should be offered to.

Several studies have looked into the motivation behind family members having mutation testing. Lafayette et al.'s (1999) study indicated that many family members chose to have carrier testing because they wanted to help their relative with CF and to further CF research. According to Sorenson et al. (1997) and Lafayette et al. (1999), relatives who perceived their chances of being carriers as high, and who were also concerned about having carrier children, were more likely to accept mutation testing. This implies that individuals choose to have carrier testing for various reasons, the majority of which are personal and dependent upon the individuals' assumed carrier status and that of their future children. Such observations again emphasise the importance of education about CF and the associated risks amongst such relatives so that they can make decisions around knowing their genetic status.

4.4 AT-RISK RELATIVES

One thousand nine hundred and ninety-one individuals, belonging to the 140 families were classified as "at-risk" according to the stipulations of this study (Table 3.4 & Figure 2.2). On average each family had 14 at-risk relatives, a figure very close to that of Sorenson et al.'s (1997) study in which an average of 15 at-risk individuals were identified per CF-affected family. From the large estimate of at-risk relatives one would expect many individuals to be attending genetic counselling. However, as the results have shown, this is not the case as only 8% (168/1991) of all at-risk relatives attended genetic counselling through our clinics. It is possible that some of these individuals received genetic counselling elsewhere but that is unlikely to account for the remainder of at-risk relatives identified.

Lafayette et al. (1999) performed a similar study to the one reported here in which the investigators assessed family pedigrees of CF-affected families and evaluated how many relatives were at 50% or greater risk of being carriers (excluding obligate carriers). They identified 238 relatives with carrier risks above 50% in 38 families. This gave an average of 6.3 individuals per family being at 50% or greater risk. The current study identified 785 relatives with carrier risks of 50% or greater (excluding obligate carriers) in 140 families (Table 3.4). This gave a similar result of 5.6 individuals per family being at a risk of 50% or greater. The results for the number of at-risk relatives per family are in keeping with previous studies.

4.4.1 Uptake of Testing Amongst At-Risk Relatives

Only 11% (217) of the 1991 at-risk relatives, including obligate carriers had mutation analysis. When obligate carriers were excluded from the data, a low 7% of at-risk relatives had testing for CF-causing mutations (Table 3.4). This is far less than the 44% acceptance rate of CF carrier testing in a clinical setting amongst relatives reported by Sorenson et al. (1997). However, a general lack of demand for CF carrier testing has been reported amongst CF-affected families (Fanos & Johnson, 1995).

Cost can influence the uptake of testing (Sorenson et al., 1997). In the current local situation, hospital patients (of which counsellees are the majority) do not pay for testing, but private patients do. However, for extended family members, testing might not be free. The cost of testing is therefore a possible obstacle preventing relatives from pursuing mutation analysis. In support of this statement, the 44% carrier testing acceptance rate amongst relatives in Sorenson et al.'s (1997) study was in an environment of free mutation testing. It is likely that the acceptance rate would have been lower if individuals had to pay for the test themselves. However, in a study performed by Lafayette et al. (1999), only 29% of at-risk relatives accepted free CF mutation testing. This therefore suggests that cost might not necessarily be a primary inhibiting factor in mutation testing of at-risk relatives and that other factors are more influential.

There are many other reasons influencing the decision to confirm one's genetic status. Some researchers say that discovering that one is a carrier can potentially threaten one's self-concept (McConkie-Rosell & DeVellis, 2000). It is possible that some at-risk relatives choose not to pursue carrier testing out of fear. The fear of social harm whereby carriers are discriminated against, through the loss of insurance or employment, might also prevent individuals from wanting to uncover their genetic status (Hulsebus & Williams, 1992). Other reasons for the recorded low uptake of mutation analysis could be due to a lack of information about CF within the family. It is also possible that certain relatives had testing elsewhere but that the individuals that attended genetic counselling were not aware of this and therefore did not report it.

Only 39% of full siblings had mutation analysis (Table 3.4). More than half of the siblings in the study conducted by Fanos and Johnson (1995) described growing up with the beliefs that they were carriers and that testing would only have confirmed their fears. Therefore, family myths and misperceptions about their genetic status could be reasons why many siblings do not have testing. In instances where a diagnosis of CF is made in a child, it would be important for that child's young siblings to be tested for CF as the phenotype can be variable and they may also have the disease and require treatment. Genetic counselling is therefore essential in promoting the uptake of mutation testing.

4.4.2 At-Risk Relatives Proven to be Carriers

Seventy-three percent of all individuals tested were proven to be carriers (Table 3.4). Despite being obligate carriers, only 87% of those at 100% risk were confirmed carriers by mutation analysis. This is likely to be a result of undetected mutations in certain individuals. Over the years the numbers of CF mutations tested for has increased. It is possible that when some of these obligate carriers had mutation analysis the laboratory was only testing for a limited number of mutations. If these individuals were retested now, it is likely that some of the previously unidentified mutations would be identified. Nevertheless, there will always be individuals whose mutations remain unknown until comprehensive mutation screening is available.

Lafayette et al. (1999) reported that 50% of the tested non-obligate at-risk relatives were proven to be CF carriers, a lower figure than that reported by the current study. In the current study, 62% (73/118) of all non-obligate at-risk relatives who were tested were proven to be CF carriers (Table 3.4). The results from both studies signify that a large proportion of at-risk individuals are indeed carriers. The considerable number of positive test results raises concern about the large number of at-risk relatives per risk category that had not pursued carrier testing. Such findings suggest that there are many more carriers who are unaware of their genetic status and are therefore at-risk of having CF-affected children. These results justify continuing with the genetic counselling service at the CF Clinics of Johannesburg Hospital.

An interesting finding was the one sibling who was supposedly unaffected but who was found to have two CF-causing mutations. With respect to carrier testing, the current policy of the Molecular Genetics Laboratory of the Division of Human Genetics, NHLS and the University of the Witwatersrand, Johannesburg, is not to test minors (under the age of 18 years). However, minor siblings of CF probands are tested for affected status. In view of the broad spectrum of clinical features of CF and the varying severity, it is possible that more individuals, including minor siblings, are potentially affected with milder symptoms but are not being diagnosed with CF. When such testing is performed, the laboratory report states that the tested individual is either affected or unaffected and therefore does not disclose carrier

status unless the individual is over 18 years of age. There is a strong argument for testing siblings of CF probands for affected/unaffected status as early treatment and intervention is beneficial for their long-term health. This is another issue that should be reinforced with doctors at the CF Clinics and families attending CF genetic counselling. In situations where familial mutations cannot be identified, linkage analysis could be offered to siblings of affected individuals if the diagnosis of CF was confirmed by other methods.

4.5 LIMITATIONS TO THE STUDY

The current study was solely dependent upon the information present within the counselling files of CF families. Consequently, data may have been limited in that information may have been incomplete, inaccurate or out-dated. With respect to pedigree analysis, it was evident that counsellors sometimes fail to draw a three generation pedigree. Incomplete pedigrees and the likelihood that families increased through births or decreased through deaths since the pedigree was constructed make it possible that the number of at-risk relatives calculated in the 140 families may indeed be more or less than 1991. It is possible that members of the families may well have had CF testing and counselling at other institutions but such information was not known at the time by the counsellee and so was not recorded in the file. In addition, a limitation to this file-based study was missing files. Twelve files could not be located for inclusion in the research. However, 11 of the 12 files were for white families and only one was a file for a black family. These files were therefore not likely to have influenced the results of the study significantly.

Furthermore, the comparison of mean data (1990-2005) versus absolute data (2006) is not ideal. However, in order to ascertain what effects the introduction of the specialist Genetic Counselling Clinics at Johannesburg Hospital's CF Clinics had on the service of genetic counselling, it was necessary to do this.

Finally, the cohort used in this study consisted only of counsellees who had been counselled at the Genetic Counselling Clinics of Division of Human Genetics, NHLS and the University of

the Witwatersrand, Johannesburg. The data generated from this study could be considered representative of the large CF referral clinics nationally. However, certain factors including the ethnicity of the patients, the referring doctors and the availability of mutation testing, as well as genetic counselling services, are not comparable among the different provinces of South Africa.

4.6 RECOMMENDATIONS

Based on the findings of this study the following recommendations can be made:

- From the increase in counsellee numbers during 2006 it is obvious that the specialist CF Genetic Counselling Clinics have been well utilised and should therefore remain in place. New patients and/or their families should enter genetic counselling as part of the broader process of management and care.
- Families previously seen for genetic counselling should be approached regularly and asked about other family members who may be reaching ages appropriate for counselling. The use of an efficient database involving up-to-date records could be used to prompt this.
- A cascade letter or booklet should be compiled and given to all families that present for CF genetic counselling. The information should be aimed at other family members informing them that they are at risk of being CF carriers and providing them with contact details for genetic counselling.
- The testing of siblings of probands for affected or unaffected status should be encouraged due to the variable phenotypic expression of CF.
- A more active approach to educate medical professionals about the importance of genetic counselling should be implemented. This could be done through workshops and presentations. Doctors treating CF-affected individuals in private practice should be targeted in order to increase private referrals. Obstetricians and gynaecologist should also be alerted to take family histories from their patients as

they too can be significant referring specialists. Nurses who have contact with CF patients should also be encouraged to refer patients to genetic counselling.

- The members of the Division of Human Genetics, NHLS and the University of the Witwatersrand need to increase their publicity in order to make the service of genetic counselling known not only to medical professionals but also to the general public. This refers not only for CF but for all genetic conditions.
- The option of incorporating a genetic counsellor into private clinics within private hospitals where CF patients are being treated should be explored.
- Similar genetic counselling clinics should be established within other specialist clinics.

4.7 SUMMARY OF FINDINGS

The study aimed to determine who uses the CF genetic counselling service and why. It also aimed to assess the number of at-risk relatives in each of the families who presented for genetic counselling, and how many relatives pursued mutation analysis. Finally, the study aimed to look at the effect of the introduction of specialist Genetic Counselling Clinics at the CF Clinics of Johannesburg Hospital with respect to the overall uptake of and referrals to CF genetic counselling. Based on the results of the study, all the described aims were achieved. In summary the following points were identified:

- Of all family members, parents of CF probands currently utilise CF genetic counselling and testing the most.
- The majority of counsellees are white but the numbers of black and coloured individuals seen for genetic counselling has increased slightly since the introduction of the specialist Genetic Counselling Clinics at the CF Clinics of Johannesburg Hospital.
- Only a small proportion of siblings and extended family members at considerable risk of being CF carriers attend CF genetic counselling and pursue mutation analysis. There is therefore a need to address ways of improving cascade screening and testing amongst at-risk families.

- Individuals attend genetic counselling in order to gather more information about the disorder and the options available to them.
- On average each family with a CF proband has 14 at-risk relatives with carrier risks of 25% or more.
- Of the at-risk relatives who are non-obligate carriers and who have mutation testing, 62% are found to be carriers.
- The introduction of the specialist Genetic Counselling Clinics at the CF Clinics of Johannesburg Hospital has been a positive experience and as a result, counsellee numbers have increased. Follow-up consultations have become more common suggesting that individuals are making use of the established genetic counselling clinic. The presence of the genetic counselling service within the CF Clinics allows for integration into the management process of CF patients and their families.

CHAPTER 5: CONCLUSION AND FUTURE RESEARCH

The current study has shown how, through the incorporation of Genetic Counselling Clinics into CF treatment clinics, counsellee numbers increase, mostly through specialist and nurse referrals within the clinics. The introduction of the specialist Genetic Counselling Clinics at the CF Clinics of Johannesburg Hospital has been effective and worthwhile and should therefore remain in place.

It remains to be seen whether counsellee numbers will remain high, but the 2007 trend suggests they will, which in turn highlights the convenience of the integrated clinics for both patients and doctors. Eventually, with time, there will be a "catch up" effect in that counsellee numbers may decrease once most of the families at the clinics have been seen for initial information giving sessions. However, the awareness of the service will have been created thus allowing individuals to return to one established central point, being the CF Clinic, for further genetic counselling such as when carrier testing or prenatal diagnosis is requested. In addition, when CF probands are at an age when they can understand the genetic information, they too can attend the established clinic.

Ongoing awareness and reinforcement of the genetic counselling service through the availability of a cascade letter or booklet as well as continued family contact at the CF Clinics, will hopefully assist in increasing the number of individuals that enter the process of cascade screening and testing for CF.

The results from this study have indicated that there is an obvious lack of participation in genetic counselling and CF mutation testing by relatives who are at risk of being carriers. This may be due to a lack of awareness of the genetic counselling and testing service as well as inadequate understanding about the condition. Poor communication between family members is likely to be a major factor inhibiting individuals from finding out more about their risks. Fears and anxieties around carrier status could also influence why many relatives do not seek CF counselling and testing. Future studies could involve exploring the reasons why at-risk relatives do not pursue genetic counselling or testing. Use of the proposed cascade letter or

booklet may alleviate some of the burden felt by parents and CF probands in having to inform their relatives of their associated risks.

With respect to individuals who do attend genetic counselling, an interesting future study would be to assess the knowledge and risk perceptions amongst South African families affected by CF prior to, and after, genetic counselling.

Genetic counselling is an essential part of the diagnosis and management of a genetic disorder. Unfortunately, other medical professionals, as well as the general public, are not aware of the importance and value of the service, and so referrals are often limited. It is therefore of utmost importance that the Division of Human Genetics advertises its counselling services, and that its members are proactive in educating medical practitioners and the general public about them. With particular reference to CF, if cascade screening and testing is to be effective, a more constructive approach to educating and inviting family members to genetic counselling needs to be employed.

Although the current study took place in Johannesburg, South Africa, the results do follow trends observed elsewhere. The genetic counselling model of 2006 described in the current study is effective and definitely results in increased numbers of counsellees. Integration of the genetic counselling service should therefore be extended into further clinics that treat patients with other genetic conditions, as well as to other CF clinics nationally. Currently, the Haemophilia Clinic at Johannesburg Hospital also incorporates specialist Genetic Counselling Clinics twice a week. It would be interesting to carry out a similar study to the one described here regarding individuals who presented at the Haemophilia Clinic.

There is great potential for genetic counselling to become part of the routine management of patients with genetic conditions as individuals do not receive detailed genetic information from other sources. This study has shown that such a system is effective and so it should be implemented elsewhere. Through increased interaction and involvement with other health professionals at treatment clinics, genetic counsellors will not only promote the service of genetic counselling but will also become accepted and established within a multidisciplinary

team treating and managing patients with genetic conditions. This is likely to promote an increase in referrals for genetic counselling and in turn will improve awareness of the service. More referrals and better awareness amongst health care professionals will result in cascade screening and testing and allow patients to make informed decisions regarding their genetic status.

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Web Resources

THE CYSTIC FIBROSIS GENETIC ANALYSIS CONSORTIUM. "Cystic Fibrosis Mutation Database." (2007) http://www.genet.sickkids.on.ca/cftr/StatisticsPage.html [Accessed 27 June 2007].

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APPENDIX A: DATA COLLECTION SHEET

Cystic Fibrosis Genetic Counselling:

An Audit of Counsellees and Their At-risk Relatives

- **File code: _____**

- **Related to other family file code: _____**

- **Date of first genetic counselling session: _____**

- **Number of counsellees: _____**

- **Description of the counsellee(s):**

1. Female CF proband ☐
2. Male CF proband ☐
3. Mother of proband ☐
4. Father of proband ☐
5. Sister of proband ☐
6. Brother of proband ☐
7. Aunt of proband ☐
8. Unrelated female individual ☐
9. Unrelated male individual ☐
10. Uncle of proband ☐
11. Female 1st cousin of proband ☐
12. Male 1st cousin of proband ☐
13. Other relative (specify)_____ ☐

COUNSELLEE CODE*	DATE OF BIRTH	AGE AT THE TIME OF COUNSELLING	EMPLOYMENT STATUS

* Counsellee code consists of the file number + the number next to the description that fits the individual in the section above

- **Ethnicity:** 1. White ☐ 2. Black ☐ 3. Coloured ☐ 4. Indian ☐ 5. Unknown ☐

- **Where did the counselling take place?**
  1. Johannesburg Hospital ☐
  2. Chris Hani Baragwanath Hospital ☐
  3. Coronation Hospital ☐
  4. Donald Gordon Medical Centre ☐
  5. TMI ☐
  6. SAIMR ☐
  7. Other (specify)_____ ☐

- **Referred to genetic counselling by:**
  1. General Practitioner ☐
  2. Specialist ☐
  3. Relative ☐
  4. Self-referral ☐
  5. Other (specify)_____ ☐

- **Reason(s) for attending genetic counselling:**
  1. CF Information gathering ☐
  2. Result giving session ☐
  3. Planning a family ☐
  4. Prenatal counselling ☐
  5. Unknown ☐

- **Were there any follow-up sessions?** 1. Yes ☐ 2. No ☐

If yes, list the dates of the follow-up sessions, who attended them and the reasons for the follow-up sessions (use same codes as used previously):

DATE	ATTENDEES	REASON

- **Does the pedigree indicate consanguinity within the family?** 1. Yes ☐ 2. No ☐

- **If yes, how are the consanguineous couple(s) related?_____**

- Pedigree drawing including the relevant at-risk individuals* prior to any molecular testing (use the most recent pedigree if the family has been seen more than once):

** "At-risk individuals" have at least a 25% risk of being carriers and include relatives from the proband's generation and below as well as from the proband's parents' generation.*

- **Was mutation analysis performed in this family?** 1. Yes ☐ 2. No ☐

- **If yes, who was it performed on?**

1. Female CF proband ☐
2. Male CF proband ☐
3. Mother of proband ☐
4. Father of proband ☐
5. Unaffected sister of proband ☐
6. Unaffected brother of proband ☐
7. Aunt of proband ☐
8. Uncle of proband ☐
9. Grandmother of proband ☐
10. Grandfather of proband ☐
11. 1st cousin (female) of proband ☐
12. 1st cousin (male) of proband ☐
13. Other relative (specify)_____ ☐

- **List the at-risk relatives in relation to the CF proband. Include their pre-testing risks of being carriers and indicate the results of mutation testing where appropriate.**

e.g.

RELATION	***PRE-TESTING RISK OF BEING A CARRIER***	***CARRIER STATUS AFTER MUTATION TESTING***
Mother	*100% (1/1)*	*Carrier*
Sister	*67% (2/3)*	*Carrier*
x3 Aunts	*50% (1/2)*	*No testing performed*
Uncle	*50% (1/2)*	*Not a carrier*

RELATION	**PRE-TESTING RISK OF BEING A CARRIER**	**CARRIER STATUS AFTER MUTATION TESTING**

....continued

RELATION	PRE-TESTING RISK OF BEING A CARRIER	CARRIER STATUS AFTER MUTATION TESTING

- **Total number of at-risk individuals in the family: _____**

- **Total number of at-risk individuals who had mutation testing**: **_____**

- **Of those at-risk relatives who had testing, how many were proven to be carriers: __**

- **Total number of at-risk relatives who attended genetic counselling at the Genetic Counselling Clinics of the NHLS and the University of the Witwatersrand:_____**

APPENDIX B: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Macauley

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M060943**
PROJECT	Cystic Fibrosis Genetic Counselling : An Audit of Counsellees and their At -Risk Relatives
INVESTIGATORS	S Macauley
DEPARTMENT	Dept of Human Genetics
DATE CONSIDERED	06.09.29
DECISION OF THE COMMITTEE*	APPROVED UNCONDITIONALLY

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE

CHAIRPERSON .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr N Gregersen

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES