Huntington's Chorea in South Africa

by

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A thesis submitted to the University of Cape Town in fulfillment of the requirements for the degree of Doctor of Philosophy in Medicine

August 1979
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For

Sandy,

my mother & father

and

to the memory of

my grandparents
Photograph of George Huntington (1850-1916), a country practitioner whose sole contribution to medical literature was an article entitled "On Chorea" in 1872.
"They reel to and fro and stagger like a drunken man, and are at their wit's end."

Verse 27, Psalm 107
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DECLARATION

This project was undertaken with the guidance of Professor P. Beighton during the tenure of the author's research fellowship in the Department of Human Genetics, University of Cape Town, from March, 1977 to June, 1979.

The neuroendocrine investigations were conducted in the Endocrine Laboratories of the Endocrine and Diabetes Research Group at the University of Cape Town, Medical School, in collaboration with Professor A.I. Vinik during the same period.

This is to certify that this thesis is my own work and has not been presented for a degree at any other university.

Signed by candidate

Signature Removed

Michael R. Hayden

ABSTRACT

South Africa offers unique opportunities for the investigation of genetically determined illnesses in view of the excellent facilities available and the different origins of the various population groups.

Huntington's chorea is generally considered to be a very rare disease in South Africa. Evidence in support of this, is the dearth of publications concerning the disorder in this country. By 1977 there had been only two such articles, in marked contrast to the plethora of reports from around the world.

This investigation was concerned with the study of many different aspects of Huntington's chorea in South Africa. The primary aims were to determine the history, frequency, clinical presentation and course of Huntington's chorea in the Republic. In the wake of the genealogical and clinical findings, interesting new observations and exploration of the established concepts of the genetics of Huntington's chorea have been undertaken.

A major attempt has been made to investigate the hypothesis that dopamine excess is important in the pathophysiology of this condition. Since dopamine has an important regulatory function on anterior pituitary hormone secretion, affected individuals might be expected to have abnormal patterns of hormonal regulation. The disturbances in prolactin, thyrotropin and growth hormone secretion reported in this thesis, support the concept of dopamine predominance. The demonstration of similar neuroendocrine abnormalities in twelve of 23 clinically normal first-generation relatives may have importance for presymptomatic diagnosis.
Although not a primary focus of the investigation, it soon became apparent that the social implications of this disorder were extremely important and largely unexplored. The attention of all health professionals is drawn to the tremendous cost of the disorder, and recommendations for improved care are proposed.

Huntington's chorea is a far more serious problem in South Africa than was initially suspected. The gene was probably introduced by the first Dutch settlers over 300 years ago, and is found today in all population groups. The South African population of mixed ancestry has amongst the highest frequency of juvenile Huntington's chorea in the world.

Even though the present study deals with only one relatively uncommon illness, the concepts presented are pertinent to numerous other unrelated chronic diseases, with which Huntington's chorea has shared concerns and needs.
ACKNOWLEDGEMENTS

In presenting this thesis I would like to express my sincere gratitude and appreciation to my supervisor, Professor Peter Beighton. It was through his inspiration that this project was initiated. He has always been available, and provided helpful and constructive criticism. His infectious enthusiasm and continual support have been a major factor in making the work for this thesis such a stimulating and enjoyable experience. I am most grateful for the privilege of being able to work in his department.

Assistance with different facets of the survey was received from a number of sources.

Professor A.I. Vinik has provided outstanding support, giving generously of his time and knowledge. The neuroendocrine investigations took place directly as a result of a discussion with him in May, 1977. It was an exciting experience to work with him as he fostered an atmosphere of free yet critical thinking. Since his departure, his advice and friendship have been missed.

I have benefitted greatly from the expert advice of Dr. J. MacGregor of the Department of Neurology, who helped with the clinical evaluation of affected patients. I am indebted to Professor S.J. Saunders Head of the Department of Medicine, and Dr. H. Reeve Sanders, Superintendent of Groote Schuur Hospital, who made facilities available and provided continuous support and encouragement.

I owe thanks to Dr. M.M. Nelson of the Department of Human Genetics, who has meticulously reviewed this manuscript, and provided useful comments and invaluable advice.
I am most grateful to all the staff of the Department of Genetics for their participation in the clinical, technical and secretarial aspects of the survey. Mrs. B. Breytenbach has volunteered on numerous occasions to provide both secretarial and technical assistance. Her dedication to perfection and efficiency has been a great asset. Sister G. Barnard during 1977, and later Sister R. Duggan and Sister M. Macrae, have given freely of their time and energy in many different ways. They have participated in this investigation with charm and efficiency.

I acknowledge with sincere appreciation the help of the staff of the Endocrine and Diabetes Research Group, including Dr. D. Levitt, Mr. M. Davids and Mr. K. Samsadien who assisted me in the blood sampling and Ms. M. Paul, Ms. S. van Tonder and Ms. E. Rawlings, who efficiently performed the immunoassay. In this regard I also wish to thank the U.S. National Pituitary Agency for the donations of human prolactin and antiserum used in the immunoassay.

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Professor M. Feldman of the Department of Psychiatry at the University of Witwatersrand, who voluntarily acted as a coordinator for the retrieval of information on affected individuals in the Johannesburg area.

Dr. D. Saffer of the Department of Neurology at Baragwanath Hospital, who provided useful clinical details of patients in his care.
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The late Professor B. Pimstone, for advice concerning the neuroendocrine investigation.

Numerous other doctors, both in hospitals and private practice who gave permission for me to study their patients.

Without the help of these colleagues the work of this thesis would not have been possible.

Different persons provided great assistance with the genealogical aspects of this study. In particular Dominee H.C. Hopkins, Chief Archivist of the Dutch Reform Church Archives in Cape Town put his facilities at my disposal and also gave freely of his own in-depth knowledge of the origins of the Afrikaner nation. His assistant, Mr. H.C. van Zyl also gave valuable help. Ms. Conradie of the Government Archives in Cape Town and Ms. M. Webb of the Cory Library for Historical Research in Grahamstown have also given practical assistance. All these persons' contributions are greatly appreciated.

I am most grateful for the photographic help that has been efficiently and expertly given by Ms. Linda Coetzee of the Department of Medicine and Mr. C. Cloe of Clinical Photography, Groote Schuur Hospital. My two good friends, Mr. John Swartz, has accompanied me on numerous trips and sensitively documented different interviews, and Mr. David Goldberg has freely given of his time and sound advice as to the presentation of this material.
I have been assisted with the illustrations by Ms. G. Beighton, Ms. M. Lipshitz and Ms. L. Coetzee who have produced these figures with great expertise and artistic flair.

Financial support for this project has been generously provided by the South African Medical Research Council, the University of Cape Town Staff Research Fund, the Baron Hartley Scholarship and the Mauerberger Foundation.

I also have four important overseas acknowledgements:

Ms. Marjorie Guthrie, Emeritus President of the Committee to Combat Huntington's Disease, has given enthusiastic support and help to this project. She has been an inspiration for me.

Professor G. Klintworth of North Caroline was the first person to do any research on this disease in South Africa. He has selflessly sent me all the excellent clinical and genealogical notes that he had in his possession, and these have been most useful. This magnanimous gesture is sincerely appreciated.

Professor G. Bruyn and Dr. L. Went of Leiden, Holland, have also generously provided important information linking affected South African and Dutch families, for which I am grateful.

I am also indebted to Dr. P. Sever of St. Mary's Hospital, London, who has kindly agreed to perform certain complex biochemical studies on blood of affected South African patients in his laboratory.

Ms. H. Parker, a social worker at Groote Schuur Hospital, has taken a special interest in Huntington's chorea and has been of great help to affected families. Her devotion and commitment is acknowledged with sincere thanks.
To Ms. Gillian Shapley, who has worked untiringly and with patience, tolerance and good humour in typing this thesis, I am especially thankful.

I am very grateful to my family and good friends, who have provided constant support and optimistic encouragement. In particular, I would like to mention my parents who have made my medical studies possible and also my grandmother who showed so much interest in this work, but did not live to see the thesis completed.

To Sandy, who has contributed in so many different ways over these years to bring this work to fruition, I am forever grateful.

Lastly, I want to acknowledge the patients themselves, who have given of their time to partake in this investigation and whose spirit, resilience and faith have been an inspiration.
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Asking patients to squeeze two of my fingers often evoked choreiform movements, when it was not obviously apparent.

The inability to perform sustained complex facial movements was a common early sign.

The picture between this man's legs was taken on his 50th birthday, one year before this photograph was shot. The rapid deterioration in this man's condition is easily discernible.

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SECTION 1

THE AIMS AND SCOPE OF THE PRESENT STUDY

"To wrest from nature the secrets which have perplexed philosophers in all ages; to track to their sources the cause of disease, to correlate the vast stores of knowledge that they may be quickly available for the prevention and cure of disease - these are our ambitions."

William Osler, (1849-1919)
SECTION I
THE AIMS AND SCOPE OF THE PRESENT STUDY

Huntington's chorea is a lethal, genetically determined, neuropsychiatric disorder which usually appears in adulthood. The main features are progressive chorea and dementia. Deterioration is inexorable and death usually occurs within 10 to 15 years of the appearance of symptoms. In a small proportion of patients, the condition has its onset before the age of 20 and in these individuals rigidity often predominates.

The disease is transmitted as an autosomal dominant trait and there is an even chance that any child of an affected individual will inherit the gene and develop the clinical manifestations. In view of the late onset, a person with the condition has usually completed his family and thus passed on the gene before the stigmata are evident in him, and in this way the disease is perpetuated in successive generations.

The constellation of these mental and physical symptoms together with the social implications for affected families conspire to make Huntington's chorea "one of the most dreadful diseases that man is liable to" (Davenport and Muncey, 1916).

In contrast with the rest of the western world there is a derth of knowledge concerning Huntington's chorea in Africa. Prior to the current investigation only seven articles on the subject had been published from this continent. Indeed, it was commonly believed that the disease was exceedingly rare in all populations of South Africa.
However, experience gained in the genetics clinic at Groote Schuur Hospital, suggested that Huntington's chorea was not uncommon in the different populations of Cape Town. In view of the serious medical and social implications of this disease an attempt was made to investigate this situation and initially to determine the minimum prevalence of the disease in the Cape Coloured community. The scope of this work was then extended to include different population groups throughout South Africa.

The aims of the current investigation as stated in 1977 and presented to the Doctoral Board of the University of Cape Town in 1978 were as follows:-

1. To determine the frequency of Huntington's chorea in South Africa.

2. To perform a genealogical investigation to identify the foreign lands of origin and earliest transmitters of the disease to this country.

3. To analyse the natural history and describe the clinical features of Huntington's chorea in South Africa.

4. To examine the established concepts of the genetics of the disorder in view of the findings of the current survey.

5. To investigate the biochemical lesion of Huntington's chorea with particular reference to the neuroendocrine status of patients and their families.

6. To examine the social implications of the disease for the patient, his family and the community at large.

This manuscript is divided into ten sections, each beginning with a review of the pertinent literature, followed by a presentation and discussion of the results of the present investigation.
Certain sections, such as biochemistry and genealogy, are considered in greater detail than others in view of the promising and interesting findings in those areas.

The results of the current study are compared to the reported observations of other works and their significance is discussed. Many new observations are reported and recommendations for further research are outlined.
"It is the method by which facts are dealt with, that forms a 'science'."

Pearson (1892)
In: The Grammar of Science.
Visits were made to all the major mental health hospitals in South Africa.
SECTION II

METHODOLOGY

II-1 COLLECTION OF DATA

II-2 AREA STUDIED: DEMOGRAPHIC DATA

II-3 ASSESSMENT OF INDIVIDUALS WITH HUNTINGTON'S CHOREA
An attempt has been made to identify all patients with Huntington's chorea in South Africa with particular reference to the Cape Province. Affected individuals were initially ascertained through the records of the Department of Human Genetics, Cape Town. Subsequently, permission was granted for a search of the neurological and psychiatric admission and discharge records of Groote Schuur Hospital, Cape Town, as far back as 1968. This was coupled with a computerized retrieval of over 55,000 records for any person admitted or discharged with the diagnosis of Huntington's chorea to Groote Schuur Hospital from 1971 to the present day.

A preliminary letter (see appendix) requesting information on persons with Huntington's chorea and their families, was sent to all psychiatrists and neurologists in the Cape Province. Thirty psychiatrists and nine neurologists were contacted in this way. Letters were also sent to selected general practitioners and physicians known to have an interest in the condition or to have come into contact with affected individuals.

The location of all the major psychiatric and mental health centres in this country is shown in Fig II-1. Letters were sent to the superintendents of all these hospitals. Other smaller psychiatric hospitals in the Cape Province, including those at Fort Beaufort, Port Alfred, Port Elizabeth, Mafeking, Kimberley and Nelspoort were also contacted in an attempt to record all known patients with Huntington's chorea.
Provincial hospitals with departments of psychiatry and neurology in all major centres, including Cape Town, Port Elizabeth, East London, Durban, Pietermaritzburg, Johannesburg, Pretoria and Bloemfontein were notified of this project in an effort to identify affected persons. Letters describing the aims of the investigation were also sent to other institutions, including homes for the mentally retarded, private nursing homes for psychiatric patients and other mental health centres in the Cape Province.

Lectures were given by the author to a meeting of all district nursing sisters in greater Cape Town and to the Departments of Social Work, Medicine, Paediatrics and Psychiatry at Groote Schuur Hospital, in an effort to stimulate interest and raise awareness of Huntington's chorea and its implications.

After replies to these inquiries had been received, a map of South Africa with the location of affected individuals was constructed. Permission was then requested from supervising doctors to visit and examine families in different parts of the country.
CHAPTER II-2

AREA STUDIED: DEMOGRAPHIC DATA

Initially, a pilot study was undertaken to identify all patients with Huntington's chorea within a well-defined area, namely the boundaries of the Divisional Council of the Cape (Fig II-2). This area includes the Cape Peninsula in the south, Swartklip in the east, Mamre in the north and Springfontein in the west. Many patients were found to have affected relatives in different parts of the country, and later the project was extended to include all provinces of South Africa.

The Republic of South Africa (R.S.A.) spans an area of 472,359 square miles. Fig II-3 shows a map with the different provinces indicated, together with their area in square miles. The route that was taken during my nation-wide survey is indicated. The population of South Africa by region and population group is shown in Table II-1. This is an estimated total for 1977, based on the May 1970 population census, taking into account the average annual growth rate for each population group. This table is constructed from data extracted from the report of the Department of Statistics, Pretoria (1978).

Over 8,000 kilometres were travelled in and around South Africa in an effort to identify and examine as many affected individuals as possible.
### TABLE II-1

**ESTIMATED POPULATION SIZE FOR SOUTH AFRICA (1977)**

*(Figures x 10^3)*

<table>
<thead>
<tr>
<th>Province</th>
<th>Blacks</th>
<th>Whites</th>
<th>Coloureds</th>
<th>Asians</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cape Province</td>
<td>1,674</td>
<td>1,207</td>
<td>2,094</td>
<td>28</td>
<td>5,002</td>
</tr>
<tr>
<td>Natal</td>
<td>1,238</td>
<td>530</td>
<td>90</td>
<td>627</td>
<td>2,484</td>
</tr>
<tr>
<td>Transvaal</td>
<td>5,131</td>
<td>2,294</td>
<td>199</td>
<td>107</td>
<td>7,731</td>
</tr>
<tr>
<td>Orange Free State</td>
<td>1,582</td>
<td>328</td>
<td>44</td>
<td>-</td>
<td>1,953</td>
</tr>
<tr>
<td>Black Homelands</td>
<td>9,516</td>
<td>17</td>
<td>14</td>
<td>4</td>
<td>9,551</td>
</tr>
<tr>
<td><strong>TOTAL (RSA)</strong></td>
<td>19,140</td>
<td>4,376</td>
<td>2,441</td>
<td>766</td>
<td>26,723</td>
</tr>
</tbody>
</table>
CHAPTER II-3

ASSESSMENT OF INDIVIDUALS WITH HUNTINGTON’S CHOREA

Patients in Cape Town and the surroundings were visited whilst replies from the rest of the country were awaited. Attempts were made to interview all living family members.

A full history of the disease and its progress were recorded on a proforma specially devised for this investigation (see Appendix). Details concerning age of onset, initial symptoms and diagnosis, the family history with details of affected individuals, any record of anti-social behaviour, particularly violence and promiscuity, together with details of any psychiatric disturbance, including suicide attempts, were noted. Where possible, hospital records were searched and results of all special investigations were documented. The family history often gave information concerning other affected individuals and the study was extended to include these persons. Pedigrees were constructed for all families.

Where possible, I made a complete general and neurological examination of each patient. Special note was taken of the severity and distribution of involuntary movements, muscle tone, tendon reflexes, dysarthria, dysphagia, the ability to perform complex facial movements and the optic fundi. Detailed psychometric testing was not performed, as this is time-consuming and special skills in psychology are required. However, the psychiatric state was assessed by observing the patient’s conversational ability and performance in simple general knowledge and
Map of South Africa, showing the route that was taken during the nationwide survey.
arithmetic questions, e.g. serial sevens, Koh's blocks.

The completeness of the clinical examination varied, depending on the patient's co-operation and the location of the survey.

After most of the patients in the Cape Town area had been examined, a nationwide trip to different institutions and families was planned. The major mental institutions that were visited during this country-wide survey are shown in Figure II-1. Patients were examined personally at all these hospitals, besides the Oranje in Bloemfontein. Lectures were given at most of these institutions. The route that was taken during the nationwide survey is shown in Figure II-3.

Professor M. Feldman, Head of the Department of Psychiatry at the University of Witwatersrand helped to collate information from the Tara General Hospital, J.G. Strijdom and T.M. Children's Hospital in the Johannesburg area. Professor Trefor Jenkins and Mrs. Jennifer Kromberg gave me permission to search through the records of affected patients who had presented to the Department of Human Genetics at the University of the Witwatersrand. Medical superintendents of the different mental institutions were particularly helpful in making all possibly useful information available for the investigation.

Home visits to affected families were made in Oudtshoorn, Heidelberg (Cape), Uitenhage, East London, Kei Mouth, Komga, Umtata, Durban, Pietermaritzburg, Johannesburg and Pretoria. Many of these families were isolated, with little or no contact with medical personnel.

Patients were directed to suitable authorities in their area to help solve any particular immediate problems. Contact was maintained
by letter or telephone with many of the persons who had been seen. Family members who were unavailable at the time of my visit and who could provide further details were contacted and some travelled to Cape Town specifically for an interview.

All information was treated confidentially and only persons directly involved in the study were allowed access to patients' records. To centralize all data a South African Huntington's Chorea Registry has been set up in the Department of Human Genetics which contains details of affected persons and their relatives.

Five affected persons in South Africa were found to be descendants of a man who lived on the island of Mauritius and the possibility that Huntington's chorea was present on that island was explored. Data on affected individuals on Mauritius was obtained with the help of a French-speaking Mauritian friend, Mr. L. de Merasez Enouf. Further information was collected at my request during the visit by a member of this Department, Dr. A.L. Berkowicz, to the island in August, 1978.
"Epidemiology is the study of disease occurrence in human populations, the primary units of concern being groups of persons, not separate individuals."

Gary Friedman
III-6  INCIDENCE OF HUNTINGTON'S CHOREA OUTSIDE SOUTH AFRICA
A. Introduction ........................................ 45
B. International comparison of incidence ............ 45

III-7  INCIDENCE OF HUNTINGTON'S CHOREA IN SOUTH AFRICA
A. Results ............................................. 47
B. Discussion .......................................... 47

III-8  THE EPIDEMIOLOGY OF HUNTINGTON'S CHOREA ON MAURITIUS
A. Introduction ........................................ 50
B. Prevalence .......................................... 50
C. Discussion .......................................... 52
A. CONCEPTS

Epidemiology has been defined as the study of the distribution, frequency and natural history of disease in man (Barker and Bennet, 1973). One of the primary aims of this project was to determine the distribution and frequency of Huntington's chorea in South Africa.

Numerous epidemiologic studies on Huntington's chorea have been performed in different parts of the world (Table III-1). These emanate largely from North America, north-western Europe and Australia. Myrianthropoulos (1973) has stated that "our knowledge of the epidemiology of this disease is by no means complete. We have no measure of its frequency in the Middle Eastern and African countries, in the large Asian populations of China and India, in South America or among the North American Indians. We have no idea whether the disease exists in primitive populations. This is a serious gap in our knowledge which could and should be bridged." The present investigation is the first of its kind in Africa and will provide information concerning the epidemiology and natural history of the disease in South Africa and also on the island of Mauritius.

Frequency of a disease may be expressed in terms of

a) prevalence: the total number of affected persons in a defined population at a specific time.

b) incidence: the total number of newly ascertained affected persons occurring in a given time period, and
c) **mortality rate**: the number of deaths due to a disease per given time per unit population.

All these parameters will be used to express the frequency of Huntington's chorea in South Africa.

In principle, there are three broad types of epidemiological investigations - retrospective, concurrent and prospective. This study contained elements of all three, with major emphasis on the first two. The retrospective aspect comprised collation of details of the natural history and clinical symptomatology in patients who had died from Huntington's chorea in South Africa. Determination of the number of affected persons living in this country was the concurrent component of the investigation. The prospective section involved maintaining a follow-up on all persons at risk of developing the disease. This will continue as an ongoing part of the project.

Each of these types of studies has inherent advantages and disadvantages. Retrospective surveys depend on respondents' memories and adequate records of events. These sources of information were sometimes found to be unsatisfactory. Concurrent studies are time consuming and are dependant on free communication and cooperation of families and members of the medical profession. Whilst these sources magnanimously provided me with much information, ignorance and misdiagnosis often unintentionally prevented complete ascertainment of data. In addition, families were sometimes less prepared to talk of a painful or socially embarrassing current event than one that had already passed. In other words, it was much less stressful for family members to describe the nature of the illness in a deceased
person than it was to give an account of their living relatives' symptoms.

Prospective investigations span many years and are complicated by patients who are lost to follow-up by moving, losing interest or refusing to continue cooperating. At this stage such handicaps have not been a major problem. The investigation of Huntington's chorea in South Africa encountered the inherent advantages and disadvantages of all three types of studies.

B. DIAGNOSTIC CRITERIA

Strict criteria were used in the current survey to determine when the diagnosis of Huntington's chorea could be made. A definitive diagnosis of the disorder was accepted if each of the following features were present:

1. Progressive motor disability, including chorea and/or rigidity, with no other obvious cause.

2. Psychiatric disturbance usually comprising progressive dementia, with no other obvious cause.

3. A positive family history of the disorder, with evidence of autosomal dominant inheritance.

Approximately 95% of patients in this survey had all three features. The remaining 5% were diagnosed on the following grounds. The diagnosis of Huntington's chorea was accepted in approximately five patients who had only features 1 and 3. One person had a progressive dementia due to no other obvious cause, together with a positive family history of the disease. Very slight involuntary
movements could be elicited on clinical provocative testing in this individual (see Fig VI-2).

The diagnosis of Huntington's chorea was approved in the absence of a family history if the disease conformed closely to the clinical features listed in 1 and 2, and if no other cause could be found for the symptoms. There were approximately ten patients in this category. A negative family history did not necessarily imply, however, that the affected person represented a mutation for the disorder. This may rather have reflected unreliable information about the health of the parents or their early accidental death before the disease became manifest. The possibility that the patient was not the offspring of both his alleged parents, but rather the illegitimate child of an unknown parent who carried the gene for Huntington's chorea was also considered.
CHAPTER III-2
PREVALENCE OF HUNTINGTON'S CHOREA IN OTHER COUNTRIES

A. SUMMARY

The reported prevalence rates per million population for different areas are summarised in Table III-1. Whilst there are substantial differences between some reported rates, most studies agree that the prevalence of Huntington's chorea is between 40 - 70 affected individuals per million population. There are, however, important exceptions and these will be discussed in Sections C and D.

B. DRAWBACKS TO COMPARISON OF PREVALENCE DATA

Caution must be exercised when comparing prevalence rates from different countries. Prior to ascribing the variation in the morbidity data to racial, ethnic or environmental factors, attention must be focused on the different methods employed in the collection of data.

Prevalence figures in the earlier surveys in particular (Critchley, 1936; Minski and Guttman, 1938) were based solely on the number of affected persons found in mental hospitals. This clearly resulted in underestimation of the true frequency. Later studies have attempted to accurately identify the number of persons suffering from Huntington's chorea in a prescribed geographical area by using multiple different methods for the collection of data. Reliance has not been solely placed on hospital records. Other sources, including private physicians, nursing homes and mental health agencies have been vigorously searched (Shokeir, 1975; Caro, 1977; Stevens, 1977). Extended family tracing has also been strictly
TABLE III - I

REPORTED PREVALENCE OF HUNTINGTON'S CHOREA (X10^{-6} OF POPULATION)

IN DIFFERENT COUNTRIES

<table>
<thead>
<tr>
<th>Location</th>
<th>Authors</th>
<th>Year of Publication</th>
<th>No. of Patients</th>
<th>Population</th>
<th>Prevalence (X10^{-6})</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNITED KINGDOM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>English counties</td>
<td>Critchley</td>
<td>1934</td>
<td></td>
<td></td>
<td>1.9 - 12.5</td>
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<tr>
<td>London</td>
<td>Minski et al</td>
<td>1938</td>
<td>43</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Cornwall</td>
<td>Bickford et al</td>
<td>1953</td>
<td>19</td>
<td>340,941</td>
<td>55.7</td>
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<td>Northamptonshire</td>
<td>Pleydell</td>
<td>1954</td>
<td>13</td>
<td>263,000</td>
<td>49</td>
</tr>
<tr>
<td>Northamptonshire</td>
<td>Pleydell</td>
<td>1955</td>
<td>17</td>
<td>263,000</td>
<td>65</td>
</tr>
<tr>
<td>Northamptonshire</td>
<td>Reid</td>
<td>1960</td>
<td>19</td>
<td>263,000</td>
<td>72</td>
</tr>
<tr>
<td>Moray Firth, Scotland</td>
<td>Lyon</td>
<td>1962</td>
<td>5</td>
<td>896</td>
<td>5600</td>
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<tr>
<td>N.E. Metropolitan</td>
<td>Heathfield</td>
<td>1967</td>
<td>81</td>
<td>3,271,000</td>
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<td>Northamptonshire</td>
<td>Oliver</td>
<td>1970</td>
<td>27</td>
<td>428,000</td>
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<td>Bolt</td>
<td>1970</td>
<td>154</td>
<td>2,959,600</td>
<td>52</td>
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<td>Bedfordshire</td>
<td>Heathfield et al</td>
<td>1971</td>
<td>30</td>
<td>427,970</td>
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<td>East Anglia</td>
<td>Caro</td>
<td>1977</td>
<td>54</td>
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<td>Leeds/Yorkshire</td>
<td>Stevens</td>
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<td>133</td>
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<td>EUROPE</td>
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<tr>
<td>Rhineeland, Germany</td>
<td>Panse</td>
<td>1942</td>
<td>242</td>
<td>7,690,266</td>
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<td>Switzerland</td>
<td>Zolliker</td>
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<td>202</td>
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<td>22.5 - 48.2</td>
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<td>Poland</td>
<td>Cendrowski</td>
<td>1964</td>
<td>2</td>
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<td>West Germany</td>
<td>Wendt</td>
<td>1972</td>
<td>869</td>
<td></td>
<td>22</td>
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<tr>
<td>Haut Vienne, France</td>
<td>Leger</td>
<td>1974</td>
<td>24</td>
<td></td>
<td>70</td>
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<tr>
<td>Belgium - Four provinces</td>
<td>Husquinet</td>
<td>1975</td>
<td>37</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Location</td>
<td>Authors</td>
<td>Year of Publication</td>
<td>No. of Patients</td>
<td>Population</td>
<td>Prevalence (X10^-6)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------</td>
<td>---------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>SCANDINAVIA</td>
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<td></td>
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<td>North Sweden</td>
<td>Sjogren</td>
<td>1936</td>
<td>18</td>
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<td>Iceland</td>
<td>Gudmundsson</td>
<td>1969</td>
<td>5</td>
<td>27</td>
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<tr>
<td>Sweden</td>
<td>Mattson</td>
<td>1974</td>
<td>362</td>
<td>7,733,853</td>
<td>47</td>
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<tr>
<td>CANADA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quebec</td>
<td>Barbeau</td>
<td>1966</td>
<td></td>
<td></td>
<td>20 - 40</td>
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<tr>
<td>Manitoba</td>
<td>Shokeir</td>
<td>1975</td>
<td>162</td>
<td>1,926,942</td>
<td>84</td>
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<td>U.S.A.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Minnesota</td>
<td>Pearson et al</td>
<td>1955</td>
<td>117</td>
<td>3,174,000</td>
<td>54.3</td>
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<td>Rochester</td>
<td>Kurland</td>
<td>1958</td>
<td>2</td>
<td></td>
<td>67</td>
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<td>Michigan-Whites</td>
<td>Reed et al</td>
<td>1958</td>
<td>200 (</td>
<td>4,932,652</td>
<td>41,2</td>
</tr>
<tr>
<td>Michigan-Negros</td>
<td>Reed et al</td>
<td>1958</td>
<td>3</td>
<td></td>
<td>15</td>
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<td>N.Y. Jews</td>
<td>Myrianthopoulos</td>
<td>1973</td>
<td>70</td>
<td></td>
<td>35</td>
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<td>Long Island</td>
<td>Korenyi et al</td>
<td>1977</td>
<td>48 - 250</td>
<td></td>
<td>33.3 - 203.8</td>
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<tr>
<td>and Borough of New York</td>
<td></td>
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<td></td>
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<td>AUSTRALIA</td>
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<td></td>
</tr>
<tr>
<td>Tasmania</td>
<td>Brothers</td>
<td>1949</td>
<td>105</td>
<td>60,344</td>
<td>174</td>
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<tr>
<td>Queensland</td>
<td>Parker</td>
<td>1958</td>
<td>31</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>Victoria</td>
<td>Brothers</td>
<td>1964</td>
<td>138</td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>Queensland</td>
<td>Wallace</td>
<td>1972</td>
<td>111</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>JAPAN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aichi district</td>
<td>Kishimoto</td>
<td>1957</td>
<td>13</td>
<td>3,916,922</td>
<td>3.8</td>
</tr>
<tr>
<td>SOUTH AMERICA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lake Maracaibo, Venezuela</td>
<td>Avila-Giron</td>
<td>1973</td>
<td>28</td>
<td>4,000</td>
<td>± 7000</td>
</tr>
</tbody>
</table>
undertaken. The results of the current investigation are comparable to these studies as similar methods of ascertainment of data have been employed.

A remote prevalence date is a prevalence day which occurs long before the time the current investigation is being conducted. Some studies (Reed et al, 1958; Bolt, 1970; Stevens, 1977) have used remote prevalence dates based on the rationale that patients with early features of this disorder may not come to medical attention for a few years after onset of the disease, again resulting in incomplete ascertainment. The major problem in the use of a remote prevalence date is that the investigator is forced to depend on respondents' memories and adequate records of past events. I chose to use a current prevalence date which allowed me personally to assess each patient and did not compel me to base my findings on records which often did not contain all necessary details.

C. AREAS OF HIGH PREVALENCE: POSSIBLE CONTRIBUTING FACTORS

Areas of high prevalence where the number of affected individuals exceeded 100 per million of the population include:

<table>
<thead>
<tr>
<th>Location</th>
<th>Author</th>
<th>Rate ($x10^6$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North Sweden</td>
<td>Sjogren (1936)</td>
<td>1,440</td>
</tr>
<tr>
<td>Tasmania, Australia</td>
<td>Brothers (1949)</td>
<td>174</td>
</tr>
<tr>
<td>Moray Firth, Scotland</td>
<td>Lyon (1962)</td>
<td>5,600</td>
</tr>
<tr>
<td>Lake Maracaibo, Venezuela</td>
<td>Avila-Giron (1973)</td>
<td>7,000</td>
</tr>
</tbody>
</table>
All these studies were performed in small, localized communities with an unusually high proportion of affected individuals. The high prevalence in Tasmania is a good example of the founder effect of a gene introduced into this isolated community by a woman who immigrated to Tasmania from Somerset, England in 1853. All 105 affected persons have been traced over numerous generations spanning 97 years to this single source.

The highest reported prevalence in the world emanates from several small communities on the shores of Lake Maracaibo, Venezuela (Avila-Giron, 1973). All 28 living patients have been traced to a sailor who arrived on a ship that was to carry fruit to Germany. The estimated population of this small community is ~4,000 (Kurtzke, 1977).

The localized pockets of unusually raised prevalence rates in the small, isolated areas of North Sweden, Australia, Scotland and Venezuela do not allow inferences to be made about the total number of affected individuals in any of these countries.

A most important factor which must be considered when assessing prevalence of a disease in any area, is the total size of the survey population. If this is small, a few affected individuals would artificially raise the prevalence. For example, in Lyons' study in the Moray Firth area of Scotland, a total of 5 affected individuals resulted in the calculated prevalence of 5,600 because the total number of inhabitants of this region was under 1,000. However, this does not explain the relatively raised rates reported by Shokeir (1975)
in Manitoba, Canada and Caro (1977) in East Anglia where the population under scrutiny was fairly large, comprising 1,926,942 and 584,415 persons and the prevalence figures were 84 and 92.4 respectively.

Both these surveys were conducted in relatively isolated farming regions. Whether the high frequency of Huntington's chorea in these areas is another example of the founder effect, where the gene was introduced to a stable, insulated community, is uncertain. Other possible factors include the fact that these studies used many different methods in the collection of their data, which thus must have been nearly complete. The great awareness of this disease, particularly in East Anglia, where there has been continued interest in the disorder over 40 years, must have led to early diagnosis and improved recognition of patients. In such an environment families are less liable to feel stigmatized and thus present themselves more readily for help and medical examination. These factors could explain the higher rates in these two investigations.

At present it is impossible to implicate any environmental factor which may increase or diminish the frequency of Huntington's chorea. It is, however, theoretically possible that a particular environmental agent could induce new mutations for Huntington's chorea in a specific area, thus changing its frequency.

It is of interest that there is an increase in prevalence rates in later epidemiological studies compared to those done earlier. This is clearly shown in the three surveys that were undertaken in Northamptonshire, United Kingdom, in 1954 (Pleydell), 1955 (Pleydell) and in 1960 (Reid). The prevalence ranges from 49 in the earliest study to 63, and finally to 72 in the latter investigation.
This discrepancy probably reflects better ascertainment of data and not a true absolute increased frequency of the disease.

D. **AREAS OF LOW PREVALENCE: CONTRIBUTING FACTORS**

Huntington's chorea would appear to be one tenth as common in Japan as it is in most western countries (Kishimoto, 1957) and one-third as common in U.S. Negroes as opposed to U.S. Whites (Reed et al, 1958). Both of these investigations were vigorously pursued by the above authors and, after examining the different methods employed by them, it can be assumed that this low frequency is not a result of under-reporting, but rather represents a real racial difference in prevalence. Data from the large medical care system of the Veterans Administration Hospitals in the U.S.A. has confirmed the fact that the risk of Huntington's chorea in U.S. Negroes is less than half that of U.S. Whites (Beebe, 1977). No adequate explanations have been forthcoming over the 20 years since these reports have been published.

One possible theory could be developed as follows. All genealogical studies (see Section IV) point to emigration from north-western Europe as being initially responsible for the spread of the gene for Huntington's chorea around the world. One could then expect to find a diminished frequency of this disorder in those races which have their origins outside north-west Europe. The lowered reported prevalence in U.S. Negroes and the Japanese is in keeping with this hypothesis. It would be important to know whether immigrants from Japan or other countries in the East and the Indian subcontinent, who migrated to the United Kingdom or the U.S.A. still have a much lower prevalence rate than the general "host" population.
Attempts to calculate mutation rates in Huntington's chorea have yielded results which are among the lowest of any human dominantly inherited condition. The mutation rate in Japan (Kishimoto, 1957) was lower than that reported in the U.S. by Reed et al (1958). This difference is, however, insufficient to account for the widely varying prevalence data.

E. CONCLUDING REMARKS

The current prevalence figures represent minimum estimates of the frequency of Huntington's chorea. The prevalence rates in more recent studies have risen because of more accurate diagnosis, greater awareness of the condition and consequent better ascertainment of data. Another factor which must not be omitted from consideration is the possibility that the true absolute frequency of Huntington's chorea is increasing. This may be particularly the case in less developed countries, where there is poor dissemination of knowledge about its genetic nature and where means of contraception and access to therapeutic abortion are less readily available. Voluntary curtailment of reproductive activity would be especially rare in these areas.

The question of increased fecundity and fertility in heterozygotes for Huntington's chorea has been the subject of many publications. Particularly in the early phases, sexual promiscuity with failure to control sexual impulses may be a feature. An increased (Shokeir, 1975; Stevens, 1977), decreased (Reed et al, 1959) and almost normal (Marx, 1973) fertility rate has been reported in affected individuals. At this stage it would be wrong to implicate increased fertility as the sole cause for the increased prevalence of Huntington's chorea mentioned in recent reports. It is far more probable that improved methods of collecting data are more significant in this respect.
CHAPTER III-3

RESULTS OF SOUTH AFRICAN INVESTIGATION: PREVALENCE

A. INTRODUCTION

The prevalence was established for the 30th December, 1977. This date was chosen, as the 1977 estimated population of South Africa was the latest available at the time of collating the data. Prevalence was calculated according to the following formula:

\[
\text{Prevalence} = \frac{A \times 10^6}{\text{Population}}
\]

where \( A \) = total number of living affected persons on prevalence day.

B. OVERVIEW

The total number of persons known to have died from or presently suffering from Huntington's chorea in South Africa is seen in Table III-II.

<table>
<thead>
<tr>
<th>TABLE III-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERSONS WITH HUNTINGTON'S CHOREA IN SOUTH AFRICA</td>
</tr>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>Living:</td>
</tr>
<tr>
<td>Deceased:</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

A total of 481 patients, of whom 153 are presently living has been recorded. A breakdown of this total according to different racial groups is seen in Table III-III.
Fig. III - 1

Provincial distribution of living affected persons with Huntington's chorea in South Africa.
### TABLE III - III

NUMBER OF PERSONS WITH HUNTINGTON'S CHOREA IN SOUTH AFRICA

(according to racial group)

<table>
<thead>
<tr>
<th></th>
<th>Whites:</th>
<th></th>
<th>Coloureds: (mixed ancestry)</th>
<th></th>
<th>African Negroes:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Live</td>
<td>21</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dead</td>
<td>26</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Subtotal</td>
<td>48</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>241</td>
<td>240</td>
<td>481</td>
</tr>
</tbody>
</table>

Most notifications of this disease (73.8%) have come from the White population, as opposed to the population of mixed ancestry (Coloured) (23.9%) and the African Negroes (2.3%). It is interesting to note that the total number of males and females recorded is almost equal, with ratios of 1,004:1,00, which is expected for a disease of autosomal dominant inheritance.

### RESULTS

The number of living affected individuals in South Africa on the 31st December, 1977 was 153.
The population figures are drawn from the 1977 estimated total, which is based on the 1970 population census, taking into account the average annual growth rate for each population group (Department of Statistics, Pretoria).

The prevalence of Huntington's chorea in South Africa according to the different racial groups is shown in Table III-IV.

**TABLE III-IV**  
PREVALENCE OF HUNTINGTON'S CHOREA IN SOUTH AFRICA

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Population x 10^3 (1977)</th>
<th>Prevalence x 10^-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites:</td>
<td>97</td>
<td>4,367</td>
<td>22,2</td>
</tr>
<tr>
<td>Coloureds (mixed ancestry):</td>
<td>53</td>
<td>2,432</td>
<td>21,7</td>
</tr>
<tr>
<td>African Negroes:</td>
<td>3</td>
<td>16,647</td>
<td>0,1</td>
</tr>
</tbody>
</table>

The number of live persons suffering from Huntington's chorea in each province of South Africa is shown in Figure III-1. The prevalence rates in these four provinces according to the different population groups is seen in Table III-V.

D. **DISCUSSION**

The prevalence of Huntington's chorea of 22,2 in the White and 21,7 in the Coloured groups is more than 200 times greater than the calculated frequency of 0,1 in the African Negro. The prevalence of the disease in the White and Coloured populations of South Africa is similar to the figures quoted by earlier reports from the United Kingdom (Heathfield, 1967), Canada (Barbeau, 1966) and Australia
### TABLE III - V

**PREVALENCE OF HUNTINGTON'S CHOREA IN DIFFERENT PROVINCES OF SOUTH AFRICA**

<table>
<thead>
<tr>
<th>Province</th>
<th>Number</th>
<th>Population x10^3</th>
<th>Prevalence x10^-6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAPE PROVINCE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>32</td>
<td>1207</td>
<td>26.5</td>
</tr>
<tr>
<td>Coloureds</td>
<td>48</td>
<td>2094</td>
<td>22.9</td>
</tr>
<tr>
<td>African Negroes</td>
<td>2</td>
<td>1674</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NATAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>16</td>
<td>530</td>
<td>30.1</td>
</tr>
<tr>
<td>Coloureds</td>
<td>-</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>African Negroes</td>
<td>-</td>
<td>1238</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TRANSVAAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>30</td>
<td>2294</td>
<td>13.1</td>
</tr>
<tr>
<td>Coloureds</td>
<td>3</td>
<td>199</td>
<td>15.1</td>
</tr>
<tr>
<td>African Negroes</td>
<td>-</td>
<td>5131</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ORANGE FREE STATE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>4</td>
<td>328</td>
<td>12.1</td>
</tr>
<tr>
<td>Coloureds</td>
<td>1</td>
<td>44</td>
<td>22.7</td>
</tr>
<tr>
<td>Africans</td>
<td>1</td>
<td>1582</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UNKNOWN LOCATION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coloureds</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africans</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>153</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(Parker, 1958) (Table III-1), but lower than more recently ascertained data in these countries (see Table III-1).

Even though the current investigation was carefully undertaken in a large population with utilization of multiple methods of collation of data, it is likely that the figures presented in Table III-IV are underestimates of the true frequency of Huntington's chorea in South Africa. Numerous factors have contributed. Ignorance of the disorder, its mode of inheritance and its implications, among both the public and the medical profession has resulted in a high proportion of initial misdiagnoses (Chapter VI.8). The current poor awareness of the disorder has added to the existing social stigma and superstition attached to the disease, with subsequent reluctance of patients to voluntarily present themselves for diagnosis. In addition, in the absence of any curative drug doctors themselves have sometimes encouraged this attitude by discharging diagnosed patients by telling them "there is nothing we can do for Huntington's chorea". Such pitfalls have prevented complete ascertainment of the frequency of Huntington's chorea in the current survey.

These problems are not peculiar to South Africa, but would seem to be accentuated in the Republic, particularly in the many rural areas, where access to medical centres and information is sometimes difficult.

The prevalence rate in South African Whites and Coloureds is similar (+ 22). It is not an unexpected finding, due to the large White contribution to the genetic constitution of the Coloureds.
The very low prevalence rate of 0.1 in the African Negro is the lowest reported figure in the world and deserves some comment. Only 11 patients, three of whom are living, are known to have the gene for Huntington's chorea. Even considering that there may have been incomplete ascertainment of data in this population group, it can be stated with confidence that Huntington's chorea is exceedingly rare in the African Negro. In this context, it is noteworthy that Dr. Guy Daynes, who has worked in the Transkei for over 20 years and who is Medical Superintendent of Umzimkulu Psychiatric Hospital, has never seen an affected patient. My findings are consistent with reports of a much lower prevalence in American Negroes (15) compared to U.S. Whites (41,2) (see Table III-I). However, the frequency of this disorder in the American Negroes is still much higher than in the African Negroes. One explanation may be that the American Negro has a much larger White genetic admixture compared to his African counterpart, who has few Caucasian genes.

Less complete ascertainment of data in this population group, particularly in remote areas of the homelands, may also contribute to this difference. It is of interest that chorea as a manifestation of rheumatic fever is significantly less common in African patients compared to Whites (Personal communication - P. Bundred, 1979). Other disorders of the basal ganglia, including Parkinsonism, are also very rare in the African Negro population (Wasserman, 1974).

The prevalence rate of Huntington's chorea in the Cape Coloured population within the boundaries of the Divisional Council of the Cape (Fig II-2) (not including the rest of the Cape Province) has
been initially reported as being $35 \times 10^{-6}$. (Hayden and Beighton, 1977). This was calculated on the basis of finding 26 living affected persons. A further seven patients have now been identified, raising the prevalence to $45.1 \times 10^{-6}$, which is the highest frequency of the disorder in South Africa.

It is clear that this finding reflects more complete ascertainment of data in greater Cape Town and the Cape Province generally, due to the fact that Cape Town is the centre from which the project began. This trend towards more complete identification of patients is illustrated in Figure III-1, where the Cape Province is shown to have the highest number of affected persons in the Republic.

The high prevalence rate in Natal (30.1) reflects 16 patients in a population of 530,000. I have had unconfirmed reports of 3 affected Coloured persons in Natal, but this figure has not been included in Table III-V. Assigning significance to the different prevalence rates in the various provinces of South Africa must be done with circumspection, as the number of patients, particularly in the Orange Free State, is small.

E. FUTURE IMPLICATIONS

Huntington's chorea is a much more important disease than would appear from estimates of its prevalence. Although only a single person in a family may be affected, all members bear the impact of the distressing social environment that often results. The state also bears a burden, through compensation for loss of earnings from productive employment, direct financial assistance and the frequent inevitable cost of hospitalization. These are some of the factors that led
Davenport and Muncie to pronounce (1916) that "it would be a work of far-seeking philanthropy to sterilize all those in which chronic chorea has developed and to secure that such of their offspring as show prematurely its symptoms shall not reproduce. That is the least the state can do to fulfil its duty towards the as yet unborn." Whilst one need not necessarily agree with this view, it is important that the state authorities in South Africa be aware of the problem and its implications.

The prevalence of Huntington's chorea in South Africa will increase, not only due to better diagnosis and identification of patients, but also as a result of an absolute increase in the frequency of the disorder, particularly amongst the Cape Coloureds, where the average annual population growth rate is 2.43 (compared to the rate of 1.93 in the Whites). Families with Huntington's chorea in this population group particularly, have not curtailed reproduction. For example on extensive investigation of three Coloured kinships, 120 persons are at risk of developing the disease by virtue of the fact that each has an affected parent. After applying appropriate correction for age of onset, it may be predicted that 48 of these have the gene for Huntington's chorea. Although not all families of mixed ancestry will have that many offspring, the problem of Huntington's chorea in South Africa is increasing and will be a growing burden to the state and the community as a whole.

Whilst it is certain that educating people of the implications of the disease will not, per se, eradicate it, it will enable all those affected or "at risk" to make more responsible decisions, taking into account their own particular circumstances.
MORTALITY DATA FROM OUTSIDE SOUTH AFRICA

A. **CLASSIFICATION OF MORTALITY DATA**

The cause of death on official death certificates is coded according to a three or four digit number, which represents a specific diagnosis within the International Statistical Classification of Diseases (I.S.C.). Huntington's chorea was assigned the number 331.0 in the 8th revision of the I.S.C. which has been in effect from 1968 until the end of 1978. The other components of the code 331 were dystonia musculorum deformans (331.1), progressive familial myoclonic epilepsy (331.2) and others (331.9) which included double athetosis, Vogt's syndrome and pigmentary pallidal degeneration.

In this country the cause of death in the Reports on Deaths from the Department of Statistics is coded only according to a three digit number. This code number 331 denotes Huntington's chorea and includes the other diseases listed above. In Denmark, where four digit coding is used, for 1969-75 there were 67 deaths coded to 331 as underlying cause and 64, or 96% of these were due to Huntington's chorea (Work Group on Epidemiology of Huntington's chorea, 1977). In Sweden only three of a total of 86 deaths coded 331 were not due to Huntington's chorea (Work Group on Epidemiology of Huntington's chorea, 1977). Thus it is apparent that the total sum of deaths coded 331 is very close (albeit somewhat higher) to the true number of persons dying from Huntington's chorea. In the current South African survey deaths coded 331 are taken to be equivalent to the number of persons dying from the disorder.
The 9th revision of the I.S.C. came into effect on the 1st January, 1979, and has coded Huntington's chorea as 333.4. The three digit number 333 will be less accurate in assessing the number of deaths from Huntington's chorea than 331 (8th revision) as the new rubric now includes many other diseases, e.g. hemiballismus, which occur with greater frequency than those which were previously listed in association with Huntington's chorea in the I.S.C. of 1968. This factor will have to be taken into account in the future when assessing mortality data for Huntington's chorea when using only the three digit code.

B. MORTALITY DATA: INTERNATIONAL COMPARISON

The importance of mortality data is that it reflects morbidity patterns and is another index of the frequency of a disease in a specific community. Table III-VI shows the number of deaths coded 331.0 as the underlying cause and the death rates per million of the population per year. In all countries except England and Wales, these figures are based on the total number of deaths specifically due to Huntington's chorea (331.0) occurring during the period 1968-1974. The results from England and Wales span 14 years from 1960 to 1973 and include all deaths under code 331. The figures shown in Tables III-VI and III-VII have been calculated by me from data presented in the report of the Work Group on the epidemiology of Huntington's chorea (1977).

The death rates for north-west Europe and for U.S.A. Whites are remarkably similar, ranging between 1 - 2 per million per year. Death rates for the Japanese and for U.S. Negroes are one-tenth and one-third of these respectively. This supports the validity of the findings of lowered prevalence data in these population groups.
### TABLE III-VI

**INTERNATIONAL COMPARISON OF NUMBER OF DEATHS CODED 331.0 AS UNDERLYING CAUSE AND DEATH RATES PER MILLION POPULATION PER YEAR (1968 - 1975)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Males</th>
<th>Rate</th>
<th>Females</th>
<th>Rate</th>
<th>Total</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.A. (Whites)</td>
<td>704</td>
<td>1.15</td>
<td>855</td>
<td>1.34</td>
<td>1559</td>
<td>1.25</td>
</tr>
<tr>
<td>U.S.A. (Negroes)</td>
<td>34</td>
<td>0.40</td>
<td>34</td>
<td>0.37</td>
<td>68</td>
<td>0.37</td>
</tr>
<tr>
<td>U.S.A. (whole population)</td>
<td>738</td>
<td></td>
<td>889</td>
<td></td>
<td>1627</td>
<td>1.14</td>
</tr>
<tr>
<td>Sweden</td>
<td>41</td>
<td>1.69</td>
<td>42</td>
<td>1.73</td>
<td>83</td>
<td>1.71</td>
</tr>
<tr>
<td>Denmark</td>
<td>31</td>
<td>1.80</td>
<td>33</td>
<td>1.89</td>
<td>64</td>
<td>1.84</td>
</tr>
<tr>
<td>Japan</td>
<td>42</td>
<td>0.12</td>
<td>57</td>
<td>0.15</td>
<td>99</td>
<td>0.13</td>
</tr>
<tr>
<td>England-Wales *</td>
<td>489</td>
<td>1.5</td>
<td>529</td>
<td>1.6</td>
<td>1008</td>
<td>1.5</td>
</tr>
</tbody>
</table>

* Code 331 - total
The rates by sex are uniformly almost equal, which would be expected for autosomal dominant inheritance. The higher mortality rates in Scandinavian countries (Denmark and Sweden) compared to the U.S.A. and England/Wales does probably not represent a truly increased morbidity or mortality, but rather indicates more accurate and meticulous collation of data in smaller populations.

Table III-VII shows the reported number of deaths in various countries due to Huntington's chorea occurring before the age of 20. Figures vary between 1 - 3 per cent of the total number.

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Total No. (all ages)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.A.</td>
<td>17</td>
<td>1,627</td>
<td>1.04</td>
</tr>
<tr>
<td>Sweden</td>
<td>1</td>
<td>83</td>
<td>1.20</td>
</tr>
<tr>
<td>Denmark</td>
<td>2</td>
<td>64</td>
<td>3.10</td>
</tr>
<tr>
<td>Japan</td>
<td>3</td>
<td>99</td>
<td>3.0</td>
</tr>
</tbody>
</table>
CHAPTER III-5

MORTALITY DATA ON HUNTINGTON'S CHOREA IN SOUTH AFRICA

A. INTRODUCTION

Information concerning the number of deaths in South Africa is published annually by the Department of Statistics in Pretoria. These reports usually appear after a delay of 2 to 3 years and the latest available publication at the time of documentation of this study was 1976. The methodologic drawbacks as to the use of the three numbered code (331 in this case) as opposed to the more specific four number rubric, have previously been mentioned (Chapter III-4 A). The reports on deaths of the Department of Statistics have been systematically searched from 1968 until the latest available publication (1976) in an effort to ascertain all mortalities noted under 331 after the first year of life. No deaths have yet been documented due to Huntington's chorea before the age of one year. The year 1968 was chosen for the commencement of this scrutiny as this was the year that the 8th Revision of the I.S.C. came into effect. The results of this study are presented in Table III-VIII.

B. RESULTS

The number of deaths and death rates in South Africa coded 331 as the underlying cause occurring between 1968 and 1978 by sex, race and age (5 year intervals) is shown in Table III-VIII.

C. DISCUSSION

The mortality figures for South African Whites are lower than those of other populations claiming European ancestry and
TABLE III-VIII


<table>
<thead>
<tr>
<th>AGE</th>
<th>WHITES</th>
<th>COLOURED</th>
<th>AFRICAN NEGROES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>0 - 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 - 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 - 14</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 - 19</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>20 - 24</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>25 - 29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 - 34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35 - 39</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>40 - 44</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>45 - 49</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>50 - 54</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>55 - 59</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 - 64</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>65 - 69</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>70 - 74</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>75 - 79</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 - 84</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>18</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>TOTAL:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average/Year:</td>
<td>4.11</td>
<td>1</td>
<td>0.33</td>
</tr>
<tr>
<td>Rate/Million:</td>
<td>1.03</td>
<td>0.46</td>
<td>0.02</td>
</tr>
<tr>
<td>Population (1972)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
higher than those peoples of African and Japanese descent. This parallels the pattern for the prevalence data presented in Chapter III-3. An interesting observation is that in South Africa 12.2 per cent of all deaths due to Huntington's chorea occurred before the age of 20 as opposed to 1 - 3 per cent in other countries (Table III-VII). If mortality data can be accepted as an index of morbidity, this may represent a higher frequency of juvenile Huntington's chorea in the Republic.

A limited opportunity to check the accuracy of the publications of the Bureau of Statistics is offered by adding the reported number of deaths due to the disease over a specific time period and comparing it with the total number of mortalities over that same time appearing in the clinical files of the current investigation, with the reservation that these notes themselves are incomplete. I have had notification of 8 deaths due to Huntington's chorea during 1975 and 1976 in the White population of South Africa, as opposed to 5 deaths in the Report of the Department of Statistics. This represents a 62% accuracy of these figures presented for the White group for those years.

It can be seen that the mortality rate for the Coloured population is less than half that of the Whites, even though the prevalence of Huntington's chorea is almost similar in these two groups (Table III-IV). This figure is unlikely to be accurate for a disease which has a similar duration and clinical course in both populations, and probably represents a poorer documentation of the causes of death in the Coloured group. I have had notification of
15 deaths occurring in the Coloured population due to Huntington's chorea between 1968 and 1976 as opposed to 9 reported mortalities. This represents a maximum accuracy of 60 per cent for those publications concerning deaths in the Coloured people during that time.

This situation in part reflects the inadequate completion of death certificates by the medical profession in this country. This situation is not peculiar to South Africa, and has also been recorded in other countries, including the United States, where in some states there were no recorded deaths due to Huntington's chorea during the same period that local health agencies reported several deaths. Another possible source of error is in the transcribing of information from the death certificates to the computer cards.

It would thus appear that mortality data are particularly unreliable parameters for assessing the frequency of Huntington's chorea in different parts of the world, including South Africa.
CHAPTER III-6
INCIDENCE OF HUNTINGTON'S CHOREA OUTSIDE SOUTH AFRICA

A. INTRODUCTION

Incidence (expressed per unit of the population per unit time) is equivalent to the prevalence of a disorder divided by the mean duration of that disease. In other words:

\[
\text{prevalence} \div \text{duration} = \text{incidence}
\]

The prevalence of Huntington's chorea has been expressed per million of the population; the duration will be defined in terms of years and thus the incidence will be denoted per million of the population per year. The expected total number of persons presenting with Huntington's chorea per year is equal to the incidence multiplied by the population (expressed in millions).

Incidence is an important parameter reflecting morbidity patterns and may be useful in planning health care and social services.

B. INTERNATIONAL COMPARISON OF INCIDENCE

The annual incidence of Huntington's chorea per million of the population has been calculated by me using the above formula from data presented by the different authors. The incidence and the expected number of new patients per year in each of those areas is shown in Table III-IX.
### TABLE III - IX

**ANNUAL INCIDENCE x 10^-6 POPULATION**

**A REVIEW**

<table>
<thead>
<tr>
<th>Author</th>
<th>Area</th>
<th>Incidence/ million</th>
<th>Expected number of new patients/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reed et al (1958)</td>
<td>Michigan (U.S.) - Whites</td>
<td>2.59</td>
<td>12.6</td>
</tr>
<tr>
<td></td>
<td>Michigan (U.S.) - Negroes</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Brothers (1964)</td>
<td>Victoria, Australia</td>
<td>3.75</td>
<td>11.75</td>
</tr>
<tr>
<td>Bolt (1970)</td>
<td>Scotland (West)</td>
<td>3.63</td>
<td>10.7</td>
</tr>
<tr>
<td>Stevens (1977)</td>
<td>England (Leeds area)</td>
<td>3.06</td>
<td>9.76</td>
</tr>
</tbody>
</table>

The mean incidence of Huntington's chorea in those populations of European origin is 3.25 as opposed to the low figure of 0.94 for the United States Negroes. This observation is in keeping with the prevalence and mortality data presented previously.
CHAPTER III-7
THE INCIDENCE OF HUNTINGTON'S CHOREA IN SOUTH AFRICA

A. RESULTS

The incidence of Huntington's chorea in South Africa and the expected number of new patients presenting each year is shown in Table III-X. Further details concerning the duration of the disease in South Africa will be given in Section IV-III.

B. DISCUSSION

The incidence of Huntington's chorea for Whites and Coloureds in the whole of South Africa is 1.5 and 1.7 respectively. In the African Negro populations the figure is 0.0046, which is exceedingly low. The highest incidence of this disorder is in the Cape Town Coloured (3.45) and Natal White populations (2.04).

The total expected number of new patients in South Africa per year is 10.76. The largest proportion of these will occur in the Cape Province and comprises 2.16 Whites and 3.65 Coloureds per year. These findings probably reflect more complete ascertainment of data in this area. It can be seen that although Natal Whites have the highest incidence, only one new patient will present each year. This reflects the small number of Whites living in that province.

A measure of the accuracy of these data would be to compare the sum of the newly ascertained patients in a year with the number of expected patients for a specific area in the given time. Between March 1978 and March 1979 there was a minimum total of 5 newly presenting Coloured and 4 White persons with newly diagnosed Huntington's chorea in the Cape Province.
### TABLE III-X

**MINIMUM INCIDENCE OF HUNTINGTON’S CHOREA IN SOUTH AFRICA**

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Prevalence Duration</th>
<th>Incidence/Year x 10^-6</th>
<th>Expected No. of New Patients/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>South Africa:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>22.2</td>
<td>1.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Coloureds</td>
<td>21.7</td>
<td>1.7</td>
<td>4.1</td>
</tr>
<tr>
<td>African Negroes</td>
<td>0.1</td>
<td>0.0096</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Cape Province</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>26.5</td>
<td>1.80</td>
<td>2.16</td>
</tr>
<tr>
<td>Coloureds</td>
<td>22.9</td>
<td>1.75</td>
<td>3.65</td>
</tr>
<tr>
<td>Coloureds (Cape Town)</td>
<td>45.1</td>
<td>3.45</td>
<td>2.51</td>
</tr>
<tr>
<td><strong>Natal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>30.1</td>
<td>2.04</td>
<td>1.08</td>
</tr>
<tr>
<td><strong>Transvaal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>13.1</td>
<td>0.89</td>
<td>2.03</td>
</tr>
<tr>
<td>Coloureds</td>
<td>15.1</td>
<td>1.15</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Orange Free State</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>12.1</td>
<td>0.82</td>
<td>0.26</td>
</tr>
<tr>
<td>Coloureds</td>
<td>22.7</td>
<td>1.73</td>
<td>0.08</td>
</tr>
</tbody>
</table>
The calculated incidence and prevalence for the Cape Province based on these figures and using the formula: incidence \times \text{duration} = \text{prevalence}, is shown in Table III-XI. These figures are compared with the reported incidence and prevalence rates as seen in Tables III-V and III-X.

**TABLE III-XI**

**EXPECTED INCIDENCE AND PREVALENCE OF HUNTINGTON'S CHOREA IN THE CAPE PROVINCE (BASED ON NUMBER OF PRESENTING PATIENTS BETWEEN MARCH 1978 AND MARCH 1979)**

<table>
<thead>
<tr>
<th>Population</th>
<th>No. of Patients</th>
<th>Expected Incidence</th>
<th>Reported Incidence</th>
<th>Expected Prevalence</th>
<th>Reported Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>White:</td>
<td>4</td>
<td>3.3</td>
<td>1.80</td>
<td>48.51</td>
<td>26.5</td>
</tr>
<tr>
<td>Coloured:</td>
<td>5</td>
<td>2.4</td>
<td>1.75</td>
<td>31.54</td>
<td>22.9</td>
</tr>
</tbody>
</table>

This is yet another indication that the reported prevalence and incidence figures for this country are artificially low. The factors which have contributed to this underestimate have been discussed in Chapter III-3 C.

The expected incidence and prevalence of Huntington's chorea in the Cape Province is shown in Table III-XI and is similar to the figures reported from around the world and is probably a more accurate representation of the situation in South Africa. Until such time as the social stigma and shame of Huntington's chorea has been overcome all statistics concerning the epidemiology of this disease will remain deceptively low.
CHAPTER III-8
THE EPIDEMIOLOGY OF HUNTINGTON’S CHOREA ON MAURITIUS

A. INTRODUCTION

Mauritius is a small island 48 kilometres in length and 38 kilometres in width, covering an expanse of 1,152 square kilometres. It is situated 800 kilometres east of Malagasy and 2,000 kilometres from the shores of South Africa, which offers the closest genetic service to the island.

Five White persons with Huntington's chorea in South Africa were found to be descendants of a man who lived on the island of Mauritius. This man was one of a sibship of eight, five of whom were males and three females (Fig IV-24). This raised the possibility that Huntington's chorea might be present on the island of Mauritius. Contact was made with an unaffected relative of this family, who provided me with initial details. Further data were ascertained, on my request, by two visitors to the island in 1977. These facts were confirmed when I interviewed Dr. C. Yiptong, psychiatrist on the island on his visit to Cape Town in January, 1979.

The genealogy of Huntington's chorea on Mauritius will be discussed in Section IV.

B. PREVALENCE

Prevalence was determined for the 30th December, 1977, according to the formula noted in Chapter III-3 A. Population figures are based on the latest official census which was drawn up on Mauritius in 1971. The results are summarized in Table III-XII.
TABLE III-XII

POPULATION OF MAURITIUS (1971)

<table>
<thead>
<tr>
<th>Population</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>230,485</td>
</tr>
<tr>
<td>Hindus</td>
<td>437,365</td>
</tr>
<tr>
<td>Muslims</td>
<td>137,760</td>
</tr>
<tr>
<td>Chinese</td>
<td>24,990</td>
</tr>
<tr>
<td>Foreigners</td>
<td>1,825</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>832,425</strong></td>
</tr>
</tbody>
</table>

The general population comprises the Creoles and the Whites. Accurate estimates of the number of Whites on Mauritius in 1977 are between 12,000 and 13,000.

The total number of persons known to have died from or presently suffering from Huntington's chorea on the island of Mauritius is shown in Table III-XIII.

TABLE III-XIII

PERSONS WITH HUNTINGTON'S CHOREA ON MAURITIUS

<table>
<thead>
<tr>
<th>Patients</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living:</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Deceased:</td>
<td>13</td>
<td>6</td>
<td>19</td>
</tr>
</tbody>
</table>

A total of 25 patients of whom 6 are presently living has been recorded.
The prevalence of Huntington's chorea in the White population of Mauritius is approximately $480 \times 10^{-6}$. I have had unconfirmed notification of one affected Creole with this disease. No other persons with Huntington's chorea have been reported.

The male to female ratio of affected persons is 1.7 : 1. This is not the ratio expected of an autosomal dominant disease. However, the number of affected individuals is too small for any conclusions to be drawn from this apparent discrepancy.

C. DISCUSSION

The high prevalence of Huntington's chorea in the White group of Mauritius reflects a total of 6 affected persons in a small population. No inferences can be made about the prevalence of the disease in other sections of the community.

This finding again illustrates the effect of introducing a relatively rare gene into a small, geographically isolated population with resulting increase in prevalence over a hundred years, i.e. in genetic terms, the founder effect.

All of the affected persons are descendants of a man, Auguste Benoni Joseph d'Agnel, who was born in Provence, France in 1804 and, dissatisfied with conditions in his country, set sail for Mauritius. He later married Elizabeth Jose Aime Bega in 1837 in Port Louis. This marriage produced eight children, five of whom carried the gene for Huntington's chorea. Auguste d'Agnel died in 1868 at the age of 64.
and apparently showed some signs of the disorder at his death. It would thus seem most probable that he passed the gene for this disease on to his children.

There are important social and medical implications of Huntington's chorea for the people of Mauritius. There are approximately 60 people at risk of carrying the gene for the condition, by virtue of the fact that they are the progeny of an affected person. Correcting for age, it may be predicted that approximately 25 individuals will develop the signs and symptoms of Huntington's chorea. The cost and burden of the disease to the state will be very high. It is imperative that those at risk be counselled of the genetic implications of the disorder, in an effort to prevent spread of the gene.

The medical profession of Mauritius must be informed that Huntington's chorea is present on the island, as the burden of providing adequate medical care for affected individuals and their families will rest on them.

This is a minimum estimate of the prevalence of Huntington's chorea on the island of Mauritius. The extent of the spread of the gene to other population groups is unknown. Certain members of this large kindred who are at risk of the condition have migrated to other small islands in the Indian Ocean. The prevalence of the disease in these places is still waiting to be determined.
SECTION IV

HISTORY AND GENEALOGY

"To understand a science it is necessary to know its history."

August Comte (1798-1857)
In: Positive Philosophy.
## SECTION IV

**HISTORY AND GENEALOGY OF HUNTINGTON’S CHOREA IN SOUTH AFRICA**

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<th>Title</th>
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</tr>
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<td></td>
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CHAPTER IV-1

HISTORICAL BACKGROUND

The word "chorea" has a long history dating back to the Middle Ages when outbreaks of involuntary movements affecting whole communities were described. The disease was named according to the locality of the attack and the shrine to which patients went to be cured, e.g. Saint Vitus' dance.

Chronic hereditary incurable chorea was recorded by many observers during the nineteenth century (Bernt, 1810; Rufz, 1834). Waters (1841) in a letter from Franklin, New York, described a disorder "which is markedly hereditary, very rarely makes its appearance before adult life, in all cases induces a state of more or less perfect dementia and never ceases while life lasts." This was the first detailed description of the disease known today as Huntington's chorea.

Gorman in Philadelphia was the second person to describe the disorder as part of his thesis "On a form of chorea vulgarly called magrums" (1846) which concerned patients observed in Wyoming County, Pennsylvania. Regrettfully, the original document has been lost.

A Norwegian district physician, Lund, reported on hereditary chorea in two families in 1860. Unfortunately this contribution failed to achieve recognition until Orbeck (1959) translated the report from Norwegian into English. In Norway this disease is sometimes still referred to as "Lund-Huntington's chorea".
THE
MEDICAL AND SURGICAL REPORTER.
No. 789. PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT.

Communication

ON ChoreA.

By GEORGE HUNTINGTON, M. D.,
Phila., Phila.

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the slow respiratory movements of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to one suffering from it, or to his friends. Its most marked and characteristic feature is a clonic spasm affecting the voluntary muscles. There is no loss of sense or of volition attending these contractions, as there is in epilepsy; the will is there, but its power to perform is deficient. The forced movements are after a manner performed, but there seems to exist some hidden power, something that is playing tricks, as it were, upon the will, and in a measure thwarting and preventing its action; and after the will has ceased to exert its power in any given direction, taking things into its own hands, and keeping the poor victim in a continual jigger as long as he remains awake, generally, though not always, granting a respite during sleep. The disease commonly begins by slight twitchings in the muscles of the face, which gradually increase in violence and variety. The eyelids are kept hanging, the brows are corrugated, and then elevated, the nose is screwed first to the one side and then to the other, and the mouth is drawn in various directions, giving the patient the most ludicrous appearance imaginable.

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, these of the face rarely being excepted. If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palm upward, and then the back. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the arms are turned in, and then inverted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through, that a complete description of the same would be impossible. Sometimes the muscles of the lower extremities are not affected, and I believe they never are alone involved. In cases of death from chorea, all the muscles of the body seem to have been affected, and the time required for recovery and degree of success in treatment seem to depend greatly upon the amount of muscular involvement. Huntington refers to two cases in which the muscles of respiration were affected.

The disease is generally confided to childhood, being most frequent between the ages of eight and fourteen years, and occurring more in girls than in boys. Du Bois and Reitz refer to 428 cases, 130 occurring in boys and 298 in girls. Watson mentions a collection of 1123 cases, of whom 733 were females, giving a proportion of nearly 6 to 2. Dr. Watson also remarks upon the disease being most frequent among children of dark complexions, while the two authorities just alluded to, Du Bois and Reitz, give as their opinion that it is most frequent in children of light hair. In every case visiting the clinic

Fig. IV - 1

Photograph of Huntington's original article—published in 1872.
Lyon (1863), while a house physician, also had contact with "magrum" families with hereditary chorea in the New York area. George Huntington was only 22 years old when he submitted his sole contribution to medical literature, "On Chorea", to the Medical and Surgical Reporter in 1872 (Fig IV-1). The pencilled remarks of his father and grandfather, both doctors, are visible in the margin of the original manuscript. Despite the previous reports, the paper which Huntington presented was the first clear and complete description of the disease. In addition to chorea, dementia and inexorable progression, three "peculiarities" were stressed, namely its hereditary nature, the tendency to insanity and adult age of onset. In Sir William Osler's words (1908) "There are few instances in the history of medicine in which a disease has been more accurately, more graphically or more briefly described."

George Huntington reported after his retirement (1910) that his medically qualified grandfather and later his father, had previously identified the features of this disease on Long Island as early as 1797. At the same time (1910) he eloquently described his first contact with the disease as follows - "Over fifty years ago in riding with my father on his professional rounds, I saw my first cases of 'that disorder' which is the way the natives always referred to the dreaded disease. Driving with my father through a wooded road, we suddenly came upon two women, mother and daughter, tall, thin, almost cadaverous, both bowing, twisting, grimacing. I stared in wonderment, almost in fear. What could it mean? My father paused to speak with them and we passed on. Then my Gamaliel-like instruction began; my medical education had its inception. From this point on, my interest in the disease has never wholly ceased."
Fig. IV - 2

Engraving by H. Hondius made in 1642 from Brueghel's drawing of 1569 (courtesy Rijksmuseum, Amsterdam).
It is only as a result of his fascination with the disorder and the close cooperation between three generations of doctors in the Huntington family stretching over nearly 100 years, that this disease was finally clearly delineated in 1872. It is fitting that the name "Huntington" be used in the eponymic designation of this disorder.

Huntington's chorea is a disorder that was certainly present for many years prior to its definitive delineation. Bickford and Ellison (1953) have noted without reference that the first patient with Huntington's chorea "was a man who imitated Christ's agony on the cross". It is possible that this disease was prevalent during the 16th century in Europe and a drawing by P. Brueghel in 1569 (Fig IV-2) concerns people suffering from "St. Jan's ziekte", which is synonymous with St. Vitus dance. Affected adults appear in Brueghel's print and it is possible that he was depicting Huntington's chorea and not St. Vitus dance, which characteristically occurs in childhood. The text of the drawing, written by Brueghel himself, indicates that if these people danced over a bridge in Meulenbeeck near Brussels they might be cured of the disease for a whole year. Dr. L.N. Went of Leiden (personal communication, 1978) has informed me that there is still a yearly procession in Meulenbeeck where everybody dances during the procession on "St. Jan's Day".
CHAPTER IV-2

GENEALOGICAL INVESTIGATIONS OUTSIDE SOUTH AFRICA

A. INTRODUCTION

Because of its long history and the fact that the mutation rate for Huntington's chorea is amongst the lowest recorded for any human dominantly inherited condition (Stevens and Parsonage, 1969) this disease offers particularly fertile ground for genealogical investigations.

B. AMERICAN GENEALOGICAL INVESTIGATIONS

The first studies into the ancestral and genealogical background of Huntington's chorea were performed by Jelliffe and Tilney (1908) and later in 1915 by Davenport. An outstanding investigation was performed by Vessie (1932) who traced the origin of a large number of affected individuals in the Eastern part of the United States to the village of Bures in East Anglia, England. The gene for Huntington's chorea was carried to the U.S.A. by three young men, Jeffrey, Nicholas and Wilkie, who embarked on the Wintrop Fleet in 1630 and landed three months later in Salem, Massachusetts.

Vessie reported that all three of these men ran foul of the law. Wilkie was charged six times for different misdemeanors, including profanity, selling beer without a licence and keeping a disorderly house. Nicholas's dishonesty caused him to be thrown in irons on the ship, while Jeffrey was charged with perjury. The sociopathic traits described are thought to be suggestive that these men were indeed suffering from
Huntington's chorea. During the intervening three centuries about 1,000 descendants of these three individuals are believed to have been affected. Recently, however, doubts have been cast on the accuracy of all of these findings by Hans and Gilmore (1969) and Caro and Haines (1975).

C. STUDIES ELSEWHERE

Further genealogical work has been carried out in other countries, including Tasmania (Brothers, 1949), Germany (Wendt et al, 1960) and Canada (Barbeau and Fullum, 1962).

Brothers (1949) traced 120 patients to a Huguenot ancestress who subsequently left her home in Somerset, England in 1848 to settle in Tasmania. She married twice, first a Mr. Lock and then a Mr. Viney and had affected descendants from both marriages.

Critchley (1964) described another Huguenot who left his native village of Montbeliard near the Franco-Swiss frontier when the Edict of Nantes was revoked in 1685. After a brief sojourn in Southern Carolina, his descendants settled in 1771 in the village of Tatamagouche, Nova Scotia. Forty-eight individuals with Huntington's chorea have been traced to this common progenitor.

D. CONCLUDING THOUGHTS

In contrast to these reports from Europe, America and Australia,
after an extensive search I was able to find only nine references to Huntington's chorea in Africa, only one of which mentioned genealogy (Table IV-1). In view of the excellent facilities for genealogical investigations (Chapter IV-4) in South Africa, a challenging task presented itself to me: namely, to attempt to determine the earliest transmitters of the gene for Huntington's chorea to this country.
### Death Notice

Pursuant to the provisions contained in Section 8 of the Ordinance No. 101 of 1999, pursuant to Section 4 of Act No. 27 of 1950.

<table>
<thead>
<tr>
<th>1. Name of the Deceased</th>
<th>Thomas Robert Hardie</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Birthplace of the Deceased</td>
<td>Cape Town</td>
</tr>
<tr>
<td>3. Day, Date, and Year of Birth of the Deceased</td>
<td>February 12, 1820</td>
</tr>
<tr>
<td>4. Age of the Deceased</td>
<td>About 74 years</td>
</tr>
<tr>
<td>5. Condition of Life, Occupation</td>
<td>Servant</td>
</tr>
<tr>
<td>6. Married or Unmarried</td>
<td>Married to Elizabeth Isabella Hardie</td>
</tr>
<tr>
<td>7. Name of Surviving Spouse</td>
<td>Elizabeth Isabella Hardie</td>
</tr>
<tr>
<td>8. Name and approximate date of death of previous spouse</td>
<td></td>
</tr>
<tr>
<td>9. The day of the decease</td>
<td>13th December 1874</td>
</tr>
<tr>
<td>10. At what house or where the person died</td>
<td>At his residence in 123, London</td>
</tr>
<tr>
<td>11. Names of Children of Deceased, and whether major or minors</td>
<td></td>
</tr>
</tbody>
</table>
- Rachel Isabella Isabella (Mrs. Hardie)  
- William Constance Hardie (married)  
- Elizabeth Mary Hardie  
- Samuel Frederick Hardie  
- Thomas Constance Hardie (married) |
| 12. Whether Deceased has left a Will | Left a Will |
| 13. Whether Deceased has left any property, and if so what kind |

Received at the Office of Registration on the 14th November 1874.  
William J. Hardie, Registrar,  
For the purposes of registration.  
[Signature]  
[Stamp]

### Fig. IV - 3

An excellent source of genealogical information —  
- The Death Notice -
<table>
<thead>
<tr>
<th>Year</th>
<th>Country of origin</th>
<th>Subjects</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1935/36</td>
<td>Kenya</td>
<td>1 affected</td>
<td>Gordon, H.L.</td>
</tr>
<tr>
<td>1937</td>
<td>Algeria</td>
<td>? affected</td>
<td>Bardenat and Sutter</td>
</tr>
<tr>
<td>1938</td>
<td>Algeria</td>
<td>? affected</td>
<td>Tordjman, J. (Thesis)</td>
</tr>
<tr>
<td>1956</td>
<td>East Africa</td>
<td>1 family - 4 affected</td>
<td>Cohen, C.</td>
</tr>
<tr>
<td>1958</td>
<td>Egypt</td>
<td>3 families - 8 affected</td>
<td>El-Garem, O.</td>
</tr>
<tr>
<td>1962</td>
<td>South Africa</td>
<td>16 families - 56 affected</td>
<td>Klintworth, G.K.</td>
</tr>
<tr>
<td>1974</td>
<td>South Africa</td>
<td>1 family - 6 affected</td>
<td>Saffer, D.S. et al</td>
</tr>
<tr>
<td>1977</td>
<td>South Africa</td>
<td>14 families - 26 affected</td>
<td>Hayden, M.R. and Beighton, P.</td>
</tr>
<tr>
<td>1978</td>
<td>Rhodesia</td>
<td>1 family - 4 affected</td>
<td>Samuels, B.L. and Gelfand, M.</td>
</tr>
</tbody>
</table>
A. REGISTRATION OF BIRTHS AND DEATHS

It is only since 1895 that it has been compulsory by law to record all births and deaths of the entire population. These events are documented on a birth or death certificate. The complete birth certificate notes the person's name, date, place of birth and names of the parents. The death certificate records the date, place and cause of death and is signed by the doctor attending the deceased.

Prior to 1895, it is possible to trace the date of death, if such a person either made a will or was the owner of valuable property. This was documented in the form of a death notice (Figure IV-3), which had to be filed with the district magistrate, and was signed by the deceased's next-of-kin. This is an exceedingly important document for genealogical research, as it discloses the names of the deceased, his parents and his children. In addition, the birthplace, date and place of death, marital status and nature of owned property of the deceased are recorded. The death notice has been obligatory since 1834. Between 1758 and 1834 deaths were registered voluntarily and usually only indicated the age and place of death. Information concerning deaths prior to 1758 could be gleaned from the burial registers of churches.

B. THE FAMILY INTERVIEW

The first step in the collection of genealogical information began with the family interview, the primary aim being to ascertain the dates of death of affected persons.

An attempt was made to draw a family tree for every kindred
who had an affected member suffering from Huntington's chorea. Many kilometres were travelled to remote areas of this land to visit isolated families who might provide a link for a missing generation. Where possible, the investigation was extended to the affected person's parents, sibs and children. Denial of the existence of the disease in their family was common, even when relatives had been admitted to mental hospitals. Many were only willing to reveal their ancestry after a relationship of trust and friendship had developed. However, once the bond of acceptance had been established, individuals in different families were then very keen to assist and some spent hours in church archives in an effort to trace their own ancestry.

The genealogical study also captured the imagination of some doctors who obtained important historical details concerning affected families under their care. In particular, kindreds in the Eastern Cape, North-Western Cape, Transkei and North-Eastern Transvaal have been traced in this way.
(Index person = A)

**Fig. IV - 4**

Plan for retrieval of genealogical data
After my first visit, memories of stories and facts long forgotten were revived, which were then transmitted to me on a return visit or by post. As a result, numerous families living in different areas and originally thought to be unrelated, have been found to be linked in previous generations. Hundreds as far apart as South West Africa and the Eastern Cape are now known to be ancestrally related.

C. PLAN FOR COLLECTION OF GENEALOGICAL DATA

After the family interview, the search was continued at the government archives where the death notices were consulted to ascertain the names of the affected person's parents. The index of death notices was then examined for the proband's parents' names, and in this way the death notice of these persons could be pursued, and thus the names of the proband's grandparents could be found. A plan for the retrieval of genealogical information is shown in Figure IV-4.

The search was continued in this way as far back as possible. When difficulties were encountered, different genealogical works were consulted. Most important amongst these was a book entitled "Die Geslacht Register der Oude Kaapsche Families" which traces many Afrikaner families from the early nineteenth century to their origins in the seventeenth century (see Chapter IV-4, E.).

In this way it has been possible to trace different affected individuals and their families to their origins at the time of the first
Dutch settlement in South Africa.

Many problems were encountered. The major obstacle was the failure of accurate documentation of important details. Some of the death notices did not contain parents' names. In this situation, the approximate date of the proband's baptism was worked out by subtracting his age from the date of death. The baptisms could then be searched for in the church registers and the parents' names found.

Another approach used when encountering difficulties with some death notices was to search the church records for the index person's marital entry. Age at marriage is always inserted. In this way the approximate date of baptism, and from there the parents' names, could be found. With this information the index person's parents' death notices could then be looked for.

Thus the church archives were valuable sources of missing details in instances when death notices were incomplete or when they were absent. This occurred either when the deceased's estate did not reach a certain sum, or when this person died prior to 1834. In these situations there was no alternative but to use the church register. Church registers were instituted in 1665, thirteen years after the first Dutch settlers under the leadership of Jan van Riebeeck arrived at the Cape.

The records of the Nederduitse Gereformeerde (N.G.) Kerk were particularly helpful. For nearly 150 years the N.G. Kerk was the only
The naming of children according to Afrikaner tradition.

The family bible also gave important genealogical facts.
officially recognised church body in South Africa and most immigrants belonged to it. I was fortunate to have free access to the Central Records of the N.G. Kerk in Cape Town and the expert attention of the Chief Archivist, Dominee J.C. Hopkins and his assistant, Mr. Van Zyl.

The Journal of Jan van Riebeeck contains important notes on persons and families, including births, baptisms, marriages and deaths in that period and was particularly important and useful for events prior to 1665.
A. NAMING OF AFRIKANER CHILDREN

Genealogical investigations in South Africa are facilitated in a number of ways. It is well known that traditional Afrikaner families have, until recently, named their offspring according to an accepted convention. The first son was named after his father's father; the second son after his mother's father and the third son after his father. The first daughter was named after her mother's mother; the second daughter after her father's mother and the third daughter after her mother (Fig IV-5). Thus, if it was known that the eldest uncle was named Jacobus Gerhardus Tobias, then the great-grandfather of the propositus (oupagrootjie) must have been named in the same way. This tradition has enabled me to locate missing links in the ancestral lineage of different families. Whilst this was a practice in the past, such a system is not in regular use today.

B. THE FAMILY BIBLE

It is common practice in Afrikaner families to have a bible that has been passed down as an heirloom from generation to generation. A pedigree was sometimes found in the first few pages with each new addition to the family carefully inscribed together with his or her progeny. Everyone that was visited was asked if they had a bible and in many instances this provided me with valuable clues as to their origins (Fig IV-6).

C. PHOTOGRAPHS

Old family albums and photographs were an unexpected source of information. Family members would often forget details such as the age
This photograph from a family album shows a gentleman with a characteristic posture, particularly marked in his hands and, together with the first appearance of a beard, suggests that the disease was already manifest.
of onset of the abnormal movements, which would only emerge as a result of this type of search. At the start of their illness patients often had difficulty shaving and the appearance of a beard on the gentleman in Fig IV-7, together with a typical posture was an important clue that the disease was indeed manifest. Sequential photographs also gave important information as to the rate of progress of the disease in an affected person (see Fig VI-4).

D. **EPITAPHS**

Epitaphs were helpful in documenting those affected persons' full names, dates of birth and death, where family members were non-contributory. Different members of a family were often buried in the same cemetery and in some instances this enabled me to construct a more complete ancestral tree. In one instance, an epitaph in a cemetery in Komga, Eastern Cape, provided me with the exact date of death and age at death of the earliest English transmitter of the gene in this country (Fig IV-8). Next to his grave was that of his brother, which gave the exact place of this family's origins in England.

E. **REFERENCE BOOKS**

The founder of genealogical research in South Africa was Christoffel Coetzee de Villiers. A book written by him and published in 1894 after his death entitled the "Geslacht Register der Oude Kaapsche Familien" traces most of the old Afrikaner families from the early nineteenth century to their origins in the seventeenth century. An alphabetical register with the names and dates of baptism of descendants of all the original Cape Settlers has been documented, which, although incomplete, has been an invaluable source of information. A revised
This tombstone in the Komga cemetery in the Eastern Cape provided the date and age at death of the earliest English transmitter of the gene to South Africa.
and updated edition of the book was published in 1966.

D.F. Du Toit Malherbe's family register of the South African Nation and other books have been important supplements to this work. In particular a recent publication entitled "Handbook for Genealogical Research" (Lombard, 1977) has added useful information.

F. PRIOR INVESTIGATIONS

The current investigation was also helped by the work of two colleagues. Doctor Geoffrey Dean's outstanding project on porphyria with the tracing of those porphyric families to a common ancestor in 1688 inspired me and provided guidelines for the methodological approach to the current study.

The only previous attempt at genealogical investigation of Huntington's chorea in South Africa was a pioneering study performed by Dr. G. Klintworth in 1960 to 1961. Unfortunately, however, this was never completed. In a short paragraph of his article (1962) Klintworth used initials of three families who all seemed to stem from an unnamed common ancestor. The initials that he quoted corresponded with surnames of affected individuals in my register and with this lead, together with my own findings and much additional information, I have been able possibly to identify the earliest transmitter of the gene for Huntington's chorea to South Africa.
Inevitably in an investigation of this nature, numerous blind alleys were explored, only to have to return to the "same place and see it again for the first time" (T.S. Eliot, 1942). It is an aspect of this study that has demanded a great deal of time, quiet, slow movements, strict attention and patience.
CHAPTER IV-5
SUMMARY OF ORIGINS OF HUNTINGTON'S CHOREA IN SOUTH AFRICA

There are multiple origins of the gene for Huntington's chorea in South Africa. The predominant source is Western Europe, the gene being brought over by carriers during the multiple waves of immigration from Holland, England and Germany.

In the early phases of this study, it was thought that there were approximately 134 independent kinships. However, as the histories of different families were unravelled, ancestral linkage was found in over 60, reducing the number of separate known kindred to 74. It is possible that, with further information, such a relationship will also be found amongst these remaining unrelated kinships.

The country of origin of the earliest known affected member has been traced in 34 of the South African kindred and is tabulated in Table IV-II. Although England was a source of most of the kinships, almost all of these families are small with only a few affected members. With only one exception (Chapter IV-7), the gene has been brought over from England during this century. Thus, although England is the country of origin of 12 kindreds, Holland is still the major source of the gene to South Africa, primarily because it was probably transmitted with the earliest Dutch settlers during the 17th century. From this single source the number of affected individuals has multiplied and today over 200 in more than 50 Afrikaner families have been traced to a common ancestor (Chapter IV-6).

Other countries are fairly evenly represented, the majority of affected persons having their origins in northern or western Europe. It
is interesting to note that the gene has also been brought to this country from islands off the coast of Africa, including Mauritius and the Cape Verde Islands. The Middle East has also contributed to the South African gene pool.

Table IV-III shows the number of separate kinships affected by Huntington's chorea according to racial groups. Only three Black families are known to be affected. Almost 70% of the White families have been traced to their foreign country of origin, in marked contrast to the poor ascertainment (12%) in the population of mixed ancestry and the African Negroes (33%). This primarily reflects the prior lack of documentation of births and deaths for the non-White population of South Africa. As further information is gathered and collated, some of the unknown sources of the remaining 40 kindred will be clarified.

The story of the origins of Huntington's chorea in South Africa is essentially a story of the multiple waves of immigration to this country, primarily from western Europe, which were the results of different accidents of history, such as the establishment of the seafaring companies, wars and the discovery of gold on the Witwatersrand.
### TABLE IV-II

**COUNTRY OF ORIGIN OF EARLIEST TRACEABLE AFFECTED MEMBER OF 34 OF A TOTAL OF 74 SOUTH AFRICAN KINDRED**

<table>
<thead>
<tr>
<th>Country</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>England</td>
<td>12</td>
</tr>
<tr>
<td>Holland</td>
<td>10</td>
</tr>
<tr>
<td>Germany</td>
<td>3</td>
</tr>
<tr>
<td>Ireland</td>
<td>2</td>
</tr>
<tr>
<td>Lithuania</td>
<td>1</td>
</tr>
<tr>
<td>Scotland</td>
<td>1</td>
</tr>
<tr>
<td>Mauritius</td>
<td>1</td>
</tr>
<tr>
<td>Cape Verde Islands</td>
<td>1</td>
</tr>
<tr>
<td>Denmark</td>
<td>1</td>
</tr>
<tr>
<td>Lesotho</td>
<td>1</td>
</tr>
<tr>
<td>Lebanon</td>
<td>1</td>
</tr>
</tbody>
</table>

Total: 34

### TABLE IV-III

**SEPARATE FAMILIES AFFECTED BY HUNTINGTON'S CHOREA ACCORDING TO RACIAL GROUPS**

<table>
<thead>
<tr>
<th>Race</th>
<th>Number</th>
<th>% of total</th>
<th>Origin of families Known (%) / Unknown(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>46</td>
<td>(62)</td>
<td>30 (65) / 16 (35)</td>
</tr>
<tr>
<td>Mixed ancestry</td>
<td>25</td>
<td>(33)</td>
<td>3 (12) / 22 (88)</td>
</tr>
<tr>
<td>African negroes</td>
<td>3</td>
<td>(5)</td>
<td>1 (33) / 2 (67)</td>
</tr>
</tbody>
</table>

Total: 74

40
From Cape Archives (1668) Kaapse Notule 611/1.

Documenting the marriage of Willem Schalcq with Elsje Jacobs, the daughter of Jacob Cloeten, on the 9th of September, 1668.

From Cape Archives (1670) Kaapse Notule 611/1.

"Den 2 Novemb: Ein dochtertje aan Willem Schalcq en Elsje zijn huysv wiert genaamt feutje tot getuigen ststanden Hendrik-Bruyn-Jocht en Marthe Tielernans."

2 November 1670: Announcing the baptism of the daughter of Willem Schalcq and Elsje, his wife, who was named Feutje, witnessed by Hendrik-Bruyn-Jocht and Marthe Tielernans.
A. THE FIRST BURGERS ARRIVE AT THE CAPE

Jan van Riebeeck wrote in his journal on Sunday, 28th April, 1658:
"Fine, clear, calm, sunny weather. In the afternoon the officers of the
ship landed and from them we understood that the ship was the 'Dordrecht'
of the Chamber Delft. She had left Goeree on 17th December last year
with 364 paid men on board of whom 14 had died and 6 had deserted at the
island of St. Vincent, where the ship had touched on 3rd February as a
result of the loss of her bowsprit and foremast."

Amongst those 344 survivors who arrived at the Cape in 1658 was a
man called Willem Schalk van der Merwe. He had left his home near
Rotterdam and was employed as a "harquebus" on the "Dordrecht". (A
harquebus is an old German word used to describe a person hired to man an
eyear type of portable gun which was supported upon a carriage.) On the
5th May, 1661 he became one of the first free burghers at the Cape.
Later, on the 9th September, 1668 he married Elsjie Cloeten, daughter of
Jacob Cloeten, who had arrived at the Cape with Jan van Riebeeck in 1652
(Fig IV-9). The first child of this marriage was a daughter named
Sophia after her maternal grandmother, according to the old Dutch tradition.
She was baptised on the 2nd November, 1670 (Fig IV-10).

Sophia married Roelof Pasman on the 12th November, 1684 (Fig IV-12,
generation III). (The key to the symbols used in pedigrees in this thesis
is shown in Fig IV-11). They had five children before he died in 1695.
In 1696 she married Pieter Robberts who was to become one of the first
magistrates in the Cape. This marriage produced only one child.
II
LANDED IN CAPE 1660
FROM OUD-BEYERLAND
HOLLAND

III
Earliest Transmitters
of Gene for H.C. to
S.A.

Fig. IV - 12
Pedigree showing the ancestral relationship of over 200 affected persons to Sophia V.D.M., the most likely earliest transmitter of the gene to S.Africa
Fig. IV - 11

The key to the pedigrees.

- ■: Affected male
- ●: Affected female
- ■*: Juvenile Huntington
- □: Male or female thought to be affected
- □: Normal male
- ○: Normal female
- /: Deceased
- ◊: Number of offspring
- ●: Proband
- †: Suicide
Together they lived on a farm "Rustenberg" in the Stellenbosch district, which was owned by Pieter Robberts from 1699. A search through old manuscripts and documents revealed a map of the Cape of Good Hope drawn between 1699 and 1713 by a cartographer named Valentyn, in which farms and the names of the owners are inscribed. The site of Pieter Robberts' farm is shown on the map depicted in Fig. IV-13. This farm is still in existence today at the foot of the Jonkershoek mountains.

Four very large Afrikaner families (RO, HU/WI, NI, HO) (Fig IV-12) previously thought to be unrelated, have been traced over 14 generations (Fig IV-16, IV-18) to these common ancestors. Three of these families are descendants of the marriage between Sophia van der Merwe and Roelof Pasman (HU/WI, HO, NI) and the other large kindred (RO) stems from the later marriage of Sophia to Pieter Robberts.

If it is accepted that there is a very low mutation rate in this disease and that affected individuals have descended from both these marriages, it is highly likely that Sophia van der Merwe carried the gene for Huntington's chorea.

The HO kindred has been found to be ancestrally related to the van der Merwe clan through a different member. Schalk was the first son born to Willem and Elsje in 1673 (Fig IV-12, generation III). Over 30 affected individuals have been traced to this common ancestor, who is the brother of Sophia van der Merwe (Fig IV-12). Affected persons in the HO kinship may thus be ancestrally related to Willem Schalk van der Merwe via two routes, namely his daughter and his son.
Map of the Cape of Good Hope, showing the farms and the names of the owners. Pieter Robbertse's name is inscribed as shown by the arrow. (Drawn by Valentyn between 1695-1713. From Cape Archives H1/1162).
Fig. IV - 14

The will of Sophia Robberts, signed in 1715 with a cross.
(From Cape Archives Testamenten CJ2651)
Taken together, there have been over 200 affected individuals in more than 50 families, which constitutes three-quarters of all the Afrikaner patients ascertained in the survey, who have been found to be ancestrally related through a common progenitor in the 17th century.

The notes relating to the earliest days in the Cape, including Jan van Riebeeck's journal, the original wills and the resolutions of the Political Council have been searched for any evidence implicating either Sophia or her parents as carriers of the gene for Huntington's chorea. In particular, a disturbance of handwriting or evidence of antisocial behaviour may suggest that that individual was, in fact, affected. It is of interest that even though both her parents signed their wills personally, Sophia Robberts (nee van der Merwe) could only sign her own will with a cross (Fig IV-14). This raises the possibility that she was in fact affected or, alternatively, she may have been illiterate, although this seems unlikely as both her parents could write.

An attempt was made to determine which of her parents may have carried the gene. Sophia's mother, Elsjie Cloeten, lived to an old age and was certainly over the age of 90 when she died. She is not likely to have suffered from Huntington's chorea. Willem van der Merwe, her father, was around 65 years of age when he died in 1716. The only mention of this man in any of the early writings at the Cape is in the Resolutions of the Political Council and refers to his occupation as a farmer, where he worked on the land - "bouwlandt heeft gearbeijt" (1663).

Contact has been made with the major Dutch centre for the investigation of Huntington's chorea in Leiden, in an effort to elicit circumstantial evidence which could either support or refute the hypothesis
Professor G. Bruyn has informed me that there is on record a large affected Dutch family which can be traced to the 17th century, originating from around Rotterdam with the name van de Merwe (personal communication, 1978). Realizing that Willem Schalk van de Merwe resided in Oud-Beyerland, near Rotterdam, prior to his departure for the Cape, this could be important collaborative evidence indicating that other members of his family were affected and supporting the hypothesis that he was the earliest transmitter of the gene to this country.

Other possible explanations are that Sophia van de Merwe was illegitimate or that neither of her parents were carriers and that Huntington's chorea arose "de novo" as a spontaneous mutation in her. Such an occurrence would be very uncommon in this disorder. The fact that affected persons have been traced to her brother, Schalk, suggests that these explanations are incorrect and rather that they both inherited the gene from their father.

B. PROBLEMS AND PITFALLS - THE WI FAMILY

Numerous blind alleys were explored in this study. It was thought for a long time that the earliest transmitter of the gene to this country was Benjamin Wiese, the grandfather of Petrus Benjamin Wiese (P.B.W.) (Fig IV-12, Fig I-16, generation 6).

Evidence supporting this hypothesis arose from the finding that this gentleman was found guilty by the Political Council of antisocial activity on two occasions around 1700. Initially he was involved in a civil case which involved objections to his application for a wine licence. The Court of Justice found against him in this matter. After this incident he insulted the judges of the time by calling them "nie regters maar geweldigers". In addition he slandered the Dutch East India Company. He was subsequently admonished for this conduct.
The perfect symmetry of B. Wiese's signature on his will, drawn up on 31st March 1718, indicates that this man was unaffected at the time.

(From Cape Archives Testamente CJ2599)
Antisocial behaviour is often present at the earliest phase of the disease and it was thought that it might have heralded onset of Huntington's chorea in this man. This was disproved when the signature with which he signed his will on 31st March, 1718 was examined (Fig IV-15). It is clearly not the signature of a man affected with Huntington's chorea!

The genealogical tree of the descendants of Petrus Benjamin Wiese (WI family) from 1751 until today is depicted in Fig IV-16. This family, with all its branches, is the single largest affected kindred in this country and patients in all provinces of South Africa have been traced to this common ancestor.

Petrus Benjamin Wiese was a citizen of Stellenbosch. His grandson, Petrus Johannes Benjamin Wiese (generation 8) married Elsie Helene Spangeberg in the Clanwilliam area in 1830. Between 1775 and 1830 members of the Wiese family migrated north along the western coast of South Africa to Namaqualand and the Calvinia area. As a result of this journey there is today a large gene pool for Huntington's chorea in the north-western Cape (Fig IV-17). It is of interest to speculate upon the factors which might have been important in stimulating this family's migration.

Many of the earliest settlers were stock farmers. As the herds expanded, so the need to find new grazing increased. The farmer inevitably became a trekboer - a nomadic farmer. Super (Ph.D. Thesis 1978) has postulated that the easy mountain passes, together with reports of large herds of game north of the Orange River, attracted the farmers into Namaqualand and the north-western Cape. A northwards movement from the Cape Colony was also encouraged by the opening of the copper mines in Namaqualand around 1850. Towards the end of the 19th century the Nederduitse Gereformeerde Kerk (N.G.K.) bought farms in the Upington area. These were cheaply leased out to impoverished farmers,
The genealogical tree of the Wi family from 1751 to the present day

THE WI FAMILY 1751 to PRESENT DAY
Map of South Africa, showing the direction of migration of the Hu/Wi family during the early part of the nineteenth century.
who were married and members of this church. Members of the WI family fell into this category.

It is possible that all the above factors played a part in the migration of this particular choreic family from Stellenbosch to the north-western Cape (Fig IV-17).

The gene for Huntington's chorea was introduced into the HU clan by Magrieta Wiese who married a German immigrant, Hermanus Husselman in 1886 (Fig IV-18, generation IX). He had previously been married to Elizabeth Marie van Wyk, with whom he had 8 children. None were affected. Seven children, of whom 5 suffered from Huntington's chorea, were born to him and Magrieta Wiese. She obviously carried the gene. Fifty-seven affected offspring have been traced to this marriage. Fig. IV-18 traces 15 of these relatives over six generations from 1864 to the present day.

The large family (HU) were and are presently members of the N.C.K. and have been farmers in the Upington area since the beginning of this century. The surname Husselman is seen printed on a map of the Kakemas-Keimoes area drawn by the war office after a reconnaissance survey of the territory in 1910 (Fig IV-19). A family graveyard in which numerous individuals who had died from Huntington's chorea have been buried is located on the farm "Warmsand" in this area.

Fig. IV-18 is a continuation from generation VIII of Fig. IV-16 which in turn is an extension of generation 6 in Fig. IV-12. These three figures together span 14 generations from 1652 to the present day.
The introduction of the gene to the Hu clan by M.W., following her marriage to H.H. in 1864 (Generation IX).

**Fig. IV - 18**
The name Husselman is seen on a map drawn as part of a reconnaissance survey of the North-Western Cape undertaken by the War Office around 1910. (From Cape Archives)
The connection of a South African family to a large affected Dutch kinship.
C. OTHER DUTCH ORIGINS FOR THE GENE IN SOUTH AFRICA

The gene for Huntington's chorea has been introduced to this country from Holland on at least six separate occasions, other than previously described in the current thesis. There are living affected persons in South Africa who can be directly traced to these independent, unrelated sources. In all instances the carriers of the gene arrived after 1930. Two families (VO, VE) emigrated from Holland to escape the suffering and poor conditions in western Europe after the Second World War. One family (PR) left Holland in the early 1960s to retire in South Africa (Fig IV-20). The exact reason for immigration in the remaining three kindred is uncertain. It is of interest, however, that one of these families (VdL) originates from Scotland. Members of the kindred spent time in Holland and subsequently migrated to this country.

The town of origin of two of the kinships (PR, VO) is Amsterdam and in one instance (VE), Vlaardingen, near Rotterdam. The towns of origin of the other three families are unknown.

The possibility that affected families in South Africa link with large, well-established choreic kinships in Holland has been explored. Dr. L. Went of Leiden has furnished information which connects three of the South African families (VdL, VE, PR) in this way (personal communication, 1978). In one instance the PR kindred has been shown to join with a large Dutch kindred which has been traced back to the early 1700s (Fig. IV-20).
D. CONCLUSION

Whilst these facts are of obvious historical interest, there are also important medical implications. Misdiagnosis is common in the early phases of Huntington's chorea, often with disastrous consequences (Chapter VI-8). A high index of suspicion of this disorder should be maintained for any individual with these or related surnames, who originate from the north-western Cape and who present with personality change, antisocial behaviour or abnormal movements.

The same concept applies to other areas of South Africa where many affected individuals are known to have descended from a common ancestor with a particular surname.

Dean (1971) has expressed the hope that "perhaps one day it will be possible to trace other genes besides porphyria to the early group of free burghers." In this study many affected Afrikaner individuals with Huntington's chorea have been traced over 14 generations to a common ancestor who was born in the Cape in 1670. It is realised that this work is still incomplete and numerous details are still outstanding. Further research will help to fill these gaps.
The suitcase containing family letters and photographs of the Tu clan found in the Cory Library in Grahamstown.
Photograph of Stephen Tu and his wife, Emily Keightley, taken at the turn of the century.

The genealogy of the Tu clan. Stephen Tu is the affected male in generation II.
TRACING OF AFFECTED SOUTH AFRICAN FAMILIES TO THE BRITISH ISLES

A. INTRODUCTION

The British Isles have been the source of most of the kinships in Canada (Barbeau and Fullum, 1962), Victoria, Australia and Tasmania (Brothers, 1964). South Africa has a similar representation with 15 separate families having their origins in the United Kingdom – 12 from England, 2 from Ireland and one from Scotland.

Fourteen of these British families arrived this century, whilst there is only one known English transmitter of the gene from the 19th century – the founder of the TU kindred, Stephen Turner.

B. THE TU KINDRED

Twenty-two affected individuals in the Eastern Cape have been traced to a common progenitor, William Turner, who arrived on the eastern shores of the Cape Province in 1840.

These findings are the result of a fortuitous discovery of an old suitcase containing a collection of family letters, documents and photographs of the Turner clan, unearthed in the archives of the Cory Library for Historical Research in Grahamstown (Fig IV-21). The contents of this suitcase have yielded important and interesting information. William Turner was a farmer near Salisbury, Wiltshire, England during the
early part of the 19th century. His grandchild recalls in a letter "that my grandfather told me all about the farming in Wiltshire, the ploughing, the horses and a favourite mare he spoke of familiarly and affectionately by name". (Family letter 17.2.1959).

He married Anne Hayter, daughter of an army officer who spent much time in India and being dissatisfied with conditions in England at that time, sailed for South Africa in 1839.

One son, Alexander, was born on board ship and subsequently died on 26th April, 1873, aged 34 years. The second son, Stephen, was born in 1843 in the Somerset East district. According to a letter written around 1935 "Stephen had a very hard, unhappy childhood and ran away from home to join the transport riders and take part in war affairs where he helped as an outpost sentry." He married a woman called Emily Keightley (Fig IV-22) and they produced 12 children (Fig IV-23, generation II and III) 8 of whom were afflicted with Huntington's chorea.

Emily Keightley was "even in her old age very attractive and she lived to 94 years" (letter 22.9.1959). Stephen Turner died in 1917 at the age of 73 years (Fig IV-8) and according to family reports he died of the disease, even though he lived to an unusually old age. Affected descendants of this man today live in different towns, villages and farms in the Eastern Cape.

For many years the persons involved have called the disease the "Turner curse". This term arose as a result of the belief that members of their family were the only affected individuals in the whole society. Misdiagnosis and incorrect information have led to much hardship for the kinship.
A high index of suspicion should be maintained for any individuals in this part of the country with related surnames who present with unusual neurological or psychiatric symptomatology.

C. OTHER ENGLISH SOURCES OF THE GENE

Other affected individuals in South Africa have been traced to different English origins.

Three affected individuals in the Durban area (family JA) have been linked to a man who left Derbyshire in the early 1900s for this country. An architect left London in 1901 and arrived here in 1902 and settled in the Oudtshoorn area. Three progeny of this man (family BR) were affected with Huntington's chorea. The family originally stems from Devonshire. Another gentleman left Manchester in approximately 1825 and settled in the Uitenhage area near Port Elizabeth in the Eastern Cape. Five affected individuals have been traced to his marriage to a Miss Mostert around 1900. None of these different families has been found to be distantly related.

In conclusion, it is clear that many English settlers left their homeland for different reasons to settle in South Africa. A small number of these people carried the gene for Huntington's chorea.
A. DID THE HUGUENOTS BRING THE GENE TO SOUTH AFRICA?

The Huguenots were Protestants who fled from religious persecution by the Catholics in France during the 17th century. They migrated to many different parts of the world, including South Africa.

It has now been established that the gene for Huntington's chorea was carried by the French Huguenots to Britain, Tasmania (Brothers, 1949), Canada (Hattie, 1909) and the United States of America (Critchley, 1964).

It has recently been suggested (Hayden and Beighton, 1977) that the Huguenots may also have brought the gene to South Africa. In the 18th century Huguenots in the Cape who committed certain crimes were banished to the island of Mauritius (Botha, 1921). The high incidence of criminality in the early phases of Huntington's chorea is well documented (Caro and Haines, 1973). It is of great interest that affected relatives of a White South African family with this disorder are presently living in Mauritius.

It was proposed that the ancestors of this family might have come to South Africa with the Huguenots and were subsequently banished because of antisocial behaviour to Mauritius, afterwards returning to South Africa, bringing the gene for Huntington's chorea with them.

In the light of new knowledge, this hypothesis has been proved to be incorrect. The French are, however, transmitters of the gene for Huntington's chorea to South Africa via another pathway.
Pierre Dagnel de Bourdon, a man of royal descent in Generation V, and the earliest definitive transmitter of the gene for Huntington's chorea on Mauritius.
B. HUNTINGTON'S CHOREA ON MAURITIUS

French origins of the gene in South Africa were traced to Mauritius. A Mauritian friend living in Cape Town performed valuable work whilst home on vacation and this helped unravel the history of Huntington's chorea on that island. Further details were obtained at my request during a visit by a member of the Department of Human Genetics, Dr. L. Berkowicz, to the island in August, 1978.

Twenty-eight related affected individuals, 19 on the island of Mauritius and 9 in South Africa, have been traced to a common ancestor Pierre Dagnel de Assigne de Bourbon, who was born on Mauritius in 1864. He had eight children, of whom five had the condition (Fig IV-24). He died in 1915 at the age of 51 of Huntington's chorea. This man's grandfather, August Benoni Joseph Dagnel de Assigne de Bourbon, a nobleman who was dissatisfied with the political situation in France after the French Revolution in 1789, set sail for Mauritius around 1800 on a boat called "Mascareynes".

Information gleaned from a family diary kept by the oldest living member on Mauritius, reveals that this kindred are direct descendants of French royalty and that they are related to Henry III and IV, kings of France. Through this diary it has been possible to trace the family as far back as 992 to François de Bourbon, the Count of Provence. The earliest known transmitter of Huntington's chorea was Pierre Dagnel de Assigne de Bourbon, born in Port Louis, Mauritius in 1864.

At present there are six living affected members of this family on the island of Mauritius with at least a further 60 potentially "at risk" individuals. This clearly has important medical and social implications.
Probable migration of the gene for Huntington's chorea to Mauritius in the early 19th century and its subsequent spread to neighbouring countries.
in a European community of less than 100,000. It can be predicted that half of those "at risk" have the gene and, correcting for age, approximately 20 to 25 individuals will be affected. Taking into account the small White community on the island this would be amongst the highest frequency of Huntington's chorea in the world. The epidemiology of the disorder on Mauritius has been discussed in more detail in Chapter III-8.

C. **SPREAD OF THE GENE FROM MAURITIUS**

This situation is an exceptionally good example of the "founder effect" where one individual who happens to be a carrier of the gene for Huntington's chorea has migrated to an isolated island and helped to found a new, small community. This gene now has an unusually high frequency amongst his descendants on the island.

Relatives of the De Bourbon family have migrated to Reunion, Madagascar (Malagasy), Seychelles and also South Africa (Fig. IV-25). At present there are four affected related offspring in South Africa. A further five relatives have already died from Huntington's chorea in this country.

In this way, albeit indirect, affected persons in this country are distantly related to French royalty of the past.
CHAPTER IV-9

OTHER POSSIBLE SOURCES OF THE GENE IN SOUTH AFRICA

A. INTRODUCTION

Patients with this disease have been described in almost every country of Europe & North and South America. It is not surprising that immigrants from these different parts of the world brought the gene for Huntington's chorea with them to South Africa.

Most patients thus far described have had their ancestral roots in Western Europe, particularly England, Holland and France. However, Eastern Europe has also contributed to the gene pool for Huntington's chorea in this country.

B. HUNTINGTON'S CHOREA IN THE JEWISH PEOPLE

Although it was initially thought that the Jewish people had immunity to the disease (Kehrer, 1940), this concept is not accepted today.

Three unrelated affected Jewish families have been encountered in South Africa. It is interesting that these three kindred are all of Ashkenazi stock and probably emigrated to this country at the turn of the century following the pogroms in Eastern Europe and the discovery of gold on the Witwatersrand (Fig IV-26). One of these families has its origin near the city of Minsk in the province of Vilna, Lithuania. The exact initial location of the other two families in Eastern Europe is at present unknown.

Holland was a haven for Jewish refugees in the 17th and 18th centuries. Wars between the Russians and the Poles in the mid-17th century spurred some Jews to leave Lithuania and travel to the enlightened
Fig. IV - 26

Genealogy of an affected Jewish family who emigrated to South Africa in 1901, following the pogroms in Eastern Europe.

Fig. IV - 27

Tracing of a large affected Coloured family to their affected White ancestor, F1-2.
new world of Holland. This coincided with the time of recruitment for service in the Dutch East India Company. It could be suggested that a few of the homeless refugee Jews were ideal candidates for such a mission. However, by law of the Dutch East India Company, no one professing the Jewish religion was allowed to be sent to the Cape. That is, however, not to say that there were no people of Jewish origin who were enlisted. Jews, who were divorced from their religion and/or who professed the established faith of their neighbours, may have been recruited by the Company and subsequently sent to the Cape Colony. Indeed, a prominent early burgher, Adam Tas, is a notable example of this state of affairs (Saron and Hotz, 1955).

An interesting thought is that the gene for Huntington's chorea in the Afrikaners may have been derived from Jewish sources, at the time of the emigration of the first burghers to South Africa three centuries ago, and that this gene reached Holland via Jews fleeing from war-torn Russia.

C. ORIGINS OF THE GENE IN THE POPULATION OF MIXED ANCESTRY

The population of mixed ancestry in South Africa has its origins in the mingling of immigrant Whites, Malays and the indigenous Khoisan people. White racial admixture has continued to the present, in recent years an element of African Negro stock has been added. The term 'Coloured' is the current term in common use to denote this population group. Numerous difficulties were experienced in tracing the ancestors of the Coloured people who were afflicted with Huntington's chorea.
Legislation making registration of births and deaths in all racial groups compulsory was passed in 1895. Prior to this time voluntary registration was practised mainly by the White and not by the Coloured sections of the community. This, coupled with a poor awareness of their own ancestry, hampered the genealogical investigation in this population group.

A total of 115 affected Coloured individuals in 25 families were ascertained during this investigation. In only 3 has it been possible to link these persons with their White ancestors. An example is shown in Fig. IV-27. It is of interest that the author has recently been notified of a large Coloured family bearing the same name as one of the largest affected White kindreds, who have previously been traced back to the earliest Dutch settlers in this country.

It is very likely that the gene for Huntington's chorea was introduced to the Coloured population as a result of European admixture. Affected Coloured families may thus also be found to be related to the earliest transmitters of the gene to South Africa in the 17th century as previously described.
"The understanding of a disease process cannot be complete without a thorough study of its behaviour in the population."

B. Nizetu (1975)
## SECTION V
### NATURAL HISTORY OF HUNTINGTON'S CHOREA

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CHAPTER V-1

AGE OF ONSET

A. PROBLEMS WITH THE CONCEPT OF AGE OF ONSET

The earliest signs and symptoms of Huntington's chorea are insidious, making accurate estimation of the age of onset most difficult. Doctors are seldom witnesses to these changes and assessment of the start of the disease often depends on the patients themselves or their families.

Numerous factors may confound the estimate. Denial of the existence of Huntington's chorea in its early phases is commonplace. Later, an attitude of acceptance supervenes and it is only at this stage that the onset of the disease is acknowledged. This clearly could result in an overestimation of the age of onset. In contrast, some families are always on guard to see which member displays any fidgetiness or clumsiness which might indicate that he or she has the gene. A history of irritability or moodiness for many years, prior to onset of the chorea may be given. In this way estimates of the time of the first appearance of symptoms may vary from family to family.

Many epidemiological studies have included mean results of ages of onset in their population surveys without accurately defining criteria for what constitutes onset of the disease. Without these specifications, comparison of results of different surveys has doubtful significance. This consideration led Caro (1977) to state that "the age of onset is a very vague retrospective point which is notoriously difficult to assess" and for this reason it was not used by him in statistical analysis.
However, the importance of this concept is that by comparison of the ages of onset in different families and areas it may be possible to determine the factors modifying age of onset and therefore the action of the Huntington's gene. Identification of possible precipitating agents may enable the utilisation of different methods to delay onset of the disease. This may also lead to an understanding of the reasons for the discrepancies in the proportions of patients with juvenile onset in different areas.

Persons who are heterozygous for Huntington's chorea have the gene from conception. It could be argued that the disease has its onset at conception. A term which could be used in place of age of onset, is the phrase "age of manifestation". This expression implies an understanding of the fact that the gene for Huntington's chorea is present from birth, but clinically dormant until later in life when the disease becomes obviously manifest. The term "age of onset" has been used by most other authors and to prevent misunderstanding when comparing data, it will continue to be used in this study.

In summary, comparison of the mean ages of onset may provide most useful information provided that there are adequate stated criteria for its determination.

B. INTERNATIONAL COMPARISON

The mean ages of onset of Huntington's chorea in reports from different parts of the world are shown chronologically in Table V-1.
TABLE V-1

AGE OF ONSET (AOO) OF HUNTINGTON'S CHOREA

AN INTERNATIONAL REVIEW

<table>
<thead>
<tr>
<th>Location</th>
<th>Authors</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Mean AOO</th>
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<tbody>
<tr>
<td>U.S.A.</td>
<td>Davenport et al</td>
<td>1916</td>
<td>138</td>
<td>37.8</td>
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<td>Literature review</td>
<td>Bell</td>
<td>1934</td>
<td>460</td>
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<td>Sweden</td>
<td>Sjogren</td>
<td>1936</td>
<td>48</td>
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<td>South Wales</td>
<td>Spillane et al</td>
<td>1937</td>
<td>21</td>
<td>41.2</td>
</tr>
<tr>
<td>London</td>
<td>Minski et al</td>
<td>1938</td>
<td>43</td>
<td>42.4</td>
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<tr>
<td>Rhineland</td>
<td>Panse</td>
<td>1942</td>
<td>446</td>
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<td>Zolliker</td>
<td>1949</td>
<td>120</td>
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<tr>
<td>Cornwall, England</td>
<td>Bickford et al</td>
<td>1953</td>
<td>21</td>
<td>42.8</td>
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<td>Michigan, U.S.A.</td>
<td>Reed et al</td>
<td>1958</td>
<td>204</td>
<td>35.3</td>
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<td>Moray Firth, Scotland</td>
<td>Lyon</td>
<td>1962</td>
<td>41</td>
<td>51.59</td>
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<tr>
<td>Victoria, Australia</td>
<td>Brothers</td>
<td>1964</td>
<td>206</td>
<td>37.2</td>
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<tr>
<td>England</td>
<td>Heathfield</td>
<td>1967</td>
<td>69</td>
<td>44.2</td>
</tr>
<tr>
<td>Scotland</td>
<td>Cameron et al</td>
<td>1967</td>
<td>230</td>
<td>43.2</td>
</tr>
<tr>
<td>France</td>
<td>Petit</td>
<td>1969</td>
<td>125</td>
<td>39.3</td>
</tr>
<tr>
<td>England</td>
<td>Oliver</td>
<td>1970</td>
<td>115</td>
<td>36.4</td>
</tr>
<tr>
<td>Scotland</td>
<td>Bolt</td>
<td>1970</td>
<td>265</td>
<td>42.7</td>
</tr>
<tr>
<td>Literature review</td>
<td>Brackenridge</td>
<td>1971</td>
<td>344</td>
<td>33.8</td>
</tr>
<tr>
<td>Belgium/France/Holland</td>
<td>Husquinet</td>
<td>1973</td>
<td>751</td>
<td>41</td>
</tr>
<tr>
<td>Sweden</td>
<td>Mattsson</td>
<td>1974</td>
<td>162</td>
<td>37.1</td>
</tr>
<tr>
<td>Canada</td>
<td>Shokeir</td>
<td>1975</td>
<td>162</td>
<td>40.54</td>
</tr>
<tr>
<td>Leeds</td>
<td>Stevens</td>
<td>1977</td>
<td>298</td>
<td>42.95</td>
</tr>
</tbody>
</table>
Marked variations in the mean age of onset have been reported ranging from 33.8 years (Brackenridge, 1971) to 51.59 (Lyon, 1962). Further details are given in Table V-I.

Before searching for other possible factors which may have caused these differences, it is necessary to examine the various methods and criteria used for determining the age of onset. Numerous studies, including those by Davenport and Muncie (1916), Bickford and Ellison (1953), Cameron and Venters (1957), Lyon (1962), Heathfield (1967), Oliver (1970) and Shokeir (1975) although stating mean ages when the disease began, do not adequately define their criteria for what constitutes onset of the disease. Reed and Chandler (1958) consider the beginning of the disease to be the time of the appearance of chorea. On the other hand, Panse (1942), Brothers (1964), Bolt (1970), Mattsson (1974) and Stevens (1977) report age of onset to be that age at which the first symptoms occur, be they neurological (usually chorea) or psychiatric (including change in personality, irritability, moodiness, any signs of a decrease in intellectual functioning and any psychotic behaviour). The different criteria used in these studies accounts in part for the marked variations in the reported age of onset.

Bell (1934) and Brackenridge (1971) have calculated their results from a survey of the literature, and thus incorporated the inherent problems of all of these studies. It is interesting to compare the mean age of onset of Huntington's chorea in those studies with carefully defined criteria (as stated above) with those investigations where these are absent. This is summarized in Table V-II.
### TABLE V-II

**MEAN AGE OF ONSET (AOO)** in investigations with and without stated criteria for its determination

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean AOO</th>
<th>Study</th>
<th>Mean AOO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davenport et al (1916)</td>
<td>37.8</td>
<td>Panse (1942)</td>
<td>37.2</td>
</tr>
<tr>
<td>Sjogren (1936)</td>
<td>41.4</td>
<td>Reed et al (1958)</td>
<td>35.3</td>
</tr>
<tr>
<td>Spillane et al (1937)</td>
<td>41.2</td>
<td>Brothers (1964)</td>
<td>37.2</td>
</tr>
<tr>
<td>Zolliker (1949)</td>
<td>40.5</td>
<td>Oliver (1970)</td>
<td>36.4</td>
</tr>
<tr>
<td>Bickford et al (1953)</td>
<td>42.8</td>
<td>Bolt (1970)</td>
<td>42.7</td>
</tr>
<tr>
<td>Lyon (1962)</td>
<td>51.59</td>
<td>Mattson (1974)</td>
<td>37.1</td>
</tr>
<tr>
<td>Cameron et al (1961)</td>
<td>43.2</td>
<td>Stevens (1977)</td>
<td>42.95</td>
</tr>
<tr>
<td>Heathfield (1967)</td>
<td>44.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shokeir (1975)</td>
<td>40.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean of total</strong></td>
<td><strong>42.58</strong></td>
<td><strong>Mean of total</strong></td>
<td><strong>38.4</strong></td>
</tr>
</tbody>
</table>

This table shows that Group B generally has a lower mean age of onset than Group A. This probably represents an acceptance of earlier subtle neurologic or psychiatric signs and symptoms denoting onset of the disease in Group B, as opposed to the more obvious later signs of Huntington's chorea accepted in Group A. The difference may also reflect more intense questioning of affected persons and the families with regard to the early changes, to see whether these correspond to the stated criteria for the beginning of the disease in a particular study.

There are many unknown variables affecting onset of this disease.
It is clear that the varying methodologies of the different studies are a potential source of bias. For comparison of these surveys, it is imperative that investigators clearly state the criteria which they use to denote the first clinical features of Huntington's chorea. In this way it will be easier to decide whether the differences noted are artefacts of variations in technique, or real.

The number of persons presenting with Huntington's chorea in each decade, as reported in different investigations, is shown in Table V-III. The total in each age group is also presented as a percentage of the sum of the whole group. It can be seen that symptoms of Huntington's chorea may appear at any stage of life. The majority of patients had onset in the fourth decade (30.0%), whilst 29.2 per cent of all persons had earliest symptoms in the fifth decade. Although figures vary for each of the 9 investigations listed above, 5.2% of all the patients had onset of the disease before the age of 20. Only 7 persons or 0.4% showed first symptoms of the disease after the age of 70.

Wendt (1959) has pointed out the danger of artificially lowering the calculated mean age of onset by including currently living persons for its determination. Siblings with later age of onset will not, at that stage, show signs of the disease, resulting in over-representation of those persons with earlier onset. Wendt showed this by listing mean ages at onset of the subjects by the decade of their birth, and noticed a lowering of the mean the nearer the decades came to the time of his investigation. Stevens (1977) has not been able to substantiate Wendt's hypothesis by finding a remarkable similarity of mean ages of onset for patients in Yorkshire, England in the four decades 1930 - 1969.
## TABLE V - III

**AGE OF ONSET IN DECADES: A REVIEW**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>0-9</td>
<td>3</td>
<td>2,2</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>2,0</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>1,9</td>
</tr>
<tr>
<td>10-19</td>
<td>2</td>
<td>1,4</td>
<td>1</td>
<td>4,7</td>
<td>22</td>
<td>4,9</td>
<td>12</td>
<td>5,9</td>
<td>11</td>
<td>5,3</td>
</tr>
<tr>
<td>20-29</td>
<td>16</td>
<td>11,6</td>
<td>2</td>
<td>9,5</td>
<td>105</td>
<td>23,5</td>
<td>42</td>
<td>20,6</td>
<td>39</td>
<td>18,9</td>
</tr>
<tr>
<td>30-39</td>
<td>50</td>
<td>36,2</td>
<td>4</td>
<td>19,1</td>
<td>129</td>
<td>28,9</td>
<td>77</td>
<td>37,7</td>
<td>65</td>
<td>31,6</td>
</tr>
<tr>
<td>40-49</td>
<td>35</td>
<td>25,4</td>
<td>8</td>
<td>38,1</td>
<td>113</td>
<td>25,3</td>
<td>61</td>
<td>29,9</td>
<td>49</td>
<td>23,8</td>
</tr>
<tr>
<td>50-59</td>
<td>25</td>
<td>18,1</td>
<td>5</td>
<td>23,8</td>
<td>53</td>
<td>11,9</td>
<td>10</td>
<td>4,9</td>
<td>30</td>
<td>14,6</td>
</tr>
<tr>
<td>60-69</td>
<td>7</td>
<td>5,1</td>
<td>1</td>
<td>4,7</td>
<td>13</td>
<td>2,9</td>
<td>2</td>
<td>1,0</td>
<td>8</td>
<td>3,9</td>
</tr>
<tr>
<td>70+</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>0,5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>138</td>
<td>100</td>
<td>446</td>
<td>100</td>
<td>204</td>
<td>100</td>
<td>206</td>
<td>100</td>
<td>230</td>
<td>100</td>
</tr>
</tbody>
</table>
The problem with Wendt's theory is that by including only the details of deceased persons, he was basing his findings on respondents' memories concerning events that occurred up to 60 years before his study was undertaken. This pitfall has to be balanced against the problem of studies of living and deceased persons with Huntington's chorea which will not include a few patients who have onset of the disease later than usual. As long as the survey population is large, ascertainment near complete and the information on onset reliable, these errors will be minimized.
CHAPTER V-2

AGE OF ONSET (AOO) IN SOUTH AFRICA

A. INTRODUCTION

For this investigation the age of onset was defined as the first time at which any signs or symptoms appeared. These could be neurological or psychiatric and represented any change from the normal state.

The age of onset was determined after speaking to affected persons, their close family and, where possible, the general practitioner. Reliance was placed on relatives' memories and hospital records with regard to details of deceased patients. Only patients with adequate documentation of clinical details were included in this calculation.

B. RESULTS

The results of the current survey for a total of 219 persons are shown in Table V-IV.

<table>
<thead>
<tr>
<th><strong>TABLE V-IV</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEAN AGE OF ONSET (AOO) OF HUNTINGTON'S CHOREA IN SOUTH AFRICA</strong></td>
</tr>
<tr>
<td><strong>Number of persons:</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Mean AOO:</strong></td>
</tr>
<tr>
<td><strong>S.E.M.</strong></td>
</tr>
</tbody>
</table>

(* This is an abbreviation for the "standard error of the mean")
This group of 219 persons comprises 147 Whites, 70 people of mixed ancestry and 2 African Negroes. The mean ages of onset in these three different population groups is shown in Table V-V.

### TABLE V-V

**MEAN AGE OF ONSET ACCORDING TO RACIAL GROUPS**

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number:</td>
<td>69</td>
<td>78</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>Mean AOO</td>
<td>37.52</td>
<td>33.81</td>
<td>35.16</td>
<td></td>
</tr>
<tr>
<td>S.E.M.</td>
<td>1.41</td>
<td>1.28</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td><strong>Coloureds</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number:</td>
<td>28</td>
<td>42</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Mean AOO:</td>
<td>31.62</td>
<td>34.78</td>
<td>33.54</td>
<td></td>
</tr>
<tr>
<td>S.E.M.</td>
<td>2.55</td>
<td>2.05</td>
<td>1.59</td>
<td></td>
</tr>
<tr>
<td><strong>African Negroes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number:</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mean AOO:</td>
<td>54</td>
<td>42</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>S.E.M.</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

A total of 95 living and 124 deceased persons were included in this survey. The mean age of onset according to these two groups is shown in Table V-VI.
TABLE V-VI

MEAN AGES OF ONSET: LIVING AND DECEASED PERSONS

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Mean AOO</th>
<th>S.E.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living:</td>
<td>95</td>
<td>33.03</td>
<td>1.65</td>
</tr>
<tr>
<td>Deceased:</td>
<td>124</td>
<td>35.43</td>
<td>1.23</td>
</tr>
</tbody>
</table>

These differences were not statistically significant.

The mean age of onset, calculated according to the decade of onset is shown in Table V-VII.

TABLE V-VII

MEAN AGE OF ONSET ACCORDING TO DECADE OF ONSET

<table>
<thead>
<tr>
<th>Decade</th>
<th>Number</th>
<th>Mean AOO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1940 - 1949</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td>1950 - 1959</td>
<td>27</td>
<td>34.88</td>
</tr>
<tr>
<td>1960 - 1969</td>
<td>50</td>
<td>35.9</td>
</tr>
<tr>
<td>1970 - 1979</td>
<td>48</td>
<td>35.8</td>
</tr>
<tr>
<td></td>
<td>144</td>
<td></td>
</tr>
</tbody>
</table>

A close similarity of the mean ages of onset for the four decades 1940 - 1979 can be seen. These results are similar to those reported by Steven (1977) and suggest that including currently living affected persons in the determination of mean age of onset will not artificially lower the result as suggested by Wendt (1959).
A histogram showing the number of persons presenting at any particular age in the total population.
The range of ages of onset together with the total number of persons presenting at any particular age in the total population, the White and the Coloured groups, is shown in Figures V-1, V-2 and V-3. This is also tabulated in Table V-VIII.

### TABLE V-VIII

**RANGE OF AGE OF ONSET OF HUNTINGTON'S CHOREA IN SOUTH AFRICA**

<table>
<thead>
<tr>
<th>Years</th>
<th>Whites</th>
<th>Coloureds</th>
<th>Africans</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>0 - 9</td>
<td>3</td>
<td>2.0</td>
<td>3</td>
<td>4.3</td>
</tr>
<tr>
<td>10 - 19</td>
<td>3</td>
<td>2.0</td>
<td>8</td>
<td>11.4</td>
</tr>
<tr>
<td>20 - 29</td>
<td>38</td>
<td>25.7</td>
<td>18</td>
<td>25.7</td>
</tr>
<tr>
<td>30 - 39</td>
<td>53</td>
<td>36.1</td>
<td>23</td>
<td>32.9</td>
</tr>
<tr>
<td>40 - 49</td>
<td>31</td>
<td>21.2</td>
<td>11</td>
<td>15.7</td>
</tr>
<tr>
<td>50 - 59</td>
<td>17</td>
<td>11.6</td>
<td>7</td>
<td>10.0</td>
</tr>
<tr>
<td>60 - 69</td>
<td>2</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 +</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>147</td>
<td>100</td>
<td>70</td>
<td>100</td>
</tr>
</tbody>
</table>

The earliest signs of the disease were documented at ages from under 10 to over 60 years. The overwhelming majority of persons (80%) developed features of the disease between the ages of 20 and 50 years. Most patients had onset during the fourth decade, while 7.7% of the total population showed signs before the age of 20. This latter group comprised 17 people, 11 from the Coloured population (15.7%) and 6 from the White group (4%). Only 2 patients (0.9%) had the first manifestations of the disease after the age of 60 years. The mean age of onset of Huntington's chorea in South Africa is 34.93 years. The difference between the figures for males (35.9) and females (33.95) is not statistically significant.
Fig. V - 2

The range of ages of onset in the White population.

Fig. V - 3

The number of affected Coloureds presenting at any particular age.
C. DISCUSSION

The cardinal finding of this investigation is that the mean age of onset of Huntington's chorea in South Africa is lower than that reported from 20 similar studies from around the world (listed in Table V-1). Only Brackenridge (1971) has documented a lower value (33,8) than the South African figure (34,9).

Before assigning real significance to this finding, it is important to exclude possible sources of bias. The danger of including live patients in this calculation, with resultant artificial lowering of the mean age of onset has already been mentioned. Although the mean result of living patients (33,03) is lower than that of deceased persons (35,43) this difference is not statistically significant. Furthermore, the mean age of onset, when calculated according to the decade of onset, is not lower the nearer the time comes to the present investigation (Table V-VIII). The inclusion of living patients is thus clearly not a major factor in the low result of this study.

The criteria for what constitutes onset of Huntington's chorea in the current survey were broad and included both psychiatric and neurological disturbances. Whilst this definition was more extensive than that used in earlier investigations, this factor could not be invoked to account for the difference, compared to later studies, where interpretation of what constitutes onset of the disease was similar.
An important factor which may have lowered the mean age of onset of Huntington's chorea in South Africa is the high proportion (7.7%) of juvenile patients (i.e. those with signs and symptoms before 20 years). This is particularly true of the Coloured population, where 15.7% of this group had onset before the age of 20, which is higher than any other reported figure. It is of interest that where the number of juvenile patients reported is low (e.g. Heathfield, 1967 - 2.9%; Stevens, 1977 - 1%) the mean age of onset is high - 44.2 and 42.95 years respectively. Conversely, a higher proportion of juvenile cases (e.g. Reed, 1958 - 5.9%; Brothers, 1964 - 7.2%; Oliver, 1970 - 9.6%) seems to parallel a decrease in the mean age of onset in these studies (35.3, 37.2 and 36.4 years respectively). Thus it could be argued that the high proportion of juvenile patients in this investigation was a major factor in producing the low mean age of onset of Huntington's chorea in South Africa.

This hypothesis, however, does not resolve all the variations between different studies. Davenport and Muncey (1916) reported low mean ages of onset (37.8) but also showed small numbers of juvenile patients (3.6%), whereas Cameron and Venters (1967) documented higher mean ages of onset (43.2) and also a relatively high proportion of juvenile cases (4.8%). The results of the latter two studies suggest that there is not necessarily an absolute linear relationship between the mean age of onset and the number of juvenile patients in any given study.

An approach to this problem would be to calculate the mean age of onset without inclusion of juvenile patients. This is shown in Table V-IX.
TABLE V-IX
MEAN AGE OF ONSET EXCLUDING JUVENILE PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Mean (years)</th>
<th>Difference (years)</th>
<th>S.E.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites:</td>
<td>143</td>
<td>37.01</td>
<td>+1.85</td>
<td>0.84</td>
</tr>
<tr>
<td>Coloureds:</td>
<td>59</td>
<td>37.18</td>
<td>+3.64</td>
<td>1.33</td>
</tr>
<tr>
<td></td>
<td>202</td>
<td>37.06</td>
<td>+2.13</td>
<td>0.70</td>
</tr>
</tbody>
</table>

The greatest difference occurs in the Coloured population, which had the greatest proportion (15.7%) of persons with onset before the age of 20. Exclusion of juvenile patients from the calculation for the White group results in an increase of only 1.85 years from the prior calculated mean age of onset (35.16) (See Table V-V). This population had a lower percentage of juvenile patients (4%). Thus, it would seem likely that the lowering of the mean age of onset in South Africans is due only in part to the high number of persons with juvenile onset of the disease. Other factors which may have contributed to this result are the broad criteria used, and possibly other genetic and environmental factors. These will be further discussed in Chapter V-5.
INTRODUCTION

The age of death of persons with Huntington's chorea is a specific point in time and is not subject to the same sources of potential bias as other measurements of the natural history of this disorder. A possible cause of underestimation of the "death age" is premature death caused by other factors, such as an accident, an unrelated intercurrent illness and suicide. Death age may also be artificially lowered if members of the affected population under study have died close to the time of the investigation. Persons with unusually long duration of the disease and thus late ages of death will not be included. These possible sources of error are minimized in a large population sample.

RESULTS OF PREVIOUS INVESTIGATIONS

The reported age of death in different surveys is shown in Table V-X. The mean age of death is fairly constant, ranging between 51.4 years (Panse, 1942) and 56.9 years (Stevens, 1977).

Those surveys with low death ages (Bell, 1935; Panse, 1942; Reed et al, 1958; Brothers, 1964; Brackenridge, 1971) also have low ages of onset. The investigations reporting higher ages of death (Zolliker, 1949; Cameron et al, 1967; Stevens, 1977) due to Huntington's chorea, also have higher mean ages of onset (see Table V-1). This would suggest that there is little variation of the duration of the disease in these different studies.
### TABLE V-X

**AGE OF DEATH - PREVIOUS REPORTS**

<table>
<thead>
<tr>
<th>Location</th>
<th>Authors</th>
<th>Year</th>
<th>No.</th>
<th>Mean AOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review</td>
<td>Bell</td>
<td>1934</td>
<td>349</td>
<td>53.27 *</td>
</tr>
<tr>
<td>Germany</td>
<td>Panse</td>
<td>1942</td>
<td>473</td>
<td>52.2 *</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Zolliker</td>
<td>1949</td>
<td>143</td>
<td>54.5</td>
</tr>
<tr>
<td>Michigan, U.S.A.</td>
<td>Reed et al</td>
<td>1958</td>
<td>262</td>
<td>53.58 *</td>
</tr>
<tr>
<td>Australia</td>
<td>Brothers</td>
<td>1964</td>
<td>123</td>
<td>51.4 *</td>
</tr>
<tr>
<td>Scotland</td>
<td>Cameron et al</td>
<td>1967</td>
<td>194</td>
<td>54.6</td>
</tr>
<tr>
<td>Belgium</td>
<td>Husquinet</td>
<td>1969</td>
<td>231</td>
<td>54.1</td>
</tr>
<tr>
<td>France</td>
<td>Petit</td>
<td>1969</td>
<td>141</td>
<td>55.6</td>
</tr>
<tr>
<td>Scotland</td>
<td>Bolt</td>
<td>1970</td>
<td>269</td>
<td>56.7</td>
</tr>
<tr>
<td>Review</td>
<td>Brackenridge</td>
<td>1971</td>
<td>403</td>
<td>51.7</td>
</tr>
<tr>
<td>Minnesota, U.S.A.</td>
<td>Marx</td>
<td>1971</td>
<td>318</td>
<td>54.1</td>
</tr>
<tr>
<td>Leeds, Yorkshire</td>
<td>Stevens</td>
<td>1977</td>
<td>256</td>
<td>56.9</td>
</tr>
<tr>
<td>East Anglia</td>
<td>Caro</td>
<td>1977</td>
<td>500</td>
<td>55.9</td>
</tr>
</tbody>
</table>

* calculated from data given.

It is interesting to note that there has been no marked improvement over 40 years in longevity of persons suffering from Huntington's chorea. The slight increase in lifespan in the seventies may reflect better nursing care and treatment of the secondary complications of this disorder, or rather general improvement of life expectancy for the community as a whole.
C. AGE OF DEATH DUE TO HUNTINGTON'S CHOREA IN SOUTH AFRICA

The mean ages of death due to Huntington's chorea in South Africa are shown in Table V-XI.

**TABLE V-XI**

| AGE OF DEATH OF PERSONS WITH HUNTINGTON'S CHOREA IN SOUTH AFRICA |
|-----------------|-----------------|-----------------|
|                  | Males           | Females         | Total           |
| Number:          | 76              | 84              | 160             |
| Mean:            | 54.13           | 50.25           | 51.87           |
| S.E.:            | 1.4             | 1.4             |                 |
| Significance:    | p<0.05          |                 |                 |

The mean ages of death for the different population groups in South Africa is shown in Table V-XII. Information on death ages from Huntington's chorea in the African Negro population is not considered to be of sufficient reliability to warrant inclusion.

**TABLE V-XII**

MEAN AGE OF DEATH (A.O.D.) ACCORDING TO RACIAL GROUPS

<table>
<thead>
<tr>
<th>Whites</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number:</td>
<td>68</td>
<td>62</td>
<td>130</td>
</tr>
<tr>
<td>Mean A.O.D.:</td>
<td>54.22</td>
<td>50.04</td>
<td>51.95</td>
</tr>
<tr>
<td>S.E.:</td>
<td>1.4</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Significance:</td>
<td>p&lt;0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coloureds</th>
<th>Number:</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number:</td>
<td>8</td>
<td>22</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>Mean A.O.D.:</td>
<td>53.38</td>
<td>50.82</td>
<td>51.53</td>
<td></td>
</tr>
<tr>
<td>S.E.:</td>
<td>4.8</td>
<td>3.0</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Significance:</td>
<td>N.S.</td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The range of ages at death of persons dying from Huntington's chorea in South Africa.

**Fig. V - 4**

AGE OF DEATH OF AFFECTED INDIVIDUALS
TOTAL POPULATION

![Graph showing the range of ages at death of affected individuals.](image-url)
The mean age of death from Huntington's chorea in South Africa is amongst the lowest in the world. There is no statistical difference in this parameter between the White and Coloured groups. Females have a statistically significant lower age of death than males in the total population, especially in the White group. The Coloured females die at a younger age than their male counterparts but this difference is not statistically significant.

The same primary mechanism operating to lower the mean age of onset in South Africa is also probably lowering the mean age of death, namely the high proportion of juvenile patients.

The difference between the ages of death in the sexes is probably due to the higher number of female persons with onset before the age of 20 (10 females to 7 males). The ratio of juveniles in the White group is 4 females to 2 males. The female preponderance of juvenile onset is not seen in the Coloured population (6:5), which is reflected in the non-significant difference between the sexes in this group.

Death from Huntington's chorea occurred at any age from 15 to 83 years. The range of ages of death, number and percentage of the total occurring at any particular time is shown in Figure V-4 and Table V-XIII.

Most persons with Huntington's chorea in South Africa die between the ages of 40 and 60 years (62.6%). The majority of deaths occur in the sixth decade (33.8%). Five percent of all patients die before the age of thirty. Another factor which may in part account for the lower age of death of patients with Huntington's chorea in South
### AGE OF DEATH DUE TO HUNTINGTON'S CHOREA IN SOUTH AFRICA

<table>
<thead>
<tr>
<th>Years</th>
<th>Whites</th>
<th></th>
<th>Coloureds</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>0 - 9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10 - 19</td>
<td>2</td>
<td>1,5</td>
<td>2</td>
<td>6,6</td>
<td>4</td>
<td>2,5</td>
</tr>
<tr>
<td>20 - 29</td>
<td>4</td>
<td>3,1</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>2,5</td>
</tr>
<tr>
<td>30 - 39</td>
<td>12</td>
<td>9,2</td>
<td>2</td>
<td>6,7</td>
<td>14</td>
<td>8,8</td>
</tr>
<tr>
<td>40 - 49</td>
<td>40</td>
<td>30,8</td>
<td>6</td>
<td>20</td>
<td>46</td>
<td>28,8</td>
</tr>
<tr>
<td>50 - 59</td>
<td>42</td>
<td>32,3</td>
<td>12</td>
<td>40</td>
<td>54</td>
<td>33,8</td>
</tr>
<tr>
<td>60 - 69</td>
<td>16</td>
<td>12,2</td>
<td>6</td>
<td>20</td>
<td>22</td>
<td>13,6</td>
</tr>
<tr>
<td>70 - 79</td>
<td>13</td>
<td>10,0</td>
<td>2</td>
<td>6,7</td>
<td>15</td>
<td>9,4</td>
</tr>
<tr>
<td>80+</td>
<td>1</td>
<td>0,9</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>0,6</td>
</tr>
<tr>
<td>Total</td>
<td>130</td>
<td>100</td>
<td>30</td>
<td>100</td>
<td>160</td>
<td>100</td>
</tr>
</tbody>
</table>

Africa compared to other reports, is the lower life expectancy of South African Whites and Coloureds, compared to the population of the U.S.A. and north-western Europe, where all the other investigations have been conducted. It could also be expected that the mean age of death of Coloured patients would be lower than those of Whites, as the life expectancy of this group is less than their White counterparts (Dick and Bourne, 1978). Although insignificant, a small difference has been found.

International comparison of the reports on parameters of the natural history of this disease must take into consideration the overall health and life expectancy of the total community as a whole.
CHAPTER V-4
THE DURATION OF HUNTINGTON'S CHOREA

A. INTRODUCTION

The duration of Huntington's chorea is derived by subtracting the age of onset from the age of death. This parameter is thus subject to the same potential sources of bias as the ages of onset and death.

B. A REVIEW

Various estimates of the duration of the disease have been previously made. This is shown in Table V-XIV.

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Year</th>
<th>No.</th>
<th>Duration (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell</td>
<td>England</td>
<td>1934</td>
<td>204</td>
<td>13,72</td>
</tr>
<tr>
<td>Panse</td>
<td>Germany</td>
<td>1942</td>
<td>446</td>
<td>13,46</td>
</tr>
<tr>
<td>Zolliker</td>
<td>Switzerland</td>
<td>1949</td>
<td>202</td>
<td>14,0</td>
</tr>
<tr>
<td>Reed et al</td>
<td>Michigan</td>
<td>1958</td>
<td>153</td>
<td>15,85</td>
</tr>
<tr>
<td>Lyon</td>
<td>Moray Firth, Scotland</td>
<td>1962</td>
<td>29</td>
<td>7,13</td>
</tr>
<tr>
<td>Brothers</td>
<td>Australia</td>
<td>1964</td>
<td>97</td>
<td>12,25</td>
</tr>
<tr>
<td>Cameron et al</td>
<td>Scotland</td>
<td>1967</td>
<td>127</td>
<td>10,6</td>
</tr>
<tr>
<td>Petit</td>
<td>France</td>
<td>1969</td>
<td>65</td>
<td>14,41</td>
</tr>
<tr>
<td>Bolt</td>
<td>Scotland</td>
<td>1970</td>
<td>176</td>
<td>14,3</td>
</tr>
<tr>
<td>Brackenridge</td>
<td>Australia</td>
<td>1971</td>
<td>191</td>
<td>11,9</td>
</tr>
<tr>
<td>Stevens</td>
<td>England</td>
<td>1977</td>
<td>180</td>
<td>13,6</td>
</tr>
</tbody>
</table>
The duration of Huntington's chorea in South Africa.

Fig. V - 5
The reported duration of the disease ranges from a mean of 7.13 to 15.85 years. Essentially, the duration of Huntington's chorea has remained constant over 50 years, reflecting failure of medical therapy to prolong affected persons' lives.

C. THE DURATION OF HUNTINGTON'S CHOREA IN SOUTH AFRICA

The calculated mean duration of Huntington's chorea in South Africa is shown in Table V-XV.

<p>| TABLE V-XV |
| DURATION OF HUNTINGTON'S CHOREA IN SOUTH AFRICA |</p>
<table>
<thead>
<tr>
<th>Number:</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43</td>
<td>51</td>
<td>94</td>
</tr>
<tr>
<td>Mean duration:</td>
<td>14,53</td>
<td>13,92</td>
<td>14,17</td>
</tr>
<tr>
<td>S.E.M.:</td>
<td>0,64</td>
<td>0,73</td>
<td>0,43</td>
</tr>
</tbody>
</table>

The difference between the sexes is not statistically significant.

The mean duration of Huntington's chorea in South Africa is similar to the reports from the rest of the world. The range of the duration of this disorder is shown in Figure V-5. It can be seen that the disease can span from 4 to 28 years. Most patients, however, live between 10 to 20 years.

The duration of Huntington's chorea according to racial groups is seen in Table V-XVI.
TABLE V-XVI
DURATION OF HUNTINGTON'S CHOREA ACCORDING TO RACIAL GROUP

<table>
<thead>
<tr>
<th></th>
<th>Whites</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Number:</td>
<td>37</td>
<td>36</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Mean:</td>
<td>14,89</td>
<td>14,46</td>
<td>14,68</td>
<td></td>
</tr>
<tr>
<td>S.E.M.:</td>
<td>0,69</td>
<td>0,87</td>
<td>0,54</td>
<td></td>
</tr>
<tr>
<td>Coloureds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number:</td>
<td>6</td>
<td>15</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Mean:</td>
<td>12,60</td>
<td>13,26</td>
<td>13,10</td>
<td></td>
</tr>
<tr>
<td>S.E.M.:</td>
<td>1,85</td>
<td>1,52</td>
<td>1,22</td>
<td></td>
</tr>
</tbody>
</table>

The mean duration of Huntington's chorea in the Coloured population is 1,58 years less than in the White group. This non-significant difference may reflect a higher number of juvenile patients who have a shorter duration of the disease in this group.

It is revealing to compare the duration of the disease in juvenile patients of the current study as opposed to those persons with adult onset. This is shown in Table V-XVII.

TABLE V-XVII
COMPARISON OF THE DURATION OF THE DISEASE
IN ADULT AND JUVENILE PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Mean</th>
<th>S.E.M.</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults:</td>
<td>86</td>
<td>14,65</td>
<td>0,49</td>
<td>p &lt; 0,001</td>
</tr>
<tr>
<td>Juveniles</td>
<td>8</td>
<td>9</td>
<td>0,46</td>
<td></td>
</tr>
</tbody>
</table>

Persons with juvenile onset of the disease have a mean duration of 9 years, which is significantly different from those of adult onset. Bolt (1970) and Stevens (1977) are in apparent disagreement, as they observed a negative correlation between age of onset and duration of
the disease. In other words, the duration of the disease is longer in those with younger age of onset. Older onset on the other hand is supposed to result in shorter duration of the disease. Whilst this also applies to the South African investigation in those with onset age over 50, a much shorter span of life is found than in those with onset under 20 years. Stevens (1977) only observed two patients with onset under 20 and Bolt (1970) does not mention what proportion of her group fell into this category. No significant comparison between the current survey and Bolt's study can be made without knowledge of this fact.

In summary, the duration of Huntington's chorea in South Africa is broadly similar to reports from around the world. A significant difference has been found in the duration of the disease between persons of adult and those of juvenile onset. This will be discussed further in Chapter VI-6.
CHAPTER V-5

POSSIBLE FACTORS MODIFYING THE ACTION OF THE GENE FOR HUNTINGTON'S CHOREA

A. INTRODUCTION

Apparent differences in the ages of onset of Huntington's chorea can partly be attributed to variations in techniques for collection of data. In this chapter possible genetic and environmental factors which may modify the action of the gene for Huntington's chorea, with particular reference to age of onset, will be considered.

An understanding of the precipitating factors of the disease at a particular age is important for several reasons. Manipulation of known environmental agents may delay its onset. Furthermore, this knowledge would be of great use in genetic counselling, where it may be possible to predict the age of onset in any particular person by taking into account his genetic and environmental background.

B. GENETIC CONSIDERATIONS

The degree of genetic determination of age of onset has been estimated using sibship data. Analysis of variance, comparing variation within and between families is probably the most convenient method of testing for the genetic contribution. Results of different studies (Reed and Chandler, 1958; Mattsson, 1974 and Stevens, 1977) have shown that within-kindred variation of age of onset is less than that between kindreds.

Reed and Chandler (1958) have suggested that this is probably due to a greater genetic similarity within kindreds than between families.
Whether this occurs as a result of the possession of common similar "background genes" against which the gene for Huntington's chorea acts, or the inheritance of the same modifying genes acting on the gene for Huntington's chorea is not yet certain.

Twin studies offer an opportunity for examining the hypothesis of genetic determination of different facets of the disease, including age of onset. A similar age of onset of Huntington's chorea in monozygotic twins would suggest that genetic factors have a major influence on this parameter.

After an extensive search I have been able to find 13 reports of twins affected with Huntington's chorea. Clinical details are shown in Table V-XVIII. The abbreviation used for monozygosity is MZ.

**TABLE V-XVIII**

<table>
<thead>
<tr>
<th>Author</th>
<th>Age of Onset</th>
<th>Sex</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russell (1894)</td>
<td>27 27</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Rosenthal (1927)</td>
<td>29 ?</td>
<td>M</td>
<td>Twin B unaffected at 40</td>
</tr>
<tr>
<td>Rosanoff et al (1935)</td>
<td>35 35</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>Entres (1940)</td>
<td>41 41</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45 45</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Jelgersma (1957)</td>
<td>45 ?</td>
<td>F</td>
<td>Details incomplete.</td>
</tr>
<tr>
<td>Parker (1958)</td>
<td>45 45</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Cepen (1973)</td>
<td>22 25</td>
<td>F</td>
<td>Discordant clinically.</td>
</tr>
<tr>
<td>Husquinnet et al (1973)</td>
<td>21 22</td>
<td>F</td>
<td>MZ proven.</td>
</tr>
<tr>
<td>Bachman et al (1975)</td>
<td>20 20</td>
<td>MZ proven.</td>
<td></td>
</tr>
</tbody>
</table>

* See text.
The reports prior to 1960 did not contain proof of monozygosity. For the later studies this has been established by means of comparison of blood groups, dermatoglyphic patterns and, in one instance, skin transplants. Of the thirteen sets of twins suffering from Huntington's chorea, nine had onset within one year of each other, one pair within two years (Bird et al, 1975) and one set within three years of each other (Oepen et al, 1973). In other words, nine of the thirteen sets of twins listed are concordant for age of onset. The twins reported by Rosenthal (1927) were discordant for the disease at age 40. However, he gave no evidence for monozygosity and in addition only examined one of the twins. Details are incomplete in Jelgersma's report (1957). Perrine and Goodman (1966) have documented twins, only one of whom died of the disease. However, they were clearly dizygotic. Bolt (1970) does not mention age of onset in her publication. All five sets of twins who were proven to be monozygous, however, were concordant for age of onset.

There would thus seem to be strong evidence for a major genetic contribution to the determination of age of onset of Huntington's chorea. It is of interest that in at least two of the later reports (Oepen, 1973; Bird and Omen, 1975) where monozygosity was proven, individual twins showed a marked difference in clinical expression of the disease in contrast to their concordance for age of onset. In Oepen's publication one of the sisters has the rigid form of the disease in contrast to the typical choreiform presentation of her sib. A disparity in the extent of chorea is also seen in the twins of Bird and Omen's report. It is thus possible that the genetic determination of the clinical features of Huntington's chorea is less than its influence on the age of onset.
Another possible explanation for the discordant neurological signs in these proven monozygotic twins is that there are non-genetic factors which can overcome the hereditary predeliction for specific clinical presentations. The extent to which the genetic components affect the age of death and duration of the disease, together with other clinical features, remains to be elucidated.

I have record of three sets of twins of whom one of the sibs is suffering from Huntington's chorea. At least six further sets, who are "at risk" of developing this disease, are living in South Africa. All of the three sets of twins with one affected member were dizygotic with premature death of the unaffected siblings due to an accident or an incidental disease. Of those at risk, three pairs are identical, whilst three sets are dissimilar. Close follow-up is being maintained on all these potential heterozygotes for Huntington's chorea.

Familial correlations for age of onset and age of death have been established by Brackenridge (1972). Prior reports have also demonstrated correlation between the onset-ages of affected parents and their children (Panse, 1942; Cameron and Venters, 1967). A genetic factor is thought to be operating. Brackenridge and Teltscher (1975) have expanded this work and suggested that the age of onset of Huntington's chorea is, in part, a function of the age of the transmitting parent at the time of birth of a subsequently affected child. They hypothesized that the younger the parent at the time of birth of the heterozygote, the later in life symptoms of disease would appear in that child. On the basis of these findings they proposed that "a general conclusion of importance in genetic counselling is the desirability of persons at risk who intend to have children to plan their families at an early age." In a later
article (1978) Brackenridge suggests that the early child acts as a deterrent from further procreation.

Burke (1976) has re-evaluated the work by Brackenridge and Teltscher and been unable to substantiate their findings. It is my impression that particularly in the group of mixed ancestry in South Africa, where teenage pregnancies are common, that low parental age does not select for onset in late adulthood in the affected progeny. Furthermore, the advice suggested by Brackenridge with regard to genetic counselling, should be withheld as it offers a false hope and may result in increasing the number of affected persons with Huntington's chorea in the community.

Whilst no significant sex difference exists as regards age of onset of Huntington's chorea, Bird et al (1974) and Brackenridge (1971) have found differences in age of death of affected offspring of males compared to those of females. The age of death of affected persons for the present study, tabulated according to the sex of the parent, is shown in Table V-XIX.

<table>
<thead>
<tr>
<th>TABLE V-XIX</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEATH AGE OF AFFECTED CHILDREN ACCORDING TO SEX OF AFFECTED PARENT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Female Parent</th>
<th>Male Parent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daughters</td>
<td>Sons</td>
</tr>
<tr>
<td>Mean (years):</td>
<td>51.8</td>
<td>57.8</td>
</tr>
<tr>
<td>S.E.M.:</td>
<td>2.52</td>
<td>8.48</td>
</tr>
</tbody>
</table>

Although progeny of females die on average 2.3 years older than children of males, this difference is not significant. However, a
statistical significance ($p = 0.02$) does emerge when comparing age of
death of daughters and sons of affected males. One possible explana-
tion for this finding is the higher proportion of female juvenile
patients.

Brackenridge (1971) had also found older ages of death in
sons of fathers, compared to their daughters. Bird et al (1974)
suggest that their findings may add further evidence for the hypothesis
of a sex-related factor in the inheritance of Huntington's chorea. The
results presented here would seem to support such a hypothesis.

In brief, there is an interrelationship between ages of onset and
death of affected parents and their offspring. Although it would seem
that a genetic factor is operating, the actual mechanism remains to be
elucidated.

C. ENVIRONMENTAL FACTORS

There is some evidence to suggest that environmental factors may
influence the age of onset of Huntington's chorea. Pregnancy has been
implicated as a precipitating agent (Spengler, 1956). Korenyi et al
(1972) found that trauma and infection were the most common identifiable
precipitants. In the present investigation patients often listed
trauma, infection and pregnancy as trigger factors for onset of the
disease.

Brackenridge (1974) has shown by analysing data from the literature
that there is a statistically significant decrease in age of onset as
the environmental temperature rises. In other words, patients in
countries in the southern hemisphere, where mean annual temperatures are
high, would be expected to have lower onset ages than those in the
northern hemisphere which are further away from the equator. The low age of onset as reported for the South African population (34.9), Victoria, Australia (37.2) (Brothers, 1964) and Venezuela (Avila-Giron, 1973) is consistent with this hypothesis.

Stevens (1977) has also pointed out that the mean ages of onset for affected individuals in Europe are higher than those from outside Europe. It would appear that patients in the northern hemisphere have older age of onset. Exceptions to this are those results of investigations in the Middle States and New England area of the U.S.A. (Davenport et al, 1916; Reed et al, 1958), where the mean ages of onset were 37.8 and 35.3 years respectively. Both these areas have low mean annual temperatures and thus would be expected to have relatively high mean ages of onset. The results do not support the observations of Brackenridge (1974) or Stevens (1977).

If it is accepted that the differences in the reported ages of onset between Europe and elsewhere are significant, some factor operating either within north-western Europe or outside of Europe should be sought to explain this phenomenon. Genetic influences can probably be discarded as people living in many of these areas, e.g. the U.S.A., are of north-western European descent.
"I were better to be eaten to death with a rust, than to be scoured to nothing with perpetual motion."

William Shakespeare
### SECTION VI

#### CLINICAL ASPECTS

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CHAPTER VI-1

INTRODUCTION

The characteristic clinical features of Huntington's chorea were described graphically by George Huntington in 1872 as follows: "It begins as an ordinary chorea might begin, by the irregular and spasmodic action of certain muscles of the face and arms. These movements gradually increase, when muscles hitherto unaffected take on the spasmodic action until every muscle in the body becomes affected, and the poor patient presents a spectacle which is anything but pleasing to witness. I have never known a recovery or even an amelioration of symptoms in this form of chorea; when once it begins it clings to the bitter end."

Despite its brevity, there have been few major additions to Huntington's original description until the present day. Two important features, however, were overlooked. Although he stated that onset is in adulthood, it has since been clearly established that a juvenile form of the disease exists. Furthermore, he failed to realize the major variations in the classical clinical presentation that occur.

It has been mentioned previously (Chapter II-2) that a full general and neurological examination was made of each patient. Over a two year period I personally examined 85 affected persons at different stages of their illness. Neurologists and general practitioners sent me full clinical reports concerning another 45 patients. Hospital records and doctors' clinical notes provided details of deceased patients. Sufficient clinical details were collected concerning 130 affected individuals to warrant inclusion in this aspect of the survey.
In this section a brief review of the clinical features of Huntington's chorea in South Africa, with special emphasis on those aspects previously unreported, will be followed by a discussion of the false diagnoses which have been made and the differential diagnosis of Huntington's chorea in this country.
This man had become generally clumsy as shown here by the spilling of his coffee into his saucer. He is closely watched by his wife, who stated that this heralded the onset of the disease.

Asking patients to squeeze two of my fingers often evoked choreiform movements, when it was not obviously apparent.
CHAPTER VI-2
THE EARLIEST SIGNS AND SYMPTOMS

There are differing opinions as to whether the earliest features of Huntington's chorea are neurological or psychiatric. The majority of investigators have reported a higher frequency of neurological presentations. The findings of various surveys are recorded in Table VI-1. Whether the differences in the various investigations are real or rather reflect dissimilar methods of collating data or the specific interests of the investigators is uncertain.

| TABLE VI-1 |
| REPORTED PERCENTAGE OF SURVEY POPULATION PRESENTING WITH NEUROLOGICAL OR PSYCHIATRIC FEATURES |

<table>
<thead>
<tr>
<th>Population Size</th>
<th>Neurological</th>
<th>Psychiatric</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oepen et al (1963)</td>
<td>219</td>
<td>34</td>
<td>24</td>
</tr>
<tr>
<td>Brothers (1964)</td>
<td>237</td>
<td>59</td>
<td>27</td>
</tr>
<tr>
<td>Heathfield (1967)</td>
<td>84</td>
<td>54</td>
<td>46</td>
</tr>
<tr>
<td>Bolt (1970)</td>
<td>68</td>
<td>54</td>
<td>27</td>
</tr>
<tr>
<td>Brackenridge (1971)</td>
<td>292</td>
<td>39</td>
<td>28,8</td>
</tr>
<tr>
<td>Mattsson (1974)</td>
<td>162</td>
<td>22</td>
<td>48</td>
</tr>
<tr>
<td>Stevens (1977)</td>
<td>102</td>
<td>65</td>
<td>35</td>
</tr>
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</table>

Of the 130 patients in the current investigation, 51% presented with psychiatric features, most commonly a disturbance of personality. Of the remainder, 39% were first noted to have neurological signs, mainly chorea. In 10% combined neurological and psychiatric...
The inability to perform sustained complex facial movements was a common early sign.
disturbances were the first features. The results of this survey are in agreement with those of Mattson (1974), who found a predominance of psychiatric symptoms in the early phase of the disorder.

The earliest signs and symptoms in 130 patients of the current investigation are shown in detail in Table VI-II. In some instances persons had two or more complaints in the prodromal phase of the illness, but the predominant symptom only has been noted.

**TABLE VI-II**

**EARLIEST SIGNS AND SYMPTOMS OF HUNTINGTON'S CHOREA IN SOUTH AFRICA**

<table>
<thead>
<tr>
<th>Neurological Features</th>
<th>Psychiatric Features</th>
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<tr>
<td>Choreiform movements</td>
<td>Personality changes</td>
</tr>
<tr>
<td>(expressed as jerkiness, incoordination, restlessness, clumsiness, slurring speech):</td>
<td>(expressed as irritability, moodiness, impulsiveness): 43</td>
</tr>
<tr>
<td>Rigidity (expressed as slowness, apathy):</td>
<td>Schizophreniform symptoms</td>
</tr>
<tr>
<td>5</td>
<td>(including paranoid delusions, auditory and visual hallucinations): 13</td>
</tr>
<tr>
<td>Facial apraxia:</td>
<td>Dementia:</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Depression:</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Anxiety (&quot;nerves&quot;):</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>(39%) 51</td>
<td>(51%) 66</td>
</tr>
</tbody>
</table>

Combined neurological and psychiatric features: (10%) 13

The single most common presenting feature was a restlessness or clumsiness which heralded the onset of chorea in 43 patients (Figure VI-I). Choreiform movements could be elicited when they were not
obviously manifest. Asking affected persons to squeeze two of my own fingers tightly often evoked spontaneous choreiform movements in that person's hand - the characteristic "milkmaid's sign" (Fig. VI-2). At this early stage almost all affected individuals were unable to perform complex facial movements such as whistling, blowing up the cheeks, frowning, putting the tongue alternatively into different cheeks or showing the teeth (Fig VI-3). The facial apraxia is a characteristic sign and may be elicited before onset of obvious chorea.

Purdon Marten (1967) has suggested that one can regard the normal "set of the facies" as a posture for which certain muscles of the face are responsible. The abnormalities in facial expression of Huntington's chorea are then a reflection of the generalized disturbance of postural reactions in the disorder, consequent to basal ganglia dysfunction.

Psychiatric symptomatology was found to be more common than neurological features in the prodromal phase of the illness. Many spouses, on close questioning, reported an early change in personality in their affected partner. This often took the form of irritability, moodiness and sometimes violence. Thirteen persons (10%) presented with a schizophreniform-type syndrome and were often mistakenly diagnosed as schizophrenic. This will be discussed in Section VI-2.

In five persons (3.8%) rigidity was the earliest sign, whilst 9 patients (6.9%) had early dementia as the presenting feature.

The importance of these data is to highlight the fact that Huntington's chorea may have a wide variety of subtle clinical presentations. Awareness of this varied initial symptomatology will hopefully lead to earlier diagnosis and more appropriate genetic counselling.
The picture between this man's legs was taken on his fiftieth birthday, one year before this photograph was shot. The rapid deterioration in this man's condition is easily discernible.
CHAPTER V-3
ON GENERAL EXAMINATION

On general examination a striking feature was the generalized loss of weight that had occurred in almost all affected persons in spite of excellent appetites and adequate intake. Bruyn (1968) has commented that none of the 100 or more patients that he examined were fat. Only two persons in the current survey were obese.

Whilst constant exercise as a result of the involuntary movements may provide a possible reason for the weight loss, I am in agreement with Whittier (1967) who has suggested that the "catabolism exceeds that which might be expected from the energy demand generated by chorea or rigidity." Oepen (1963) has reported that the generalized emaciation also manifests in brown atrophy of the heart and liver. Bruyn has suggested (1968) the term "metabolic marasmus" to denote a possible underlying metabolic defect which could account for all these findings. This defect has not been elucidated.

Almost all adult patients looked older than their chronological age. Once the disease had manifest, premature greying, loss of skin turgor and a generalized aging effect were commonly seen. The appearance of an affected person 5 years after the onset of the disease, and one year after the photograph placed between his feet was taken, is shown in Figure VI-4. The rapid deterioration in this man's condition is easily discernible.

Six patients complained of excessive sweating, for which no cause could be found. Refsum (1938) and Aminoff and Gross (1974) have reported vasomotor abnormalities in patients with Huntington's chorea.
The hyperhidrosis in some affected persons in the current survey may be further evidence of autonomic dysfunction.

It is my impression that many unrelated patients bore a remarkable similarity to each other. Only Heathfield (1967) has commented on this finding. This resemblance is not unexpected, as patients have a similar progressive pathological process, due to a common genetic defect.
A. CHOREA

One hundred and eighteen individuals (91%) in this survey had chorea at some stage of their illness (see Fig I-2). The extent and severity of these movements varied from person to person. The restlessness and clumsiness of the early phase progressed and the involuntary movements generally increased in severity. Early incoordination resulted in one patient "often covering himself in blood" whilst shaving. Most subjects had more marked movements distally, whilst others showed gross facial twitching and incoordination. Excitement, tension and walking exacerbated the chorea, whilst the movements disappeared during sleep. In many, the chorea became less conspicuous towards the end of the illness, a feature commented on previously by Denny-Brown (1962).

It is possible to distinguish this form of chorea from that seen in Sydenham's chorea. The movements of Huntington's chorea are slower, almost athetoid in nature, as opposed to the brusque, abrupt and jerky motions of Sydenham's chorea.

Twelve people (9%) did not have any abnormal involuntary movements at any stage of their illness. A further 18% had only mild chorea. Thus, the term Huntington's chorea is a misnomer, not taking into account the fact that the disease may appear without its cardinal feature, namely chorea. Huntington's disease is now becoming the accepted term for the disorder in the United States of America. English and South African neurologists continue to use the expression "Huntington's chorea".
This man has a mask-like facies, together with a positive glabellar tap and lead-pipe rigidity, reminiscent of Parkinsonism.
B. RIGIDITY

The rigidity in Huntington's chorea may either be extrapyramidal (lead pipe) or cortical (clasp knife) in origin. Rigidity occurred in three different clinical situations:

Group A. **Rigidity ab initio without chorea** (5 persons, 3.9%)

Group B. **Rigidity occurring simultaneously with chorea** (25 persons, 19%)

Group C. **Choreiform movements being superceded by rigidity**, usually in association with other signs of pyramidal tract dysfunction (43 persons, 33%).

Whilst it was occasionally difficult to differentiate between extrapyramidal and cortical rigidity, in most instances this was usually possible, taking into account the nature of the rigidity and the associated signs. On this basis it can be stated that most persons in Groups A and B had signs suggestive of extrapyramidal damage, which included lead pipe rigidity, a mask-like facies (Fig VI-5), bradykinesia, lack of associated movements on walking and a flexed posture. A positive glabellar reflex was elicited in half of these patients. It is easy to understand why Parkinson's disease was a relatively common misdiagnosis (Table VI-X).

Twenty-five persons had the simultaneous appearance of extrapyramidal-type rigidity together with choreiform movements. The co-existence of rigidity and chorea in any one person is contrary to the concept that Parkinsonian-like features are due to dopamine deficiency, whilst dopamine excess underlies chorea. It is not
This photograph, taken two months before her death, shows a young girl with markedly flexed arms and hyperextended legs and feet.
feasible to postulate a simultaneous occurrence of dopamine deficiency and dopamine excess in the corpus striatum of patients with Huntington's chorea. These clinical features suggest that the underlying pathophysiological basis for chorea or rigidity is more complicated than a simple dopamine deficiency or excess. This will be further developed in Section VIII.

Hamilton in America (1908) was the first to document Parkinsonian-like features in patients with Huntington's chorea. Since that time comparable observations have been made in over 90 different reports. One of the most comprehensive studies was performed by Bittenbender and Quadfasel (1962) who, in addition to their own series, reported on 70 rigid patients from the world literature. In their investigation 12 - 14% of persons had Parkinsonian-like rigidity. The results of the current investigation (23%) are similar to those of Stevens, who found that 25% of his patients had a similar pattern of rigidity.

Rigidity occurred more commonly at both ends of the age spectrum. The presence of hypertonicity in juvenile patients will be discussed in Chapter VI-5. Forty-three patients (33%) developed increased tone in association with other signs of pyramidal tract dysfunction in the final phases of the disease. This often occurred in persons whose predominant initial sign was chorea (Fig VI-6) and is in accordance with Denny-Brown's concept (1962) that there is a natural evolution of this disease towards a more rigid state.
A detailed description of these features is seen in Table VI-III. Many different signs were commonly seen in one patient.

| TABLE VI-III |
| SIGNS OF PYRAMIDAL TRACT DYSFUNCTION |
| No. | % |
| Hypertonicity (clasp knife): | 14 | 10.7 |
| Hyperreflexia: | 37 | 26 |
| Extensor plantars response: | 10 | 7.6 |
| Absent abdominal reflexes: | 22 | 17 |
| Clonus: | 16 | 12.3 |

The signs listed above are indicators of cortical atrophy which is a characteristic pathological feature of the disease. The number of persons with signs of pyramidal tract dysfunction in the current survey is similar to the percentage of 33% and 47% reported by Heathfield (1967) and Stevens (1977). Bittenbender and Quadfasel (1962) have warned that the "frequency of occurrence of the rigid form of Huntington's chorea is greater than is generally appreciated". The findings of this study support their conclusion.

C. DYSARTHRIA

Seventy-three or 56% of affected persons had a disorder of speech, with a difficulty in articulation. This is lower than the
figure (73%) reported by Heathfield in 1967. The severe dysarthria may mistakenly lead the examiner to conclude that the patient is far more demented than he really is. This pitfall has also unfortunately resulted in some family members giving up talking to their affected relative, on the assumption that if they could not express themselves, they could therefore no longer comprehend what is said to them.

The dysarthria resulted from an incoordination of the muscles of articulation, probably reflecting the combined effects of cortical and extrapyramidal damage. Dysarthria was present to a similar degree in patients with rigidity and chorea and usually occurred early in the disease as opposed to the late presentation of dysphagia.

D. DYSPHAGIA

Dysphagia is not uncommon in the terminal phases of Huntington's chorea. In the present survey, twenty-three persons (19.3%), all of whom had shown symptoms for over five years, complained of this symptom. During the course of the survey one patient who was having great difficulty in swallowing, in spite of a good appetite, aspirated food, developed bronchopneumonia and died. This mode of death is a common occurrence in Huntington's chorea. Edmonds (1966) reported that 12 of the 14 patients in his study died from a respiratory cause, probably secondary to aspiration of fluids or solids.

The dysphagia is in part consequent to involuntary movements affecting the muscles of deglutition. Another possible contributing factor is bilateral damage to the cortical origins of the pyramidal
This 53 year-old lady developed increased tone and incontinence as a late feature of the disease. Note the pressure sore over the right femoral head.
tracts, resulting in a pseudobulbar palsy. Evidence excluding the latter as the sole cause is that only 13 (56%) of the total of 23 suffering from dysphagia had other signs of pyramidal tract dysfunction.

Heathfield (1967) found that 15 of 25 patients (60%) complained of dysphagia, whilst Stevens (1977) reported that 35 of 100 persons (35%) were affected. The figure of 17.3% noted in the present series may reflect the inclusion of a greater proportion of persons at earlier phases of the illness when dysphagia is uncommon.

E. OTHER NEUROLOGICAL SIGNS

Another late feature of Huntington's chore is incontinence. Twenty persons (15.3%) were incontinent of urine (Fig VI-7), whilst eight of these were incontinent of urine and faeces. The inability to control bladder and rectal function did not occur in any persons who had symptoms for less than five years. Whether the underlying mechanism for impaired sphincter function is involuntary movement of the controlling muscles, bilateral pyramidal tract dysfunction, or the consequence of frontal cortical atrophy, is uncertain. This symptom has received scant attention from other authors.

Ataxia was a clinical feature in 34% of persons of the current survey. All patients had associated chorea. The disturbance of gait was not cerebellar in origin, but rather the consequence of choreiform movements of the trunk, head and limbs. In fact, the gait of persons with Huntington's chorea was characteristic. At rest, most patients stood on a wide base. When walking involuntary movements were greatly increased and displacement of the trunk from side to side was prominent, resulting in what Heathfield has termed (1967) "zig-zag" progression.
Associated movements whilst walking were also abnormal and the arms were either kept rigidly at the sides or held in abduction to accommodate the choreiform movements of the trunk. Patients with severe chorea could not walk unaided. In three instances, fractures were sustained as a result of falling. Other injuries occurred in four persons. These signs are consistent with the theory proposed by Purdon Martin (1967) that the caudate nuclei are concerned with the regulation of locomotion, with particular emphasis on the control of the centre of gravity and the balance of the body.

Abnormal sensory signs and symptoms were a distinctly uncommon finding. Two persons were found to have a peripheral neuropathy due to other causes.

Ocular signs, including disturbance of ocular movements, optic atrophy and minor pupillary changes, have been reported by different authors. The pupillary changes (Merskey, 1958) and optic atrophy (Stevens and Parsonage, 1969) are probably coincidental findings, whilst the disturbance of ocular movements is a feature of Huntington's chorea (Petit and Milbled, 1973), manifested as a disorder of upward gaze and a generalised slowing of ocular movements. Ocular reflexes were normal. Where possible, external ocular movements were examined clinically. Abnormalities in conjugate gaze and paucity of eye movement were seen in a total of 22% of patients. Bruyn has suggested that these disturbances may be due to an oculomotor apraxia (1968).

Fundoscopy was performed on all patients personally examined. No specific abnormalities were found.
Cerebellar signs including nystagmus, dysdiadokokinesia and minimal dysmetria were noted in three patients, all of whom had juvenile onset of the disease. This is in accordance with reports of cerebellar signs in the juvenile form of Huntington's chorea (Jervis, 1963; Byers and Dodge, 1967).

Three persons (2.5%) with adult onset of the disease had grand mal seizures. Oepen (1963) has found a frequency of 3% in 3,443 patients with Huntington's chorea, which is higher than the figure of 2% reported by Entres (1940). A total of 35% of the patients in the current survey with onset before the age of 20 had epilepsy. The association between juvenile onset disease and epilepsy will be discussed in Chapter VI-6.

F. VARIANTS OF HUNTINGTON'S CHOREA

Stevens (1973) has described the conditions under which variants of any disease may be defined. "A variant should be a distinct form of the disease and ideally there should be little overlap between that variety under consideration and any other form of the disorder." The purpose of delineating variants of any disorder is to document the different forms and determine the reasons for these differences.

There is at present much confusion in the literature concerning the delineation of the variants of Huntington's chorea. Bruyn (1968) has described the juvenile type, denoting patients with undeniable onset before the age of 20, and also the Westphal variant which depicts the hypokinetic, rigid group. Westphal (1883) called the hypertonic, hypokinetic variant "pseudosclerosis". Bruyn has pointed out that
Westphal failed to realize that the father of the described patient as well as four brothers and sisters were suffering from chorea, and that this person, in fact, had a variant of Huntington's chorea. Semantic confusion surrounds the eponym "Westphal's variant" and it is suggested that this term be replaced by the phrase "the rigid form of Huntington's chorea".

Bruyn (1968) suggested another variant, the "status subchoreaticus" which describes patients either with onset very late in life or in a considerably mitigated fashion. The term was first used by Patzig (1935). Using one expression to describe two clinical presentations which are distinctly different is misleading. Patients may have late onset with gross clinical signs or early onset with very few signs.

Other authors have attempted to define variants of this disease according to the presenting feature (Chandler et al, 1960), the occurrence of rigidity (Stevens, 1973) or the absence of chorea ("Chorea Huntington sine chorea") (Curran, 1930). None of these delineations meet the criteria described above, as these groupings are not mutually exclusive.

All attempts to describe the variants of Huntington's chorea have been made from a clinical standpoint. A more useful classification of the disease awaits a more accurate understanding of the different patho-physiological mechanisms underlying the various clinical features. Until then all delineations will be arbitrary. In this survey patients have been grouped according to the dominant clinical signs, be they chorea, rigidity or psychiatric features. Patients with onset below the age of 20 have all been grouped together and will be discussed in Chapter VI-6.
A. INTRODUCTION

Mental change as an integral part of the clinical features of Huntington's chorea was recognized as early as 1898, when Hallock suggested that the title of Huntington's chorea be replaced by the term "dementia choreica". Later Kehrer (1940) and Panse (1942) proposed the names "choreopathy" and "choreophrenia" respectively.

It has already been noted that the majority of patients in South Africa had psychiatric symptoms as the earliest feature of Huntington's chorea. During the course of their illness, all persons had some psychiatric disturbance which embraced many different types of mental illness, including dementia, the affective disorders and psychotic states.

B. DEMENTIA

Confusion surrounds the concept of dementia. An excellent definition, which was used for this survey, was proposed by Pearce and Miller (1973) as follows - "Dementia is a symptom, characterized by a decline of intellect and personality, which reflects a disturbance of memory, orientation and capacity for conceptual thought."

As stated previously, detailed psychometric examination was not undertaken and the degree of dementia was judged by patient's conversational ability and by simple arithmetic and memory tests.

Second to chorea, dementia is the most common clinical feature of Huntington's chorea. In the present investigation approximately
90% of affected persons were suffering from some form of dementia.

The dementia varied considerably from patient to patient in respect of its severity, natural history and stage at which it became manifest. In general almost all persons with chorea had some intellectual deterioration. However, the extent of the chorea was not found to closely approximate the degree of dementia. Brothers (1964) came to a similar conclusion. This is in contrast to the report by Heathfield (1967) who found a parallel course of chorea and dementia.

Nine patients presented with a decline of intellect as the first feature of the disorder. In seven this was followed in a short time by the onset of abnormal movements. One young patient later developed a paranoid psychosis which necessitated hospitalisation. The remaining person presented at 15 years with organic dementia. She is now 22 and still has no choreiform movements, though she has signs of pyramidal tract dysfunction. The diagnosis of Huntington's chorea has been suggested, in the absence of choreiform movements, in view of her positive family history for the disorder.

In different families the mimetic nature of the disease was apparent, with some having minimal dementia, whilst other families showed gross dementia in almost all affected persons.

Intellectual deterioration was manifest in the early phases by defects of memory and errors of judgement. For example, patients often forgot where they had put their belongings. One patient, even though he had gross choreiform movements, still bought a car without realizing he would never be able to drive. Numerous accidents resulting from
impaired judgement whilst driving were recorded. Individuals of great intellectual ability prior to onset, after a few years had a deterioration of general knowledge, with disinterest in everyday events. These changes merged imperceptibly with the change of personality and disorder of affect to be discussed in Sections C and D.

Huntington's chorea is an example of a presenile dementia. Its differentiation from other examples of early dementia is possible on clinical grounds alone and this will be elaborated in Chapter VI-8.

C. CHANGE OF PERSONALITY

According to the broad definition of dementia adopted for this study, the personality change is really a feature of the dementia. Almost all patients' relatives recognized this symptom. In some the person's premorbid personality was exaggerated, with the quiet individual becoming more introverted, whilst those more extroverted became sometimes aggressive and violent. Most distressing to families was the lack of control of affected persons "who would smash crockery", "pull up all the plants in the garden" and "threaten to chop their relatives up with an axe". In some instances, the natural personality trends were completely reversed. One patient, a priest, who was always a kind, quiet, benevolent gentleman, became angry, cursing and violent.

Lack of inhibitions was a problem in many families. One affected individual was constantly lifting up her dress in the streets of Pretoria, which necessitated admission to an institution. In other persons this change in personality was manifested as moodiness, with frequent outbursts of anger. Many patients who had previously been neat and well dressed, now totally neglected their clothing, shaving and
cleanliness. Incontinence occurred without embarrassment.

Personality change is an invariable accompaniment of Huntington's chorea. Environmental factors may influence the expression of these disturbances. Poverty and social isolation exacerbated the problem for the affected person, whilst patients in a caring home environment generally fared better.

D. THE AFFECTIVE DISORDER - DEPRESSION

Depression was a common affective state, particularly at the onset of their illness, and occurred in almost 20% of all patients. It is very difficult to give an accurate estimate of the extent of depression in Huntington's chorea owing to the vagueness of the symptoms and the inadequate documentation. Suicide and attempted suicide rates are one crude measure of its frequency. Eleven affected persons in South Africa died as a result of suicide, whilst a further 27 people are known to have attempted suicide. This will be further discussed in Chapter IX-2C.

In the early phases depression led to withdrawal and feelings of inadequacy. It is difficult to differentiate dementia from depression at this stage, as clinical features may be similar. However, the occasional psychotic manifestations of the depressive state are useful distinguishing characteristics.

Different writers have drawn attention to the high frequency of depression in Huntington's chorea (Brothers, 1964; Heathfield, 1967; Bolt, 1970). However, it has not been adequately recognized that this mood disorder may respond to conventional anti-depressive treatment.
(McHugh and Folstein, 1975). This mode of therapy should be an integral part of the treatment of patients with Huntington's chorea.

Mania was not seen in any affected individuals. However, mania has been reported in a total of eight patients by Heathfield (1967), Bolt (1970) and McHugh and Folstein (1975). There were no features to distinguish this from an endogenous manic-depressive illness. Only the family history suggested that the psychosis was a symptom of Huntington's chorea and not idiopathic manic-depressive illness.

E. SCHIZOPHRENIC-LIKE PSYCHOSIS

The commonest misdiagnosis in the current survey was schizophrenia. In 10% (13 persons) schizophrenic-like symptoms, including delusions, commonly paranoid in nature, auditory and visual hallucinations were the presenting feature of Huntington's chorea. Another 15 patients (11.5%) had psychotic episodes during the course of their illness.

Paranoid delusions were the most common symptoms in this group of patients. The delusions often centred around the unaffected spouse's infidelity or attempts by their partners to kill them. In three instances patients refused hospital tablets as they were supposedly "poisoned". One affected person pulled out all the plants in his garden because "al die mense plant dagga om haar huis en hulle is aangetrek soos beeste wat daar rondloop" (All the people plant dagga around his house, where they wander dressed as animals). Less commonly, auditory and visual hallucinations were present. One patient heard "messages from General Smuts that were poisoning him and the whole country". Others heard voices threatening to kill them.
There was no obvious relationship between this symptom and others such as chorea and dementia. The psychotic episodes occurred before, simultaneously with, and after these other signs appeared. However, it was apparent in a few persons that, as a result of their intellectual fall-off, they misunderstood and misinterpreted certain situations with resultant false assumptions, e.g. accusations of infidelity if the spouse spoke to any member of the opposite sex. In these instances it could be argued that the paranoid delusions derived from the patient's underlying dementia.

Other authors, including Brothers (1964), Heathfield (1967), Bruyn (1968), Bolt (1970) and Garron (1973) have reported the high frequency of schizophrenic-like syndromes in Huntington's chorea. Heathfield (1967) and Bolt (1970) specifically mention paranoid features.

Signs and symptoms of patients with these features in the current survey have been alleviated by therapy with dopamine antagonists. It has been established that the paranoid psychosis induced by amphetamines is mediated by dopaminergic mechanisms (Gershon and Angrist, 1973). In Section VIII the factors suggesting that dopamine excess is important in the basal ganglia dysfunction of Huntington's chorea will be shown. An interesting possibility is that the net dopamine excess in some affected patients is important in mediating their paranoid behaviour.

F. OTHER PSYCHIATRIC SYMPTOMATOLOGY

Psycho-somatic complaints, including headaches, chest and abdominal pain, were occasional features of the early stage of the illness. In one family all affected members complained of chest pain, for
which no underlying cause could be found. These symptoms are features of latent anxiety, which is a common accompaniment of the earliest stage of Huntington's chorea, when the person 'at risk' realizes he may indeed be affected.

G. CONCLUDING REMARKS

In this chapter I have reported my clinical experience with affected persons in South Africa. The predominant psychiatric symptom was dementia in almost all patients. The affective disorder, change in personality and schizophrenic-like syndrome may derive in part as a result of the dementia but can also arise de novo. The biochemical bases for these syndromes are at present unclear.
A. INTRODUCTION

Although Huntington's chorea is generally considered a disease of adulthood, seventeen juvenile patients (7.8% of total) were ascertained during the South African investigation. The term "Juvenile Huntington's chorea" pertains to those patients with definitive signs and symptoms present before the age of 20. It encompasses both the childhood (with onset before 10) and the adolescent forms of the disease (earliest clinical features in the second decade).

In spite of a report by Lyon which recorded the first juvenile patient in 1863, Huntington in his classic paper of 1872 failed to recognize this form of the disease. In fact he stated emphatically that a peculiarity of the disorder is that "it manifests itself as a grave disease only in adult life". Bruyn et al (1974) in their centenial bibliography list 133 separate references to Juvenile Huntington's chorea in support of the concept that this is, indeed, a distinct entity.

The purpose of this chapter is to highlight the differences between the juvenile and adult form of the disorder in terms of epidemiology, natural history, clinical features and mode of transmission. Possible reasons for these differences will be discussed.

B. THE EPIDEMIOLOGY OF JUVENILE HUNTINGTON'S CHOREA

A total of 481 persons with Huntington's chorea in South Africa were recorded. Sufficient details concerning age of onset were noted in 219 persons. Of these, 17 had onset before the age of 20.
The number and proportion of juvenile patients in investigations from 1916 till 1979, including the current study, is shown in Table VI-IV.

### Table VI-IV

<table>
<thead>
<tr>
<th>Age of onset:</th>
<th>0 - 9</th>
<th>10 - 19</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Davenport (1916)</td>
<td>3</td>
<td>2,2</td>
<td>2</td>
</tr>
<tr>
<td>Spillane (1937)</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Panse (1942)</td>
<td>9</td>
<td>2,0</td>
<td>22</td>
</tr>
<tr>
<td>Reed (1958)</td>
<td>-</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>Brothers (1964)</td>
<td>4</td>
<td>1,9</td>
<td>11</td>
</tr>
<tr>
<td>Cameron (1967)</td>
<td>2</td>
<td>0,9</td>
<td>9</td>
</tr>
<tr>
<td>Heathfield (1967)</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Oliver (1970)</td>
<td>4</td>
<td>3,5</td>
<td>7</td>
</tr>
<tr>
<td>Mattson (1974)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stevens (1977)</td>
<td>1</td>
<td>0,3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Current study (1979)</strong></td>
<td><strong>6</strong></td>
<td><strong>2,7</strong></td>
<td><strong>11</strong></td>
</tr>
<tr>
<td>Whites</td>
<td>3</td>
<td>2,0</td>
<td>3</td>
</tr>
<tr>
<td>Coloureds</td>
<td>3</td>
<td>4,3</td>
<td>8</td>
</tr>
</tbody>
</table>

The number of juvenile patients in different series varies from 1% (Stevens, 1977) to 9,6% (Oliver, 1970). The percentage of 7,7 for the South African study lies between these figures. The racial distribution of these patients shows that whilst the White group has a figure of 4%, the number of persons with Juvenile Huntington's chorea in the population of mixed ancestry is 15,7% of the total, which is higher than any reported figure in the literature.
Numerous factors may be suggested to account for this finding. It is unlikely that it reflects a bias in the ascertainment of data, as similar methods were applied to all population groups with divergent results. It has already been mentioned that Brackenridge (1974) has shown a statistically significant decrease in age of onset as environmental temperature rises. If climate were a factor, the White group would also be expected to have an unusually high proportion of juvenile patients. This is not so. Furthermore, 4 of the 11 Coloured persons with Huntington's chorea come from the Transvaal where the climate and environment is different to that in the Cape where the remaining 7 patients reside. It is difficult to postulate an environmental mechanism for the reported result. If it can be accepted that these findings are valid and do not reflect a bias in the collection of data, genetic factors may be invoked to account for the racial difference in the distribution of juvenile patients.

The Whites of South Africa are predominantly of north-western European origin. The Coloured population, however, is a unique genetic group, resulting from intermingling between the Whites, Khoisan (Hottentot and Bushmen) and Malaysian slaves in the 17th and 18th centuries. In most instances, it was the White males who procreated with Khoisan and Malaysian females (Jenkins, personal communication, 1979).

Thus the gene for Huntington's chorea was probably first introduced to the Coloured population by males of European origin. Since the father is the transmitter of the gene to affected juveniles 3 to 4 times more commonly than the mother, it could be argued, taking into account the origins of the Coloured group, that one would expect a
higher frequency of juvenile patients in this group.

The Whites of South Africa have a prevalence of Juvenile Huntington's chorea similar to those populations of north-western European origin (see Table V-IV). The high proportion of juvenile patients in the Coloured population may be a manifestation of their unique genetic constitution, whereby this group's inherent genotype interacts with the gene for Huntington's chorea, modifying the phenotypic expression of the disease, with earlier age of onset. This process is termed epistasis. There is no way to test this hypothesis but, in the absence of any known environmental agents, it is most likely that genetic factors are important in the pathogenesis of the high proportion of juvenile patients in the population of mixed ancestry in South Africa.

The Coloured group have a larger proportion of their population below the age of 20. It could be argued that one would thus expect a higher absolute number of persons with juvenile Huntington's chorea in this group. One way to correct for any possible bias is to determine the absolute rate ($x 10^{-5}$) of juvenile Huntington's chorea in the different populations. This is shown in Table VI-V.

**TABLE VI-V**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>AGE</th>
<th>NO. OF PATIENTS</th>
<th>0-20 yr POPULATION</th>
<th>TOTAL POPULATION</th>
<th>RATE ($x 10^{-5}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites</td>
<td>0-20</td>
<td>6</td>
<td>1,599,513</td>
<td>4,050,079</td>
<td>0,37</td>
</tr>
<tr>
<td>Coloureds</td>
<td>0-20</td>
<td>11</td>
<td>1,232,962</td>
<td>2,273,000</td>
<td>0,89</td>
</tr>
</tbody>
</table>
Correcting for the shift in the Coloured population structure shows that the rate of juvenile Huntington's chorea is still 2.4 times more frequent than that of the White group.

Samuels and Gelfand (1978) have recently published a report of Huntington's chorea in a Black Rhodesian family, including 4 juvenile patients. The diagnosis was made in the absence of a positive family history. The father, however, may have had the gene, having died at the age of 40 years before the disease became manifest. Klintworth (personal communication, 1978) also documented another 4 affected Black persons with juvenile onset in South Africa, who were all from one kinship. I have no details concerning these patients. However, the finding of 8 juvenile patients in the African Negro population of Southern Africa, where the disease is extremely rare, is an unexpected finding. If one accepts that the diagnosis is correct, one possible reason is that both these families, although phenotypically African Negro, are of a mixed racial ancestry, and that the same factors operating to produce a high proportion of juvenile patients in the Coloureds are functional in these families. Another possibility is that there is an unknown environmental agent, such as a contaminant in the traditional diet, which is acting on both these populations. It is difficult, however, to identify an environmental factor which is operating selectively on specific groups in this subcontinent.

C. CLINICAL FEATURES OF JUVENILE HUNTINGTON'S CHOREA

There is a striking clinical disparity between the features of Huntington's chorea in children as opposed to adults, with particular
This 15 year-old girl (E.M.) had onset at 8 years with gait disturbance and intellectual deterioration, followed by generalized increased tone and the onset of seizures.
L.J., a 14 year-old, had onset at 8 years with rigidity and failure at school. The scar on his right shin is as a result of a fall into a fire at the age of 9.

Fig. VI - 9
regard to the principal motor abnormalities (Fig VI-8, Fig VI-9), the rate of progression and the occurrence of seizures.

The mean duration of Huntington's chorea in patients diagnosed before the age of 10 has been calculated from reports cited by Perretti (1885), Bielschowsky (1922), Spielmeyer (1926), Pleydell (1955), Campbell et al (1961), Jervis and Thiells (1963), Brion and Comoy (1965), Markham and Knox (1965) and Byers et al (1973). In the 16 reported cases, the mean duration of this form of the disease is 6.9 years. The mean duration of the illness in juvenile and adult patients in the current survey is shown in Table VI-VI.

<table>
<thead>
<tr>
<th>TABLE VI-VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DURATION OF HUNTINGTON'S CHOREA IN THE CURRENT SURVEY</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Adult patients:</td>
</tr>
<tr>
<td>Adult patients:</td>
</tr>
<tr>
<td>Juvenile patients:</td>
</tr>
<tr>
<td>a) Childhood form:</td>
</tr>
<tr>
<td>b) Adolescent form:</td>
</tr>
</tbody>
</table>

The duration in juvenile onset patients is significantly different to that in adults. Separation of the juvenile group into those with childhood and adolescent onset, shows that the mean duration of those with onset before the age of 10 is less than at any other time. This confirms the finding calculated from the different reports, mentioned above.

The clinical features of the 17 juvenile patients of the current investigation is shown in Table VI-VII.
### TABLE VI-VII

**CLINICAL FEATURES OF JUVENILE HUNTINGTON'S CHOREA IN SOUTH AFRICA**

<table>
<thead>
<tr>
<th>Initials</th>
<th>Sex</th>
<th>Age of onset/death</th>
<th>Presenting symptoms</th>
<th>Chorea</th>
<th>Rigidity</th>
<th>Dementia</th>
<th>Cerebellar signs</th>
<th>Epilepsy</th>
<th>First Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coloured</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V.v.W.</td>
<td>M</td>
<td>14</td>
<td>Mental fall-off</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>Huntington's chorea</td>
</tr>
<tr>
<td>M.v.W.</td>
<td>F</td>
<td>12</td>
<td>Clumsiness</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td>Huntington's chorea</td>
</tr>
<tr>
<td>B.v.W.</td>
<td>M</td>
<td>16</td>
<td>Ataxia</td>
<td>-</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Huntington's chorea</td>
</tr>
<tr>
<td>K.v.W.</td>
<td>F</td>
<td>15</td>
<td>Mental fall-off</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Huntington's chorea</td>
</tr>
<tr>
<td>E.M.</td>
<td>F</td>
<td>8</td>
<td>Clumsiness</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>Hyperactivity</td>
</tr>
<tr>
<td>(Fig VI-8)</td>
<td></td>
<td></td>
<td>Mental fall-off</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>E.M.</td>
<td>F</td>
<td>12</td>
<td>Mental fall-off</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>Infantile autism</td>
</tr>
<tr>
<td>I.M.</td>
<td>F</td>
<td>5</td>
<td>Dysarthria</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>C.D.</td>
<td>M</td>
<td>16</td>
<td>Psychosis</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>&quot;</td>
</tr>
<tr>
<td>L.D.</td>
<td>M</td>
<td>19</td>
<td>Psychosis</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>&quot;</td>
</tr>
<tr>
<td>L.J.</td>
<td>M</td>
<td>8</td>
<td>Social withdrawal</td>
<td>-</td>
<td>++</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>Minimal brain damage</td>
</tr>
<tr>
<td>(Fig VI-9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Kinnier-Wilson Disease</td>
</tr>
<tr>
<td>J.S.</td>
<td>F</td>
<td>17</td>
<td>Irritability</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>&quot;</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D.D.</td>
<td>F</td>
<td>9</td>
<td>Mental fall-off</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>&quot;</td>
</tr>
<tr>
<td>A.H.</td>
<td>F</td>
<td>5</td>
<td>&quot;</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>? S.</td>
<td>F</td>
<td>10</td>
<td>?</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>&quot;</td>
</tr>
<tr>
<td>S.S.</td>
<td>F</td>
<td>15</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&quot;</td>
</tr>
<tr>
<td>J.V.</td>
<td>M</td>
<td>13</td>
<td>?</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>&quot;</td>
</tr>
<tr>
<td>J.d.T.</td>
<td>M</td>
<td>5</td>
<td>?</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

+ = mild  ++ = moderate  +++ = severe
HUNTINGTON'S CHOREA

COMPARISON OF ADULT AND JUVENILE PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>CHOREA</th>
<th>RIGIDITY</th>
<th>SEIZURES</th>
<th>DURATION</th>
<th>CEREBELLAR SIGNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADULT</td>
<td>± 90%</td>
<td>± 10%</td>
<td>Seldom</td>
<td>13 - 15 yrs</td>
<td>RARE</td>
</tr>
<tr>
<td>JUVENILE</td>
<td>± 50%</td>
<td>50%</td>
<td>Commonly</td>
<td>8 - 10 yrs</td>
<td>OCCASIONAL</td>
</tr>
</tbody>
</table>

Fig. VI - 10

Comparison of the clinical features between adult and juvenile patients
Table VI-VII lists the clinical features of juvenile Huntington's chorea at all stages of the illness. Although a history of chorea could be elicited in 82% of these patients, it generally occurred early, was mild and was superseded by rigidity which was the predominant physical finding in 10 patients (58%).

Epilepsy, which often proved difficult to control with routine antiepileptic medication, occurred in 6 persons (35%). Generally this was a late phenomenon.

Cerebellar signs (which were not seen in affected adults) were demonstrated in three juvenile patients and included dysmetria, adys-diadochokinesis and intention tremor. Intellectual deterioration with failure at school and difficulty in concentration was present in 16 (94%) children. In at least 35% mental fall-off was the presenting manifestation of the disease.

This is the largest reported series of juvenile Huntington's chorea in the world literature. Jervis (1963) published details of 4 patients with childhood Huntington's chorea and compared these with 17 other reports. Table VI-VIII summarizes his findings together with the results reported by Markham (1969) and Byers et al (1973).

It can be seen that the results of the current survey are similar to those reported by these other authors. It is clear that juvenile Huntington's chorea differs from adult chorea with regard to its duration, predominant motor abnormality, frequency of seizures and cerebellar signs (Fig VI-10). Various theories have been invoked to account for these differences.
**TABLE VI-VIII**

COMPARISON OF DIFFERENT REPORTS OF JUVENILE HUNTINGTON'S CHOREA

<table>
<thead>
<tr>
<th>Author</th>
<th>Number</th>
<th>Predominant Motor Abnormality</th>
<th>Dementia</th>
<th>Epilepsy</th>
<th>Cerebellar Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Chorea</td>
<td>Rigidity</td>
<td>Combined</td>
<td></td>
</tr>
<tr>
<td>Jervis (1963)</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>(own series)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jervis (from literature)</td>
<td>17</td>
<td>4</td>
<td>8</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Markham (1969)</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Byers et al (1973)</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Total (%)</td>
<td>34</td>
<td>8</td>
<td>21</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(23.8%)</td>
<td>(61.7%)</td>
<td>(14.7%)</td>
<td>(82.3%)</td>
</tr>
<tr>
<td>Current survey</td>
<td>17</td>
<td>5</td>
<td>10</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(29.4%)</td>
<td>(58.8%)</td>
<td>(11.7%)</td>
<td>(94%)</td>
</tr>
<tr>
<td>Grand Total:</td>
<td>51</td>
<td>13</td>
<td>31</td>
<td>7</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(25.4%)</td>
<td>(60.7%)</td>
<td>(13.7%)</td>
<td>(86.2%)</td>
</tr>
</tbody>
</table>

Attempts to correlate severity of destruction of the caudate nucleus, putamen and globus pallidus with chorea or rigidity (Denny Brown, 1962) have not been conclusive (Byers et al, 1973). The morphologic abnormalities in affected juveniles as a rule conform to the findings seen in affected adults. Exceptions are the more common findings of cerebellar inferior olivary and globus pallidus lesions in juvenile patients. The former would account for the signs of cerebellar disease, whilst the gliosis of the globus pallidus could account for the increased frequency of rigidity in the juvenile group (Byers et al, 1973).
Approximately 50% of all affected children have seizures. In the present investigation 6 of 17 juvenile and 2 of the 113 adults were epileptic. No pathological differences, such as focal cortical scarring, have been demonstrated which might explain the variation in seizure frequency. I am in agreement with Markham (1967) who has suggested that this probably represents the increased likelihood of epilepsy in children generally, when exposed to a variety of stresses. The increased susceptibility to seizures in affected juveniles is probably not the result of any specific difference in the childhood form of the disease, but rather the pattern of reaction to the degenerative process in the developing, as opposed to the developed, brain of affected adults. The fact that adults with the rigid form of the disease do not have an increased frequency of epilepsy would suggest that the occurrence of seizures is unrelated to the clinical presentation of rigidity.

The shorter span of juvenile Huntington's chorea may also reflect the process of systemic degeneration in a brain still undergoing growth and development. A less mature central nervous system may be less able to withstand the destructive process of Huntington's chorea, as opposed to the adult brain, with consequent shorter duration of the disease.

In summary, the different clinical features of juvenile, as opposed to adult, chorea may be explained in terms of pathologic, developmental and genetic factors. Unusual aspects of the genetics of juvenile chorea will be discussed in Chapter VII-2.
The brain of the patient seen in Fig. VI-8, showing bilateral ventricular dilatation and cortical atrophy.
D. CONCLUSION

Juvenile Huntington's chorea is not as rare as is generally supposed. In the current study 7.7% of the total had onset before the age of 20. Diagnostic difficulty may occur if it is not realized that rigidity, and not chorea, is the principal motor abnormality of the disorder.
A. INTRODUCTION

The diagnosis of Huntington's chorea is primarily made on clinical grounds. Different special investigations are employed to confirm the diagnosis. In a few situations where there is uncertainty these techniques may be of special use.

The neuropathological examination of the brain of affected individuals post mortem may be a most important means of establishing a definitive diagnosis. The results of such an investigation have obvious implications for genetic counselling.

In this chapter, a brief review of the pathology of Huntington's chorea will be followed by a summary of the different diagnostic techniques that have been used in South Africa.

B. POST MORTEM STUDIES

Attempts were made to arrange post mortems on patients dying of suspected Huntington's chorea in the Cape Town area. During the course of the survey 4 persons who were known to have the disease died in this region. Due to administrative difficulties a post mortem was organized through the courtesy of the Pathology Department on only one patient. She suffered from the juvenile form of the disease.

Post mortem examination revealed a brain which was smaller than normal, weighing only 997 grams (Fig VI-11). Coronal sectioning of the brain revealed symmetrical enlargement of both lateral ventricles, with bilateral atrophy of the caudate nucleus and putamen. The cortex of the frontal lobes appeared thin. The cerebellum was normal. The
results of light and electron-microscopy are at present unavailable. Macroscopically, these abnormalities confirm the clinical diagnosis of Huntington's chorea.

Light microscopy findings reported elsewhere (Klintworth, 1973; Goebel et al, 1978) include loss of small and large neurons in the atrophic areas, with astrocytic proliferation. It is the anatomical distribution of these lesions that distinguishes Huntington's chorea from several other degenerative disorders of the nervous system. The most striking abnormalities involve the caudate nucleus, globus pallidus, putamen and cerebral cortex. Within these areas neurons are not equally affected. The small neurons bear the brunt in the caudate nucleus, whilst the third, fifth and sixth layers are most commonly affected in the cerebral cortex. The ultrastructural characteristics of the brain have been extensively reviewed by Goebel et al (1978) and Forno et al (1978) and will not be discussed further.

An important finding is that the different clinical variants of Huntington's chorea have similar neuropathological abnormalities. However, in the juvenile type, minor histopathologic differences include more pronounced neuronal cell loss, gliosis in the cortex and neuronal depletion of the cerebellum, dentate and inferior olivary nucleus (Klintworth, 1973).

C. ELECTROENCEPHALOGRAPHIC STUDIES (EEG)

There have been numerous accounts of the EEG findings in Huntington's chorea. The most comprehensive review is that reported by Scott et al (1972) who studied 95 patients. The most common finding of all these investigations was a low voltage, poorly formed EEG. In
A normal pneumoencephalogram. The arrow shows the indentation due to the caudate nucleus.
Scott's survey, one third (31) of affected individuals had a low voltage EEG with no alpha rhythm over 10 mV in amplitude. The remaining 64 persons either had a normal EEG or showed non-specific changes. Scott has suggested that the low voltage record, though not absolutely specific in Huntington's chorea, is rare in other disorders, never occurs in normal subjects and thus may be of value as a diagnostic technique in this disorder.

I have reports of the EEGs of 45 affected individuals in South Africa. A low voltage record was the most common finding, being present in 19 persons (42%). In 13 patients (28%) the EEG was reported as normal, despite the fact that these persons had obvious neurological abnormality. In other words, the EEG changes are not directly related to neurological signs and do not seem to have a constant relationship to the duration of the illness. Other non-specific disturbances, including an excess of theta activity or generalised slowing, were seen in the EEGs of the remaining 13 persons.

Not too much reliance should be placed on the EEG in the diagnosis of Huntington's chorea. False negatives are common, with a normal EEG being found in up to 50% of affected individuals (28% in the current survey).

D. THE PNEUMOENCEPHALOGRAM (PEG)

The PEG has much greater value in substantiating the diagnosis of Huntington's chorea than the EEG. However, as it is an invasive technique it still should not be used routinely and can only be justified if the results offer useful diagnostic information.
Fig. VI - 13
The P.E.G. of an affected 50 year-old man. The arrow points to the ventricular dilatation consequent to caudate nucleus atrophy.

Fig. VI - 14
The filled arrow marks the lateral ventricular dilatation, whilst the unfilled arrow points to the air over the frontal lobes indicative of cortical atrophy.
As mentioned previously, caudate nucleus atrophy is a cardinal pathological feature of the disorder, resulting in dilatation of the lateral ventricles, which can be seen on the PEG. Another important feature of the PEG of patients with Huntington's chorea is the widening of the cerebral sulci, indicating cortical atrophy.

I have PEG reports of 25 affected persons in South Africa. A normal PEG is seen in Fig VI-12. The most common finding in the current study was a flattening or loss of convexity of the caudate nucleus with consequent ventricular dilatation (Fig VI-13). Cortical atrophy, particularly over the frontal lobes, was also reported (Fig VI-14). These abnormalities were present to different degrees in 23 of the 25 persons (92%). Two patients had perfectly normal PEGs in spite of the fact that, in both instances, they had clinical features of the disease. In both these persons, however, symptoms were mild, of less than 2 year's duration, predominantly psychiatric in nature and only minimal choreiform movements could be elicited.

There would seem to be little correlation between the duration or severity of the illness and the PEG. Some patients with advanced disease had mild abnormalities, whilst others with early Huntington's chorea had severe degrees of caudate atrophy. This is consistent with the reported findings of Blinderman et al (1964), Gathe and Vinje (1968) and Fahn et al (1973).

Another drawback, in addition to the finding that a normal PEG pattern does not exclude a diagnosis of Huntington's chorea, is that the reported abnormalities are not pathonomonic of the disorder. Pick's and Wilson's diseases may give identical PEG patterns (Blinderman et al,
1964). Notwithstanding these problems, the PEG is still a valuable aid in substantiating the diagnosis of Huntington's chorea.

E. COMPUTED AXIAL TOMOGRAPHY (CAT)

The advent of the CAT scan has offered a non-invasive, relatively harmless method for assessing ventricular dilatation.

At this early stage it would seem that the CAT scan is a more accurate diagnostic technique than others mentioned previously. Terrence et al (1977) studied 12 affected persons. Neophytides et al (1978) investigated 42 patients and caudate nucleus atrophy was found in all patients. Barr et al (1978) scanned 7 patients with Huntington's chorea, 20 persons with cerebral atrophy and 20 normal controls. The bicaudate index - the ratio of the width of both lateral ventricles at the level of the caudate nuclei to the distance between the outer tables of the skull at the same level - significantly discriminated between the three groups. Taken together, reports of CAT investigation of 61 persons with Huntington's chorea have been published. There have been no false negatives.

The CAT scan became functional at Groote Schuur Hospital, Cape Town in 1977, during the course of this investigation. Owing to technical problems it was often difficult to obtain accurate scans in patients with abnormal movements. In those instances, where it was deemed necessary, patients were anaesthetized prior to CAT scan. One patient, in whom the diagnosis was certain and who had symptoms including chorea for over five years, had a normal CAT scan on two occasions. This would be the first report of a false negative CAT scan in an affected person.
Computed tomography is an important advance in the possible diagnostic methods for Huntington's chorea. Further investigations are needed to determine whether false positives or false negatives will be the drawback to the utilization of CAT scans as the most accurate diagnostic technique for the disorder.

F. CEREBRAL ANGIOGRAPHY

Fahn et al (1973) are the only group who have reported results of cerebral angiography in Huntington's chorea. They made an attempt to visualize the vasculature of the neostriatum which is derived almost entirely from the lenticuloostriate arteries. A consistent decrease in the caliber and number of these vessels was found in patients with Huntington's chorea, as opposed to the normal distribution in diffuse cerebral atrophy and Parkinson's disease. Whether these changes are primary or secondary to neuronal loss is uncertain.

This technique, with its hazards, offers no advantage over the other methods previously discussed.
A. INTRODUCTION

The protean clinical symptomatology of Huntington's chorea has resulted in the disorder being misdiagnosed on many occasions. This has occurred particularly in the early or late phases of the disease and in patients presenting with the juvenile or rigid variants. Problems of diagnoses are compounded by the relative rarity of the disorder, with the result that many doctors may not have encountered an affected person.

In this chapter a review of the misdiagnoses in South Africa will be followed by a discussion of the differential diagnosis of inherited chorea.

B. MISDIAGNOSIS

Misdiagnosis can occur in two ways. Firstly, patients with Huntington's chorea may be misdiagnosed as suffering from some other disease. Secondly, patients with some other condition may be wrongly diagnosed as being affected with Huntington's chorea.

Although less common, the latter is particularly serious in view of the important clinical and genetic implications of Huntington's chorea. Corsellis (1976) has found that about 7% of patients diagnosed as having Huntington's chorea have some other neurological condition, most commonly Alzheimer's disease. In the South African survey 4 patients with Alzheimer's disease were wrongly diagnosed as having Huntington's chorea. Confusion arose as both conditions may be inherited as autosomal dominant traits and may present with a change in
personality. However, there are important differentiating features which are summarized in Table VI-IX.

**TABLE VI-IX**

**DISTINGUISHING FEATURES BETWEEN HUNTINGTON'S CHOREA AND ALZHEIMER'S DISEASE**

<table>
<thead>
<tr>
<th></th>
<th>Huntington's chorea</th>
<th>Alzheimer's disease (Pearce &amp; Miller, 1973)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset:</strong></td>
<td>+ 35 years</td>
<td>+ 55 years</td>
</tr>
<tr>
<td><strong>Genetics:</strong></td>
<td>Autosomal Dominant</td>
<td>Multifactorial. AD occasionally.</td>
</tr>
<tr>
<td><strong>(AD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>+ 14 years</td>
<td>+ 8 years</td>
</tr>
<tr>
<td><strong>Extrapyramidal</strong></td>
<td>Chorea in + 90%</td>
<td>Parkinsonism in + 70%</td>
</tr>
<tr>
<td><strong>features:</strong></td>
<td>(adults)</td>
<td></td>
</tr>
<tr>
<td><strong>Dysphasia:</strong></td>
<td>Rare</td>
<td>+ 90%</td>
</tr>
<tr>
<td><strong>Astereognosia:</strong></td>
<td>Rare</td>
<td>+ 70%</td>
</tr>
<tr>
<td><strong>Epilepsy:</strong></td>
<td>1% of adult patients</td>
<td>+ 14%</td>
</tr>
</tbody>
</table>

The neurological features of Alzheimer's disease are primarily the consequence of cortical atrophy, as opposed to the features of caudate nucleus destruction and cortical atrophy in Huntington's chorea.

Another 3 patients were misdiagnosed as having Huntington's chorea whilst they were suffering from spinocerebellar ataxia. Confusion arose here, as a result of failure to recognise that cerebellar ataxia can be inherited, both as recessive and dominant traits. The cerebellar signs with the evidence of pyramidal tract dysfunction should serve to distinguish this condition from Huntington's chorea.
It is as a result of these problems that Bird (1978) has urged that "every patient diagnosed as having Huntington's chorea should have this confirmed by autopsy" to help those physicians caring for the offspring.

The most common situation, however, is that patients with Huntington's chorea are misdiagnosed as having other neurological or psychiatric conditions. In the current investigation 40% of those whose case records were available were initially diagnosed as suffering from some other condition. These misdiagnoses are tabulated in Table VI-X.

**TABLE VI-X**

**MISDIAGNOSES OF HUNTINGTON'S CHOREA IN SOUTH AFRICA**

(Number of persons in brackets)

<table>
<thead>
<tr>
<th>Misdiagnosis</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia (23)</td>
<td></td>
</tr>
<tr>
<td>&quot;Nervous breakdown&quot; (7)</td>
<td></td>
</tr>
<tr>
<td>St. Vitus Dance (5)</td>
<td></td>
</tr>
<tr>
<td>Behaviour disorder (4)</td>
<td></td>
</tr>
<tr>
<td>Mental retardation (3)</td>
<td></td>
</tr>
<tr>
<td>Spinocerebellar ataxia (2)</td>
<td></td>
</tr>
<tr>
<td>Shell shock (2)</td>
<td></td>
</tr>
<tr>
<td>Depression (10)</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism (6)</td>
<td></td>
</tr>
<tr>
<td>Wilson's disease (5)</td>
<td></td>
</tr>
<tr>
<td>Organic brain syndrome (3)</td>
<td></td>
</tr>
<tr>
<td>Senile psychosis (2)</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis (2)</td>
<td></td>
</tr>
<tr>
<td>Alcoholism (2)</td>
<td></td>
</tr>
</tbody>
</table>

The most common misdiagnosis was schizophrenia. The advent of choreiform movements in these patients was often regarded as "schizophrenic mannerisms" or side effects of neureleptic therapy, with the result that the wrong diagnosis persisted. In many instances and only some years later, when the patient's condition deteriorated and information that there was a positive family history for the disorder became
available, was the diagnosis changed to Huntington's chorea.

This situation is not peculiar to South Africa. Heathfield (1967), Bruyn (1968), Oliver (1970) and Bolt (1970) have all stressed the frequent occurrence of misdiagnosis of the disease. In Bolt's study (1970) 29% were thought to have another condition, most commonly schizophrenia.

The confusion between Huntington's chorea and psychiatric conditions in the early stages is understandable in view of the wide variety of presenting mental symptoms. It must also be realized that 'at-risk' individuals are not immune to other neurological and psychiatric illnesses and not every 'at-risk' person who presents with neuropsychiatric symptomatology will be suffering from Huntington's chorea. Furthermore, individuals in this group may present with choreiform movements in association with some other condition. Chorea is really a non-specific sign of basal ganglia dysfunction due to many different causes. Other diseases which are not known directly to affect the basal ganglia, such as thyrotoxicosis, systemic lupus erythematosus, cirrhosis, polycythemia and many others may also present with chorea. A full list of causes of this sign has been drawn up by Greenhouse (1966) and Godwin-Austin (1979).

The criteria for the diagnosis of Huntington's chorea have already been mentioned. The positive family history is an extremely important feature. However, it is now clear that there may be many causes of inherited chorea, only one of which (albeit the commonest) is Huntington's chorea.
# TABLE VI-XI

## THE CAUSES OF INHERITED CHOREA

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Age of onset</th>
<th>Course</th>
<th>Clinical features</th>
<th>Associated findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huntington's chorea</td>
<td>AD</td>
<td>About 35</td>
<td>Progressive</td>
<td>Chorea ementia</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>AR</td>
<td>Variable, usually childhood</td>
<td>Progressive</td>
<td>Tremor, dysarthria, rigidity</td>
</tr>
<tr>
<td>Lesch-Nyhan syndrome</td>
<td>X-linked recessive</td>
<td>Infancy</td>
<td>Progressive</td>
<td>Choreo-athetosis</td>
</tr>
<tr>
<td>Familial paroxysmal choreo-athetosis</td>
<td>AD, AR</td>
<td>Childhood</td>
<td>Non-progressive</td>
<td>Bouts of choreo-athetosis</td>
</tr>
<tr>
<td>Familial degeneration of basal ganglia with Acanthocytosis</td>
<td>AR ?, AD</td>
<td>Early adulthood</td>
<td>Slowly progressive</td>
<td>Chorea</td>
</tr>
<tr>
<td>Familial non-progressive chorea</td>
<td>AD, AR</td>
<td>Early childhood</td>
<td>Non-progressive</td>
<td>Chorea</td>
</tr>
<tr>
<td>Pseudohypoparathyroidism</td>
<td>X-linked domin.</td>
<td>variable</td>
<td>Parkinsonian features</td>
<td>Skeletal anomalies, chorea, mental retardation, microcephaly</td>
</tr>
<tr>
<td>Familial calcification of the basal ganglia</td>
<td>AR</td>
<td>variable, usually adulthood</td>
<td>Non-progressive</td>
<td>Parkinsonian features</td>
</tr>
<tr>
<td>Hallervorden-Spatz syndrome</td>
<td>AR</td>
<td>Childhood</td>
<td>Progressive</td>
<td>Dementia, choreo-athetosis</td>
</tr>
<tr>
<td>Pallidal atrophy</td>
<td>AR</td>
<td>Adolescence</td>
<td>Slowly progressive</td>
<td>Parkinsonian features</td>
</tr>
</tbody>
</table>
C. THE DIFFERENTIAL DIAGNOSIS OF INHERITED CHOREA

The differentiation between the multiple causes of inherited chorea is most important in terms of different inheritance, course, treatment and prognosis. A list of the causes of inherited chorea with their distinguishing features is shown in Table VI-XI.

Huntington's chorea is by far the commonest cause of hereditary chorea. No accurate figures are available concerning the frequency of the other disorders. However, Bearn (1960) estimates the prevalence of Wilson's disease in the U.S.A. to be $0.025 \times 10^{-5}$, whilst Harper (1978) has suggested that familial non-progressive chorea is around 20 times less common than Huntington's chorea. Until recently only about 20 instances of the Hallervorden-Spatz syndrome had been described (Pratt, 1967). The entity of familial degeneration of the basal ganglia with acanthocytosis was first documented by Estes et al in 1967. Since then only another 5 affected families have been reported. Whilst the precise frequency of this condition is unknown, it is distinctly uncommon.

There are three main causes of autosomal dominant inherited chorea, namely Huntington's chorea, familial paroxysmal choreoathetosis and familial non-progressive chorea. These three disorders have important differentiating characteristics. The latter two conditions have onset in the first ten years of life, as opposed to the usual adult onset in Huntington's chorea. Furthermore, they are both non-progressive. Familial paroxysmal choreoathetosis is characterised by bouts of involuntary movements of arms, legs and trunk with grotesque posturing and grimacing. Patients are perfectly normal between attacks. Familial non-progressive chorea has been known by the name 'benign hereditary chorea' (Harper, 1978), 'hereditary chorea without dementia'
(Behan and Bone, 1977) and 'familial non-progressive chorea' (Bird et al, 1976). Bird et al (1976) have suggested the latter name in the light of the finding that the disease is certainly not benign in a social context, causing considerable emotional and psychological distress. The non-progressive nature of this illness, with the absence of dementia, clearly distinguishes it from Huntington's chorea.

Familial degeneration of the basal ganglia is similar to Huntington's chorea in that there is a familial occurrence of adult onset of progressive chorea. The mode of inheritance of the disorder is not yet clearly established. Estes (1967) and Levin et al (1968) have suggested that this condition is also inherited as an autosomal dominant. Later reports from Critchley and Nicholson (1970) and Bird et al (1978) clearly support autosomal recessive inheritance. The abovenamed disorder is dissimilar to Huntington's chorea in view of the presence of acanthocytes, decreased deep tendon reflexes and relative lack of severe mental deterioration.

The patient who presents with the classical signs and symptoms of Huntington's chorea is not a diagnostic problem to the physician. However, confusion can arise when an affected person has the less common symptomatology of the disorder. In these instances careful inquiry as to the familial pattern, age of onset and course of the illness, together with a thorough clinical examination will differentiate between most causes of inherited chorea.

* During the latter weeks of the current investigation a family with this disease was encountered in the Cape Town area.
"Alas our frailty is the cause not we, for such as we are made of such we be."

William Shakespeare
Twelfth Night, Act II, Scene ii, 32.
SECTION VII

GENETICS

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CHAPTER VII-1

INTRODUCTION

A. THE MODE OF INHERITANCE OF HUNTINGTON’S CHOREA

Huntington’s description of the hereditary nature of the disease in his essay of 1872 was remarkably accurate. He stated "When either or both the parents have shown manifestations of the disease, one or more of the offspring invariably suffer from the disease. It never skips a generation to again manifest itself in another. Once having yielded its claims, it never regains them.” These remarks were based on his own empirical observations and unfortunately did not take cognizance of Mendel’s paper establishing the laws of inheritance in 1866. This is understandable as Mendel published his findings in an obscure journal. The interpretation of the familial aggregation of Huntington’s chorea in Mendelian terms took place 36 years later in 1908 (Jelliffe, 1908; Hamilton, 1908).

The results of the current investigation support the concept that the disorder is inherited as an autosomal dominant. This implies that the gene has no sex preference, is carried on the autosomes and that the gene for the disease dominates the other normal allele, resulting in the heterozygote being clinically affected. Each child of an affected parent has an even chance of inheriting the gene. If that individual does not carry the gene the disorder cannot be transmitted to his or her children. An impression of skipping of generations may occur if the child of a clinically normal parent develops features of the disease prior to onset in the parent. This happened in two instances in this survey and was definitive proof that the clinically normal parent was also an unsuspected heterozygote for Huntington's chorea.
B. CONCEPTS CONCERNING AUTOSOMAL DOMINANT INHERITANCE

Tremendous progress has been made towards elucidating the precise biochemical defect of some autosomal recessive (AR) diseases. This is in striking contrast to the paucity of knowledge concerning the 583 proven autosomal dominant (AD) diseases listed in McKusick's 1975 catalogue of genetic disorders.

Certain broad concepts are emerging. As opposed to the clinical specificity of AR disease, there is a marked variation in the clinical expression of AD disease. Huntington's chorea is a prime example. Furthermore, whilst AR disorders generally involve enzyme defects, in particular metabolic pathways, AD diseases are often due to defects in structural proteins. (There are many exceptions to this concept, including AD inherited porphyria varigata, McArdle's syndrome and familial hyperlipoproteinemia, all of which are due to specific enzyme deficiencies).

Goodman (1973) has suggested that the basic defect in Huntington's chorea lies not in the metabolic pathways of the bioamines and other substances, but rather that the mutant gene works on the metabolic pathways. A regulator or modifying gene may alter the control of a given pathway, with resulting accumulation of some substances and early demise of specific central nervous system cells. Whilst this seems plausible it is as yet an untested hypothesis.

C. UNRESOLVED ISSUES

Whilst the autosomal dominant mode of inheritance of Huntington's chorea has clearly been established, there remain a few important unresolved issues regarding the genetics of this disorder.
These are:-

a) The finding of the father being the transmitting parent to affected juveniles 3 to 4 times more commonly than the mother.

b) The familial aggregation of juvenile patients.

c) It is unclear whether more than one allele or more than one locus is involved in different affected persons.

d) There is no knowledge of the heterozygote frequency or the mutation rate of Huntington's chorea in South Africa.

e) The clinical expression of the homozygous state has not yet been determined.

These issues will now be discussed.
CHAPTER VII-2

UNUSUAL ASPECTS OF THE GENETICS OF JUVENILE HUNTINGTON'S CHOREA

A. INTRODUCTION

Juvenile Huntington's chorea is inherited as an autosomal dominant. The sex distribution of affected persons has been reported as equal in numerous surveys, the largest being those of Merrit et al (1969) - 106 cases, and Myrianthopoulos (1973) - 43 cases.

Of the 17 affected juveniles in the current investigation, 10 were female and 7 were male, yielding a ratio of 1.4:1. Bruyn (1968) has also reported a female sex preponderance among the juvenile patients with a ratio between 1.5:1 and 2:1. He does not, however, specify the number of patients in his sample from which this is calculated. These ratios are in marked contrast to other reports where the sex ratio has been shown to be equal (Myrianthopoulos, 1967, 1973; Merritt et al, 1969). Because of the inconsistency of this finding and the fact that the current survey population under scrutiny is small (17) it is most probable that the female preponderance is a chance finding. With a larger population the sex ratio will probably equalise.

However, certain results of the current survey support a constant finding of all known series, namely that irrespective of sex, children with Huntington's chorea have an affected father approximately four times as frequently as an affected mother.
B. PREDOMINANCE OF PATERNAL DESCENT IN JUVENILE CHOREA

As Huntington's chorea is inherited according to the law of autosomal dominant transmission, it could be expected that the affected parent of any affected offspring would, with equal probability, be the mother or the father. This is true with regard to adult-onset patients. However, it has repeatedly been shown that the affected parent of a child with juvenile chorea is 3 to 4 times more commonly the father. Table VII-1 summarises these reports. In the current investigation this trend is substantiated, the father transmitting the gene 2.4 times more commonly than the mother.

**TABLE VII-1**

SEX OF AFFECTED PARENT OF PATIENTS WITH JUVENILE HUNTINGTON'S CHOREA

<table>
<thead>
<tr>
<th>Author</th>
<th>Number</th>
<th>Affected parent</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merrit et al (1969)</td>
<td>106</td>
<td>84</td>
<td>3.8 : 1</td>
</tr>
<tr>
<td>Barbeau (1970)</td>
<td>33</td>
<td>26</td>
<td>3.7 : 1</td>
</tr>
<tr>
<td>Myrianthopoulos (1973)</td>
<td>34</td>
<td>27</td>
<td>3.9 : 1</td>
</tr>
<tr>
<td>Current survey (1979)</td>
<td>17</td>
<td>12</td>
<td>2.4 : 1</td>
</tr>
<tr>
<td><strong>TOTAL:</strong></td>
<td>190</td>
<td>149</td>
<td>3.6 : 1</td>
</tr>
</tbody>
</table>

The constancy of this unexplained and unexpected finding in different reports suggests that it is not likely to represent a bias in the ascertainment of data. Affected parents were identified in large surveys in which no possible sex bias could have been exerted.

Penrose (1948) has suggested that an allelic gene from the unaffected parent may precipitate the clinical symptoms in juvenile patients.
Fig. VII - 1

In this family, four sibs in generation III had juvenile onset.

Fig. VII - 2

In generation IV, 2 affected sisters (46, 48) both had onset before the age of 20.
The reports by Byers and Dodge (1967) and Delmas-Marsalet et al (1968) describes two juvenile patients who were half brothers, children of the same father and different mothers and renders this theory most unlikely. Myrianthopoulos (1973) has suggested that if modifying genes of the affected parent are responsible, they must somehow be sex-associated. It is obvious that these modifiers could not be assigned to either the X or Y chromosome as the sex distribution among juvenile patients is essentially equal. Therefore these modifiers must be located on one of the autosomes. In some, at present unexplained way these modifiers are also sex associated.

Another possibility is that the predominance of parental descent in the childhood form is a localized example of a more general phenomenon with higher fertility of affected males than females. This was first suggested by Merrit et al (1969) and proven to be incorrect by Jones (1973) who showed the women with chorea are more fertile than men at all ages of onset.

The high frequency of paternal descent in the juvenile form of Huntington's chorea remains an unexplained statistical fact with no adequate biological explanation.

C. FAMILIAL AGGREGATION OF JUVENILE HUNTINGTON'S CHOREA

In view of the relative rarity of this condition it is surprising to find that the 17 juvenile patients of this survey came from only 8 different kindreds. In other words, there is a familial aggregation of these patients. Four affected sibs with juvenile Huntington's chorea are shown in Figure VII-1, whilst another 2 affected sibs (Generation IV 46, 48) and 3 affected first cousins (V 3,4,19) are
The three affected juveniles in generation V (3, 4, 19) are first cousins.
shown in Figures VII-2 and VII-3 respectively. Even though related sibs with juvenile Huntington's chorea were noted as early as 1892 (Schmidt) (and numerous subsequent publications have documented this), the phenomenon of familial aggregation of juvenile Huntington's chorea has not been adequately discussed.

It could be argued that environmental factors are responsible for this phenomenon, but they are unlikely to have a major influence as there are examples in the current study and elsewhere of sibs separated at birth into different environments, who developed the same form of the disease. This would support the postulate that genetic factors are most important in determining the age of onset of this disease (Section IV-V).

It is feasible that the factors responsible for the early development of the disorder in a given sibship operate in regard to all those who inherit the defective gene. This could either be in the form of allelic genes, linked modifying genes or unlinked modifiers. The reports of two sets of half-brothers of different mothers and an affected father would seem to refute the possibility that the normal parent contributes an allelic gene. If the modifying gene were closely linked to the gene for Huntington's chorea, one would expect all sibs of a given patient with the defective gene, also to inherit the linked modifier and thus have early onset of the symptoms. In the present study I have record of a patient, J.D.T., who in 1938 developed signs of the disorder at 5 years of age. His sister, H.M.G., however, only showed features of Huntington's chorea at the age of 43 in 1960. On this basis it is likely that in this family the possible genetic
factors operating to precipitate early onset are not closely linked to the gene for Huntington's chorea.

Close examination of Fig VIII-2 and VIII-3 shows that in each family there are 12 and 10 affected persons respectively (personal communication Nelson, 1979). Of these in the DA kindred there are 10 males and 2 females, whilst examination of the MA family tree reveals 9 affected females to 1 affected male. In both families patients with juvenile Huntington's chorea received the gene from a parent of the less common sex. In other words both affected females in the DA kindred produced children with juvenile onset of the disorder, whilst the one afflicted male in the MA family had 2 children with the juvenile form of the disease. This is a new observation. It does not apply to the other juvenile families, but in many instances those family trees are incomplete. The findings in the DA and MA families may be the result of chance. However, on the other hand, these observations in the two kindreds may be a localized expression of a more widespread phenomenon, namely that a) families with unequal sex ratios of affected persons are more likely to produce patients with juvenile onset, and b) the less well represented sex in these families is more commonly the transmitter of the gene of juvenile Huntington's chorea.

The significance of these observations is uncertain, but they are further evidence as to the complexity of the inheritance of Huntington's chorea.

The factors which are modifying the action of the main gene for Huntington's chorea seem to be largely genetic, but there may also be some gene-environment interaction. The problem of elucidating the operant genetic factors is compounded by the dearth of knowledge as to the possible presence of heterogeneity in the disorder.
CHAPTER VII-3

HETEROGENEITY

Genetic heterogeneity refers to the phenomenon of more than one gene producing the same clinical phenotype. It will be shown that mutations do occur in Huntington's chorea (Chapter VII-5). It is theoretically feasible that these mutations have occurred at entirely different loci, thus resulting in heterogeneity in the disorder. The great variation in the clinical presentation of affected patients in different families is thought to be evidence supporting this possibility (Wallace and Hall, 1972).

The determination of the existence of heterogeneity in Huntington's chorea would have widespread implications. It may be the underlying cause for the differing clinical (Section VI) and biochemical responses (Section VIII). Furthermore, such information may be an important aid to the planning of therapy for the disease, with different genetic forms responding to different medications.

The only definitive way of establishing the presence of multiple genes for the phenotype of Huntington's chorea is by gene mapping. Genetic linkage is the most efficient way at present of chromosomal assignment of the locus of Huntington's chorea. Numerous linkage studies have been designed and performed without being able to designate accurately the locus of the gene for Huntington's chorea. The most comprehensive report is from Pericak-Vance et al (1978) who attempted to link the gene to 27 polymorphic marker systems. No significant linkage was found. However, several markers were excluded and the beginnings of an exclusion map for the gene of Huntington's chorea has been established.
The Coloured population of South Africa has a unique genetic admixture. In addition they have large families and it is not uncommon to have two living generations of affected individuals. For these reasons genetic linkage studies in South Africa may prove to be extremely valuable. Unfortunately, such a project was beyond the scope of this thesis.

Wallace and Hall (1972) have suggested that the magnitude of the variation in the symptom complex of the disease between different families is sufficient to provide possible evidence for genetic heterogeneity. They particularly looked at data concerning the natural history of Huntington's chorea and established that the differences between individuals within pedigrees are less than the differences between pedigrees. Whether this is due to different genes for Huntington's chorea or rather due to similarities in the genetic background in families is not clearly established.

The familial aggregation of patients with juvenile Huntington's chorea reported in the current investigation may also reflect heterogeneity or the results of a specific interaction of the gene for Huntington's chorea with the inherent genotype of that group of individuals.

The elucidation of the biochemical defect in Huntington's chorea would enable the search for the assignment of the locus of the gene for the disorder to be pursued via somatic hybridization techniques.
The heterozygote frequency of Huntington's chorea refers to the number of individuals in a given population who carry the gene for the disease, such persons being either clinically affected or asymptomatic.

The importance of the heterozygote frequency is that it indicates the total number of persons in the community who either have or eventually will develop the disease, and will consequently need medical and social services. As a result, planning for the provision of health care facilities can take place. Four previous estimates of the heterozygote frequency in other countries have been made and are shown in Table VII-II.

**TABLE VII-II**

**ESTIMATES OF HETEROZYGOTE FREQUENCY**

<table>
<thead>
<tr>
<th>Author</th>
<th>Area</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson et al (1955):</td>
<td>Minnesota</td>
<td>$21.23 \times 10^{-5}$</td>
</tr>
<tr>
<td>Reed and Chandler (1968):</td>
<td>Michigan</td>
<td>$10.1 \times 10^{-5}$</td>
</tr>
<tr>
<td>Stevens (1973)</td>
<td>Leeds, England</td>
<td>$10.77 \times 10^{-5}$</td>
</tr>
<tr>
<td>Shokeir (1975)</td>
<td>Manitoba, Canada</td>
<td>$23.3 \times 10^{-5}$</td>
</tr>
</tbody>
</table>

Different methods have been used to calculate this value (Stevens, 1973). A relatively simple and efficient method is that employed by Reed and Chandler (1958). They used the following formula:
where \( H \) is the number of observed patients with Huntington's chorea, \( N_x \) the total number of individuals in the area at age \( x \) and \( P_x \) the proportion of heterozygotes where chorea is recognised by age \( x \). The heterozygote frequency has been calculated for the White and Coloured populations of this country using the following data.

The values for \( N_x \) and \( P_x \) are given in Table VII-III. The figures for \( P_x \) are derived from Table IV-VIII and Figs IV-1, 2 and 3 by calculating the proportion of heterozygotes who were clinically affected at the end of each 5 year period. \( N_x \) has been determined from the report of the Department of Statistics, Pretoria, 1975.

### TABLE VII-III
VALUES FOR \( N_x \) AND \( P_x \)

<table>
<thead>
<tr>
<th>Age</th>
<th>( N_x )</th>
<th>( P_x )</th>
<th>( N_x \times P_x )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 4</td>
<td>729,850</td>
<td>0.014</td>
<td>1,021.7</td>
</tr>
<tr>
<td>5 - 9</td>
<td>734,685</td>
<td>0.027</td>
<td>19,836.4</td>
</tr>
<tr>
<td>10 - 14</td>
<td>714,044</td>
<td>0.05</td>
<td>35,702.2</td>
</tr>
<tr>
<td>15 - 19</td>
<td>653,896</td>
<td>0.07</td>
<td>50,349.9</td>
</tr>
<tr>
<td>20 - 24</td>
<td>555,936</td>
<td>0.168</td>
<td>93,397.2</td>
</tr>
<tr>
<td>25 - 29</td>
<td>422,254</td>
<td>0.33</td>
<td>139,343.3</td>
</tr>
<tr>
<td>30 - 34</td>
<td>420,412</td>
<td>0.515</td>
<td>216,512</td>
</tr>
<tr>
<td>35 - 39</td>
<td>366,988</td>
<td>0.68</td>
<td>251,019</td>
</tr>
<tr>
<td>40 - 44</td>
<td>326,001</td>
<td>0.78</td>
<td>254,280</td>
</tr>
<tr>
<td>45 - 49</td>
<td>288,759</td>
<td>0.881</td>
<td>254,396</td>
</tr>
<tr>
<td>50 - 54</td>
<td>256,967</td>
<td>0.96</td>
<td>246,648</td>
</tr>
<tr>
<td>55 - 59</td>
<td>216,150</td>
<td>0.99</td>
<td>213,988</td>
</tr>
<tr>
<td>60 +</td>
<td>576,391</td>
<td>1</td>
<td>576,391</td>
</tr>
</tbody>
</table>
From the above formula the heterozygote frequency is calculated to be $6.7 \times 10^{-5}$. The minimum number of heterozygotes in South Africa at present is equal to the heterozygote frequency times the total for the White and Coloured populations. Using the latest report of the Department of Statistics (1978) the number of heterozygotes for Huntington's chorea is estimated at 456, which is approximately equal to one affected person per 13,000 of the population. The total number of clinically affected persons ascertained during this survey was 153. Thus, there are at present a minimum of a further 303 persons in South Africa who, although at this stage not showing any clinical features, are nevertheless heterozygotes for the gene of Huntington's chorea.

The disadvantage of this formula is that with incomplete ascertainment (this has been acknowledged in the current study) H will be too low and thus the heterozygote frequency will also be artificially lowered.

It is interesting to speculate on the true number of heterozygotes in South Africa. Table III-XI lists the expected prevalence in the Cape Province for the White and Coloured populations, assuming ascertainment to be nearly complete. The number of affected persons and the heterozygote frequency, based on these figures, is shown in Table VII-IV

**TABLE VII-IV**

**HETEROZYGOTE FREQUENCY IN SOUTH AFRICA**

<table>
<thead>
<tr>
<th>Minimum:</th>
<th>No. of patients (H)</th>
<th>Heterozygote frequency</th>
<th>No. of heterozygotes in South Africa</th>
<th>Population ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>153</td>
<td>$6.7 \times 10^{-5}$</td>
<td>456</td>
<td>1:13,866</td>
</tr>
<tr>
<td>Based on expected prevalence rates:</td>
<td>292</td>
<td>$12.4 \times 10^{-5}$</td>
<td>845</td>
<td>1: 7,483</td>
</tr>
</tbody>
</table>
The estimated heterozygote frequency of $12.4 \times 10^{-5}$ is nearer the calculated values for this parameter as reported by Reed and Chandler (1958) and Stevens (1973). Even if it is accepted that the latter figure, calculated for the heterozygote frequency may be slightly high, these results again confirm that Huntington's chorea is not a rare disease in South Africa and should alert the health authorities to the problem of providing health care facilities for these patients.
The very low frequency of spontaneous mutations in Huntington's chorea has been of major importance in making it possible to trace the gene for the disease back over many generations. In view of the rarity of mutations, a high index of suspicion has been advocated when finding symptom-free parents of an affected child. In this regard Bruyn's (1968) aphorism "Pater semper incertum est" (Paternity is always uncertain) is a useful one.

The criteria to be fulfilled prior to acceptability of a mutation which has been critically suggested by Stevens and Parsonage (1969) and later modified by Stevens (1977) are as follows:-

1. The disease must be Huntington's chorea and descend for more than one generation from the mutant.
2. The parents of the mutant must have died after the age of 70 years and must have been symptom-free.
3. The apparent mutant must be the child of his alleged parents and not the illegitimate issue of an unknown choreic.

In this investigation a family history of Huntington's chorea could not be obtained in 15 persons. However, in 13 of these, no adequate details of the parents were available. Three were illegitimate and the remaining 10 patients either had been separated from their parents in early childhood or had no knowledge of one or both of their parents due to their early death.
The remaining two persons were isolated examples of the disease within their families. I personally examined one of these patient's (M.S.) parents, and both did not have signs of the disease at the ages of 61 and 59 respectively, whilst the other patient's father and mother died symptom-free at the ages of 59 and 81 respectively. Paternity was not confirmed by blood group or HLA studies. It can thus be seen that none of the patients in the survey conform to all the strict criteria stated above.

Previous authors have used two different methods for estimation of the mutation rate. The easiest and most direct means uses the formula:

\[ \mu = P \times \frac{f}{2} \]

where \( \mu \) is the mutation rate, \( P \) is the proportion of affected individuals without heterozygous parents, and \( f \) is the heterozygote frequency. \( \left( \frac{f}{2} \right) = \text{gene frequency} \).

The second method is less direct and takes into account that the disease may not be in balance in the population. The indirect method only gives an approximate estimate of the mutation rate because it depends on the assessment of biological fitness, which is difficult to determine with any accuracy. For this reason the former formula was employed in this survey.

Results of prior estimates of the mutation rate using both methods are shown in Table VII-V.
**TABLE VII-V**

**MUTATION RATE OF THE GENE FOR HUNTINGTON'S CHOREA**

<table>
<thead>
<tr>
<th>Direct estimate</th>
<th>Indirect estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kishimoto et al (1957)</strong></td>
<td>-</td>
</tr>
<tr>
<td><strong>Reed and Neel (1959)</strong></td>
<td>5.4 x 10^{-6}</td>
</tr>
<tr>
<td><strong>Mattson (1974)</strong></td>
<td>5.0 x 10^{-6}</td>
</tr>
<tr>
<td><strong>Stevens (1977)</strong></td>
<td>4.0 x 10^{-6}</td>
</tr>
<tr>
<td></td>
<td>4.22 x 10^{-7}</td>
</tr>
</tbody>
</table>

Stevens (1977) employed the direct method, initially only including one mutant in his estimation, to give the result 4.0 x 10^{-6}. Less strict criteria were then employed by him, enabling 11 possible mutants to be included, with a resultant rate of 4.22 x 10^{-7}.

If less stringent requirements were to be applied in South Africa, two possible mutants could be used in the estimation of the mutation rate. The proportion of affected persons without a heterozygous parent = \( \frac{2}{481} \) whilst the heterozygote frequency has already been determined as 6.7 x 10^{-5}. Therefore according to the formula:

\[
\text{Mu} = \frac{2}{481} \times \frac{6.7 \times 10^{-5}}{2} = 1.3 \times 10^{-7}
\]

This figure is lower than that from other studies. It is possible that this is artificially decreased. Some of the other 13 patients for whom there were no details concerning their parents and who for that reason were not included in this estimate, in fact may have been mutants for the gene of Huntington's chorea. What emerges, however, is that the findings of this investigation support the concept that the occurrence of spontaneous mutations in Huntington's chorea is very rare and is amongst the lowest recorded rate for any dominantly inherited condition.
The family tree of two affected heterozygotes.

The expected mode of inheritance in the offspring of two heterozygous parents for Huntington's chorea,
CHAPTER VII-6

THE HOMOZYGOUS FORM OF HUNTINGTON'S CHOREA

Two individuals (W.d.B. and S.d.B.) at risk of developing Huntington's chorea by virtue of the heterozygous state of both of their parents were identified during the investigation. They married and produced 5 children (Fig VII-4). Unfortunately, detailed clinical information is lacking with respect to this family. However, it is established that both persons (Generation II) were heterozygous for Huntington's chorea. The husband (W.d.B.) developed symptoms in his early thirties and was killed shortly after this in a railway accident. His wife (S.d.B.) had onset of the disease around the age of 30 and died approximately 18 years later in 1938 in Weskoppies Hospital, Pretoria.

Four of their five children were clinically affected. From the incomplete details available there would seem to be no difference between them and other patients in this series with regard to age of onset, duration or clinical symptomatology. There was no history of miscarriages or early infant death.

According to classical Mendelian principles (Fig VII-5) the offspring of two heterozygous parents carrying the gene for Huntington's chorea would have a 50% chance of being heterozygous, a 25% chance of being homozygous for the gene and a 25% possibility of not inheriting the gene at all.

Due to the rarity of such matings only two prior occurrences of this nature in Huntington's chorea have been well documented. In 1935 Hindringer reported the marriage of two cousins, both of whom developed
the disease. Of their offspring, 3 had clinically typical Huntington's chorea, one died in infancy (? cause) and one was unaffected at the age of 36.

Eldridge et al (1973) reviewed Hindringer's patients and also reported a second kindred in which a consanguineous union took place between a couple who developed Huntington's chorea and produced three children, one of whom was typically affected. The remaining two died young, one a young man dying in combat in the Second World War and the other a term infant girl, dying a few days after birth. No cause was given.

There is no way at present of knowing whether the offspring of affected couples are heterozygous or homozygous for the Huntington's chorea gene. There were no unusual clinical or laboratory features in the abovementioned patients. It is interesting to note, however, that in both families reported by Hindringer (1935) and Eldridge et al (1973) there was an infant who for no stated reason did not live more than a few days. Whether these offspring were homozygous for the gene is uncertain, but this could possibly be evidence for very early death of persons in the homozygous form of the disease.

The possibilities of the range of effects of a "double dose" of the Huntington's chorea gene are:-

a) It is lethal and induces spontaneous abortion.

b) It is incompatible with survival past infancy.

c) It induces a more severe or atypical clinical form of Huntington's chorea.

d) It may be no different from the heterozygous state.
The precise identification of those homozygous for the gene will only occur after there is biochemical definition of the heterozygous state. On the other hand, clinical and biochemical investigation of individuals possibly homozygous may be of tremendous value in identifying the possible biochemical defects of the heterozygous state.

Avila Giron (1973) has reported that 30% of the patients in Venezuela are offspring of two affected parents. This population should be further investigated to identify, if possible, the characteristics of the homozygous state for Huntington's chorea.
"My intention is not to prove that I have been right, but to discover whether I am right. Yes, we will question everything, everything once again. And what we find today we shall strike out from the record tomorrow, and only write it in again when we have once more discovered it."

Bertolt Brecht (1938)
In: The Life of Galileo.
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The basic defect in Huntington's chorea is unknown. Pharmacological evidence, including the observation that drugs which prevent or antagonize cerebral actions of dopamine lessen chorea (Lazarte et al 1955; Whittier and Korenyi 1968) while those which increase or potentiate dopamine aggravate the condition (Klawans et al 1972; Kartzinel et al 1976) has implicated dopaminergic predominance in this disorder.

The finding of pathological changes in the hypothalamus (Klintworth 1969) together with disturbance in weight and sweating in affected individuals (Bruyn 1968) has suggested hypothalamic dysfunction. Interest in the hypothalamic-pituitary axis has been further stimulated by the finding that dopaminergic pathways in the hypothalamus modulate the synthesis and release of different pituitary hormones (Smythe 1977). Thus examination of pituitary hormone release in Huntington's chorea may yield important information as to the state of functional activity of the dopamine-containing pathway of the tuberoinfundibular system which is involved in neuroendocrine regulation.

The recognition of the vital interrelationship between Huntington's chorea and dopaminergic pathways on the one hand and dopamine and pituitary hormone regulation on the other, is the fundamental concept which stimulated the examination of prolactin,
thyrotropin and growth hormone regulation in this disorder. In this section, following a brief review of previous biochemical studies, three consecutive investigations will be described, followed by a presentation and discussion of the results and the development of concepts attempting to explain the mechanisms of disturbances in hypothalamic-pituitary hormonal regulation in Huntington's chorea.

The potentially important findings of neuroendocrine abnormalities in first-generation, clinically normal relatives and their significance in terms of developing a possible means for presymptomatic diagnosis will be discussed in the closing chapter of this section.
CHAPTER VIII-2

REVIEW OF PREVIOUS BIOCHEMICAL STUDIES

A. INTRODUCTION

The report of the Commission for the Control of Huntington's Disease presented to the President of the United States in October 1977, and subsequent acceptance of many of its proposals, has given new impetus and financial support to research on Huntington's chorea around the world. There has been a remarkable and continuous increase in the number of published papers on the various aspects of this disorder in the last few years. A total of 32 and 41 publications are listed in the Index Medicus of 1971 and 1972, respectively, as opposed to 67 and 81 for 1976 and 1977.

However, despite intensive ongoing research the primary biochemical defect in this disorder is still to be discovered. Although there have been numerous essentially negative biochemical investigations carried out in the past, different promising avenues of biochemical research are now being explored, including examination of immunological, tissue culture and generalised cell membrane abnormalities in the disease.

B. TRACE METALS

After the breakthrough in the understanding of the biochemical basis of hepato-lenticular degeneration of Wilson's
The metabolism of dopamine.
disease (Cumings, 1959), a similar line of reason was invoked for other disorders involving the basal ganglia, including Huntington's chorea. Numerous investigations into the role of trace metals such as copper (Forrest, 1957), strontium (Courville et al, 1963), calcium and magnesium metabolism (Bruyn et al, 1965; Kenyon, 1969), proved inconclusive. Klintworth (1969) reported high iron concentrations in the pallidum and substantia nigra of 23 patients with Huntington's chorea studied at autopsy. This finding is not only found in the above named disorder, but probably represents a nonspecific feature of the aging brain.

At the present time it is impossible to implicate a defect in the metabolism of the trace elements in the pathogenesis of Huntington's chorea. It is noteworthy that three important steps in dopamine metabolism are dependent on trace metals (Barbeau, 1973). Dopamine beta-hydroxylase, which converts dopamine to noradrenaline, is a copper containing enzyme, while mono-amine oxidase and catechol-O-methyl transferase, enzymes essential for the degradation of noradrenaline, are dependent on iron and magnesium respectively (Fig VIII-1). It can be seen that abnormalities of metabolism of these trace metals could lead to irregular functioning of these enzyme systems and subsequent imbalances between dopamine synthesis, turnover and inactivation. It is possible that more extensive investigations of brain trace metal metabolism may yet show significant abnormalities.
C. MUCOPOLYSACCHARIDE, LIPID, STEROID AND PROTEIN STUDIES

Miscellaneous approaches involving mucopolysaccharide (Delbruck and Oepen 1964) and lipid metabolism (Oepen and Kreutz 1964) have yielded negative results.

On the basis of the observation that disturbance in sexual behaviour and progressive loss of weight may be early symptoms in Huntington's chorea, adrenal function was investigated by Bruyn et al in 1972. These studies were further prompted as a result of the observation by Oepen (1970) that urinary excretion of dehydroepiandrosterone (DHEA) was significantly reduced in the disease. The plasma testosterone, cortisol and DHEA levels were found to be normal in all patients. However, dehydroepiandrosteronesulphate (DHEA-S) was considerably reduced. The discrepancy between normal DHEA and markedly reduced DHEA-S led Bruyn et al (1972) to postulate a defect of sulphation in the adrenal reticular zone.

The observation that patients with chorea are usually very thin and age prematurely also led to studies attempting to implicate defects in protein and amino acid metabolism in this disorder. Bruyn and Lequin (1964) have reported elevated serum alpha-2-globulins and haptoglobulin in Huntington's chorea. Perry et al (1969) reported that the concentrations of six aminoscids (proline, alanine, valine, isoleucine, leucine and tyrosine) in the plasma of a group of 19 affected individuals fasting overnight were significantly reduced when compared with
those found in either a group of healthy control subjects or a group of hospitalised patients with chronic schizophrenia. The decreased concentrations of tyrosine, valine, leucine and isoleucine — all ketogenic amino acids — are similar to that seen in prolonged starvation states, such as kwashiorkor (Holt et al, 1964). Plasma alanine is usually only depressed late in malnutrition as a consequence of increased gluconeogenesis. It is unlikely that the results of Perry's study can be explained on a nutritional basis, as the patients were seemingly adequately nourished.

A later project was performed by Watt and Cunningham (1978) who controlled for diet by keeping 9 patients and 9 controls on a constant daily protein intake for ten days. They confirmed a decrease in the concentration of alanine, isoleucine and leucine, but did not find a significant difference in the concentrations of proline, valine or tyrosine. In addition, statistically important decreases in threonine, lysine and histidine were found in patients with Huntington's chorea. Since different investigators have failed to establish a consistent pattern of abnormality, it is likely that in spite of careful precautions, these findings are due to non-specific influences and not primary factors in the disease.

D. CELL CULTURE ABNORMALITIES

A major problem in all C.N.S. research is the difficulty in obtaining readily available brain tissue during life. However, the biochemical abnormality of Huntington's chorea may not be localized to brain cells and could very possibly be expressed in tissues outside the central nervous system. This is the underlying concept that has stimulated different workers to undertake studies of cell culture properties in this disorder.
Differences in growth of Huntington's chorea and control fibroblasts during their replicative lifespan in vitro has been shown by numerous authors (Goetz et al, 1975; Barkley et al, 1977; Kirk et al, 1977; Brown et al, 1978). The cell density of Huntington's chorea fibroblasts was 25 to 160 percent greater than normal fibroblasts in these studies. These results must be viewed in the light that normal fibroblasts vary considerably in their growth potential. Brown and his co-workers (1978) have attempted to understand the biochemical basis for this difference by undertaking a study of the incorporation in vitro of radio-labelled aminoacid precursors into protein. They found decreased levels of incorporation of \( ^{35} \text{S}-\text{methionine} \) into total cell protein in Huntington's chorea patients as compared to controls, giving possibly some explanation for the decreased cell growth.

An interesting finding has been reported by Tourian et al (1978) who found differential qualitative (morphological) and quantitative (cell viability) toxic effects of glutamine on Huntington's chorea fibroblasts, compared to controls, with the former showing increased sensitivity. This is particularly important as glutamine is a neurotransmitter and one suggested hypothesis is that the disease may result from specific preferential neurone sensitivity to some excitotoxictic compound such as glutamate.

E. CELL MEMBRANE ABNORMALITIES

Although Huntington's chorea has been considered a defect of the basal ganglia, recent work by Butterfield et al (1977) has suggested that a more widespread membrane involvement may be present. Using complex spin resonance techniques he has observed alterations in the physical state of membrane proteins in Huntington's chorea erythrocytes compared to controls.
A reasonable generalisation in human genetics is that recessive disorders involve enzyme proteins, while dominant disorders usually involve structural proteins, such as collagen, elastin and membrane proteins. As an autosomal dominant disease, a structural protein is likely to be affected in Huntington's chorea. Recent findings as described above highlight the possibility of a membrane protein as the candidate for the altered protein of the disorder.

F. IMMUNOLOGY

Both cellular and humoral immune abnormalities have been implicated in Huntington's chorea.

Barkley et al (1978) have investigated the possibility that the pathological changes in the brain of patients with Huntington's chorea produce new antigens that sensitize their lymphocytes. They showed that the migration of lymphocytes from these patients was inhibited by exposure to brain extracts from Huntington's chorea patients, in contrast to normal progression when confronted with normal control brain extracts. In other words a migration inhibitory factor was directed against antigen found in Huntington's chorea, but not normal brain. Barkley has speculated that the late appearance of the clinical signs in the disorder may be due to the late appearance of the disease antigen, to which the immune system responds as it would to an infectious agent.

Husby et al (1977) have studied serum samples from 78 patients for presence of antineural antibody by immunofluorescence of frozen sections of the normal central nervous system. 50% of patients with Huntington's chorea had IgG antibodies to neuronal antigens. The
test was positive in 25% of family members at risk and also positive in 30% of unaffected spouses and only 5% of controls. This surprising finding was interpreted as suggesting that an environmental agent may be important in the pathophysiology of the condition.

Further studies are needed to confirm the immunological abnormalities in the disease and to elucidate the role they play in its pathogenesis.

G. NEUROCHEMISTRY

Tremendous progress has been made in the elucidation of the neurochemical defects of Huntington's chorea over the last three years. Post mortem analysis of the basal ganglia and other areas of the brain has revealed abnormalities in different neurotransmitter systems, including gamma-aminobutyric acid, acetylcholine, dopamine, serotonin, angiotensin and substance P. This will be discussed in detail in Chapter VII-8 after the neuroendocrine results of the current project have been presented.
CHAPTER VIII-3

THE IMPLICATION OF DOPAMINE IN THE BASAL GANGLIA DYSFUNCTION OF HUNTINGTON'S CHOREA

A. INTRODUCTION

After a dopamine deficiency was identified and confirmed in Parkinson's disease (Ehringer and Hornykiewicz, 1960; Hornykiewicz, 1966) attention was drawn to the role of dopamine and other neurotransmitters in the pathophysiology of Huntington's chorea. It was suggested that hyperfunction of striatal dopamine may account for the extrapyramidal signs of the disorder. This hypothesis was based in part on the observation of the effects of a number of pharmacologic agents on the clinical manifestations of the disease.

B. DOPAMINE AS AN IMPORTANT NEUROTRANSMITTER IN THE CENTRAL NERVOUS SYSTEM

The neurochemical finding of dopamine deficiency in the nigrostriatal pathways of Parkinsonian patients led to the effective utilisation of L-dopa in the amelioration of these persons' symptoms. The efficacy of this drug has been attributed to its ability to restore function to the partially degenerated nigrostriatal dopaminergic pathways. L-dopa crosses the blood-brain barrier and is decarboxylated to form dopamine, which now serves as an important transmitter.

At presynaptic sites dopamine is concentrated in storage vesicles (Bloom, 1972), released into the synaptic cleft by electrical stimulation (Chiueh and Moore, 1973), followed by vigorous re-uptake by the presynaptic neuron and/or enzymatic catabolism (Pelton and Chase, 1975). Dopamine is then catabolized to homovanillic acid and secreted into
Release and re-uptake of dopamine at a brain synapse.
the cerebrospinal fluid where it can be measured. A diagrammatic representation of metabolism at a dopamine synapse in the brain is presented in Figure VIII-2.

Three main dopamine-containing neuronal pathways have been identified in rat brain (Fuxe et al, 1970). The nigrostriatal system arises from cell bodies in the pars compacta of the substantia nigra and terminates in the corpus striatum. There is a close relationship between the activity of this system and motor function. Pharmacological evidence presented suggests there is hyperactivity of this pathway in Huntington's chorea.

Another dopamine-containing pathway is the tuberoinfundibular system with cell bodies in the arcuata and anterior periventricular nuclei of the hypothalamus and terminates in the capillary flexus supplying the pituitary. This is involved in neuroendocrine function.

The third dopaminergic tract, the mesolimbic pathway, has its cell bodies dorsal to the interpeduncular nucleus and terminates in the nucleus accumbens and olfactory tubercle. This system plays a part in the modulation of behaviour.

The importance of dopamine as a neurotransmitter in the central nervous system is clearly established. Whether abnormalities of one of these dopamine systems is associated with irregular functioning of the other pathways is, however, not established.
Specific dopamine receptors have been identified in different organs, and in the peripheral nervous system (Thorner, 1975). These receptors are similar to those within the central nervous system in that they are stimulated by dopamine and blocked by dopamine antagonists. Whether the primary defect in Huntington's chorea, which seems to result in net functional dopamine excess acting on the nigrostriatal pathway, is also present, producing the same effect outside the central nervous system, has not been examined.

C. PHARMACOLOGICAL EVIDENCE

Three classes of drugs, including rauwolfia alkaloids such as reserpine, phenothiazines such as chlorpromazine and butyrophenones, including haloperidol, have been used with some degree of success in the treatment of Huntington's chorea.

The first agent to be used was reserpine (Lazarte et al, 1955) which depletes the brain of dopamine, noradrenaline and serotonin (Bein, 1956). The reversal of the reserpine effect by L-dopa and not serotonin favours a catecholamine mechanism in the pathophysiology of chorea (Roos and Steg, 1964). This conclusion receives support from the results obtained with more specific catecholamine depleters or antagonists. Of these the phenothiazines, particularly chlorpromazine and later trifluoperazine, has been used extensively with reduction of chorea (Vaughn et al, 1955; Whittier and Korenyi, 1968). Neuroleptics, including phenothiazines and butyrophenones, act by blocking dopamine (Van Rossum, 1966), but not noradrenaline or serotonin receptors in the central nervous system (Anden et al, 1966). As shown in Figure VIII-3, dopamine can be almost perfectly superimposed upon a portion
DRAWINGS of MODELS of the MOLECULAR STRUCTURES of

A CHLORPROMAZINE
B DOPAMINE as determined by X-ray crystallographic analysis
C DOPAMINE superimposed on a portion of the CHLORPROMAZINE MOLECULE

Fig. VIII - 3

The similarity of dopamine to part of the chlorpromazine molecule.
of the chlorpromazine molecule. The similarity of the dopamine conformation to part of the chlorpromazine structure suggests that phenothiazines exert their effect by interacting with dopamine receptor sites (Horn and Snyder 1971).

If the improvement in chorea seen with these agents is in fact due to decreasing the concentration of dopamine acting at striatal dopamine sites, then increasing dopamine reaching these sites should worsen chorea. This concept is supported by the finding that levadopa, which increases striatal dopamine, with little effect on striatal concentrations of noradrenaline (Bertler and Rosengren 1959), markedly exacerbates the involuntary movements of Huntington’s chorea (Barbeau 1969). Furthermore, bromocryptine, a dopamine receptor agonist, also aggravates chorea in these patients (Kartzinel et al 1976).

It is therefore surprising that apomorphine, another dopamine agonist, has been found to reduce the involuntary movements in Huntington’s chorea (Tolosa and Sparber; 1974; Corsini et al, 1978). This is in apparent conflict with the view that increased dopaminergic activity may account for the extrapyramidal signs of this disease. Bunney and Aghajanian (1975) have shown that low doses of apomorphine administration preferentially result in stimulation of those dopamine receptors whose excitation leads to inhibition of dopaminergic neurons. These receptors have been termed autoreceptors or self-inhibitory dopamine receptors (Carlsson, 1976). In higher doses, apomorphine and other dopamine agonists exacerbate chorea.
Thus the finding that low doses of apomorphine ameliorate the abnormal, involuntary movements in Huntington's chorea by stimulating receptors which inhibit dopamine function and synthesis, is not contradictory to the hypothesis of increased dopamine activity in the disease.

Observations in the experimental animal indicating that an increase in dopamine-mediated synaptic activity leads to hyperkinetic states, whereas hypofunction favours hypokinesis, are consistent with the concept (Pelton and Chase, 1975).

D. CONCENTRATIONS OF DOPAMINE AND METABOLITES IN THE CENTRAL NERVOUS SYSTEM IN HUNTINGTON'S CHOREA

Numerous postmortem investigations of brains of patients with Huntington's chorea, where the concentrations of dopamine, its metabolites and enzymes involved in its synthesis and degradation were determined (Fig VIII-1) have failed to yield uniform results.

Bernheimer and Hornykiewicz (1973) measured dopamine and homovanillic acid (HVA) concentrations in post mortem choreic brains and found a significant decrease in dopamine and HVA in the choreic caudate nucleus with a non-significant decrease in the putamen. Mattson (1974) could not confirm this finding in his examination of 15 choreic brains. Bird and Iverson (1974) found an insignificant decrease in caudate nucleus dopamine concentration in 17 choreic post-mortem brains. Subsequent examination of 33 choreic brains showed the decrease to be significant (Bird and Iverson, 1976). Tyrosine hydroxylase, the biosynthetic enzyme for dopamine, dopamine-hydroxylase, its degradative enzyme and noradrenaline
have also been measured in the choreic brain and no significant differences of activity have been found between affected choreics and controls (Bird and Iverson, 1974).

Spokes (1978) has recently reported results in contrast to these earlier studies. In a series of 70 Huntington's chorea brains he found significant elevations in striatal dopamine concentration compared to controls and a large series of schizophrenics. This latter group of psychiatric patients was deliberately included to see whether neuroleptic administration could be implicated for any abnormal findings that occurred.

Studies on the level of monoamine metabolites in the cerebrospinal fluid (CSF) of Huntington's chorea patients have shown a significant fall in CSF homovanillic acid, the metabolite of dopamine, with no change in 3-methoxy 4-hydroxy-penylethylene glycol, the product of noradrenaline metabolism (Chase, 1973).

The inconsistent findings of decreased, normal and increased levels of dopamine in the brain highlight the difficulties and caution that must be exercised in interpreting these results. Variance of results may be due to many factors, including different laboratory assay techniques, post mortem delay prior to receipt of brains, and incorrect selection of controls.

E. CONCLUSIONS

In summary, these findings suggest that dopamine is incriminated in the pathophysiology of Huntington's chorea. The hypothesis of striatal dopamine hyperfunction is supported by observations of the effects of a number of pharmacologic agents. However, most workers
have reported a normal or decreased dopamine concentration in post mortem examinations of basal ganglia of affected individuals. Functional activity of neurotransmitters may not be accurately assessed by measuring their absolute concentrations, but may rather reflect a balance between secretion, turnover, inactivation and relative concentration of antagonistic neurotransmitters.
CHAPTER VIII.4

INVESTIGATION OF DISTURBANCES IN HYPOTHALAMIC-PITUITARY HORMONAL DOPAMINERGIC REGULATION IN HUNTINGTON'S CHOREA: IMPAIRED PROLACTIN RELEASE

(A) GENERAL INTRODUCTION

In the following four chapters, ideas concerning dopamine influence on the regulation of the endocrine system in Huntington's chorea with particular reference to prolactin, thyrotropin and growth hormone are formulated. Consecutive investigations undertaken by the author are then described followed by presentation of results and development of concepts attempting to explain the mechanisms of disturbances in hypothalamic-pituitary hormonal regulation in Huntington's chorea.

(B) DOPAMINE, THYROTROPIN RELEASING HORMONE (TRH) AND PROLACTIN SECRETION

The high concentration of monamines in the hypothalamus, particularly dopamine (Brownstein et al 1976) raises the possibility that the substance has important regulatory functions for secretion of hypothalamic releasing hormones. This is clearly extremely important in relation to Huntington's chorea where dopamine excess is thought to account for some of the manifestations.
Relationship between Dopamine and Prolactin secretion

Dopamine inhibits prolactin secretion.
There is little doubt that dopamine is the principal brain catecholamine controlling prolactin secretion (Fig VIII-4). Prolactin release is generally accepted to be under tonic inhibitory control by the hypothalamus at the level of the tuberoinfundibular dopaminergic neurons (Hokfeldt and Fuxe, 1972). Elevation of human brain dopamine activity by the administration of L-dopa and dopamine infusion causes a significant suppression of prolactin secretion (Leblanc et al, 1975), whilst hypothalamic dopamine receptor blockade by chlorpromazine stimulates prolactin release (Kleinberg et al, 1971). L-dopa is the amino acid precursor of both dopamine and noradrenaline and its administration to rats increased the brain levels of dopamine, but even in very high doses only slightly raised the level of noradrenaline (Weiss et al, 1972). This suggests that dopamine and not noradrenaline is responsible for inhibition of prolactin secretion.

The finding that prolactin release is blocked by dopamine in isolated pituitary gland preparations (MacLeod et al, 1970) and that L-dopa administration blocks prolactin secretion following pituitary stalk section in humans (Woolf et al, 1974) has led to the suggestion that dopamine itself may be the prolactin inhibitory factor (PIF). Further support for this concept comes from Schally and his colleagues (1976), who found that the most potent fraction of pig hypothalami with PIF activity contained only catecholamines, noradrenaline and dopamine.
Thyrotropin releasing hormone is a potent stimulus to prolactin release in normal individuals (Jacobs et al, 1973). This effect is due to a direct action of TRH on the anterior pituitary. L-dopa pretreatment significantly suppresses this prolactin rise following intravenous TRH, when it is administered one hour before TRH testing (Noel and Frantz, 1973). In other words, a relative dopamine excess would diminish the prolactin response to TRH.

Phenothiazines raise prolactin concentrations in blood by inhibiting the action of dopamine (Steinberg et al, 1971; Tolis et al, 1973). If dopamine predominance is implicated in Huntington's chorea, affected individuals may be expected to have lowered prolactin levels, poorly responsive to phenothiazine administration and a blunted prolactin response to TRH. An investigation was undertaken by the author to test this hypothesis.

(C) PATIENTS AND METHODS

Three affected females and five affected males aged 27 to 70 years were studied. Choreiform symptoms predominated. A boy and a girl aged 14 in the rigid phase of the condition were also investigated. Twenty-three potentially affected first generation relatives of these patients, either sibs or children, comprising ten males and thirteen females aged 14 to 50 years were studied. The project was approved by the Hospital Ethics Committee and after careful explanation of the details and nature of the study, each patient gave written
An affected woman lies at rest in bed. The needle is kept patent via a slow saline infusion.
consent (see appendix). Each person was requested to discontinue all medication for at least two weeks before the investigation. None had any other intercurrent illness.

With the person at rest in bed or in a comfortable chair an indwelling needle was placed in an antecubital vein and kept patent with a slow saline infusion. After a baseline venous blood sample had been taken 100 μg of synthetic TRH was given intravenously (IV) and further venous blood samples were obtained every 30 minutes for the next two hours. Twenty-four hours later, the same individuals received a single intramuscular (IM) injection of chlorpromazine (25 mg) (CPZ) and blood samples were taken every 30 minutes for two hours (Fig VIII-5).

These two tests were also carried out in 12 volunteer controls, six males and six females (19 to 50 years old) who had no evidence of endocrine or metabolic disease.

Blood samples were immediately centrifuged and the plasma was separated and stored at -20°C until assayed for human prolactin by radioimmunoassay as described by Vinik et al (1974). Significance of differences in results were determined by Student’s t test.

The lowest detection limit of the assay was 1 ng/ml. The within-assay coefficient of variation was 8.4% at 40 ng/ml and the between-assay coefficient of variation (%) was 16% at 40 ng/ml.
Fig. VIII - 6

Prolactin responses to 100μg intravenous TRH. Asterisks indicate significance of difference from controls.
The fundamental organisation pertaining to ethical approval, patient and control selection, and methods of obtaining, separation and storage of blood samples were similar in the succeeding investigations, and mention will only be made of differences in procedure.

(D) RESULTS: EFFECT OF TRH ON PROLACTIN SECRETION

In controls TRH administration caused a significant increase in serum prolactin from a mean basal concentration of $4.6 \pm 0.9$ ng/ml (mean $\pm$ SE) to $15.3 \pm 1.9$ ng/ml at 30 min and $14.8 \pm 2.1$ ng/ml at 60 min (Fig VIII-6). In contrast the adults with chorea had a lower mean basal level of $1.5 \pm 0.3$ ng/ml. After TRH this rose to $10.7 \pm 2.2$ ng/ml at 30 minutes, fell to $6.3 \pm 1.4$ ng/ml at 60 minutes, $4.5 \pm 1.1$ at 90 minutes and $1.8 \pm 0.5$ at 120 minutes. The mean basal prolactin and the concentration at 1 hour ($p = 0.004$ in both instances), 90 and 120 minutes ($p = 0.01$ in both instances) were significantly less than in controls. The two young patients with rigidity had basal levels of 1 and 3.2 ng/ml which rose to 9.6 and 39.7 ng/ml respectively 30 minutes after TRH. There were no significant differences between these results and those of choreic or control patients (Fig VIII-6).
Fig. VIII - 7

Prolactin responses to TRH in controls and five out of twenty-three potentially affected first generation relatives.

Fig. VIII - 8

Mean ± S.E. prolactin responses to 25 mg intramuscular chlorpromazine.
The first generation relatives had a mean basal prolactin of $3.0 \pm 0.5$ ng/ml, the concentration rose to $16.7 \pm 1.4$ ng/ml at 30 minutes and fell to $10.2 \pm 1.1$ ng/ml at 60 minutes. These values were similar to those in controls. However, of these relatives, five had intact initial responses to TRH (Fig VIII-7) but the concentrations were unsustained compared with the response in controls. These results are summarized in Table VIII-1.

The mean peak prolactin increment of the choreic patients was $8.9 \pm 1.9$ ng/ml which was significantly different ($p < 0.05$) from $14.3 \pm 1.9$ ng/ml in the controls (Table VIII-III).

**EFFECT OF CHLORPROMAZINE ON PROLACTIN SECRETION**

The mean basal prolactin of the controls was $4.4 \pm 1.1$ ng/ml with a rise to $6.8 \pm 0.9$ ng/ml at 30 minutes, a further rise to $9.2 \pm 1.2$ ng/ml at 60 minutes and a sustained rise to $9.5 \pm 0.8$ ng/ml at 90 minutes (Fig VIII-8). In adult choreic patients prolactin levels were significantly lower than controls. The mean basal level in choreic patients was $1.3 \pm 0.1$ ng/ml ($p < 0.001$), with a rise to $1.8 \pm 0.3$ ng/ml at 30 minutes ($p < 0.001$), $3.9 \pm 0.8$ ng/ml at 60 minutes ($p = 0.002$) and $5.6 \pm 0.9$ ($p = 0.005$) at 90 minutes (Fig VIII-8).
Mean S.E. prolactin responses to chlorpromazine in first generation relatives and controls. Impaired prolactin responses are seen in 6 individual at risk relatives. Shaded area equals two standard deviations of the mean.

Excessive prolactin responses in five first generation relatives.
The mean basal concentration of the two rigid juvenile patients was 3.3 ± 2.3 ng/ml with a rise to 19.5 ± 1.4 ng/ml at 30 minutes and 19.0 ± 0.8 ng/ml at 60 minutes (Fig VIII-8). This was significantly higher than values in controls at 30 minutes (p<0.001) and 60 minutes (p<0.005) and higher than values in adult choreic patients at 30 and 60 minutes (p<0.001), 90 minutes (p = 0.004) and 2 hours (p = 0.003).

The potentially affected relatives of the patients with Huntington's chorea had a mean response to chlorpromazine which was similar to controls (Fig VIII-9). However, 11 individuals had responses which were more than 2 S.D. from those of controls. In 6 responses were poor and similar to those in adult choreic patients (Fig VIII-9) and in 5 the responses were excessive, resembling those in rigid juveniles (Fig VIII-10). The above results are summarized in Table VIII-11.

The mean peak increment in prolactin of the choreic patients was 6.8 ± 1.2 ng/ml which was not significantly different from that in controls (6.6 ± 0.8 ng/ml).

The mean peak increment of the juvenile patients (16.3 ± 0.9 ng/ml) was significantly different from the control patients (6.63 ± 0.8 ng/ml) (p < 0.001) (Table VIII-III).
**TABLE VIII-I**

PROLACTIN RESPONSES (mean ± SE) to 100 μg IV TRH

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Basal</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>4.6 ± 0.9</td>
<td>15.3 ± 1.9</td>
<td>14.8 ± 2.10</td>
<td>9.8 ± 1.6</td>
<td>6.1 ± 1.5</td>
</tr>
<tr>
<td>Adult chorea</td>
<td>1.5 ± 0.3***</td>
<td>10.7 ± 2.1</td>
<td>6.3 ± 1.4**</td>
<td>4.5 ± 1.1***</td>
<td>1.8 ± 0.5**</td>
</tr>
<tr>
<td>Juveniles</td>
<td>2.1 ± 1.1</td>
<td>24.6 ± 15.1</td>
<td>1.6 ± 13.3</td>
<td>9.1 ± 8.1</td>
<td>5.6 ± 4.6</td>
</tr>
<tr>
<td>First generation relatives</td>
<td>3.1 ± 0.5</td>
<td>16.7 ± 1.4</td>
<td>10.2 ± 1.1</td>
<td>5.62 ± 0.8</td>
<td>3.9 ± 0.5</td>
</tr>
</tbody>
</table>

Asterisks indicate significance of difference from controls

* p < 0.001
** p < 0.005
*** p < 0.05
### TABLE VIII-II

PROLACTIN RESPONSES TO 25mg IM CHLORPROMAZINE

<table>
<thead>
<tr>
<th>GROUP</th>
<th>PROLACTIN LEVELS NG/ML</th>
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<tbody>
<tr>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td>Control:</td>
<td>4.3 ± 1.0</td>
</tr>
<tr>
<td>Adult chorea:</td>
<td>1.2 ± 0.1*</td>
</tr>
<tr>
<td>Juveniles:</td>
<td>3.3 ± 2.3</td>
</tr>
<tr>
<td>First generation relatives:</td>
<td>4.2 ± 0.8</td>
</tr>
</tbody>
</table>

Asterisks indicate significance of difference from controls:

* $p < 0.001$
** $p < 0.005$
*** $p < 0.05$

### TABLE VIII-III

MEAN ± S.E. PEAK INCREMENTS IN PROLACTIN

<table>
<thead>
<tr>
<th>Group</th>
<th>After T.R.H.</th>
<th>After chlorpromazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls:</td>
<td>14.3 ± 1.9</td>
<td>6.6 ± 0.8</td>
</tr>
<tr>
<td>Chorea:</td>
<td>8.9 ± 1.9*</td>
<td>6.8 ± 1.2†</td>
</tr>
<tr>
<td>Juveniles:</td>
<td>22.6 ± 13.9</td>
<td>16.8 ± 0.9*</td>
</tr>
<tr>
<td>First-generation relatives:</td>
<td>12.8 ± 1.4</td>
<td>8.6 ± 1.3†</td>
</tr>
</tbody>
</table>

Significantly different from controls: $* p < 0.05$, $+ p < 0.001$

Significantly different from rigid patients: $† p < 0.001$
E. DISCUSSION OF RESULTS

The cardinal observations in this study were the significantly lower mean basal and poor prolactin responses to chlorpromazine and TRH in adults with Huntington's chorea compared to controls.

Since chlorpromazine permits unrestrained prolactin secretion as a result of blocking the dopamine receptors in the hypothalamus, the impaired response to chlorpromazine in adults with Huntington's chorea suggests that dopaminergic activity, at least in the hypothalamus, is enhanced. The blunted prolactin response to TRH adds further support to this hypothesis.

The prolactin response to TRH may be impaired in patients with hyperthyroidism (Snyder et al, 1973), primary pituitary failure (Tolis et al, 1973) and after a 36 hour fast (Vinik et al, 1974). None of these factors could be invoked to account for the blunted response in our patients.

It should be noted that the mean prolactin level at 30 minutes after TRH in affected individuals, though decreased, was not statistically different to that of controls. The response in patients, however, was not sustained and differences in prolactin concentrations were highly significant at 60, 90 and 120 minutes. This pattern of late impairment is different to that seen with the conditions listed above.

The two rigid juvenile patients had normal basal prolactin levels but were hyper-responsive to chlorpromazine, with abnormally high prolactin concentrations at 30 and 60 minutes. This is not the expected serum prolactin pattern of dopaminergic excess and there
is no adequate explanation for the exaggerated response. It emerges that great differences in the clinical expression of the disease may be paralleled by varying biochemical responses. Failure to accurately define the clinical status of these patients with subsequent pooling of data from rigid and choreic individuals, would mask possible differences between these groups and controls. It is vitally important to take cognizance of this possible pitfall when assessing these and other investigators' results.

The potentially important observation that approximately half of the potentially affected clinically normal first generation relatives had abnormal prolactin responses will be discussed in Chapter VIII.10(D).

F. PROLACTIN REGULATION: COMPARISON AND CONTRAST WITH OTHER STUDIES

Just after this study was published in the Lancet (1977), Caraceni et al also reported results of an investigation into prolactin and growth hormone regulation in Huntington's chorea (1977). Subsequently two other groups, namely Chalmers et al in Glasgow (1978) and Caine et al (1978) in Bethesda, Maryland, published data of similar experiments. Paulson et al (1978) have measured serum prolactin in 11 patients with the disease in the course of other investigations (1978).

Whilst these studies are not in complete agreement with each other or the investigation in Cape Town, all point to some disorder of neurotransmitter regulation of the hypothalamic pituitary axis in patients with Huntington's chorea.

A summary of the findings of all the studies is seen in Table VIII-IV.
TABLE VIII-IV

REVIEW OF PROLACTIN REGULATION IN HUNTINGTON'S CHOREA

PUBLISHED REPORTS

<table>
<thead>
<tr>
<th>INVESTIGATORS</th>
<th>PROLACTIN RESPONSES AFTER DIFFERENT AGENTS COMPARED TO CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal Levels</td>
</tr>
<tr>
<td>Hayden et al (1977)</td>
<td>↓</td>
</tr>
<tr>
<td>Caraceni et al (1977)</td>
<td>↑</td>
</tr>
<tr>
<td>Chalmers et al (1978)</td>
<td>Normal</td>
</tr>
<tr>
<td>Caine et al (1978)</td>
<td>Normal</td>
</tr>
<tr>
<td>Paulson et al (1978)</td>
<td>↓</td>
</tr>
</tbody>
</table>
Normal, decreased and increased basal prolactin levels have been reported. Paulson et al (1978) confirmed the decreased basal concentrations found in this study. He was careful to accurately define the patient's clinical features. Caine et al (1978) are in agreement with the finding of impaired prolactin release in adult choreics after dopamine receptor blockade by chlorpromazine, seen in the author's investigation. There have been no other studies of TRH stimulated prolactin release in Huntington's chorea.

I am particularly concerned about the use of dopamine agonists in these neuroendocrine investigations in view of the possible exacerbation of choreic symptoms. For this reason, dopamine antagonists were chosen for the study in Cape Town.

Possible sources of differences between this investigation and the other reported studies will now be discussed. Caraceni et al (1977) and Chalmers et al (1978) have examined growth hormone and prolactin responses in patients with Huntington's chorea after oral ingestion of 2.5 mg bromocryptine, a dopamine receptor agonist. Baseline prolactin levels in both reports are at variance with the findings of significantly reduced basal prolactins in our patients.
Unfortunately Chalmers et al (1978) and Caine et al (1978) fail to accurately specify whether rigidity or chorea predominated in their patients. This is most important as the author has shown that patients with rigidity (Fig VII-8) have diametrically opposite prolactin responses after chlorpromazine injection, compared to patients with chorea as the predominant manifestation. This may have masked differences as the mean of both rigid and choreic patients together would parallel the results seen in controls.

Caraceni et al (1977) found significantly elevated basal prolactin in his patients. Even though he has clinically defined his patients, he chose 7 control patients of whom 4 were in severe pain. This may have artificially lowered the prolactin levels in these persons as a result of catecholamine release consequent to the pain. Further evidence supporting this suggestion derives from the fact that the controls had a mean basal growth hormone level which was more than three times greater than that seen in the choreic patients. Thus, the lowered prolactin levels in controls could have given a spurious impression that basal prolactin levels in patients with Huntington's chorea were raised.

A major problem in these studies has been to determine the effects of long term neuroleptic therapy on pituitary hormone release. Phillipson et al (1978) have shown recently
that plasma chlorpromazine and its metabolites were no longer measurable in plasma of 17 persons who had been on phenothiazine therapy for extended periods after only 8 days. Blood levels may, however, not be an accurate measurement of biological effect which may persist long after the drug can be assayed in the plasma. Chalmers (1978) stipulated that patients stop drug therapy for a minimum of 72 hours prior to his investigation. The mean basal prolactin level in patients off therapy for at least three days was nearly four times higher than the mean basal prolactin concentration of patients never treated with phenothiazines, suggesting that 72 hours is much too short a period to reduce the effects of neuroleptic therapy on prolactin release investigations. At least two to three weeks are required to achieve more accurate results.

Another important consideration is the normal individual variability in responses. Even though one may find statistical significance between two measurements, this does not always imply that the differences are indeed relevant. Placebo administration as done by Caine et al. (1978) is a useful adjunct in assessing individual variability and could be used as another safeguard before wrongly assuming positive significance of results.

Subjects in the studies of Caraceni et al. (1977) and Chalmers et al. (1978) were given low doses (2.5 mg) bromocryptine and prolactin responses were measured. One mg bromocryptine was used in the study of Caine et al. (1978).
chorea were a manifestation of dopamine excess, or receptor hyper
sensitivity, it could rationally be expected that there would be
an exaggerated fall in prolactin secretion following bromocryptine
administration in these patients compared to controls. This
would be consequent to bromocryptine stimulated dopamine receptor
activity.

No consistent results were found. Plasma prolactin
fell after bromocryptine in all reports in both controls and
patients. However, no increased sensitivity to dopamine
stimulated prolactin depression was found. In fact, Caraceni
et al (1977) demonstrated a clear-cut prolactin hyporesponsiveness
in affected individuals compared to controls. This was also found
in Caine's study at 180, 240 and 360 minutes. The poor efficacy
of bromocryptine, a dopamine agonist, to suppress prolactin levels
in patients with Huntington's chorea, is difficult to understand.

Post et al (1976) and Di Chiara et al (1977) have
recently reported that low doses of dopamine agonists such as
bromocryptine seem to have a preferential action on the self-
inhibitory dopamine receptors termed autoreceptors, whose stimula-
tion results in inhibition of the activity of the dopaminergic
neurons. Furthermore, Kartzinel et al (1976) have shown that the
chorea in this disorder is only exacerbated by doses of bromocryptine
greater than 45 ng/day. Lower doses produced no significant changes. They also reported that only chronic high doses of bromocryptine significantly reduced plasma prolactin levels in 6 choreic patients.

Thus it could be deduced that the prolactin hyporesponsiveness in Caraceni's study is possibly due to the fact that low doses (2.5 mg) of bromocryptine were used which subsequently stimulated the self-inhibitory dopamine receptors, resulting in an impaired prolactin response in choreics compared to controls.

Another suggested explanation for the impaired prolactin response to bromocryptine is that patients with Huntington's chorea may have a diminished number of hypothalamic-pituitary dopamine receptors for the regulation of prolactin secretion (Caine et al 1978). This awaits clarification.

Markedly reduced dehydroepiandrosterone sulphate (DHEAS) has been reported in Huntington's chorea (Bruyn et al 1972). No adequate explanation has been formulated, though Bruyn suggested that this could be due to a defect of sulphation in the adrenal cortex, as DHEAS is abnormal in the presence of normal levels of DHEA. The effects of human prolactin on the human adrenal cortex have until recently been little investigated. Bassi et al (1977) recently reported that plasma DHEAS was increased in 10 women affected by amenorrhea with hyperprolactinemia.
Furthermore, treatment with bromocryptine, a dopamine agonist, caused a clear decrease of DHEAS correlating with a decrease in plasma prolactin. This study was confirmed by Vermeulen and Ando (1978). It is thus possible that the reported reduced level of DHEAS in Huntington's chorea is due to the reduced level of prolactin in this disease and both are secondary to dopamine hyperfunction.

(G) SUMMARY

In summary, a project was devised to determine whether dopamine excess could be implicated in the pathophysiology of Huntington's chorea. Dopamine control of prolactin release is more clearly understood than the role of dopamine in the regulation of other anterior pituitary hormone release and for this reason prolactin was the hormone chosen for such a study. The impaired prolactin release to TRH stimulation and chlorpromazine injection support the hypothesis of dopamine predominance in this disease. It remains to be determined whether patterns of release of other anterior pituitary hormones in Huntington's chorea will substantiate the proposed dopamine excess.
CHAPTER VIII.5
DOPAMINERGIC INHIBITION OF THYROTROPIN (TSH)
SECRETION IN HUNTINGTON'S CHOREA

A. DOPAMINE AND TSH SECRETION

The finding that patients with Huntington's chorea had impaired prolactin release, suggesting dopaminergic excess, prompted investigations into patterns of secretion of other pituitary hormones, in particular thyrotropin (TSH) and growth hormone (GH).

Administration of synthetic thyrotropin releasing hormone (TRH) causes a dose-related release of TSH by the pituitary (Hall et al, 1970). It has been demonstrated in man that this response can be blunted by dopamine infusion (Besses et al, 1975) and chronic L-dopa ingestion (Spaulding et al, 1972). This effect may be due either to dopamine directly or to its metabolite, noradrenaline. However, the fact that metaclopramide, a specific dopamine receptor antagonist, overcomes the suppressive effects of dopamine on the TSH response to TRH (Scanlon et al, 1977) implicates dopamine directly. The concept of inhibitory dopaminergic control over TSH release in man has also been supported by the report of Kirkegaard et al (1978) who have shown that administration of dopamine receptor blockers resulted in a significant increase in basal serum TSH levels.

An impaired TSH response to TRH in patients with Huntington's chorea would suggest that TRH receptors as well as prolactin receptors are under the influence of the proposed dopamine excess. A study was initiated by the author to test this hypothesis.
B. PATIENTS AND METHODS

Three affected females and four affected males, 25 to 65 years old were studied. As it has previously been shown in the prolactin study that clinically hypertonic patients may have an unexplained biochemical response which is diametrically opposed to that of chorea patients (Fig VIII-10), rigid patients were excluded and only those where choreic symptoms predominated were included in the investigation. The procedure for this study was similar to that described in Chapter VIII.4(C).

After a baseline blood sample was taken 100 µg of synthetic TRH was given intravenously and further venous blood specimens were obtained every 30 minutes for the next two hours. For comparison with choreics the test was carried out in 11 normal people, 6 males and 5 females, 21 to 60 years old. These individuals were of normal physique and good nutritional status.

Blood samples were centrifuged without delay and the plasma was separated and stored at -20°C until assayed for human TSH (hTSH) by radioimmunoassay (Phadebas Kit). Serum T₄ and T₃ concentrations were measured by radioimmunoassay (Amersham Kit) and T₃ resin uptake by the Thyropac kit. All samples from any single test were assayed simultaneously. The significance of differences in results was determined by the Student's t-test, and changes in the same individual by the paired t-test.

C. RESULTS: EFFECT OF TRH ON TSH SECRETION

The mean basal TSH in controls of 1.5 ± 0.2 was similar to that of 1.3 ± 0.2 ng/ml in adult patients with chorea. In both groups TRH administration caused a significant (p < 0.05) rise in TSH concentration which reached a peak at 30 minutes and returned towards the basal
Patients with chorea had an impaired TSH response to 100μg intravenous TRH compared to controls.
at 120 minutes. However, in controls there was a 4 to 5 fold increase above the basal, whereas in patients the rise was impaired and was only 2 to 3 times the basal concentration (Table VIII-V, Fig VIII-11).

There was no significant difference in serum T₄ and T₃ concentrations and T₃ resin uptake between patients and controls. The results of these tests are shown in Table VIII-VI.

D. DISCUSSION OF RESULTS

The cardinal finding in this study is the impaired TSH response to TRH stimulation in adults with Huntington's chorea. Other factors which might be associated with a blunted TSH response include prolonged fasting (Vinik et al, 1974), elevated T₃ or T₄ (Snyder et al, 1973), drugs such as aspirin (Ramey et al, 1976) or dexamethasone (Re et al, 1976), advanced age and hypothalamic-pituitary disease. The patients with chorea were not fasting, did not have raised T₃ or T₄ levels and all medication had been discontinued for at least two weeks before the investigation. The mean age of the patients was similar to that of the control group.

In the absence of other known factors the impaired TSH response to TRH stimulation in these patients suggests that pituitary TSH receptors as well as prolactin receptors are under the influence of dopaminergic excess. This gives considerable support to the hypothesis of dopaminergic predominance in Huntington's chorea.

The interaction between TRH and the central nervous system has recently been examined. It has been noted that TRH increases the minimum lethal dose of barbiturates and increases the toxicity of
strychnine (Brown and Vale, 1975). It has also been used in the treatment of depressive disorders (Coppen et al, 1974). The possibility that this and other peptides play a role in the regulation of central nervous system function and the modulation of behaviour, has been suggested (Venebey et al, 1978).

Depression with a tendency to suicide is a relatively common feature in the early phases of Huntington's chorea and was commented on in the original description of the disease (Huntington, 1872). Patients with depression (Hollister et al, 1970; Kirkegaard et al, 1978) unrelated to other diseases have also been reported to have an impaired TSH responsiveness to TRH administration in depression. Gold et al (1977) have proposed that this reflects the alteration in functional activity of dopaminergic systems seen in depression.

The author tentatively suggests that the reduction in TRH effectiveness in Huntington's chorea may be a contributing factor to the high frequency of depression in the disorder.

In conclusion, the findings of impaired human prolactin responses to chlorpromazine, and blunted TSH responses to TRH suggest hypothalamic and pituitary dopaminergic predominance in Huntington's chorea. Whether or not these observations can be extended to include other anterior pituitary hormone and dopaminergically regulated systems throughout the body remains to be established.
TABLE VIII-V

MEAN ± S.E. TSH RESPONSES TO 100 μg INTRAVENOUS TRH

<table>
<thead>
<tr>
<th>Group</th>
<th>TSH levels ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td>Control:</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>Adults with chorea:</td>
<td>1.3 ± 0.2</td>
</tr>
<tr>
<td>Significance:</td>
<td>NS</td>
</tr>
</tbody>
</table>

TABLE VIII-VI

THYROID FUNCTION IN ADULTS WITH CHOREA & CONTROLS

<table>
<thead>
<tr>
<th>Total T4 (ng/ml)</th>
<th>T3</th>
<th>T3 Resin Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls:</td>
<td>6.1 ± 0.5</td>
<td>1.6 ± 0.1</td>
</tr>
<tr>
<td>Choreics:</td>
<td>7.1 ± 0.4</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>Significance:</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
CHAPTER VIII.6

PARADOXICAL GROWTH HORMONE (GH) RESPONSES TO TRH AND CHLORPROMAZINE IN HUNTINGTON'S CHOREA

A DOPAMINE AND GROWTH HORMONE SECRETION

There is evidence to suggest that catecholamines, particularly dopamine, are important in the regulation of growth hormone secretion (Martin 1976).

Oral administration of L-dopa (Boyd et al 1970) causes release of growth hormone in man. This effect could be mediated by either noradrenergic or dopaminergic mechanisms. Dopamine is clearly in part responsible, as sub-emetic doses of apomorphine, a centrally active dopamine agonist, also causes release of growth hormone in man (Lal et al 1973). Furthermore, the dopamine blocking drug chlorpromazine inhibits growth hormone release in man (Sherman et al 1971). Thus it is clear that dopamine acts as a stimulus to growth hormone secretion in normal individuals. Other monoamines, particularly noradrenaline and serotonin may also play an important part in growth hormone stimulatory mechanisms, but their exact roles are not understood.

Although thyrotropin releasing hormone (TRH) has no apparent effect on growth hormone secretion in normal individuals it can stimulate its release in depression (Maeda et al 1975), acromegaly (Faglia et al 1973) and anorexia nervosa (Maeda et al 1976). It has recently been shown that TRH can inhibit the L-dopa induced release of growth hormone in man (Maeda et al 1975) and can cause a paradoxical fall in dopamine stimulated growth hormone secretion in baboons (Steiner et al 1977). It would be
of great potential importance to determine whether TRH can cause a fall in growth hormone secretions in humans who seem to be under constant influence of dopaminergic excess.

The aim of this investigation was to determine the effects of TRH stimulation and dopamine receptor blockade by chlorpromazine on growth hormone release in adults with Huntington's chorea.

B. PATIENTS AND METHODS

Three affected females and four affected males with Huntington's chorea, 25 to 55 years old, were studied. The patients were non-obese and taking a balanced diet. Clinically rigid patients were excluded and only those with choreic symptoms were included in the study. The procedure for this investigation was similar to that described in Chapter VIII.4(C). TRH administration was followed 24 hours later by chlorpromazine injection.

These two tests were carried out in twelve controls, six males and six females (19 to 55 years old) who had no evidence of endocrine or metabolic disease. These individuals were of normal physique and good nutritional status.

Blood samples were immediately centrifuged and the plasma was separated and stored at -20°C until assayed for human growth hormone by radioimmunoassay (Cea Sorin kit).

The lowest detection limit of the assay was 0.02 ng/ml. The within-assay coefficient of variation (%) was 13.5, 8.8 and 7.8 at 1.85, 18.2 and 30.8 ng/ml respectively and the between-assay coefficient of variation (%) was 18.0, 12.8 and 10.5 at 2.11, 16.4 and 31.4 ng/ml.
Mean ± S.E. growth hormone responses to 100 μg TRH.
All samples from each test were assayed simultaneously. Significance of differences in results were determined by the paired t-tests for within-group comparisons, while the between-group differences were assessed by Student's t-test.

C. RESULTS: EFFECT OF TRH ON GROWTH HORMONE SECRETION

In adults with chorea, TRH administration caused a fall in serum growth hormone from a mean basal concentration of $1.4 \pm 0.4$ ng/ml to $1.1 \pm 0.3$ ng/ml at 30 minutes, a further drop to $0.7 \pm 0.1$ ng/ml at 60 minutes, and $0.6 \pm 0.1$ ng/ml at 90 minutes, and a subsequent small rise to $0.7 \pm 0.1$ ng/ml at 120 minutes (Fig VIII-12). In contrast, the mean basal concentration of $1.9 \pm 0.9$ ng/ml in controls did not fall after TRH administration. Although the response in patients with chorea appeared to differ from that in controls, at no time did the differences reach statistical significance (Fig VIII-12, Table VIII-VII).

### TABLE VIII-VII

<table>
<thead>
<tr>
<th>Group</th>
<th>Growth Hormone Levels ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td>Control:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$1.9 \pm 0.9$</td>
</tr>
<tr>
<td>Adults with chorea:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$1.4 \pm 0.4$</td>
</tr>
<tr>
<td>Significance:</td>
<td>NS</td>
</tr>
</tbody>
</table>
Fig. VIII - 13

Mean ± S.E. growth hormone responses to 25 mg intramuscular chlorpromazine.
EFFECT OF CHLORPROMAZINE (CPZ) ON GROWTH HORMONE SECRETION

The mean basal growth hormone level of the controls was 2.1 \( \pm \) 1.0 ng/ml. CPZ administration induced a rise to 4.7 \( \pm \) 1.6 ng/ml at 30 min., a further rise to 6.2 \( \pm \) 1.8 ng/ml at 60 min. and a subsequent fall to 3.2 \( \pm \) 1.0 ng/ml at 120 min. (Fig VIII-13). None of these changes were, however, significantly different from the mean basal levels.

The mean basal level in the choreic patients of 1.9 \( \pm \) 1.0 ng/ml was similar to controls. In contrast with the controls CPZ caused a fall to 0.8 \( \pm \) 0.2 ng/ml at 30 min and a subsequent rise to 4.1 \( \pm \) 1.7 ng/ml at 120 min. (Fig VIII-13). Although these changes were not significant per se, the concentrations at 30 and 60 minutes were significantly (\( p < 0.05 \)) less than those of the controls. These results are summarized in Table VIII-VIII.

### TABLE VIII-VIII

**MEAN ± S.E. GROWTH HORMONE RESPONSES TO 100 µg INTRAMUSCULAR CHLORPROMAZINE**

<table>
<thead>
<tr>
<th>Group</th>
<th>Growth hormone levels ng/ml.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td><strong>Control:</strong></td>
<td>2.1 ( \pm ) 1.0</td>
</tr>
<tr>
<td><strong>Adults with chorea:</strong></td>
<td>1.9 ( \pm ) 1.0</td>
</tr>
<tr>
<td><strong>Significance:</strong></td>
<td>NS</td>
</tr>
</tbody>
</table>
D. DISCUSSION OF RESULTS

The cardinal observation in this study was the fall in growth hormone levels following chlorpromazine administration in adults with Huntington's chorea. The apparent fall in hGH concentration after TRH administration failed to reach significance.

There have been previous reports of disturbed control of hGH secretion in Huntington's chorea: an exaggerated response to arginine infusion (Leopold and Podolsky, 1975), bromocryptine (Caraceni et al, 1977) and L-dopa, non-suppressibility of GH after glucose and a paradoxical fall in GH after L-dopa and glucose administration (Podolsky and Leopold, 1974).

The hGH responses to oral bromocryptine were studied by Caraceni et al (1977) and Chalmers et al (1978) with great variation in results. Caraceni et al (1977) found mean peak GH levels which were significantly higher than in controls, indicating hyper-responsiveness to bromocryptine administration. Chalmers et al (1978) showed a reduced hGH response to bromocryptine in adults with Huntington's chorea. These differences are difficult to reconcile, but may indicate different control selection, variations in the assay and failure to adequately define clinical data.

L-dopa administration causes release of growth hormone in man (Boyd et al 1970). If dopaminergic predominance is a major factor in the pathophysiology of this condition, it could rationally be expected that affected individuals would have an abnormally elevated hormone level. There have been differing reports of both an abnormally raised (Phillipson and Bird 1970) and normal
basal growth hormone levels (Podolsky and Leopold, 1974; Caraceni et al, 1977; Chalmers et al, 1978) in adults with chorea. Patients in this study had a normal mean basal hGH level. Results of these different studies are summarised in Table VIII-IX

### TABLE VIII-IX

REVIEW OF GROWTH HORMONE (GH) REGULATION IN HUNTINGTON’S CHOREA

#### PUBLISHED REPORTS

<table>
<thead>
<tr>
<th>INVESTIGATORS</th>
<th>GH RESPONSES AFTER DIFFERENT AGENTS COMPARED TO CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal Levels</td>
</tr>
<tr>
<td>Phillipson et al (1976)</td>
<td></td>
</tr>
<tr>
<td>Keogh et al (1976)</td>
<td>Normal</td>
</tr>
<tr>
<td>Caraceni et al (1977)</td>
<td>Normal</td>
</tr>
<tr>
<td>Chalmers et al (1978)</td>
<td>Normal</td>
</tr>
<tr>
<td>Hayden et al (1979)</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Although acute administration of dopamine (Burrow et al., 1977) and L-dopa (Boyd et al., 1970) stimulates hGH secretion, this response is not sustained and the pituitary becomes refractory to continued dopamine (Burrow et al., 1977) and frequent L-dopa administration (Eddy and Parker, 1976). It has been shown that pituitary hormone receptors in Huntington's chorea are probably under the influence of chronic dopaminergic excess, which might explain the normal basal concentrations found in the current study.

The patients in this investigation had an abnormally marked fall in hGH levels, following dopamine receptor blockade by chlorpromazine as compared to controls (Fig VIII-13). Even though the fall in hGH concentrations in the patients is not significant, it is statistically different from the concentration in controls at 30 and 60 minutes and is further evidence for a disturbance in the control of GH secretion in this disorder. The exaggerated fall in hGH is consistent with the suggested hypothesis of enhanced dopaminergic sensitivity in Huntington's chorea (Klawans et al., 1972).

Dopamine receptor blockade by chlorpromazine did not drop the mean hGH levels in controls as might have been expected. In fact, there was a slight but insignificant increase in hGH concentration. This may have been the result of an inadequate dosage (25 mg) of chlorpromazine which was sufficient in patients with chorea, but inadequate to elicit a similar response in controls. Indeed, inhibition of dopamine mediated locomotor activity in rats by low doses of the dopamine agonist, apomorphine, and stimulation by higher doses (Carlsson, 1976) would suggest that activation and inhibition
of dopamine receptors is dependent on drug dosage. The non-significant increase in hGH secretion following a small dose of chlorpromazine may reflect stimulation of dopamine receptors in these normal individuals.

TRH alone does not normally affect growth hormone release. However, the finding that TRH caused a paradoxical fall in dopamine stimulated GH release in baboons (Steiner et al, 1977) and also blocked the GH release induced by oral L-dopa in man (Maeda et al, 1975) suggests that TRH inhibits exogenous dopamine mediated GH release. These observations, together with the finding that TRH caused a depression in GH levels in patients with Huntington's chorea in this study, a disease in which dopaminergic predominance has been implicated, may suggest that TRH has an inhibitory effect on hGH release in the presence of endogenous dopaminergic excess. Further studies are warranted using a placebo control to determine whether the GH fall after TRH is due to TRH or rather represents a spontaneous decrease from a slightly stress-increased basal sample.
CHAPTER VIII-7

SUMMARY OF BIOCHEMICAL FINDINGS AND CONCLUSIONS

There is convincing pharmacological evidence of hyperactivity of the nigrostriatal dopamine system in Huntington's chorea. The neuroendocrine findings of an impaired PRL response, together with a blunted TSH response to TRH suggest that there is a corresponding increase in the activity of the tuberoinfundibular dopamine system, which invests the hypothalamus.

Eleven of 23 clinically normal first generation relatives had abnormal PRL responses to CPZ, which corresponded with those with the manifest disease. This may indicate that neuroendocrine studies could be valuable markers in the preclinical stage of Huntington's chorea.

Rigid juvenile patients had unexplained exaggerated PRL responses to CPZ blockade, diametrically opposed to those of adults with chorea. It is important that cognizance be taken of these differences if our understanding is to be more complete.

The problem of difficulty in the interpretation of data presented, due to effects of prior drug therapy deserves mention. The marked fall in growth hormone levels following dopamine receptor blockade by chlorpromazine in adults with chorea compared to controls would suggest that striatal receptor hypersensitivity to normal dopamine input is present. One possible explanation for this phenomenon is that this striatal dopamine hypersensitivity may represent a form of tardive dyskinesia following cessation of drug therapy only two weeks before these neuroendocrinological investigations were undertaken.
Marsden et al (1975) have reported that the clinical findings in tardive dyskinesia may represent a state of relative dopaminergic hypersensitivity. Most of the patients in this study who were on drug therapy were taking phenothiazines and butyrophenones which are also the most commonly implicated drugs in tardive dyskinesia.

There are important objections to this hypothesis. Firstly, patients who were on no drug therapy at all had similar neuroendocrinological responses to those who had been on long term therapy. Furthermore, none of those patients taking drugs had dystonic reactions which could be related to cessation of therapy. This hypothesis would also not explain who almost 50% of clinically normal first generation relatives who were at risk of developing this disorder and who were on no therapy at all, should have biochemical responses similar to those individuals with Huntington's chorea. For these reasons prior drug therapy can probably not be implicated in the abnormal patterns of hormone release seen in these patients.

Emotional and behavioural changes in Huntington's chorea are common and may herald the onset of the disease. Hormones exert influence on conduct and mood, quite apart from their classic endocrine effects (Nemeroff et al, 1978). The mechanisms by which these peptides exert their effects is not understood. Since these hormones play a role in behavioural homeostasis, disturbed hormonal release as reported may participate in the pathophysiology of the psychiatric symptomatology of Huntington's chorea.

The proposed dopamine excess may not be due to an absolute increase in hypothalamic dopamine, but may reflect an imbalance between dopamine secretion, turnover, inactivation, interaction with receptors
and relative concentrations of antagonistic neurotransmitters such as gamma-aminobutyric acid, acetylcholine, serotonin, noradrenaline and substance P. The task of unravelling the nature of the interactions between biogenic amines and the endocrines is complex and conclusions must be viewed in this light.
CHAPTER VIII-8

IN VolVEMENT OF NON-DOPAMINERGIC NEUROTRANSMITTER SYSTEMS IN HUNTINGTON'S CHOREA

A. INTRODUCTION

Postmortem analyses of the basal ganglia of Huntington's chorea patients have shown abnormalities in dopamine and each of the following other neurotransmitter substances: gamma-aminobutyric acid, acetylcholine, serotonin, angiotensin and substance P.

Numerous substances such as somatostatin, vasopressin, endorphins, gastrin, vasoactive intestinal polypeptide, the enkephalins and others are also now considered to function as neurotransmitters and have not been measured in this disease.

Involvement of the non-dopaminergic neurotransmitter systems will be described in this chapter. Whether the changes described are primary or secondary to other pathological processes is uncertain. Furthermore, the extent to which these changes are reversible and/or counteracted with drug therapy remains to be determined.

B. GAMMA-AMINOBUTYRIC ACID (GABA)

GABA was the first amino acid shown to function as a neurotransmitter in both vertebrate and invertebrate nervous systems.

There is strong evidence that GABA acts as a central inhibitory neurotransmitter (Curtis 1976). Perry and his colleagues (1973) have noted that GABA levels of the substantia nigra and
GLUCOSE

TRICARBOXYLIC ACID CYCLE

SUCCINIC SEMIALDEHYDE

GABA Transaminase

GLUTAMIC ACID

Glutamic Acid Decarboxylase

GABA

Fig. VIII - 14

The metabolism of GABA.
striatum were considerably reduced in patients with Huntington's chorea (Fig VIII-15). This same group have recently reported a decreased GABA in the nucleus accumbens and thalamus of schizophrenic patients which was as marked as that found in Huntington's chorea (Perry et al, 1978). The decreased GABA could be due to decreased synthesis, or increased GABA catabolism by GABA transaminase (Fig VIII-16). GABA receptors are apparently normal in this disease (Enna et al, 1976). Other investigators have subsequently reported a significant decrease in glutamic acid decaboxylase (Fig VIII-15) (GAD) activity which is the enzyme converting glutamic acid to GABA (Fig VIII-14), and is a stable and specific marker for GABA containing neurons (Bird and Iversen, 1974; McGeer et al, 1973).

However, GAD activity has also been found to be decreased (although not as severely) in patients dying with Parkinson's disease (Lloyd and Hornykiewicz, 1973) and with senile dementia (Bowen et al, 1974).

Homocarnosine, a dipeptide derived from GABA is also reportedly reduced in the basal ganglia of patients with this disorder (Urquhard et al, 1975). Whether this is secondary to a deficiency of GABA is uncertain.

Therapeutic endeavours to augment brain GABA levels in Huntington's chorea by administering this neurotransmitter have been impractical as GABA does not cross the blood brain barrier. Drugs such as sodium valproate (Symington, 1978), which elevates brain GABA levels by inhibiting its degradative enzyme, GABA transaminase (Fig VIII-14) and isoniazid (Perry, 1979), which inhibits another degradative enzyme, GABA aminotransferase, have been used with contradictory
Fig. VIII - 15

Neurochemical profile of the basal ganglia in Huntington's chorea compared to controls.
results. Only isoniazid (Ferry et al, 1979) has been shown to help some patients with Huntington's chorea and since this drug also inhibits the enzyme in the brain that synthesizes GABA, namely GAD, it is possible that it was mediated by some totally different and unexpected mechanism.

Thus it is likely that GABA deficiency in Huntington's chorea is only part of a complex biochemical disturbance and imbalance in several neurotransmitter systems. Furthermore, if the primary gene defect in this disease were related to the GAD/GABA system, it is possible that its effects would be demonstrated in non-neural tissue since GAD and GABA occur outside the CNS, especially in the kidney. However, Bird (1976) found normal GAD activity in kidneys from four patients with Huntington's chorea.

Although disorder brain GABA metabolism may be a consistent and important feature in this disorder, it is not specific to Huntington's chorea and is probably only a part of a complex biochemical imbalance in several neurotransmitter systems. Its relationship to the underlying genetic defect remains to be elucidated.

C. ACETYLCHOLINE

The corpus striatum contains high concentrations of both acetylcholine and its synthesizing enzyme, choline acetyltransferase. Biochemical evidence of cholinergic neuron involvement in Huntington's chorea derives from the finding of marked reduction (50%) in the activity of choline acetyltransferase in the striatum and globus pallidus (Bird and Iversen, 1974; McGeer et al, 1973) of affected individuals (Fig VIII-15). A 50% decline in binding at muscarinic cholinergic receptors in the caudate nucleus of affected individuals has also been
reported (Enna et al, 1976).

Pharmacologic attempts to alleviate the abnormal movements of this disorder by using drugs which act at acetylcholine receptors or modify the activity of cholinergic neurones have not been convincing. Physostigmine and other agents which increase brain acetylcholine by interfering with its enzymatic degradation have failed to obtain consistent effects in diminishing chorea (Tarsy, 1974). It is therefore likely that a defect in the cholinergic system in this disorder is not the primary defect, but rather secondary to abnormalities in other chemical systems.

D. NORADRENALINE

The importance of noradrenaline lies in its role in the control of elementary locomotor activity (Barbeau, 1973). Concentration of noradrenaline in the basal ganglia of patients with Huntington's chorea lies within the normal range (Bernheimer and Hornykiewicz, 1973). In addition, normal spinal fluid levels of noradrenergic catabolites (Chase, 1973) fail to provide support for the notion of altered noradrenergic systems in this disorder.

E. SEROTONIN

Serotonin systems interact with dopamine and noradrenaline in the control of motor behaviour. A 50% decrease in the serotonin receptor sites in the basal ganglia of patients with Huntington's chorea was reported by Enna et al (1976). In addition administration of the precursor of serotonin, tryptophan, has exacerbated chorea in some instances (Lee et al, 1968). However, the demonstration of normal serotonin concentration in the caudate
nucleus and globus pallidus (Bernheimer and Hornykiewicz 1973) (Fig VIII-15), together with other clinical pharmacologic studies involving drugs which antagonise serotonin effects (Ringel et al 1973) have failed to implicate serotonin as a primary factor in the pathogenesis of this disorder.

**(F) SUBSTANCE P**

Substance P is an excitatory neurotransmitter (Fig VIII-16) whose role in Huntington's chorea has only recently been examined.

The concentration of substance P is highest in the substantia nigra of the central nervous system (Kanazawa and Jessell 1976). Kanazawa et al (1977) reported evidence for a decrease in substance P content of substantia nigra in Huntington's chorea which paralleled the decrease in GAD (Fig VIII-15). The significance of this finding remains to be elucidated.

**(G) ANGIOTENSIN AND ANGIOTENSIN CONVERTING ENZYME (ACE)**

ACE is a specific dipeptide which converts the decapeptide angiotensin I to the octopeptide angiotensin II. Arregui et al (1977) have recently shown that there is an 83 - 92% reduction of ACE in the globus pallidus in Huntington's chorea (Fig VIII-15). The possibility that an abnormality in the renin-angiotensin system plays some role in the disorder is suggested by the finding that patients with Huntington's chorea, despite normal resting blood pressure and normal responses to the
Valsalva manoeuvre, have a defect in postural vasoregulatory mechanisms (Aminoff and Gross, 1974).

Bradykinins play a major role in the maintenance of postural control of blood pressure. Recently it has been shown that kininase which metabolises bradykinin, has a similar substrate and antigen specificity to homologous renal and lung ACE (Oparil, 1977). Whilst it is not yet possible to equate kininase and ACE, the finding of deficient ACE in the striatum in patients with Huntington's chorea may parallel a deficiency of kininase, which in turn is an important factor in the mediation of impaired postural regulatory mechanisms seen in this disorder.

Blair et al (1977) have shown in dogs that catecholamines, including dopamine, formed within the central nervous system can act to lower renin secretion in the peripheral circulation. An important line of research to be pursued in Huntington's chorea is the examination of the effect of proposed dopamine excess, both on the renin-angiotensin system in the brain and the peripheral circulation.

At the present time, in collaboration with Dr. P. Sever's laboratory at St. Mary's Hospital in London, samples drawn from patients and controls in this country by the author, are being assayed for renin, ACE, angiotensin I and II and peripheral catecholamine levels, including dopamine, noradrenaline and adrenaline in an effort to answer some of these problems.
Interactions of multiple neurotransmitters in the brain,
A. INTRODUCTION

It is clear that multiple neurotransmitter systems are disturbed in Huntington's chorea. An exciting and important proposition is that these several transmitters interact, and that disturbance of one of the chemical systems in the basal ganglia may be followed by changes in several other interrelated neurotransmitter systems, with which it is in contact.

The successful treatment of Parkinsonism, a disease of dopamine deficiency, with L-dopa or anticholinergic drugs, suggests that there is a delicate balance between the state of functional activity of cholinergic and dopaminergic systems, particularly in the striatum. There is now considerable experimental evidence to support this clinical observation.

B. INTERACTION BETWEEN NEUROTRANSMITTER SYSTEMS

It appears certain from histochemical studies that the nigrostriatal dopaminergic neurons form direct synapses on cholinergic interneurons of the striatum (McGeer et al, 1976). Pharmacological studies suggest that dopamine exerts an inhibitory action on cholinergic systems (Fig VIII-16). Agents that enhance dopamine activity (L-dopa, amphetamine, apomorphine) cause a decrease in acetylcholine release in this region, whilst drugs blocking dopamine receptors in the striatum (such as most
neuroleptics) as well as cholinergic agonists, increase the synthesis and release of dopamine in the striatum (Bartholini et al, 1975).

It is also likely that acetylcholine has, possibly by way of a positive feedback, a mild enhancing action on striatal dopaminergic mechanisms, whilst inhibiting the nigral dopamine system (Fig VIII-16). Evidence supporting the positive feedback is that anticholinergics in high doses (Hornykiewicz, 1976) seem to decrease striatal dopamine turnover (Bartholini et al, 1975).

Thus, when the dopamine is diminished as in Parkinsonism, there is less inhibition and a consequent overactivity of cholinergic neurons. However, when the dopaminergic system is excessive as in Huntington's chorea, decreased cholinergic activity as shown by the decreased levels of choline-acetyltransferase in the striatum is present (Fig VIII-16).

These findings are consistent with the hypothesis of dopamine excess in Huntington's chorea. However, an important question still needs to be answered - What is the evolution of the net dopamine excess in relation to the described neurotransmitter interactions?

Recent pharmacological evidence suggests the possibility of a dopamine-GABA interrelation at the level of the basal ganglia. Drugs increasing GABA concentrations in the brain reduce dopamine turnover in the striatum (Anden, 1974). In addition intranigral injections of picrotoxin, a GABA receptor-blocker, produced a reversible contralateral turning syndrome analogous to that seen after unilateral intracaudate injection of dopaminomimetic drugs (Tarsy et al, 1975). From this it
can be concluded that increased GABA activity inhibits striatal dopamine activity, whereas blocking GABA receptors stimulates striatal dopamine receptors. In other words, the GABA system impinges on the dopamine system in the striatum to exert an inhibitory effect (Fig VIII-16).

Conversely, there seems to be a feedback system which suggests that dopamine itself may influence GABA activity. Acute administration of L-dopa inhibits GABA activity (Fig VIII-16) whilst prolonged administration of this drug increases the activity of the GABA-synthesizing enzyme, glutamic acid decarboxylase (GAD) in the striatum (Lloyd and Hornykiewicz, 1973).

C. THE HYPOTHESIS

It is now possible to postulate a mechanism which explains the development of dopamine excess in Huntington's chorea. Decreased activity of the GABA system in this disorder as evidenced by reduced levels of GABA and GAD, may result in less inhibition of the dopaminergic neurons in the basal ganglia and consequent dopamine hyperactivity. This functional excess may then act to suppress cholinergic receptors and mechanisms. It seems likely that these striatal cholinergic neurons play some role in regulation of the GABA-mediated system, but this remains to be confirmed.

Whilst absolute levels of dopamine may be normal or even reduced in the basal ganglia, it is clear that these absolute concentrations may have little functional significance and that the clinical features of this condition arise as a result of complex changes in
several neurotransmitter systems, the net effect being one of dopamine excess.

This is certainly an oversimplification, but it is clear that in considering Huntington’s chorea and other diseases of basal ganglia dysfunction, it is useful to think in terms of multiple neurotransmitter interactions.

It would be a great misconception to conclude that the defect in the metabolism of dopamine and other neurotransmitters is the cause of Huntington’s chorea. These abnormalities are the secondary effect of a primary defect that is still unknown.

The basal banglia are particularly rich in other neurotransmitters besides dopamine, acetylcholine and gamma-aminobutyric acid and these systems may also play an important role in control of dopaminergic systems. Most transmitter substances have yet to be studied in this disorder. Pharmacological data suggest that substance P, which is decreased in Huntington’s chorea, is an excitatory transmitter influencing dopaminergic neurons (Magnusson et al 1976), whilst serotonin (5HT) inhibits these neurons (Hornykiewicz 1976) (Fig VIII-16). Interaction between the renin-angiotensin and dopaminergic system still awaits clarification.

In this chapter I have postulated a unifying hypothesis based on different neurochemical findings to explain the evolution of the net functional dopamine excess in the nigro-striatal pathways in Huntington’s chorea. The neuroendocrine findings presented previously, support the hypothesis of dopamine excess, extending to
the tuberoinfundibular dopamine system as well. Whether the unifying hypothesis relating to striatal dopamine predominance can be invoked at the level of the hypothalamic–pituitary axis is not clear.

Recent studies suggest that GABA may play a role in the neural modulation of certain pituitary hormones. Mioduszewski et al (1976) and Pass et al (1977) have reported an elevation of serum PRL following intracerebral administration of GABA in the unanaesthetized rat. Tamminga et al (1978) have shown using a GABA agonist, muscimol, that GABA exerts a stimulatory role in the regulation of human PRL. Several possible mechanisms exist for this effect. GABA could act directly on the pituitary. This is unlikely as GABA does not stimulate PRL release or interfere with dopamine induced inhibition of PRL release from rat anterior pituitary cells in culture (Tamminga et al, 1978). It is possible that GABA stimulates PRL secretion by decreasing synthesis and release of dopamine in the hypothalamus, thus decreasing PIF. The striatal GABA system has already been shown to exert an inhibitory effect on striatal dopaminergic neurons. The decreased basal prolactin shown in the current study thus could be due to increased PIF consequent to the reported decrease in GABA in Huntington's chorea.

This is preliminary evidence that the postulated model for the basal ganglia may well be applicable to the tuberoinfundibular dopamine system. Further knowledge concerning the nature of the interaction between other neurotransmitter systems and pituitary hormone release is needed to clarify this issue.
CHAPTER VIII-10

PRESYMPTOMATIC DETECTION OF HUNTINGTON'S CHOREA

A. INTRODUCTION

There is still no reliable method of determining whether a symptom-free descendant of a person with Huntington's chorea carries the gene for the disorder. Different attempts to diagnose Huntington's chorea before the onset of obvious clinical signs have been based on the hypothesis that abnormal findings in an affected individual may be found (perhaps to a lesser degree) in a presymptomatic carrier of the gene.

It was this concept which stimulated the neuroendocrine investigation of first generation relatives of affected individuals who were found to have abnormal patterns of pituitary hormone release.

B. ETHICAL ISSUES

The possible advent of a successful, reliable predictive test poses numerous ethical problems. It could be argued that these issues are at present irrelevant, as there is no safe, established method for presymptomatic identification of the carrier. I am, however, in agreement with the editorial in the British Medical Journal (1978) which proposed that "the time has come when we should debate guidelines for handling the results before the test is introduced."

Whilst acknowledging the major ethical problems that such a test would pose, identification of the genetic carrier would have enormous medical and social significance and could constitute the most promising step towards the understanding of the pathophysiological basis of the disease. Advances in presymptomatic detection and
treatment may not occur concurrently. For this reason Stevens (1971) has argued that the potential harm of such a test would outweigh the benefit accrued. At this stage, whilst no adequate therapy is available, he proposed that it would be better for 50% of the "at risk" individuals to be encouraged by false hope than to know for certain that they are carriers of the gene.

Hemphill (1973), on the other hand, has given three different motivating considerations for continued research in this area — a drop in the frequency of the disease in future generations, the removal of the uncertainty for those free of the gene, and allowing those who have the gene to plan their lives and act responsibly in the light of such knowledge.

Ethical guidelines for the current neuro-endocrine investigation of patients and families were carefully determined. Each individual was contacted personally prior to the investigation. They partook in the project voluntarily and were free to withdraw at any stage. Each person was told of the experimental nature of this research. A critical issue that ensued was what to tell the subjects subsequent to testing. In view of the inability to determine the significance of the findings, it was decided that it would be immoral and unethical to disclose any results. Patients were informed of this policy prior to the beginning of the project, and were told that the procedure would be of no immediate benefit to them, but may help in the long term search for the biochemical parameters of this disorder. No persons refused to partake in the study.

The problem of possible stigmatization of these individuals by employers and others as "at risk for Huntington's chorea" was avoided
by strict confidentiality. Letters to employers requesting time off work were written in broad outline without mention of the disease itself.

After the study participants were contacted to determine whether they were in need of any special support. The project did provoke anxiety in two subjects who asked me to disclose the results of their studies. On careful reiteration of the conditions under which they participated, and with further psychosocial support, their anxiety was alleviated.

Whilst these are the guidelines employed for this research, other issues will ensue if a safe and reliable method is developed. Important considerations will include the timing of such a test, to whom it should be given and by whom it should be administered.

It is hoped that the principles for the use of a presymptomatic test will be clearly evolved by the time a reliable, safe method for identification of the genetic carriers has been developed.

The Commission for the Control of Huntington's Disease (1977) has suggested preliminary broad guidelines for the utilization of a predictive test as follows:-

1. All presymptomatic testing must be entirely voluntary.

2. All presymptomatic testing must be accompanied by pre- and post counselling to ensure that subjects and their families are fully informed as to the nature of the test, its possible outcome and the impact of that information on the lives of those concerned.
3. Legislative measures should be enacted to guarantee that results of any test be kept confidential and private.

4. Legislative protections should be instituted to prevent public or private organizations, agencies or corporations from requiring that individuals undergo presymptomatic testing as a condition for employment, insurance coverage, or qualifications for services or benefits.

Implementation of these guidelines would protect those "at risk" who volunteer for such a test. A major problem has arisen with regard to further research on patients "at risk" for Huntington's chorea in the U.S.A. According to a recent law, investigators in that country are legally bound to advise persons of the outcome of their predictive tests, notwithstanding the fact that these results may be of doubtful significance. This has severely discouraged many workers in the U.S.A. from doing any testing on "at risk" individuals. It is hoped that there will be some reasonable resolution of this impasse which will protect volunteering subjects and also allow investigators to continue the search for a predictive test and the underlying biochemical aberration of Huntington's chorea.

C. PREVIOUS ATTEMPTS AT PRESYMPTOMATIC DIAGNOSIS

The earliest method of presymptomatic diagnosis was in 1948 when Patterson et al suggested that the excess of slow activity on the electroencephalogram in children of affected patients might predict those individuals who would later develop chorea. In 1966 twenty-three of the original 26 persons tested were followed up by
Chandler. The prediction proved wrong in 50% of these people and showed the test to have no clinical application.

Numerous clinicians have reported that mothers have a very keen premonition as to which of their children will be affected long before the onset of clinical features. This has also been my experience during this study. Goodman et al (1966) investigated offspring of affected individuals through the use of various psychological, speech, language and hearing tests. While results allowed separation of the unaffected "at risk" children into different groups based on their performance in psychological tests of speech and language, it is not apparent whether the abnormalities represented disordered function as a result of a disturbed environment, or rather the earliest manifestations of Huntington's chorea. It is unlikely that psychological methods will provide the answer, as there are too many undetermined immeasurable variables.

Individuals with established disease have abnormal eye and finger movements. This observation prompted Falek (1969) and Petit and Milbled (1973) to examine these movements in possible carriers of the gene. Although changes were found in some members of the "at risk" population, these were non-specific and do not help to divide this group into heterozygous and non-heterozygous siblings.

Other methods to detect minor neurological abnormalities in muscle activity, and the visually evoked potential employing electromyography (Baro, 1973) and electroencephalography respectively (Ellenberger et al, 1978) have been inconclusive.
The best known and most controversial attempt at presymptomatic diagnosis is the L-dopa provocative test. This was based on the rationale that stimulation of receptors hypersensitive to dopamine might elicit chorea in those who have the gene (Klawans et al, 1973). It has now fallen into disrepute for numerous reasons. Whilst false positives occurred rarely, false negatives have been reported. The test may be non-specific and may apply to those who are susceptible of developing tardive dyskinesia following prolonged neuroleptic exposure and not to persons affected with Huntington’s chorea. Furthermore, the effect of this test on the time of onset and the rate of progress of the disease is unknown. The development of symptoms in an asymptomatic individual at risk allows the subject as well as the investigator to read the results. This could impose severe psychological stress. For these reasons workers have been discouraged from using this method.

More recent studies include those involving genetic linkage, computerized axial tomography and measurements of gamma aminobutyric acid in the cerebrospinal fluid of affected individuals.

Genetic linkage studies in Huntington’s chorea have been inconclusive. Went (1977) excluded linkage with 30 markers. Pericak-Vance et al (1978) using 22 marker loci were able to begin delineation of an exclusion map in relation to the gene for Huntington’s chorea. Linkage analysis could lead to division of asymptomatic family members into high and low risk groups. Problems with this method include necessary availability of large families with, optimally, three involved generations and large numbers of siblings. Linkage studies may also be
complicated by possible heterogeneity in this disorder.

In the South African context, prospects for linkage studies are good as large families with both affected parents and affected children are fairly commonly encountered.

Although computerized axial tomography is useful in showing basal ganglia atrophy in affected persons, Neophytides et al (1978) have been unable to show any changes in "at risk" individuals with this method.

Manyam et al (1978) have recently found a bimodal distribution of cerebrospinal fluid GABA levels in individuals "at risk" for the disease. This approach arose from the finding of significantly reduced GABA levels in patients with Huntington's chorea (Enna et al, 1977). The validity of this method awaits long term follow-up.

Numerous attempts at presymptomatic diagnosis have been described. At this time no single test is reliable, none have been validated and the problem of false positives and false negatives remains.

D. POSSIBLE MEANS OF DISCRIMINATION BETWEEN CARRIERS AND NON-CARRIERS BY NEUROENDOCRINE INVESTIGATION

In the current study 23 unaffected first generation relatives of persons with Huntington's chorea were included in the neuroendocrine investigation of prolactin release. Of these, 13 were females and 10 males. Thirteen were children of affected parents, whilst 10 were either brothers or sisters of affected sibs.
A major problem in projects designed for presymptomatic diagnosis is that studies have used children of patients with chorea, which means that many years will have to pass before the disease manifests in those who carry the gene. Siblings of known affected persons were deliberately included in this study, with the realization that these individuals (should they indeed carry the gene) might develop the clinical manifestations in the very near future. In this way it may be possible to obtain a result more quickly and thus reduce the need for long term follow-up.

The rationale for this investigation was as follows: Since impaired prolactin regulation had been a feature in adults and children with this condition, it is possible that biochemical changes, resulting in the same abnormality, may precede the clinical manifestations and thus be present in those who have the gene for Huntington's chorea.

The methods used have been described in Chapter VIII-4(C). After chlorpromazine injection, the potentially affected "at risk" individuals had a mean prolactin response to chlorpromazine which was similar to controls (Fig VIII-9). However, examination of individual curves revealed that 11 relatives had responses which were more than 2 S.D. from those of controls. In 6 responses were poor and similar to those in adult patients with chorea (Fig VIII-9) and in 5 the responses were excessive, resembling those in rigid juveniles (Fig VIII-10).

After TRH administration the first generation relatives had mean prolactin responses which were not significantly different to those seen in controls. Examination of individual responses, however,
Fig. VIII - 17

Prolactin response to TRH in E.S. compared to controls.
revealed that of these relatives, 5 had intact initial responses to TRH (Fig VIII-7) but the concentrations were unsustained at 60, 90 and 120 minutes compared with the response in controls. Adults with chorea also had initial responses which, although, impaired, were not significantly different from controls. However, these responses in affected adults were significantly blunted at 60, 90 and 120 minutes (Fig VIII-6). Thus 5 clinically normal individuals at risk also had prolactin curves after TRH which were similar to adults with chorea.

It is of great interest that this group of 5 with impaired prolactin responses to TRH, is part of the very same set of 6 individuals who had blunted prolactin responses to chlorpromazine injection. On close examination of the TRH-prolactin curve of the remaining individual (E.S.) who had an abnormal prolactin curve after chlorpromazine, but was not included in those with abnormal TRH-prolactin responses, it could be seen that she had an intact response to TRH at 30 and 60 minutes. However, the TRH response at 90 and 120 minutes in this person was certainly not sustained compared to controls, and thus this pattern of impaired release may also be significant (Fig VIII-17).

Even excluding this patient, the results of the investigation have revealed that five out of six patients who had blunted prolactin responses after chlorpromazine, also had impaired prolactin responses after TRH, with both curves being similar to those seen in affected adults with Huntington's chorea.

The salient fact that emerges from this study is that approximately 50% of clinically normal first generation relatives (11 out of 23), corresponding to predicted autosomal dominant inheritance,
had abnormal prolactin responses to chlorpromazine injection. These findings suggest it may now eventually be possible to discriminate between heterozygotes for Huntington's chorea and their non-heterozygous siblings. Whether those "at risk" persons with the chorea-like curves will develop the disease with chorea as its predominant manifestation and those with rigid-like curves will have rigidity as the main feature is an intriguing possibility.

Only 6 out of 23 "at risk" individuals tested had abnormal TRH-prolactin curves. It would seem that chlorpromazine induced prolactin release may be more accurate in the assessment of the "at risk" population. Other, as yet undiscovered factors may have an important role in the regulation of TRH induced prolactin release, which prevented division of this potentially affected group according to accepted Mendelian principles for this disease. This also raises the possibility that there are distinct subpopulations in affected families, with unique hormonal responses. The disparate literature reports of endocrine function in Huntington's chorea may be a reflection of this phenomenon.

The assumption that the gene for Huntington's chorea is present and causing detectable changes in those clinically normal individuals who have the gene is supported by the finding of abnormal hormonal regulation in asymptomatic, potentially affected persons similar to that found in adults with chorea. Only a prospective longitudinal study will determine whether the impaired or exaggerated responses have predictive value for presymptomatic diagnosis of this condition.
The significant findings of other neuroendocrine abnormalities in this condition (Caraceni et al, 1977; Caine et al, 1978), together with the important developments in the field of psycho- and neuroendocrinology suggest that this approach may be useful in the development of a reliable predictive test in Huntington's chorea.

E. SOME PSYCHOSOCIAL PERSPECTIVES

The development of a safe, reliable method to identify the genetic carrier of Huntington's chorea has important social implications. A discussion of the implications of the "at risk" state is presented in Chapter IX-3.

Whilst it would be of tremendous importance that 50% of "at risk" individuals would be found to be free of the disorder, it would now be possible to know which 50% will develop the disease. The hope of those in this group will be blighted at a time when they still may have 15 to 20 productive, creative years ahead of them and could result in a lifetime of dread, anxiety and possibly even suicide.

Numerous questions arise and need to be considered. What would the impact of such a test be should it be positive, on social issues such as marriage and reproductive behaviour? When should the test be done? What will the effect be on parents and siblings watching a known "carrier" grow up? How will the knowledge alter families' responses to that child's behaviour and moods? Would it not be difficult to learn to separate normal errors in judgement, clumsiness and mistakes from the early symptoms of the disease? What effect will it have on economic issues such as employment?
possibilities and life insurance? Should employers be told the results of the test? Would these patients be further discriminated against in terms of entrance to university, job opportunities and, for example, car insurance? How would the knowledge that one is a carrier influence that person's motivation in terms of further study and involvement in long term projects? Whilst many of these questions have no easy answers, they highlight some of the complex, important social issues that should be considered prior to utilization of a safe, reliable predictive test.

F. ATTITUDE OF FAMILIES TO A PREDICTIVE TEST

Whilst scientific progress is made in an effort to presymptomatically diagnose Huntington's chorea, the attitude of affected families to the possible advent of a reliable predictive test remains largely unexplored.

In an effort to answer this, individuals in such families were asked during the course of the investigation in South Africa whether they would themselves, or if they were not "at risk", whether they would wish their family members "at risk" to have a predictive test should it be 100% safe and reliable. The responses are recorded in Table VIII-V. Whilst almost all affected individuals indicated they would have such a test, almost 50% of those "at risk" indicated they were not sure that they would themselves participate.
TABLE VIII-X
RESPONSES TO THE POSSIBLE UTILIZATION OF A HYPOTHETICALLY
100 PERCENT SAFE AND RELIABLE PREDICTIVE TEST

<table>
<thead>
<tr>
<th>Responses</th>
<th>Yes</th>
<th>No</th>
<th>Uncertain</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected persons</td>
<td>30</td>
<td>3</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>&quot;At risk&quot; persons</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(White)</td>
<td>33</td>
<td>10</td>
<td>13</td>
<td>56</td>
</tr>
<tr>
<td>(Coloured)</td>
<td>34</td>
<td>23</td>
<td>19</td>
<td>76</td>
</tr>
<tr>
<td>Unaffected spouse</td>
<td>15</td>
<td>3</td>
<td>8</td>
<td>26</td>
</tr>
</tbody>
</table>

This contrasts with the study of Stern and Eldridge (1974) in America and Barrett (1977) in England, who found that those at risk were overwhelmingly in favour of a predictive test. Only 20% of those at risk in America and 16% in England would refuse such a procedure. Wexler (1977) reported that approximately two-thirds of the 35 potentially affected persons she interviewed in depth would take the test. In this country, one of the reasons for the high percentage refusal includes the belief that uncertainty is preferable to being informed that Huntington's chorea is the certain prospect. An unaffected spouse (M.T.) expressed it in this way - "I don't think my children should be told as there is no point. The less they know about these things the better." A daughter "at risk" (L.F.) would refuse the test on the grounds that giving the results would be "like telling you it's ten more years to live with no future for your family."
Fifty-five percent of the respondents at risk in the group of mixed ancestry did not want the test, as opposed to 41% for the similar White population. It is well known that voluntary hospital attendance is low in this population (Gillis et al, 1968). This is in part due to suspicion, distrust and fear of modern medical practice. These factors, together with ignorance, may play a part in the lower acceptability of a predictive test in lower socio-economic groups of this country, compared to Western European and North American families. However, once presymptomatic detection is coupled with the hope of more effective treatment, it is likely that a much higher percentage of "at risk" persons would choose to have the test.
"A cyclone had hit our home, and it was ripping and tearing away our family and scattering it in the wind."

Fig. IX - 1

A photographic representation of the shadow that constantly haunts those 'at risk'.
# SECTION IX

## SOCIAL PERSPECTIVES

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INTRODUCTION

In contrast to the great strides that have been made with regard to the biochemistry of Huntington's chorea, very little attention has been paid to understanding the social consequences of the disorder. Whilst there is no available drug to restore normal function, appropriate community resources could be mobilized in an attempt to alleviate some of the social problems of patients and their families. In other words, with no available medical cure, the major task in the management of Huntington's chorea is to provide improved care. The prospects of social isolation and emotional deterioration are often more feared than the progressive motor impairment.

The purpose of this section is to provide a better understanding of the social consequences of Huntington's chorea which were encountered in the current study, in the hope that this will contribute to the wellbeing of all those living under the shadow of the disorder. (Fig IX-1). Quotations from family members will be included, where possible, to illustrate some of the common problems.
CHAPTER IX-2
PSYCHOSOCIAL CONSEQUENCES FOR THE AFFECTED PERSON

A. THE REALIZATION

Many patients in the earliest phase of their illness express great apprehension at the possible social implications of being afflicted with "that dreadful hereditary disease, the slow killer, which slowly and inexorably disintegrates the mind and body". They fear the physical and mental disability, economic impoverishment and social stigma of the "disease of inherited madness". Many also feel guilty, firstly for not giving their offspring a stable home base and secondly for possibly giving their offspring the gene for Huntington's chorea.

The tragedy of this disorder is that it strikes in the prime of life, when social responsibilities and personal and financial possibilities are greatest. Patients "grow senile without growing old" (Wexler, 1974). The affected person dreads losing his personal dignity, exemplified by the failure of control of bladder and bowel function. At the same time that they most need support, there is the unvoiced fear of anticipated abandonment and consequent loneliness. All these factors stimulate an attitude of extreme dependence.

A woman at risk describes these feelings about her father - "Dit was pateties om te sien hoe die onbefreesde, positiewe mens verander het na 'n sukkelende, afhanklike, onsekere persoon." (It was pathetic to see how a fearless, positive man changed into a struggling, dependent, uncertain person).

Patients with this embarrassing disease are ostracised not only
by old friends, but also by their own children. One mother with fairly severe choreiform movements was forbidden by her son to attend his wedding, as this would frighten his friends and future parents-in-law.

Patient's despair is also compounded by the knowledge that has accrued from watching "other members of the family wasting to an existence almost too horrible to contemplate". They find themselves in a hopeless situation. For many this terrifying realization signals the start of an attempt to cope.

B. PSYCHOLOGICAL DEFENCE MECHANISMS

For an affected person the devastating realization that he/she has the illness invariably results in the development of different psychological defence mechanisms. Kubler-Ross (1970) has described the various psychological stages experienced by patients who are dying. In many ways, these parallel the phases through which patients with Huntington's chorea pass.

The earliest and most common defence employed by those affected is denial. Some persons will categorically state that "members of our family are all perfectly well" when it is clear that there is a strong family history of Huntington's chorea. Others will distort information given in an attempt to allay their own anxiety. "I have been told that blond hair protects you from this disease. Therefore I have nothing to worry about."

One member of a well established affected family with a particularly ethnic surname changed his name to that of a totally different culture, emigrated from this country and gave up all contact with his
relatives in an attempt to escape the family curse. Unfortunately he carried the gene for Huntington's chorea with him. This was also a form of denial.

The negation of the existence of the disease is an attempt to safeguard employment and insurance possibilities, social acceptability and marriage prospects. In some persons, however, denial of a family history may be an honest representation of the known facts. The parents may have died before the symptoms were obvious or the patient may be unaware of his own illegitimacy and thus the diagnosis in his natural parent.

Unfortunately, however, denial has serious implications as patients fail to come to terms with the disease.

Denial is superseded by the second stage of defense, namely anger. Anger, sometimes violent, is often directed at the unaffected spouse. An affected person may injure his loved ones. A father may become a baby batterer. There are unfortunately very few instances where this rage has been directed into creative channels.

The patients then often passed into a phase of bargaining - trading in their disease, if they comply with relatives and doctor's wishes. Some patients feel that if they take the prescribed medication they will be cured. When this fails depression supervenes. In this phase suicide is a very real possibility.

C. SUICIDE

"Insanity with a tendency to suicide" was one of three features mentioned by Huntington (1872) in his definitive description of the illness.
I have had notification of 11 affected persons who have died from self-inflicted wounds. This is equivalent to 3.35% of all deaths due to Huntington's chorea in South Africa. Suicide and self-inflicted injuries are coded E950-E959 in the International Classification of Diseases (I.C.D.). Based on reported rates for 1976 the chance of an affected person with Huntington's chorea in South Africa committing suicide is over 2,200 times more likely than in the general population.

Reed and Chandler (1958) have reported that 7.8% of deaths in non-institutionalized affected males and 6.4% in non-institutionalized females with Huntington's chorea were due to suicide. Bolt's (1970) rate of 1.75% is not comparable as this reported figure for deaths due to suicide is calculated from the total number of all known cases, including those who have died and also many still living and thus is an underestimate.

Affected males in South Africa commit suicide ten times more commonly than affected females. A further 24 persons have made serious attempts on their lives. Females predominate in this latter group and are likely to attempt suicide twice as commonly as males. In other words, males are more likely to ensure that they die from their suicide attempts, in contrast to the greater frequency of attempted suicide in affected females. Whilst no definitive pattern has emerged, patients are more likely to commit suicide in the early phases of the illness when depression is severe and dementia is minimal.

One man at risk, who was suffering from insomnia and hypogogic gyrations, committed suicide on the assumption that he was now affected.
Medical examination two days prior to death, together with inspection of this man's handwriting in his suicide letter (Fig IX-2) confirm that at the time he was, in fact, unaffected. Although some commit suicide, others do come to terms with their situation.

D. COPING

With adequate support a patient can be encouraged to openly express his/her fears, anxiety and regrets. In so doing an affected person is not isolated from family and friends and may develop an attitude of calm acceptance. Such a person now learns to use his resources as fruitfully as possible, sharing in a communicating environment. A daughter at risk explains how these channels were kept open right to the end with regard to her affected father. "Tot op die laaste, al het dit some gelyk of my vader in 'n koma was, het hy nogtans geweet wat om hom aangaan. My moeder wat op 'n manier met hom kon kommunikeer was bewus daarvan en voor hy na die hospitaal is, het hy saam met haar gereel vir sy eie begrafnis." (Till the last moment, even when he sometimes appeared to be in a coma, he still knew what was going on around him. My mother, who could still communicate with him, was aware of this and before he went to hospital he made arrangements with her for his own funeral.") Another patient expressed his acceptance in this way - "The most important thing is that everything I do from now on, I do with as much dignity as possible, so my family can remember me living with a little extra dignity."
The first page of this man's suicide letter. In the fourth paragraph, he explains that he is taking his life "voordat hierdie kanker van slaaploosheid my dalk 'n swakkeling maak." ("before this cancer of insomnia reduces me to a weakling.")
Every child of an affected parent has an even chance of inheriting the gene for Huntington's chorea. The inability to escape from the unacceptable reality that they may be "passive victims of a totally random genetic accident" (Wexler, 1977) over which they exert no control is devastating for all concerned. "It's like living under a cliff, waiting for a landslide" was the way one 28 year old woman described it. A man at risk, aged 40, in a letter to his children wrote as follows - "For all the joy and happiness I have had from you, my children, is clouded by the ever-present, dreadful "if" always hanging overhead like a sword of Damacles. The fear is quite inescapable - it smothers you like a black, choking snake. It clouds the reason and you tend to become conscious of every little action, wondering if this is the beginning of it." (Fig IX-1). Others have described the experience of being at risk as "living with a time bomb" (Pines, 1977) and "playing Russian roulette with a two-barrelled gun and somebody else's hand on the trigger" (Wexler, 1977). Anxiety was expressed at one time or other by many persons at risk in South Africa. Pearson (1973) has stated that 40% of such people suffered from overt anxiety neurosis.

For those who understand the implications of being at risk, denial is often the only way they can continue enjoying constructive, creative lives. Some of these persons marry and produce children without informing their spouses of the disease in their family, even though they are aware of its genetic implications. In this way, denial propagates the disease.
Anger, directed against the affected parent for transmitting this unwanted legacy, is expressed by only a few persons. More often feelings of warmth and sadness are voiced, as with this woman who said "I just felt overwhelming pity and love" when talking of her affected mother.

Some subjects feel that onset of the disease can be prevented or delayed by different methods, e.g. prayer, or yoga. In other words, a positive mental state can preclude the symptoms of the illness. Other people are less positive and become depressed as they are sure they will inherit the gene. Clumsiness, moodiness and an appearance similar to their parents are thought to be definitive pointers. Unaffected relatives can sometimes be cruel by reinforcing such beliefs. For example, two girls aged 12 and 14 were sterilized as a result of the family belief that they would inherit the gene. Their two siblings were not subjected to a similar procedure.

Some people see the inheritance of the gene for Huntington's chorea as a punishment for some unsuspected wrongdoing. "I used to look at other families and wonder what I had done to deserve this. I only wanted to be normal". A few refuse to marry or have children.

In many instances feelings of anxiety and fear can be sublimated into more creative channels, e.g. painting, writing or business. In other countries, as a result of these people's efforts, organisations to promote research and support families with this disease have been formed. At present attempts are being made to stimulate formation of a similar organization in South Africa.
The woman on the right has spent much of her life looking after family members affected with Huntington's chorea; first her husband and now her two children.
All at risk individuals have to live with the long-term threat of inheriting the gene for Huntington's chorea. Medical and paramedical personnel can be of much greater help if there is an awareness and sensitivity to their experience of being "at risk".
CHAPTER IX-4
THE BURDEN OF THE UNAFFECTED SPOUSE

The unaffected spouse has unique concerns and needs. He or she is often alone, having to cope with the patient at home. The change of marital role, with the husband having to deal with increasing domestic chores or the wife now being forced to become the breadwinner for the family, is most difficult for the respective spouses. This difficulty is compounded by the inevitable isolation that ensues following repeated social embarrassments and rejection by old friends.

The hardest fact for the unaffected partner to assimilate is that they have been unwittingly involved in the transmission of the disease to their children. Many unaffected spouses name this as their heaviest burden, for which they feel guilt. They often resent that they have not been told of the family illness prior to marriage, and certainly prior to parenthood. Almost all partners (80%) say they would still have entered the marriage if they had known of the illness, but could then have planned for responsible parenthood. The unaffected spouse is often the one confronted with the intolerable task of having to inform the children of the implications of their at-risk status. In one instance the partner was witness to the development of changes in her only two children similar to those she had seen in her deceased husband. This woman, with her two children, is shown in Fig IX-3 approximately five years after her husband's death.

One woman, whose husband has been suffering from the illness for five years, describes her anguish in this way - "Niemand wil my help nie. Wat moet ek doen? Is daar dan niemand om to help as sulke dinge plaasvind? Waarheen moet ek my wend? Ek moet kos voorberei
vir die kinders. Hier loop hulle nog met hulle skool tasse rond. Die psigiaters het gesê hy het Huntington's chorea. Hy kan nie 'n oomblik stil sit nie. Hy moet gehelp word. Ag, dis 'n haartseer storie. Ek het ses kinders - drie dogters en drie seuns. Ek het gehoor die siekte is oorerflik. Wat lê nog alles vir ons voor? Wie gaan getref word? Ek is uitgeput. Ek kan nie slaap nie." (Nobody will help me. What must I do? Is there nobody to give help when such things happen? Where can I go? I have to prepare food for my children. Here they are, still walking around with their school cases. The psychiatrists said he has Huntington's chorea. He cannot sit still for a moment. He must be helped. Oh, this is a heart-breaking story. I have six children, three daughters and three sons. I heard this disease is inherited. What lies ahead of us? Who will be affected? I am exhausted. I cannot sleep."

The unaffected spouse often becomes the target for the patient's delusions, abuse and sometimes violent attacks. "He used to hit me with his fist and on occasion threw his teacup at me."

Whilst divorce ensues in some families, in many others the spouse chooses to stay with his or her partner. A feeling of acceptance and strength is expressed. "I married him, and it is my duty to look after him." Within these families the spouse becomes a source of great strength and comfort to all around them.

Many partners complain of the indifference of the medical profession to their problems. "Doctors just seem to be not interested." One woman explains "The doctor at the hospital told me to take her home as I probably knew more about this Huntington's chorea than he did."
What must I do? I go to the doctors for help and they can do nothing for me."

Whilst the afflicted patient is the person who first draws medical attention to these families, it is often the unaffected spouse who needs the most attention and help to cope with his or her problems.
Fig. IX - 4

A family photograph, showing the patient surrounded by his wife, his 6 children, 5 grandchildren and the dog.
CHAPTER IX-5
HUNTINGTON'S CHOREA: A FAMILY DISEASE

The purpose of this chapter is to reiterate that Huntington's chorea is a prime example of a family disease. Data concerning the number of affected persons in South Africa must be seen in their correct perspective. For every affected individual there are approximately ten people in the immediate environment who suffer from the social consequences of the disorder. Whilst only half the offspring inherit the gene, all bear the impact of the illness as a result of the inevitable social upheaval and consequent deprivation.

This is poignantly described by a family member at risk as follows: "To watch one's loved ones suffering this disease is a 'hell on earth' existence. We, his family, are suffering as much as he is. The heartache it brings is worse than any physical pain."

The repercussions of the disorder are felt beyond the boundaries of the immediate blood relatives. Some "in-laws" have made significant contributions by way of emotional and financial support. An uncle by marriage "adopted" his three nieces and a nephew after their affected father died. Two of the nieces have now also developed features of the disorder. The uncle continues to support the whole family.

A family photograph is shown in Fig IX-4. The patient (middle of back row) is surrounded by his children and grandchildren, all of whom are in some way bearing the consequences of their father's or grandfather's illness. The problems are particularly acute in under-privileged sections of society, where there is less financial support and also less access to community resources. Such a family
is shown in Fig IX-5. The father, who was the breadwinner until the onset of his illness, now needs daily care, preventing his wife from seeking employment. The disease has impoverished the family.

Ideally, all these factors should be given consideration when caring for patients with Huntington's chorea.

**Fig. IX - 5**

Huntington's chorea has aggravated this family's poverty by preventing the father from being employed. The white bowl is used for washing.
CHAPTER IX-6

ANTISOCIAL BEHAVIOUR : HUNTINGTON'S CHOREA AND THE LAW

It is on record that the earliest transmitters of the gene to the United States of America had problems with the legal system of their adopted country, as a result of repeated crimes and misdemeanours (Vessie, 1932).

In the current survey of Huntington's chorea in South Africa there have been repeated instances of antisocial behaviour, including suicide, assaults, stabbings, shooting, theft, two reports of murder and other more minor crimes such as offences against property. Sexual aberrations have included indecent exposure, prostitution and rape. Similar offences have been reported by numerous other authors (Parker, 1958; Hans and Gilmore, 1968; Dewhurst et al, 1970).

The presence of antisocial behaviour in Huntington's chorea is clearly established. What is more difficult to ascertain are the precise determinants of such conduct. Is it possible that the biochemical defect of the disorder produces such behaviour, or is this rather the result of the disturbed social environment? Neurologic syndromes have been described which are associated with specific patterns of conduct, e.g. the frequent presence of religiosity and a deepened interest in moral and ethical issues in some patients with temporal lobe epilepsy (Waxman and Geschwind, 1974). In other words, specific diseases may be associated with predictable modes of behaviour, which are directly related to the ongoing pathological process. Is this also true for Huntington's chorea?
These Cape Town newspaper headings document the plight of one man afflicted with Huntington's chorea and his conflict with the law.
A good group for comparison with Huntington's chorea patients are the unaffected members of the family, as they are exposed to a similar psychological, social and biologic environment. Although no formal study has been performed, it is my impression that antisocial behaviour is less common in this "control" group. Oliver and Dewhurst (1969) have reported on one large family where, even though the children of affected persons did not carry the gene, the consequences of their disturbed upbringing resulted in psychiatric and antisocial sequelae in adult life. However, these misdemeanours seemed less prevalent than in their affected ancestors.

It is thus possible that the different offences committed by affected persons are consequent to disinhibition or lack of control of aggressive impulses, which are certainly, in part, the result of the characteristic degenerative process of Huntington's chorea. The fact that most patients who perform antisocial acts come from disturbed home environments suggests that the socially impoverished surroundings may also have contributed to their causation.

The newspaper headings, shown in Fig IX-6, relate to a man in Cape Town who committed murder, was found guilty and because no mitigating circumstances could be found, was sentenced to be hanged. This man came from a well-known choreic family and was found to be suffering from early Huntington's chorea by a neurologist, a psychiatrist and myself. The sentence was upheld against appeal and at this stage the State President is being asked to grant clemency.

Whilst accepting that criminals should be dealt with according to the laws of a country, a more human approach should be employed when
dealing with patients suffering from Huntington's chorea. Caro and Haines (1973) have expressed these thoughts when they stated "It can be seen, therefore, that we have been persecuting this particular group of unfortunates for a very long time, but now instead of burning them at the stake, we simply lock them up for rape or attempted murder rather than understand that their problems are not of their own making". 
CHAPTER IX-7
PROSPECTS FOR RESPONSIBLE PARENTHOOD

Many parents, ignorant of the hereditary nature of Huntington's chorea, produce offspring and thus propagate the disease. The argument against reproduction in affected families is particularly strong in view of the mode of inheritance, the lack of a reliable predictive test and the absence of any known cure in Huntington's chorea. Yet in spite of this many parents, aware of the risk they are taking, choose to procreate. Advising patients to refrain from procreation would be much easier if there were viable alternatives. What are the options in South Africa?

By virtue of their at-risk status such people are not usually accepted as adoptive or foster parents, in order to protect the child if the new parent does in fact develop Huntington's chorea. A possible alternative to adoption arises if the potential carrier is a male. In such a case artificial insemination of his wife would ensure that the gene would not be transmitted to the next generation and, at the same time, allow her the fulfilment of pregnancy. This method has not been sanctioned by the Medical Association of South Africa, and by itself raises important psychological and moral issues.

The dilemma of whether or not involved couples should have children has often been presented to me. I have been guided in this matter by others, e.g. Pearson (1974) who has had over 25 years of experience counselling affected families, and feels convinced that "more people are happier longer when the decision against reproduction is made at the outset of the childbearing years." For this reason he
has become more directive in his counselling techniques, advising prospective parents of the different options, but mentioning that in that situation he himself would refrain from procreation. During the course of this survey two terminations of pregnancy were performed in Cape Town on persons at risk for Huntington's chorea, while others in full knowledge of the risk, refused termination. Whilst counselling is important in this situation the final choice always remains a personal matter between the patient and spouse.

Whilst it is true that offspring of an affected parent in South Africa and elsewhere have contributed greatly in the fields of science, art and the humanities, it could also be argued that there would be no Huntington's chorea (apart from the rare, spontaneous mutations) if such parents had not procreated.

The problem of reconciling couples to their childlessness would be made easier if alternatives such as adoption existed. Potential carriers have adopted children in other parts of the world, such as the U.S.A. Such a possibility has not been explored in South Africa.

Huntington's chorea poses other difficulties in regard to adoption in that, as a result of the disturbed and often impoverished social environment, affected parents are often unable to look after their at risk children and put them out for adoption. No adequate family history of the illness is given to the adoption societies. The rights of prospective adoptive parents should, where possible, be protected and parents adopting offspring of affected persons should have a full understanding of the implications of the disease and be willing to accept the calculated risks.
CHAPTER IX-8
COUNSELLING IN HUNTINGTON'S CHOREA

In the past the main thrust of genetic counselling in Huntington's chorea has been directed towards the reduction of the frequency of the disorder. It had been hoped that giving the genetic facts to those at risk would, per se, decrease reproduction. As mentioned previously numerous individuals in the current study who understood the implications of such information, still chose to have children. It is clear that eugenic genetic counselling will not eradicate the disease in the community. Whilst efforts should still be directed to this end, a much broader, more holistic view of the function of the genetic counsellor in Huntington's chorea is necessary.

A slightly modified definition of genetic counselling drawn from the American Workgroup on Guidance and Counselling (1977) reads as follows: "Counselling is a communication process that has as its goal the alleviation of human suffering associated with the occurrence or the risk of occurrence of a genetic disorder in a family. The counsellor tries to achieve this goal by helping the counsellee

1. Comprehend the medical facts, including the diagnosis, probable course of the disorder and the available management.
2. Appreciate the risk of recurrence in specified relatives.
3. Understand the choices for dealing with the risk of recurrence.
4. Choose the option which seems appropriate to them in view of their risk and their values and act in accordance with that decision.
5. Make an optimal adjustment to the disorder, be that person affected or at risk of developing the disease."
To achieve the above goals it is clear that different skills are necessary. The counsellor must have sufficient experience to make a definitive diagnosis of Huntington's chorea. Persons with a knowledge of genetics are needed to collect accurate family history data. Furthermore, individuals skilled in psychotherapy and aware of the repercussions of Huntington's chorea on all family members are needed to provide psychosocial support. Whilst one clinician may have all these skills, the optimal approach is a multidisciplinary one, utilizing a team of professionals. This is the underlying concept that stimulated the formation of the Huntington's Chorea Clinic at Groote Schuur Hospital at the beginning of 1979 (see Chapter X-4).

During the course of the survey affected persons, individuals at risk, unaffected spouses and other family members, each with their own specific problems were counselled in an effort to relieve their burdens. The problems of each of these patient populations have been described previously in this section.

The policy adopted during the survey was that the extent of the information given depended on the level of awareness of the person and his or her readiness to receive further details. Counselling was based on the specific needs and concerns of each individual in an affected family. What has clearly emerged is that appropriate counselling can exert a considerable influence on the behaviour and wellbeing of the patient and his family.

Power and Sax (1978) have performed a unique study on the effects of timely discussion of all facets relating to Huntington's chorea on the behaviour of the patient and different family members.
They assert that early, honest confrontation with the facts of the disease generates constructive attitudes and maintains patient productivity commensurate with the stage of the illness. The home environment is crucial to his coping and, if adequate, insures against premature, unnecessary institutionalization. The findings of the present investigation support this view.

In many instances the tragedy for the affected person is that their families tend to ostracize them when they most need support. The aim of all counselling is to "include these patients among the living until the moment of their dying". (Wexler, 1974).
SECTION X

CONCLUDING THOUGHTS AND RECOMMENDATIONS

"We can no longer afford in any science to focus exclusively on one region and to leave the rest of the universe out of account until we complete our investigations. We never actually complete our investigations, the nature of science being a continuous process of inquiry."

SECTION X

CONCLUDING THOUGHTS AND RECOMMENDATIONS

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HUNTINGTON'S CHOREA - A PROTOTYPE FOR RESEARCH

Huntington's chorea has clinical features which are similar to those found in many other neurological and psychiatric diseases. This is an important factor in the finding of a high frequency of initial misdiagnosis of the disorder.

Great advances in the understanding of the pathophysiology of Huntington's chorea were originally made as a result of the discovery of dopamine deficiency in Parkinson's disease. It is possible that further elucidation of the causes and effects of Huntington's chorea will, in turn, benefit and enhance the understanding of other diseases with shared clinical features, amongst which are the presenile dementias, chorea due to other causes and schizophrenia.

Of the 2,350 described genetic diseases, 583 are inherited as autosomal dominant traits. A further 675 disorders are thought to be transmitted in this manner. Elucidation of the primary defect in Huntington's chorea could provide a conceptual basis for the investigation of other autosomal dominant disorders.

The current thesis has provided evidence for the concept of dopamine excess in Huntington's chorea. If this hypothesis is correct, then Huntington's chorea could serve as a model for the understanding of the interactions between different neurotransmitters and the dopamine system, by examining the effects of dopamine excess on these different neurochemicals. Furthermore, the effects of dopamine on other
hormones such as the renin-angiotensin system and the encephalins, could be explored by investigation of patients with Huntington's chorea.

In other words, Huntington's chorea could serve as a prototype for research into other psychiatric, neurologic and genetic diseases, and also provide greater insight into the interaction between dopamine and the endocrines (Fig X-1).

The social concerns and needs of patients with Huntington's chorea are shared by persons suffering from numerous other unrelated chronic diseases. Awareness of the need for comprehensive care with mobilisation of appropriate community resources for patients with Huntington's chorea would also highlight the shared requirements of other chronic long-term disorders.

**Fig. X - 1**

Huntington's chorea as a prototype for research into other neurologic, psychiatric and genetic diseases, and dopaminergic mechanisms.
The scope of the current investigation has been extended to include workers in different parts of the world. Biochemical studies have been undertaken in collaboration with Dr. P. Sever of St. Mary's Hospital, London to investigate different aspects of amine metabolism and the renin-angiotensin mechanisms. Studies into the immune mechanisms have been undertaken in conjunction with Dr. D. Doniach of the Middlesex Hospital, London to determine whether auto-immunity could be the underlying factor in the impaired prolactin release in Huntington's chorea patients.

As a result of careful explanation to affected families of the need for organ donors, I have been able to send Dr. E. Bird, Head of the Brain Bank in Boston, U.S.A. the brain of a young girl who died of juvenile Huntington's chorea. The brain will be subjected to complicated histochemical and histopathological examination. Other affected South African families have been interested to hear of the Brain Bank and have expressed their desire to become organ donors in the hope that they could contribute personally to a greater understanding of the disorder.

Professor G. Bruyn and Dr. L. Went of Holland have provided me with important data on affected families in their country who linked up with patients in South Africa.

As a result of the interest generated in the different aspects of the current survey, I was an invited guest to a conference on the genetic and social implications of Huntington's chorea in London in
December, 1977 and the Second International Symposium on Huntington's Disease in San Diego, U.S.A. in November, 1978. At the latter meeting an international collaborative neuroendocrine investigation of patients with Huntington's chorea was proposed, including workers in the U.S.A., Italy and South Africa. This has still to be implemented.
CHAPTER X-3

AN ASSOCIATION TO COMBAT HUNTINGTON'S CHOREA

The first association of this kind was formed by Mrs. Marjorie Guthrie (widow of Woody Guthrie, the legendary American folksinger who died of Huntington's chorea) in June, 1967 in the U.S.A. Initial objectives were to help research into the causes, effects and treatment of the disease, to aid the patients and their families and to educate the professional and the lay public. Similar organisations have since been formed in Australia, Belgium, Britain, Canada, France and Holland. At a meeting of the Southern African Inherited Disorders Association (SAIDA) on April 25, 1979 in Johannesburg specifically organised for patients suffering from this disorder and their families, the author proposed that an association to combat Huntington's chorea in South Africa be formed with the following aims:

1. To give help, advice and moral support to Huntington's chorea families.

2. To provide an opportunity for affected families to meet each other, share experiences and discuss common problems.

3. To support research into different aspects of Huntington's chorea.

4. To educate medical bodies, Huntington's chorea families and the public about all aspects of the disease. In so doing medical and paramedical personnel will become more aware of difficulties facing affected families.

5. To mobilize community resources by making the government and Department of Health aware of the problem of Huntington's chorea in South Africa.
Whilst numerous persons expressed great enthusiasm for such an association, fear and anxiety has prevented others from volunteering to be of help in its formation. At the present time a South African association to combat Huntington's chorea has not yet been formed.
Although not fully anticipated at its inception this investigation has precipitated a service commitment to patients with Huntington's chorea in South Africa. During the survey numerous functions have been fulfilled, including counselling, diagnosis, treatment and, where necessary, referral of patients to appropriate clinics. I have also dealt with numerous social problems, including arrangement of disability grants, insurance and provision of alternative housing and employment. Requests for information have been received from doctors and patients all over South Africa and from South West Africa, Zimbabwe-Rhodesia and Mauritius.

As described earlier, it was felt that patients' interests would best be served by a multidisciplinary approach to the disease, with simultaneous attendance of all necessary experts at a formal clinic. With the support of the Medical Superintendent, Dr. H.R. Sanders, Professors Ames, Beighton and Gillis, a special Huntington's Chorea Clinic has been established at Groote Schuur Hospital, the first one being held on January 9th, 1979. The staff of the clinic comprises a neurologist (Dr. McGregor), a psychiatrist-on-call, the author, a social worker (Ms. Parker) and a genetics nursing sister. The clinic has proved to be most successful.

It has become apparent that a very neglected group of persons in the family setting is the unaffected spouse. Group therapy sessions specifically for these persons are being arranged through the Department of Social Work.
CHAPTER X-5

THE SOUTH AFRICAN HUNTINGTON'S CHOREA REGISTRY

An attempt has been made to establish a South African Registry of patients with Huntington's chorea.

In this way families and patients can be easily located and notified of any major breakthrough in the disease.

Referral to the register may also provide important information in relation to a person who presents with personality problems, dementia or chorea, yet denies the family history of the illness. In this way such a register may be of help in diagnostic problems.

It must be emphasized that confidentiality remains a pre-eminent consideration. The register will be maintained in the Department of Human Genetics at the University of Cape Town.
CHAPTER X-6

RECOMMENDATIONS FOR FURTHER RESEARCH

The current study has been limited by time and available funds. The results of the investigation, by answering some questions, have posed numerous others. Furthermore, many problems, although mentioned, have not been dealt with in great detail as they have been deemed to be outside the scope of this thesis.

Recommendations for ongoing research projects include:

1. Determination of the changing frequency of Huntington's chorea in the various ethnic groups in South Africa. It will be of great interest to find out whether those of Eastern origin, such as the Malays and Asiatics have a low prevalence of the disease similar to other Eastern populations, e.g. the Japanese.

2. A formal study of Huntington's chorea on Mauritius, including its history, frequency and social implications for the island.

3. Genealogical investigations into the undetermined origins of over half the families in the current study.

4. Investigations into the reasons for the relatively low frequency of Huntington's chorea in South Africa, considering that the gene was probably introduced over 300 years ago.

5. Examination of the reasons for the low age of onset and age at death of Huntington's chorea in South Africa compared to other countries.

6. Determination of the possible factors modifying the action of the gene for Huntington's chorea.
7. Investigation of juvenile Huntington's chorea in South Africa, with particular reference to its
   a) frequency,
   b) aetiology,
   c) genetics,
   d) clinical presentation, and
   e) morbid pathology.

Regular follow-up of families with juvenile patients should be maintained.

8. CAT scans in Huntington's chorea and those at risk.

9. Genetic linkage studies, particularly on the juvenile patients and those affected from the Coloured population.


11. Investigation of other neurotransmitters in Huntington's chorea, e.g. somatostatin, neurotensin and the enkephalins.

12. Close follow-up of those at risk of inheriting the gene who were found to have impaired, exaggerated and normal prolactin responses to chlorpromazine, in an effort to determine the efficacy of neuro-endocrine determination of the clinically normal heterozygote.
CHAPTER X-7
ON A PERSONAL NOTE

Fig. X - 2

Two sibs at risk for Huntington's chorea next to the sign denoting the name of their home.

The photograph above shows the name of a home of a large family in the Western Cape with Huntington's chorea — a single, poignant example of the courageous spirit that I have so often encountered during this work. These people unwittingly continue to be a source of inspiration for me.
"The power too, to study correctly what has been written, I consider to be an important part of the art of Medicine."

Hippocrates (460-377 B.C.)
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PROFORMA USED FOR SURVEY.
HUNTINGTON'S CHOREA

Date: 
Name: 
Sex: D.O.B.: 
Address: 
Postal Code: 
Phone No.: 
Folder No.: 
Ethnic Group: Birthplace: 
Referring Consultant: 

HISTORY: 

Initial Symptoms
Psychiatric
Neurologic
Combined

A.O.O.
Initial Diagnosis: 

S. & S.:

Psychiatric:
Depressive - Anxious
Schizophrenic
Paranoid
Personality Disorder

Any attempts at suicide - explain: 
Neurologic:

- Hypertonic - Rigid
- Hypotonic
- Chorea
- Dementia

Any other abnormal movements:

Any fits:

Signs of cerebellar involvement:

Social:

- Any criminal offences
- Violence
- Sexual aberrations
- Promiscuity
- Illegitimacy
- Drinking

Results of SJ:

- Blood
- CSF
- EEG
- AEG
FAMILY TREE: D.O.B.

D.O.D. in all affected individuals
A.O.O.
28th June, 1977.

Dear Dr.

The Department of Human Genetics is currently undertaking an investigation into Huntington's chorea. Because of the important social and medical implications for the individual with this disease, and for society as a whole, an attempt is being made to locate all carriers of the gene.

Another facet of this project is to determine the origin of the disease in this country. At this stage, it is already clear that the gene has been in South Africa for at least 300 years. The Dutch, the British and the Huguenots have been implicated as possible origins of the gene.

At present, there is no reliable method for recognizing the gene carrier before symptoms become apparent. The detection of the carrier state would be a highly significant development in the control of the disease. Certain biochemical and neuro-endocrine studies have been undertaken as part of this project and preliminary results have been most encouraging.

I am writing to give you this information because it is very probable that you have patients with Huntington's chorea under your care. I would also appreciate it if you could give us particulars of any patients with this disease that have come to your attention. This information will, of course, be treated with strict confidentiality.

This department will be only too happy to give any further assistance or information that you might require.

Yours sincerely,

[Signature Removed]

Dr. Michael Hayden
I hereby consent to being investigated by means of blood tests involving injection of 100 mg TRH, IV, followed by IM injection of 25 mg chlorpromazine the following day. Blood samples will be taken every 30 minutes for 2 hours.

I realise these tests will not necessarily benefit me directly, but that they may lead to a better understanding of other patients' illnesses.

The nature and risks of the test have been explained to me.

Signed ............................................

Witnesses: 1. Signature Removed
(Doctor)

2. Signature Removed
(Technician)
Huntington's Chorea in the Cape Coloured Community of South Africa

M. R. HAYDEN, P. BEIGHTON

SUMMARY
Huntington's chorea is a grave genetic neurological disorder which appears to be a more serious problem in South Africa than has generally been recognized. The minimum prevalence of the disease in the Cape Coloured is 3.5/100 000 of the population. Sixteen per cent of patients were younger than 20 years at the time of onset of the disease. This is among the highest incidence of juvenile Huntington's chorea in the world.

The gene for Huntington's chorea has been in South Africa for 300 years. It was first introduced into this country from Holland in the middle of the 17th century and then later from England in the middle and end of the 19th century.

The number of affected individuals appears to be on the increase in South Africa. Unfortunately, at present, no methods are available for effective control of this disorder.

GEOGRAPHICAL BACKGROUND
Huntington's chorea has a long history and it is found throughout the world. The gene was introduced to the eastern seaboard of America in 1635 by immigrants who came from Suffolk, England, and the condition was eventually delineated following a classic description by an American physician, George Huntington, in 1872.

It would be of considerable interest to determine the origins of this disease in South Africa. However, in the Cape Coloured families whom we have studied it has been impossible to trace the family tree further back than 100 years. This group has considerable ethnic admixture, and since the gene has a very low mutation rate, it is possible that they have received the gene from more than one source.

The gene for Huntington's chorea certainly reached South Africa by at least 2 routes. When Jan van Riebeeck set sail from Amsterdam in 1651, he took with him a young Hollander at the Cape. Klintworth has traced 3 Afrikaner choreic families to this marriage. Similarly we have encountered choreic individuals who had their origins in Salisbury and Cornwall, southern England. The ancestors of one of these families came to South Africa just after the 1820 settlers, while the other kindred arrived in 1890.

Another probable source of Huntington's chorea in South Africa is the Huguenots, who have also taken the disease to Britain, Canada, and Tasmania. In the 18th century, Huguenots in the Cape who committed certain crimes were banished to the island of Mauritius. The high incidence of criminality in the early phases of this disease is well known and it is of great interest that affected relatives of a White South African family with Huntington's chorea are presently living in Mauritius. It can be postulated that the ancestors of this family came to South Africa with the Huguenots, were then banished to Mauritius, and subsequently returned to South Africa, bringing the gene for Huntington's chorea with them.

In any event, it is reasonable to assume that the gene for Huntington's chorea has been in South Africa for at least 300 years. This alone would add considerable support to the notion that Huntington's chorea is a relatively common disease in South Africa.

METHODS
An effort was made to identify all patients with Huntington's chorea within the boundaries of the Divisional Council of the Cape. In 1976 there were 730 306 Coloured people in this area, which includes the Cape Peninsula in the south, Swartklip in the east, Mamre in the north.
and Springfontein in the west. Affected individuals were
initially ascertained through the records of the Department
of Human Genetics. Home visits were made, family
members were interviewed and pedigrees were constructed.
Subsequently, neurological and psychiatric records were
searched, as far as this was possible, and a personal
approach was made to neurologists, psychiatrists and
physicians in an attempt to obtain additional information.
The diagnosis in all patients was made either by a neuro-
logist or a psychiatrist.

Fig. 1. Pedigrees of 3 Cape Coloured kindreds with Huntington's chorea.
RESULTS
A total of 26 living persons with Huntington's chorea in 14 separate Cape Coloured kindred were examined. Fifteen females and 11 males aged between 12 and 68 years were seen. On the basis of these 26 patients, a minimum frequency of 3.5 overt cases of Huntington's chorea per 100,000 of the Coloured population can be estimated. Sixteen per cent of these individuals had developed symptoms before the age of 20. There were 2 females and 2 males in this group. Two more children probably had early signs of Huntington's chorea but the diagnosis awaits confirmation. In 3 large families the disease has been transmitted through at least 4 generations, and no less than 120 people in these kindreds are at risk of inheriting the gene (Fig. 1).

Huntington's chorea is not confined to the Coloured community and patients from other racial groups were encountered during the investigation. Ten Whites and 1 Black with Huntington's chorea were found within the Cape Town area. Information was also received concerning numerous patients in the eastern Cape, and it seems likely that the condition is particularly common in the White population of that area.

DISCUSSION
The prevalence of Huntington's chorea has been estimated in many countries. The figures are not strictly comparable because of diversity of methods in collection of data, but in most populations the prevalence ranges from 3 to 7 per 100,000. There have been no previous estimates from Africa, but the prevalence which we have calculated is in keeping with these figures.

It is inconceivable that the ascertainment, although carefully undertaken, was complete. It is well known that voluntary hospital attendance is very low in the Coloured population. Furthermore, a disorder of this nature may easily be accepted in the community without coming to medical notice. Similarly, because of the wide spectrum of clinical presentation, the diagnosis of Huntington's chorea is often missed. For these reasons, it is possible that the prevalence of Huntington's chorea in the Cape Coloured community is much higher than the figure which we have estimated.

Presentation in childhood occurs in about 5% of cases. The prevalence at this stage in our series is among the highest in the world. This is a most interesting observation which requires some explanation. One possibility is that there was a bias of ascertainment of juvenile cases and that the true prevalence of adult patients is much higher. However, Saffer et al. have documented 4 juvenile Coloured patients with Huntington's chorea, and thus seems that the juvenile form is relatively common in the Coloured community. It is possible that this is the result of epistasis, whereby the inherent genotype alters the phenotypic expression of the gene and results in the onset of the disease at an earlier age. In this context, it has been reported that children with Huntington's chorea have an affected father 4 times as frequently as an affected mother. Our own findings were in accordance with this observation.

Huntington's chorea will become more common in South Africa in the future. For instance, on extensive investigation of 3 kindreds shown, 120 people are at risk of developing the disease by virtue of the fact that each had an affected parent. After applying appropriate correction for age of onset, we may predict that 48 of these individuals carry the gene for Huntington's chorea. They will all develop the disease at a later stage in their lives. By extrapolation from our own figures for the White population, there must be a minimum total of 200 Coloured and White people with Huntington's chorea in this country. Since little is known about this disease in the African Negro, this population group has not been included in this estimate.

Huntington's chorea is a much more important disease than would appear from estimates of its prevalence. Even though only half of the offspring of a choreic patient are at genetic risk of developing the disease, all members of the family bear the impact of the distressing social environment which results from the progressive physical and mental disablement of an afflicted parent. The financial liability to the family and the state includes compensation for loss of earnings from productive employment and direct financial assistance to dependent children. Finally, the cost of hospitalization, which is often inevitable in the late stages of the disease, is enormous and will also increase.

The only effective method of controlling Huntington's chorea at the present time is by abstinence from procreation on the part of those individuals who have the gene. Unfortunately, presently there is no accurate or reliable method for recognizing the gene carrier before symptoms become apparent. However, with the explosion of genetic and biochemical knowledge, it is not inconceivable that such a method will be developed in the near future.

We are grateful to the South African Medical Research Council and the University of Cape Town Staff Research Fund for grants which supported this project. Our thanks are also due to the neurologists, psychiatrists and physicians who co-operated in this study, in particular Dr J. MadGregor, who examined patients, and Dr T. Zabow for information concerning numerous patients in the eastern Cape, and it seems likely that the condition is particularly common in the White population of that area.

REFERENCE
IMPAIRED PROLACTIN RELEASE IN HUNTINGTON'S CHOREA
EVIDENCE FOR DOPAMINERGIC EXCESS

M. R. HAYDEN  A. I. VINIK
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Summary

Eight individuals with Huntington's chorea had low basal and impaired human prolactin responses to both chlorpromazine and thyrotrophin-releasing hormone. These findings are compatible with enhanced hypothalamic dopaminergic activity in this disease. Two juvenile rigid patients with Huntington's chorea had excessive prolactin responses to chlorpromazine. Approximately half of the twenty-three potentially affected first-degree relatives of patients with Huntington's chorea had normal prolactin responses to chlorpromazine. However, twelve had significantly abnormal responses—seven in one direction, and five in the other. The predictive value of these findings in terms of presymptomatic diagnosis will be revealed by a longitudinal study. A biochemical method for the early recognition of the condition would have profound implications for genetic counselling.

Introduction

Huntington's chorea is a lethal genetic neurological disorder. Chorea usually appears in middle age, and the condition runs a progressive course, with dementia, personality deterioration, incontinence, and death in 10–15 years. In view of the late onset, affected individuals have completed their families by the time signs of the disorder develop. Occasionally the disease starts before the age of 20, when rigidity often predominates.

The basic defect is unknown but it has been suggested that the condition may have a neurochemical basis.1 Because of observations that drugs which prevent or antagonise the cerebral actions of dopamine lessen the chorea2,3 while those which increase or potentiate dopamine aggravate the condition, a dopaminergic predominance has been implicated.4
10·7±2·2 ng/ml at 30 min and fell to 6·3±1·4 ng/ml at 60 min. The mean basal prolactin and the concentration at 1 h were significantly less than in the controls (*p=0·004 in both instances). The two young patients with rigidity had basal levels of 1 and 3·2 ng/ml which

**Mean±S.E. Peak Increments in Prolactin**

<table>
<thead>
<tr>
<th>Group</th>
<th>Controls</th>
<th>Chorea</th>
<th>First-generation relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16±3±1·9</td>
<td>6±6±0·8</td>
<td>8±1±2±3·4</td>
</tr>
<tr>
<td>Controls</td>
<td>16±3±1·9</td>
<td>6±6±0·8</td>
<td>8±1±2±3·4</td>
</tr>
<tr>
<td>Rigid juveniles</td>
<td>22±6±17·9</td>
<td>16±6±0·9</td>
<td>8±2±1·3±3</td>
</tr>
<tr>
<td>First-generation relatives</td>
<td>12±6±1·4</td>
<td>8±6±2·3±3</td>
<td></td>
</tr>
</tbody>
</table>

Significantly different from controls: *p<0·05, **p<0·001. Significantly different from rigid patients: ***p<0·001.

rose to 9·6 and 39·7 ng/ml, respectively, 30 min after T.R.H. There were no significant differences between these results and those of the choreic or control patients.

The first-generation relatives had a mean basal prolactin of 3·0±0·5 ng/ml; the concentration rose to 16·7±1·4 ng/ml at 30 min and fell to 10·21±1·1 ng/ml at 60 min. These values were similar to those in controls. However, of these relatives, five had intact initial responses to T.R.H. (fig. 2) but the concentrations were unsustained compared with the response in controls.

The mean peak prolactin increment of the chorea patients was 8·8±1·3 ng/ml which was significantly different (*p<0·05) from 14·3±1·9 ng/ml in the controls (table).

**Effects of Chlorpromazine**

The mean basal prolactin of the controls was 4·4±1·1 ng/ml with a rise to 6·8±0·9 ng/ml at 30 min, a further rise to 9·2±1·2 ng/ml at 60 min sustained level at 9·5±0·8 ng/ml at 90 min (fig. 3). In adult choreic patients, prolactin levels were significantly lower than controls. The mean basal level in choreic patients was 1·3±0·1 ng/ml (*p<0·001) with a rise to 1·8±0·3 ng/ml at 30 min (*p<0·001), 3·9±0·8 ng/ml at 60 min (*p=0·002), and 5·6±0·9 (p=0·003) at 90 min (fig. 3). The mean basal concentration of the two rigid juvenile patients was 3·3±2·3 ng/ml with a rise to 19·5±1·4 ng/ml at 30 min and 19·0±0·8 ng/ml at 60 min (fig. 3).

This was significantly higher than values in controls at 30 min (*p<0·001) and 60 (p<0·005) and higher than values in adult choreic patients at 30 and 60 min (*p<0·001, 90 min (p=0·004), and 2 h (p=0·003).

The potentially affected relatives of the patients with Huntington's chorea had a mean response to chlorpro-

**Discussion**

The cardinal observations in this study were the poor prolactin responses to chlorpromazine and T.R.H. in adults with Huntington's chorea.

Chlorpromazine and other phenothiazines raise plasma-prolactin in man. It is believed that these agents block the inhibitory action of dopamine on its receptors in the hypothalamus, thereby permitting unrestrained prolactin secretion. The impaired response to chlorpromazine in Huntington's chorea suggests therefore that dopaminergic activity, at least in the hypothalamus, is enhanced.
Dopaminergic pathways in the hypothalamus play a part in the regulation of pituitary hormone release. Treatment of levedopa stimulates the release of growth hormone in man and other species, and it has been reported that growth-hormone secretion is abnormally high in Huntington's chorea. However, growth-hormone concentrations are also raised with hypoglycaemia, malnutrition, muscular exercise, and other stimuli, all of which may have contributed to the findings in Huntington's chorea. Dopamine inhibits human prolactin release, and it may be the prolactin-inhibiting factor. Phenothiazines raise prolactin concentrations in blood by inhibiting the action of dopamine. If dopaminergic predominance is implicated in Huntington's chorea, affected individuals might be expected to have lowered prolactin levels, which are poorly responsive to phenothiazine administration. We report here observations which support this hypothesis.

Patients and Methods

Reected a total of 1,365; thus, treatment is more effective than is currently recommended for hyperprolactinaemia. In controls, T.R.H. administration caused a significant increase in serum prolactin from a mean basal concentration of 4.6 ± 0.9 ng/ml (mean ± s.e.) to 15.3 ± 1.9 ng/ml at 30 min and 14.8 ± 2.1 ng/ml at 60 min (fig. 1). In contrast, the midline with clomipramine and a lower mean elevation of T.R.H. administration in patients with Huntington's chorea, surgical treatment is not currently recommended. The project was approved by the hospital ethics committee, and, after careful explanation of the details and nature of the study, each participant gave written consent. Each person was requested to discontinue all medication for at least 2 weeks before the investigation. None had any other intercurrent illness.

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The brains of affected patients is, however, lacking, but an altered dopamine/α-aminobutyric-acid ratio has been found. Furthermore, it may not necessarily be the absolute levels of these neurotransmitter substances which are deranged, changes in secretion-rate, metabolism, receptor binding, or activity could be at fault. Indeed, in our patients the prolactin response was impaired mainly in the first 60–90 min after chlorpromazine administration, but by 2 h the concentration was almost normal. It may thus be that defective rather than excessive dopaminergic regulation is the hallmark of this disease.

The action of T.R.H. is presumed to be direct stimulation of pituitary release. The impaired prolactin response in the patients with Huntington’s chorea suggests that they have abnormal pituitary function. However, the prolactin response to T.R.H. can be inhibited by administration of levodopa which is converted in the hypothalamus to dopamine. In other words, a relative dopamine excess would diminish the prolactin response to T.R.H. Hence we suggest that the impaired prolactin response to T.R.H. supports the notion that patients with chorea have enhanced brain dopaminergic activity.

The two rigid juvenile patients had normal basal prolactin levels but were hyperresponsive to chlorpromazine, with abnormally high prolactin concentrations at 30 and 60 min. These patients do not reveal the expected serum-prolactin pattern of dopaminergic excess. We cannot explain this exaggerated response.

Approximately half of the potentially affected first-generation relatives in our series had entirely normal responses to both agents, and the mean for all twenty-three was normal. However, an analysis of individual results revealed that seven had impaired serum-prolactin response to chlorpromazine. Five of these also had unsustained responses to T.R.H. These results were similar to those of the adult choreic patients. In contrast, the remaining first-generation clinically normal relatives had exaggerated responses to chlorpromazine which resembled those of the rigid juvenile patients. We acknowledge that these findings may not be true prognostic indices but simply reflect the variability of the prolactin responses and differences in drug metabolism in these individuals. Only a longitudinal study will determine whether the impaired or exaggerated responses have predictive value for presymptomatic diagnosis of the condition.
In conclusion, the demonstration of lowered prolactin levels, which were poorly responsive to T.R.H. and phenothiazine administration, supports the hypothesis of dopaminergic predominance in Huntington’s chorea. Furthermore, the observation that approximately 50% of the clinically normal first-generation relatives had abnormal prolactin responses offers hope for eventual development of a means for identifying genetic carriers of this disease. This would be of tremendous practical importance, as it would facilitate effective counselling of these individuals in whose families the disease is present.

This work was supported by a grant from the South African Medical Research Council and the University of Cape Town staff research fund. We thank the physicians for permission to study patients under their care, the staff of the endocrine and diabetes research group and the human genetics department who assisted in blood-sampling, and the U.S. National Pituitary Agency for donations of human prolactin and antiserum used in the immunoassay.

Requests for reprints should be addressed to A.I.V.

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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National Institutes of Health
Estimates of the prevalence of Huntington's disease in Africa have not previously been established. South Africa offers a unique opportunity for investigation of genetically determined illnesses. We have shown that the minimum prevalence of Huntington's chorea in the White community and the population of mixed ancestry in South Africa is 4.3/100,000. However, 10% of all patients had onset of the disease before the age of 20. Because many communities are isolated, intermarriage is not uncommon, and one individual is known to be at risk of developing the homozygous form of this disease. It is very likely that the gene for Huntington's disease has been in this country for over 300 years. In an early pioneering study, Klintworth traced three Afrikaner choreic families to a common ancestral couple who came to South Africa with the initial Dutch settlers in 1652. The gene subsequently arrived in this country with the British immigrants in the early 19th century and with the French via the island of Mauritius. The Huguenots, who have taken the disease to Britain, Canada and Tasmania, are another probable source of the gene. The problems of patients and their families with Huntington's disease in South Africa are compounded by socio-cultural factors and this situation offers unique insights into the means employed in coping with this disorder and its consequences.

Disturbances in Hypothalamic-Pituitary Hormonal Dopaminergic Regulation in Huntington's Chorea; Michael R. Hayden, Aaron I. Vinik, Peter H. Beighton, Dept. Human Genetics and Endocrine & Diabetes Research Group, Univ. of Cape Town, South Africa

Dopaminergic pathways play an important part in the regulation of pituitary hormone function. Dopamine inhibits human prolactin (hPRL) release, stimulates release of growth hormone (hGH) and blunts the thyrotropin (hTSH) response to thyrotropin-releasing hormone (TRH). There is evidence for dopaminergic predominance in Huntington's chorea. The hPRL response to a dopamine antagonist, chlorpromazine (CPZ) in adults with Huntington's chorea was impaired, indicating enhanced hypothalamic dopaminergic activity. Mean peak increment in hPRL after TRH of 8.9 ± 1.9 was significantly (P<0.05) less than 14.3 ± 1.9 ng/ml in controls, suggesting excess dopaminergic action on the pituitary. The peak hTSH response to TRH in adult choreics of 12.3 ± 3.0 was significantly (P<0.05) less than that in normal controls of 23.6 ± 3.03 mIU/ml, suggesting further that pituitary TSH receptors are also influenced by the dopaminergic excess. CPZ (25mg IM) caused a rise in both from 2.12 ± 1.09 to a peak of 6.21 ± 1.83 in controls and a fall from 1.95 ± 1.09 to a nadir of 0.86 ± 0.21 ng/ml in choreics. The differences were significant (P<0.05). These findings suggest that the dopaminergic predominance in Huntington's chorea is not due to absolute dopamine excess but rather due to increased sensitivity to endogenous dopamine. Similar neuro-endocrine abnormalities demonstrated in 12 of 23 clinically normal first generation relatives may have importance for presymptomatic diagnosis.
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KONGRESBROSCJUIRE
HUNTINGTON'S CHOREA IN SOUTH AFRICA: A UNIQUE AND NEGLECTED PROBLEM

M. R. HAYDEN, A. I. VINIK, Department Human Genetics/Endocrine & Diabetes Research Group University of Cape Town, Cape Town

Huntington's chorea is a grave genetic neurological disorder, which is a more serious problem in South Africa than has generally been recognised. Our epidemiological survey revealed a minimum prevalence of the disease in the Cape Coloured and White populations of 4.5/100,000; South Africa has among the highest incidence of juvenile Huntington's chorea with onset before the age of 20, in the world. In our detailed genealogical studies, it was found that the gene for the condition probably arrived in this country in the 17th century with the Dutch, in the 18th century with the Huguenots, and in the 19th century with the British. Since dopaminergic predominance has been implicated and as dopamine has an important regulatory function on prolactin, growth hormone and thyrotropin secretions, affected individuals might be expected to have abnormal hormonal functions. In our study of 8 affected adults, impaired prolactin response to chlorpromazine injection and a blunted thyrotropin release to thyrotropin releasing hormone stimulation has been shown. Furthermore, growth hormone hypersensitivity to dopamine blockade in adult choreics has confirmed the hypothesis of dopamine predominance. The demonstration of similar abnormalities in 12 of 23 clinically normal first generation relatives may have important implications for presymptomatic diagnosis.