GENETIC AND SOCIAL ASPECTS OF

HUNTINGTON'S CHOREA

DECLARATION

I declare that this thesis has not been submitted elsewhere for a degree and that it has been composed by myself.

SIGNED:

GEORGE A. VENTERS.

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Natural/

SUMMARY

SUMMARY

The thesis is concerned with the investigation of Huntington's chorea in South East Scotland. It outlines the difficulties encountered in such an investigation and provides a history of the study of heredity to facilitate an understanding of problems concerning the inheritance of the disease.

A detailed description of the history of the study of the condition is given in addition to current theories on its pathology, pathophysiology, and inheritance.

The method of ascertainment of cases, of the formulation of an approach to, and the interviewing of, affected individuals, their spouses, and persons at risk of the condition, is described. Tables are provided of the sources of ascertainment of cases and their yield, on hospitalisation of choreics and clinical features of illness, on reproductive performance of choreics and controls, and on education and occupation of choreics and individuals not at risk of developing the disease.

Discussion/

Discussion is undertaken on the relative under-reporting of cases and possible reasons for this. Difficulties in diagnosis are considered and case histories provided to illustrate how misdiagnosis can occur. Suggestions are made as to how diagnosis may be improved and the nature and source of the information on the disease held by those at risk or affected.

An estimate of the prevalence of the condition is obtained and this is found to be higher than that of other studies. Reasons for this are discussed.

There is detailed clinical description provided of the course of the disease and explanation attempted of the causes of some of the changes observed.

Genetic aspects of the condition are examined. Its inheritance is found to be compatible with mendelian dominant inheritance. The relevance of some genetic concepts that have been used in study of the condition is evaluated.

Social aspects of the condition are discussed in terms/

terms of their influence on the course of the illness and also the social problems it engenders. The latter are considered from the standpoint of the choreic, the spouse, the children and the medical practitioner. Suggestions are made as to how the management of the disease can be improved and the possibility is raised of the formation of an association for those interested or involved with the condition.

CHAPTER ONE

INTRODUCTION

INTRODUCTION

Heredity, the transmission of similarities from parent to child, has been of interest to man since prehistoric times and studied for millennia. Much religious and scientific endeavour has been devoted to an explanation of the phenomenon, particularly in mankind. However, the study of the processes of heredity in the human species presents problems of a biological nature in that the number of offspring is usually comparatively limited and the lifespan long. Therefore much of our enlightenment on the matter of inheritance has been obtained from observation of organisms with more convenient characteristics for study than man.

Further, in many instances laws of inheritance determined from experiment in animals have been applied to mankined, particularly in the case of inherited disease. That condition providing the subject of study of this thesis, Huntington's chorea, is such a disease. It is a chronic progressive neurological disorder whose mode of inheritance is in conformity with principles of heredity formulated on a basis of observation and experiment in non-human organisms. The/

The pattern of occurrence of cases in families is typical of that observed in Mendelian dominant inheritance (discussed below). However its straightforward mode of inheritance belies the complexity of reality. There may be a wide range of clinical conditions that are included under the rubric of Huntington's chorea and also of variability in the clinical features of conditions with the same genetic basis. The clinical features of the disease may be very dissimilar in different members of the same family.

Any inherited disease raises social problems for the persons at risk or suffering from the condition, those involved in the treatment and care of sufferers, and those who wish to investigate such disease. Huntington's chorea generates difficulties common to all inherited disease and some specific to the condition. Because of the nature of the disease and its severity these problems may be particularly acute. My experience of the condition has consolidated my belief that it is the most dreadful of all diseases.

Some aspects of social problems raised by the condition

As it is intended to discuss the problems and management/

management of those individuals affected or at risk, and their families, at length below, this preliminary discussion will be directed towards problems encountered in the investigation of the condition.

The range of techniques and aspects of investigation of the disease is limited by social considerations, particularly where study of inheritance is concerned. Breeding experiments are unethical or illegal in mankind. Consequently, in the study of the inheritance of Huntington's chorea, the orientation is towards observation of patterns of occurrence and features of the disease in families. In this condition social factors exert an important influence beyond the definition of what is acceptable methodology of investigation to affect the investigator's identification of, and access to, the population of choreics and their families.

For any investigation into the disease we must be able to identify those persons suffering from it or at risk of developing it. The main criteria for diagnosis of the condition are the presence of progressive chorea and dementia whose frequency of occurrence in a family is not incompatible with that observed in Mendelian dominant inheritance. Because of the wide range of variability in the/

the clinical manifestations of illness, misdiagnosis is possible and very much related to the knowledge of a family history of the disease (as discussed below). Obtaining a family history will depend upon the degree of co-operation the doctor elicits from the patient and also the amount of knowledge the patient has of the disease and his family. The extent to which patient and doctor or members of a family communicate with each other must be determined by social factors to a great extent.

In many cases there is a reluctance to volunteer information on known or suspected family history of illness. However the withholding of information on familial disease is not the prerogative of the patient. Knowledge about the disease may be withheld from family members by medical practitioners in an attempt to prevent the emotional stress engendered by the prospect of hereditary disease. Thus various contingencies can obscure patient and family awareness of and communication about the disease and lead to erroneous diagnosis.

Misdiagnosis of the disease does occur and must preclude the ascertainment of all choreic families in a region/

region. However a more serious obstacle to identifying which families bear the diathesis is the great variability in the quality of the records kept by the multiplicity of persons and agencies that can be involved in the care of such families. Deficiencies in records are, to some extent, compensated for by this diversity of sources of care in that many patients have contact with a number of medical practitioners and institutions. Defective records in one may be made good by those of the others. Nevertheless it is to be expected that ascertainment of cases or families in any region must be incomplete for the reasons given. Further reasons are that there is no restriction on the geographic mobility of choreics in and out of regions under study nor is there any guarantee that the sexual activities of members of such families are confined within the bounds of matrimony. This last fact also creates difficulties in the study of certain aspects of the genetics of the condition.

When an index population has been identified the inherited nature of the condition raises great difficulties if it is intended to approach such cases and, or , their families. People are justifiably afraid of the disease and/

and for any investigator to come to remind them of the shadow they live under, or even unwittingly reveal that they are at risk, may be distressing. No ethical investigator wishes to cause such distress and some medical practitioners would tend to disallow any approach to their patients on these grounds.

The inherited nature of the disease also creates specific problems in the management of such patients and their families in addition to those of caring for a chronic sick person and they are related to the information the patient may have on the condition. When a patient knows about the disease, or a sib or child of his risk, his expectations, his behaviour, even his style of life may be changed. If a patient or someone at risk does not know about the nature of the disease the question arises as to what, if any, information should be given. If information is withheld then those at risk may be spared the dread of the disease but also of the opportunity to plan their lives and their family in such a way as to minimize the impact of the illness should it develop. For every person who wishes that he had never learned of his risk of the condition is another who wishes that he had learned earlier so that he could have made better provision for the eventuality of the/

the disease. My bias is towards providing a maximum of information for patient and family because of my interpretation of the ethics of the situation and also because thus we can be sure of the quality of information they obtain. To me it seems unethical to withhold information of such potential importance for the future life of those persons at risk. This question has been discussed in a previous paper (see Appendix) and further debate is necessary to allow the formulation of what and how advice should be given to those at risk.

Difficulties in the study of genetic aspects of the condition

At the outset it was stated that man was an inconvenient animal in which to study heredity. The laws of Mendelian inheritance which the disease appears to follow, although determined from animal experiment, may be considered validly applicable to the case of Huntington's chorea. However, when we wish to consider more sophisticated questions such as how do cases arise and persist in the population concepts valid in the laboratory may be less so when applied to the human situation.

Huntington's chorea is subject to the arrogant "omniscience"/

"omniscience" of the scientist. At any point in time there is a tendency to seek to interpret observations and obtain explanations in terms of extant knowledge rather than admit that current knowledge is inadequate to explain observed phenomena. Reluctance to accept that this may be the case for heredity leads to attempts to fit the body of observed facts into current genetic theory somewhat after the manner of Procrustes. This tendency is observable in some studies on genetic aspects of Huntington's chorea (discussed below) and investigation of the history of the study of heredity reveals how ancient this tendency is.

Some knowledge of the history of the study of heredity is desirable so that a further understanding may be obtained of the origins and basis of current genetic theory. Such understanding is necessary if we wish to examine the limitations of the application of some genetic concepts to the case of Huntington's chorea.

Study of the history of the investigation of heredity provides an insight into another social aspect of scientific investigation in that scientific theory often reflects/

reflects current political and social ideas. Every scientist is a product of his social and cultural milieu and examination of the history of the study of inheritance demonstrates that no scientist is an island.

CHAPTER II

CONCEPTS OF INHERITANCE IN HISTORIC TIMES

CONCEPTS OF INHERITANCE IN HISTORIC TIMES

Although glimpses of concepts of the nature of heredity can be obtained from references in ancient literature the earliest propounded hypothesis on biological inheritance appears to be that of Empedocles, a pre-Socratic Greek philosopher. Only fragments of his writings survive and translations (Leonard 1908, Burnet 1920) reveal that he considered the male and female to contain different parts of the unborn child. This state of disintegration in the child was the cause of sexual desire in the parent (Burnet 1920) the inference being that there was a mutual attraction of the separated parts of the child drawing the potential parents together. The entry of the mixed seed, paternal and maternal, into the uterus gave rise to either a boy or girl depending upon the heat therein. If the womb was hot a boy developed, if cold, a girl. He also admitted that thoughts even pictures and statues seen at the time of conception would influence the nature of the conceptus. This belief is of extreme antiquity that has held currency even/

even in scientific circles until less than 150 years ago and perhaps still in superstition. It is mentioned in the book of Genesis, Chapter 30 - 37-41, in which Jacob is said to have had Labon's cattle bear distinctively marked calves by exposing them to bundles of peeled twigs when they conceived. In the notes of W.A. Cook (1927), on Robertson Smith's "Religion of the Semites", it is stated that it was a Semitic belief that parental thoughts at the time of conception will influence the inheritance of the child. The heroine, Chariclea, of Helidorus's novel "The Ethiopians" (translated by Lamb, 1962) was of European colouring, yet the daughter of two Ethiopians. Her dissimilarity to the parents was explained by the fact that her mother had been envisaging a statue of Andromeda at the time of conception and the striking resemblance of the girl to the statue verified this. Although the work was fiction the provision of such an explanation as credible indicates that Roman society at that time (in the first century A.D.) accepted that thought would influence conception. Galen believed this (Adams, 1837), but it was never mentioned in the works/

works attributed to Hippocrates. In the pamphlet on super-foetation by a member of the Hippocratic school it is stated that if a pregnant woman thought of eating coals during pregnancy then the child would have the marks of coals on his head (Adams, loc. cit.), which shows that the Hippocratic school believed that the maternal imagination could affect the physical attributes of the child. This belief was maintained over the centuries and an explanation for the phenomenon was given even as late as 1825. Sir Everard Hone (1825) in the Croonian lecture that year, claimed that the innervation he found in the placenta provided a direct link with the maternal nervous system through which physical changes in the child could be effected. He cited instances of how maternal psychiatric upset, mainly fright in pregnancy, was accompanied by deformity in the child and he chose to assume that the fright was causal. This concept is reflected in current superstition, e.g. the welter of old wives tales concerning birth marks, etc., in which a fright to the pregnant mother or her seeing a black cat, etc., could lead to deformity in the child.

THE THEORY OF PANGENESIS

Origin of the Theory:

One of the most durable of hypotheses on inheritance appears to have been formulated by Hippocrates although it is not explained in detail by Hippocrates himself. It is summarised in his pamphlet on the Sacred disease (Hippocrates, Works, translated by Francis Adams, 1849) and explained fully in the work of the Hippocratic school, "De Generatione" (cit. Needham, 1959). This is considered by Adams (1849) to have been written by Polybus, Hippocrates' son-in-law. Darwin (1882) re-iterated it in his work "The Descent of Man" and the theory, variously modified, had its adherents over more than two thousand years.

It is obvious from the summary given that the pangenetic scheme of inheritance was well known to Hippocrates/

Hippocrates and his writings are the earliest in which it is described. Consequently it is valid to ascribe the hypothesis to him although Zirkle (1945) believes that Anaxagores should be regarded as the formulator. He (Anaxagores, translated by Burnet, 1920) did provide a philosophical basis on which the Empedoclean theory could be developed into that of pangenesis. His concepts of objects was that they were made up of infinitely small units each being a microcosm containing an infinite series of microcosms of ever decreasing size. Each of these particles had a representative particle of every other type of object that existed. Objects that we see were the results of the arrangements of these constituent particles. To demonstrate the argument he said that hair cannot develop from anything but hair yet we never eat hair as such, therefore, how can hair grow? His hypothesis was that the food we eat, because it contains representative substituents of all things must contain the elements of hair. It was an atomic theory and the atoms, in addition to containing an infinite series of constituent particles/

particles of decreasing size, are assorted and arranged to form objects by the effect of an indefinable, omnipresent, omniscient, omnipotent force called 'nous'. Maupertuis (1746) outlined a similar theory which will be discussed in more detail in the section on preformation.

In pangenesis the semen is considered to derive from all parts of the body each part contributing a tiny particle to the semen. This particle contained the potential to develop another part similar to the derived part and did so in the foetus. The similarity between the pangenetic particle and the Anaxogorean 'atom' is obvious in that both have the potential to develop into things and both are small. Modifications of the Empedoclean theory in the light of the Anaxagorean concept of objects could lead to the development of the pangenetic theory. Hippocrates would have been acquainted with the writings of both and either he or some unknown thinker must have performed the transformation of Empedocles' theory in the light of Anaxagores which resulted in that explanation of the nature of inheritance called pangenesis.

The/

The Theory:

The main features of the pangenesis theory are: that semen is a fluid to which all organs of the body contribute particles; that these particles have the potential to develop into an organ of the type whence they were derived; that both parents secrete semen and the child is developed from the mixture in which aggregation of particles will occur in such a way that the child will have a similar organ structure and appearance to its parents. Suppression of maternal menstruation was considered to occur because the menstrual blood became the food supply for the developing child. It was also believed that different organs appeared at different times and that embryonic development was completed more rapidly in the male than the female. Both parents were considered to have contributed equally to the inheritance of the child in this system.

Aristotle, dismissing the Empedoclean theory as impossible, examined the theory of pangenesis in detail and demonstrated/

demonstrated its inadequacies convincingly. Yet the basic theory was intermittently in favour until the turn of the present century its only serious rivals being that of preformationism and the Aristotelean concept of inheritance. Galen adhered to it (Needham, 1959) and his support ensured its preferment until the advent of microscopy ushered in preformationism. Yet even during this latter period pangenesis had its adherents. When preformation was discredited pangenesis was restored and believed in by the major biologists of the nineteenth century, including Lamarck (translated 1929) and Darwin (1889). De Vries also postulated an intra-cellular form of pangenesis towards the end of the nineteenth century. However, the re-discovery of Mendel's work provided a more consistent explanation of hereditary phenomena and has now gained common acceptance.

The case against pangenesis:

Aristotle devoted several pages of his treatise on the generation of animals to refuting the hypothesis of pangenesis/

pangenesis. Some of his arguments could have been accommodated in the light of increased biological knowledge but many incontrovertibly demonstrate the fallaciousness of the theory. He tendered the following observations that could not be accommodated by the theory of pangenesis: the deformed parents could have normal children; that children resemble their parents in tissues that are dead, e.g. hair and nails which could not contribute particles to the semen; that the sex organs are different in both parents yet the child is either male or female, never both; that two animals should be formed as the parts are available for two; and that plants can be mutilated yet produce normal seeds. He also clearly saw that the scheme provided no explanation as to how the particles aggregated together accurately to form the parts and then the complete individual; that the theory implied some organising force controlled the assembling of constituent particles into the appropriate form. On this concept of an organising force Aristotle erected his own hypothesis of inheritance.

Aristotle's/

Aristotle's Concept of Inheritance

Aristotle considered that the mother contributed only the raw material of the embryo and that the semen of the father provided the force dictating the form and development of the child. The mother provided the "nutritive soul" which can be equated to potentiating life, and the father gave the "sentient soul", equivalent to the psyche and that his semen controlled development of the child. Combining both aspects of inheritance it is obvious that the male is placed in a dominant role in Aristotle's concept of inheritance; he is considered comparable to a sculptor modelling the child from the maternal menstruum and bestowing a personality on this living but psychologically undeveloped individual. Parallels may be drawn between the male and female roles in Greek society of that time in which the woman was regarded as subservient to the male. Aristotle extrapolated this subservience extending it into the realms of biology. To this extent biological theory mirrored social conditions and demonstrates that scientific theories can be misconstructed under the influence of socially acquired bias. This concept of male dominance/

dominance in inheritance occurred in other societies in which women were allocated inferior social roles (Needham, loc cit p. 43). It was the case in Egypt around the time of Christ. (Diodorus Siculus, translated, 1933). At that time the Egyptians believed that the woman provided only a nutritive nidus for the child deposited by the father. Hence no stigma attached to illegitimacy as the child bore no relation to the mother. This concept of lack of biological kindred with the mother was resurrected and held in the animalculist version of preformation (Cole, 1930).

Although Aristotle refuted the hypothesis of pangenesis his theory failed to provide a generally acceptable alternative and pangenesis was the preferred doctrine until the advent of mendelism. Only during the period when preformation was in vogue did any theory resembling Aristotle's gain acceptance. Harvey (translated by Willis, 1847) demonstrated the fallacy of Aristotle's hypothesis. His dissection of pregnant does dispelled the misconception that a mass of maternal menstruum and/

and male semen were the raw material of the embryo. He showed that the embryo developed from an 'egg' implanted in the uterus and an orderly sequence of appearance and development of organs (epigenesis) led to the formation of the individual. In his belief in epigenesis he followed Aristotle and this he acknowledged. However, he was at a lost to explain how this egg appeared in the uterus and disbelieved that the ovary was the source. He also failed to find semen in the uterus (loc cit p. 575) and so believed that no physical constituent of semen was involved in procreation. Again living in a male dominated society he ascribed priority of importance to the male in formation of the foetus. Although he stressed the tenuousness of his hypothesis he considered it no more remarkable than any others postulated at the time. His theory was that contact of women with semen conferred a property on the uterus of generating and moulding a foetus. This property was an attribute of the male and required an appropriately mature uterus for the formation of a fertile egg. There is the concession that the female must be in the proper receptive state but he reverts to the true Aristotelean concept when he speaks (loc cit p. 578) of/

of the imprinting of the uterus with the idea of the father directing the 'formative faculty' to produce an offspring like himself. This phraseology is obscure but it can be simplified to the basic Aristotelean theory that the father dictated the form of the embryo.

Harvey's reliance on his own observations led him to reject that the ova were formed in the ovary and he died twenty years before Ham observed the presence of animalculae in semen. Consequently the difficulties he had in envisaging how conception could occur are understandable and though he contributed no satisfactory theory of inheritance he did help re-establish the value of direct observation as a technique for the explanation of natural phenomena. His dictum of 'Ex ovo omnia' was to be taken literally by the protagonists of preformation.

The Preformation Theory:

Preformation was essentially an embryological concept in which it was believed that the entire structure of the embryo is determined at a single point in time. It is/

is in contrast to the theory of epigenesis in which it is believed that the different tissues and organs of the body appear and develop sequentially as a result of the growth and modification of tissues of the developing foetus.

Empedocles provided a preformationist theory in that his disconnected limbs and parts of the body were all formed and extant in the parents pre-natally and at conception they were magically reassorted to give the formed child. Thus it can be seen that the doctrine is of great antiquity. Aristotle recognised and rejected it as a theory of production of the embryo. So convinced was he of epigenesis as a result of his observations on eggs that he was able to refute preformation which would have been a possible mechanism whereby pangenesis could credibly lead to the production of the foetus. Adherents of pangenesis however had also observed embryonic development in eggs and no more adhered to preformation than Aristotle. Galen also believed in epigenesis and only when his authority was overthrown was the concept of preformation resurrected.

Cole (1930) considers the original resurrectionist to be Joseph of Aromatari who claimed in 1625 to have seen the rudimentary embryo in the unincubated egg. Others followed in that century with the same claim and soon the theory gained credence that the process of development in the embryo was merely the increase in size of pre-existing structures. Increase in growth would result in the most miniscule of organs eventually becoming apparent - invisibility of an organ in the embryo was the result of its smallness or insubstantiality, not its absence. There appears, at that time, to have been a readiness to believe that increasingly small and smaller particles could exist conceptually similar to Anaxogorean 'atoms'. The ultimate development of the theory was that each seed would contain the seed containing the seeds of all subsequent generations. This process of successive encapsulation of successive generations was called 'emboitement' and was first stated by the philosopher, Malebranche (Cole loc cit p. 50).

Development/

Development of the concept of preformation is understandable in the light of inaccurate observation and generalising from botanical to animal reproduction. Wheen seeds were examined they could be seen to have the rudiments of the plant. Therefore there was some justification of the theory provided by observation. However, the concept of emboitement was a philosophical one based more on current religious ideas than scientific thought. Belief in the hypothesis of creation that God made all animals at one point in time could substantiate the doctrine and the Bible was cited as evidence of preformation (Hebrews VII, 9-10) by Swammerdam (Cole, loc cit). In these verses Levi is represented as having paid tithes before his birth as he was in the loins of his father Abraham when he paid tithes to Melchisedek. Swammerdam also revealed that discussions with Malebranche had provided a biological reason for the justification of the doctrine of original sin. The reasoning was that the original progenitors of the human race, Adam and Eve, contained all the subsequent progeny of the human race and that extinction of the human species would occur when this store was exhausted. Death of the species was the penalty/

penalty implied by the doctrine of original sin and this was the ultimate fate of the human race.

Emergence and tenure of the hypothesis of preformation was very much dependent on the theological climate of the period illustrating once more how much scientific theory can be a product of social non-scientific ideas. In spite of Harvey's observation on the development of the embryo, in spite of calculations revealing that astronomical numbers of humunculi would be necessarily contained in the primigenitor of a species, the concept of preformation was adhered to for nearly two centuries. However, early in the history of the theory controversy arose as to whether the ovum or the spermatozoon contained the homunculus, that is, the individual in miniature.

Maupertuis (1746) provides a lucid summary of the ideas held by the rival theorists. Ovists held that the ovum was the source of homunculi, that the semen awakened and invigorated whichever dormant homunculus was most ready/

ready for development. If a male homunculus was stimulated then he would develop to produce only semen not homunculi. Direct descent was possible only through the female line and should a female homunculus be selected then she could provide the ova containing the ova of all subsequent generations. Children resembled the father only in so far as the excitatory force in the semen could modify the homunculus. This half-denial of a biological basis for paternity is a retrograde step. It is observed in some current cultures (Hartland, 1910), but was believed only in prehistoric times in the countries where civilisation first appeared. Venus figures as fertility symbols antedate phallic symbols by millenia (Childe, V.G. 1961) but the latter can be identified in neolithic cultures indicating the antiquity of the recognition that the male intervention was essential for procreation.

The animalculists believed that the male carried the store of homunculi and that each homunculus contained the seeds of subsequent generations. Each spermatozoon was believed to contain a homunculus with its/

its encapsulated progeny. If a female homunculus gained access to the nidus of the maternal uterus and developed into a woman she would only act as a receptacle for the homunculi provided by the male. She could not reproduce. Resemblance to the mother was possible only in so far as her providing the food and environment for the growing foetus would allow.

Maupertuis rejected both hypotheses on the grounds that children could resemble both parents and neither ovism nor animalculism could satisfactorily explain this. An homunculus was considered preformed and the animalculist theory of maternal environmental modelling of the foetus to resemble the mother was considered by Maupertuis no more logical than that it should resemble the food the mother ate or the place she lived. Ovists who invoked a paternal modelling force derived from the semen were using a further mystery as an explanation of the phenomenon of generation. Maupertuis considered this concept no advance in thinking and was disinclined to accept it. He was a convinced epigenesist believing that Harvey's observations provided/

provided irrefutable evidence of this and resurrected a pangenetic schema of inheritance. His hypothetical particles aggregated under the influence of a mutual attraction and were similar to Anoxagorean atoms in that on death they dispersed only to be absorbed and integrated into another individual. He postulated two levels of attraction. One was organ specific in which he likened the constituent particles to citizens of a republic equivalent in status cohering to form the organ. A higher level of attraction was postulated also in which the organs (equivalent to republics) were mutually attracted and arranged to produce the individual under the influence of an organising attractive force. This force he likened to the power exercised by a king welding separate republics into a kingdom.

It is a semi-philosophical explanation his mysterious attractive forces being only slightly nearer observational verification than Anaxagores' 'nous' or the ability to dictate foetal development conferred on the semen by Aristotle. Some observational foundation for/

for his hypothesis was provided by study of the process of what we know to be crystallisation and the complex forms this could take. His specific argument was that the mixture of silver, spirits of nitre, mercury and water give rise to a structure extremely like a tree. Maupertuis stated that chemists were constantly observing and using the concept of attractive forces. These facts he cited as evidence for the hypothesis he offered which he made clear was only tentative.

Observation by Wagner and Leuckart of fertilisation of the ovum by contact with the spermatozoon provided the ultimate refutation of both ovist and animalculist theories but the illogicality of the principle of emboitement and the increased development of observational biology were the major factors causing the discrediting of the hypothesis of preformation as envisaged by biologists of the seventeenth and eighteenth centuries.

Pangenesis/

Pangenesis was re-established as the preferred theoretical explanation of inheritance after the demise of preformationism. Maupertuis had re-iterated it and it was generally accepted by biologists of the nineteenth century. Lamarck (translated 1912), and Darwin (1889) specifically stated versions of the theory but they adhered fundamentally to the Hippocratic doctrine. Darwin admitted his admiration of Aristotle (Needham, loc cit p. 42) but obviously his reading did not extend as far as Aristotle's refutation of pangenesis or he could never have seriously propounded the hypothesis. He was able to establish the theory on a cellular basis, that every cell had particles he called gemmules which were carried via the blood into the gametes. Galton (1889) was aware of the limitations of the hypothesis but accepted it as a suitable foundation for the mathematical treatment of hereditary phenomena. Spencer, a la Descartes, via Maupertuis, postulated that such units had some mysterious affinity for those of a similar nature, like the molecules of a crystal, and organogenesis was analogous to the process of crystallisation (cit Weisman 1893). Weismann (1893) proposed that particles were grouped on the chromosomes and had/

had a topographical pattern which would dictate the form of the individual. These particles were the raw material of inheritance. The genealogy of the organism would specify how these particles were arranged in the germ plasms and thus how the embryo would develop. His theory of the continuity of the germ plasm illustrates a stage of transition from the concept of direct inheritance towards indirect inheritance. His basic units of inheritance were biophors which aggregated to form ids. These were situated on the chromosomes (which he called idants). He believed that the source of the sex cells, the germ plasm, persisted unmodified in a line of cells direct from the fertilised egg. All other body cells used up their allocation of biophors in becoming transformed into specific tissues but the sex cells maintained a full complement of hereditary particles. Consequently the body was the vehicle whereby this germ plasm was maintained and reproduced. It was the product not the producer of the germ plasm. Hence inheritance was not of discrete particles deriving from parental organs but of the potential to develop characteristics i.e. indirect inheritance. Weismann also recognised/

recognised that a reduction in the amount of hereditary material was logically necessary otherwise the progeny would be accumulating more hereditary material than the parents in ever increasing amounts. He predicted that this reduction would occur and observed this happen during oogenesis.

Mendel firmly declared that inheritance was indirect and that there was reduction of the amount of hereditary material in the gametes. (Mendel, 1865).

MENDELISM

Mendel's experiments breeding peas enabled him to deduce the laws of inheritance from his observations. He observed that when he crossed strains of peas bearing differences in single characteristics such as seed coat colour or shape he could discern patterns which enabled him to predict what would happen in subsequent generations. When two plants differing in a single characteristic were cross-fertilised all the progeny of the first mating showed only one characteristic. This characteristic was considered to be 'dominant' and was developed in preference to its 'recessive' partner. On self-fertilising this first generation the progeny obtained varied in that some demonstrated the dominant, others the recessive characteristic. The ratio of these with the dominant to those with the recessive character was constant at about three to one. When the second generation progeny were self-fertilised those with the recessive character bred true, one third of those with the dominant character bred true, and two thirds of those plants with the dominant characteristic gave the three to one ratio of dominant to recessives.

These/

These observations led Mendel to postulate that each plant inherited the potential to develop either characteristic i.e. indirect inheritance. He further postulated that the agents of inheritance, those attributes which specified what characteristics would be observed in the progeny, were particulate units which segregated in the sex cells. On fertilisation the segregated units were brought together in pairs once more. Thus each parent contributed one member of each pair of particles to their progeny. The dominant characteristic would be observed in the individual if the members of a pair were dissimilar and the recessive characteristic would appear only when both units of the pair specified the recessive characteristic. If the fertilised egg contained a pair composed of identical units it was called homozygous; if they were non-identical it was called heterozyous for the appropriate units. These units were later called genes by Johanssen and members of a group of genes affecting the same characteristic were called alleles. Mendel declared his units, genes, to be transmitted unaltered from generation to generation. If the physical appearance of the plant (the phenotype),

/g

demonstrated/

demonstrated a dominant characteristic, and if the genetic constitution (the genotype) was heterozygous, the recessive gene was unaltered by its sojourn in the "wrong" phenotype. Should gametes subsequently be produced bearing the recessive genes and unite to form a homozygous recessive zygote, then the phenotype would demonstrate the characteristic specified by the recessive genes.

Consideration of the results obtained when crossing plants showing two differing pairs of characteristics led Mendel to postulate that each pair of genes segregated independently of all other pairs.

Prior to the rediscovery of Mendelism advances in the understanding of cell behaviour had provided insight into the anatomy of inheritance. Von Baer* observed the cleavage and development of the fertilised mammalian egg in the third decade of the nineteenth century. In I850 Warneck,* and later Hertwig,* observed that contact with spermatozoa was necessary to initiate the development/

* all cit. in "The Rise of Embryology", by Meyer, A.W. London I939.

development of the ovum. Van Beneden* observed the behaviour of chromosomes and their reduction in number during oogenesis in I879 and by the early I880's, Van Beneden*, Hertwig*, Strasburger*, Boveri* and Weissmann (loc cit) had all independently postulated that the chromosomes contained the hereditary material of the cell. When Mendel's work was rediscovered Boveri* then Sutton* postulated that the chromosomes were the structures containing the genes. Morgan* developed chromosome studies in drosophila and the major task of genetics has been detailed study of the nature and behaviour of chromosomes in all manner of organisms.

It is now known that the raw material of chromosomal heredity is de oxyribonucleic acid (D.N.A.). A sequence of 3 base pairs (triplets) in the chains of D.N.A. occurring in chromosomes appears to code for a specific amino acid. A sequence of triplets will specify a polypeptide chain which will be the constituent of some cell enzyme. Thus the chromosomal D.N.A. is a source of information providing in detail the chemical composition of much of the cell and some information on the controlling of the metabolic activity of the cell, qualitatively, quantitatively/

* All cit. in "Towards an understanding of the mechanism of Heredity", by Whitehouse, H.L.K., London I969.

quantitatively and perhaps even temporally. We have some insight as to how such information is used by the cell but this is limited. Comparison with micro-organismal systems is of debatable validity. However the postulated scheme is that the genetic D.N.A. is made accessible to molecules of ribonucleic acid, R.N.A. These R.N.A. molecules are grouped linearly along a length of chromosomal D.N.A. so that they form a long molecule which will be released as "messenger" R.N.A. and will correspond in base sequence with chromosomal D.N.A. The messenger R.N.A. becomes attached temporarily to a cytoplasmic particle, a ribosome. There amino-acids are assembled according to the sequence specified in the messenger R.N.A. and when assembly is completed the appropriate polypeptide chain is released.

This scheme of inheritance relegates the Mendelian gene from a deterministic particle to an item of information. This deterministic ethos implied that genes created whatever character they were concerned with/

with. They controlled the appearance of specific characteristics which would appear only if, and because, the appropriate gene was present.

The foundations of the concept of deterministic particles were inherited from prehistory. It is essentially a sub-division of the seed into "Mini-seeds" each sub-unit creating a particular characteristic. There is a personalisation of the gene in so far as the role it is ascribed is that of an operator. Deterministic particles were the raw material of the pangenetic schemes of inheritance. The most extreme case of particulate determinacy was that of the homunculus beloved of the preformationists.

Experimental confirmations of the fundamental hypotheses were soon abundant and the investigation of the mechanics of inheritance had a firm basis from which further hypothecation could be made and tested. Since then the discipline has developed steadily and logically/

logically, exploring the mechanismal possibilities and revealing the extent of our ignorance.

Initially the science was confined to observation of the appearance and behaviour of differences between parents and progeny. Unless differences are present we cannot observe patterns of heredity. However, as the powers of resolution of the science have been extended to the cellular level the mechanisms of information transfer from parent to progeny have been accessible to study. Those processes whereby differences in information (different genes) are serially transmitted from parent to child are thought to be common to all genes. The mechanisms of interpretation and use of genetic information are also available for study. This enlarges the field of genetics considerably as it brings study of the inheritance of invariable gene dependent characteristics within its compass, characteristics common to all cells. There can be no denial that invariable characteristics exist. No cell exists without a cell membrane/

membrane but the presence of such integral cell structures may be largely independent of chromosomal genetic hereditary mechanisms.

HUMAN GENETICS

The vast majority of concepts applied and upheld in human biology are inferences, the result of conclusions drawn from animal experiments. In many cases this can be rationalised because th animals or tissues studied are phylogenetically close enough to human for analogy to be credible. In addition some techniques of study can be applied equally to man and the experimental animal. Validity of applicability of concepts will be in proportion to the degree of biological similarity between man and the organism studied. Because of the foundations of human genetics being entrenched in formal genetics conceptualisation is in animal genetic terms. Their applicability is broadly justifiable but may be the reverse when particularised. Many animal genetic concepts have been formulated from experiments unrepeatable in the human situation. At present genetic homogeneity of a condition can only be verified by breeding experiments. These are precluded in human investigation. This fact vitiates many conclusions on inheritance of disease in which phenotypic similarity is equated with genetic identity.

There is a need for the elaboration of techniques that can be credibly applied in the field of human genetics. Mankind's peculiar advantages and disadvantages for study should be evaluated and appropriate techniques evolved rather than inadequate modifications of those productive in the context of animal genetics.

It is undeniable that a considerable amount of knowledge has been gathered providing insight into a biochemical basis of heredity, of how/

how information is contained in genes, how they are replicated, transcribed and translated. How these processes are organised in the cell, topographically and temporally is not known. Apparently reasonable hypotheses can be made on the nature and raw material of the genome but we have only limited insight as to how it is operated in organisms larger than bacteria. Yet for the practical scientist knowledge of the modus operandi is essential.

The aim of scientific investigation is to acquire knowledge. Motives towards its acquisition are either for the sake of knowledge itself or for its practical consequences for mankind. In human genetics the latter motive is of prime importance. Only by understanding the modus operandi can we use knowledge practically in exerting control over hereditary processes.

Every scientist is a product of his cultural milieu and this can be a potent source of bias. (Needham, loc cit p. 242), (Reed, 1956). When science examines areas of general social interest differing cultural backgrounds can give rise to different hypotheses. This is especially the case when facts are scarce and consequently the scope increased for variation in hypothesis. In human genetics facts are scarce and, because of the social connotations/

connotations of the discipline, there may be a tendency toward premature hypothesis.

It is hoped that this thesis will illustrate difficulties in methodology and concepts of human genetics by study of a particular condition, Huntington's chorea. Some interesting social and clinical aspects of the disease are also studied.

CHAPTER III

BACKGROUND OF INVESTIGATION OF HUNTINGTON'S CHOREA

HISTORICAL BACKGROUND

Chorea is a latin transliteration derived from the Greek word Χορεα which means a communal dance. In modern times it is used to specify a type of involuntary movement first described by Sydenham in I686 (translated by Swan, I769) as chorea Sancti Viti. Prior to then that term had been applied to an assortment of epidemic diseases, the dancing manias, (Hecker, I844) which had flourished in the Middle Ages. They originated probably from a variety of causes (such as ergotism or encephalitides) but the most common cause appeared to be mass hysteria in a susceptible population (Hecker, I844).

Generally it was not so much the physical activity that was involuntary as the state of mind by which they were compelled to cavort. In such epidemics a sufferer suddenly felt an irresistible desire to perform various acrobatic feats and the sight of the afflicted caused any onlooker to becaome similarly affected. These epidemics came in the wake of the Black Death and periodically/

periodically scourged the continent of Europe. The name Grand Danse de St. Guy or St. John resulted from the celebration of that Saint's day with mystic customs, probably preserved heathen rituals and bacchanalian revels. The association of epidemic chorea with festal revelry is easy to understand. According to Hecker there was a medieval legend about St. Vitus in that when he was martyred he pleaded to be allowed to intercede for these afflicted with the dancing mania. Hence the other name used for the disease was Chorea St. Viti (or St. Witt).

These epidemics gradually diminished in severity and frequency and after the beginning of the 16th century rarely occurred and were never extensive.

Sydenham's use of the term chorea differed greatly from the previous usage. His description was of involuntary movements of the limb and trunk muscles, a dance of the muscles in which the sufferer had no desire to perform such antics but was powerless to prevent them. He established that muscular movement occurred independent of/

of the will of the sufferer whereas in the dancing manias such movement was intentional.

Nosological inexactitude in the seventeenth, eighteenth and early nineteenth centuries led to a more general application of the term than to the random jactitious movements described by Sydenham. Parkinsonism, (Bouteille, 1810, See 1850) essential tremor, (Bouteille, 1810) post-traumatic or infective encephalitic motor disorders, (Bouteille, See, loc cit, Sandras 1851) and Gilles de la Tourette's syndrome (Bouteille, Sandras, loc cit) were categorised as chorea. This hyper-- inclusiveness was also accompanied by extension of the age limits within which choreic symptoms were recognised as occurring. What had originally been considered as a symptom - complex of childhood (Sydenham, Bouteille, See, loc cit) and puberty or pregnancy was recognised as occurring in older age groups and even in the senium (Sander 1870). On the continent, especially in Germany, the concept of "chorea magna" (chorea Germanorum) evolved. This became established as an alternative to chorea minor/

minor and came to be a "dustbin" term. All hypermotile disorders in adults that were not identifiable as chorea minor could be, and frequently were, diagnosed as chorea magna. The heterogeneity of such conditions was apparent in Britain and the term was never generally used. This came to be the case on the continent by the end of the nineteenth century.

As disease syndromes crystallised the limits of application of the term chorea became increasingly confined to those disorders of which jerky, involuntary movements were a feature no matter what age of the sufferer.

During the epoch of the dancing manias the majority of the populace, including physicians, considered the cause of the disease to be demoniac possession. According to Hecker, Paracelsus did not subscribe to this view preferring to attribute disease to natural processes rather than divine intervention or lack/

lack of it. But belief in the supernatural causation of disease dies hard. Lyon (1863) stated that families suffering from hereditary chorea were considered as cursed and their affliction just retribution for their distant forebears having mocked Christ on the cross. Similarly Huntington (1872) stated that the affected families were commonly regarded to be suffering under a curse imposed for their mockery of the sufferings of a certain cleric.

Chorea and Heredity:

It is probably that heredity was regarded as a contributory or causal factor long before any comment was published mentioning it. The earliest traceable reference is in a pamphlet on chorea Sancti Viti by John Ewart (1786) published in Edinburgh in 1786. This dissertation on chorea minor contains the comment that in cases of chorea where there is an hereditary taint they are healed straightforwardly but with more difficulty than those with no hereditary predisposition. Berndt mentioned hereditary chorea in 1810 (cit Bell 1934) and Antoine Portal (1808) stated that some spasmodic disorders/

disorders of the nervous system were inherited. In 1833 Dr. Eliotson described chorea in adults which he said was hereditary, progressive and incurable (Eliotson 1833). By the mid nineteenth century acute chorea was postulated (See loc cit) to be a familial condition and chronic adult chorea was established (Sandras, loc cit).

Huntington's Chorea:

The Rev. C.O. Waters (1848) wrote a letter to Dunglison in 1841 describing a chronic hereditary chorea occurring in adults. This provides the first clear description of the condition now known as Huntington's chorea and the letter contained an accurate account of the heredity and the clinical features of the disease. Gorman (article in Neurographs by The Editor (1908)) described the disease before Huntington but his communication was destroyed. I.W. Lyon (loc cit) also described chronic hereditary chorea before Huntington but did not state that dementia occurred. Sander also mentioned hereditary chorea (loc cit). In 1872 George Huntington published a paper on chorea minor and appended a section on chronic hereditary chorea. This paper was the one medicine chose to recognise as definitive and/

and the accolade was accordingly bestowed of the eponym "Huntington's" to the disease.

His paper contained a description of the disease in which a progressive chorea started in adulthood and inexorably worsened. It was accompanied by dementia and a tendency to suicide. This condition was inherited and occurred only in families that had choreic forebears. He asserted that once a family line escaped the disease for one generation then it never recurred in that line and was of the opinion that it was a local affliction occurring only in a few families in the New England States. However once the syndrome was defined, the abundance of reports of choreic families in several countries showed that it was a disease of universal occurrence. (Editor, Neurographs, 1908). It has now been reported as occurring in every continent. (Barbean, 1962, 1964; Bayulken, 1961; Chuttani, 1957; Beaubrun, 1962; Brothers, 1964; Kishimoto, 1957; Klein, 1964; Klintworth, 1962; Murakami, 1964; Zhivkov, 1964).

Initial/

Initial observations on the disease were of its clinical features and its inheritance by means of family and pedigree studies. At an early stage autopsy studies were made in attempts to establish the pathological basis of the disease. Unfortunately in the earlier cases described there was no uniformity of pathological findings just as there was no guarantee that the autopsies were of cases of Huntington's chorea.

Pathophysiology of Chorea:

The brain had been recognised as controlling the motor activity of the body since the work of Hippolytus and Erisitratus at Alexandria. That part of the brain giving rise to choreic involuntary movements was first recognised as the striatum by Broadbent (1869). He recognised that chorea was symptomatic only of the site of the disease and not the manifestation of a general condition of the brain or blood or any other organ. He also noted that if impairment of intellect occurred then the cerebral hemispheres were also affected. Hence he provided a rationale for the neuropathological investigation/

investigation of the cerebral lesion in Huntington's disease for subsequent investigators. This was overlooked on the continent. Golgi commented on the basal ganglia being affected in a case of progressive chorea in 1873 (Golgi 1873). This patient had been ravaged by syphilis and this could have caused the striatal and cerebral lesions described.

Huntington's Chorea - Neuropathology:

In the early autopsy studies the striatum was generally ignored and the meninges and cerebral cortex investigated. Some investigators supported the view that a chronic pan-cerebral encephalitis was demonstrable. (Huber, 1887; McLaren, 1885; Jolly, 1891; McLeod, 1882; Clarke, 1897).

Jelgersma (1908) is credited by the majority of authors with the focussing of attention on the striatum and with describing the cerebral atrophy. He was antedated by Harbinson, (Harbinson, 1881) who had been/

been influenced by Broadbent's paper and confidently sited the lesions in the striatum and cerebral cortex. Pierre Marie and Lhermitte (1914) confirmed the observations of Jelgersma. Pathological investigations were undertaken notably by Dunlap (1927) Stone and Falstein (1938) and more recently by McCaughey (1961).

As stated by McCaughey there is a spectrum of changes in the central nervous system in Huntington's chorea. Though they may differ on minutiae, pathologists are generally agreed that the major depradations of the disease are in the caudate nucleus and putamen and the cerebral cortex.

The main neuropathological features of the disease are cortical, striatal, and subthalamic nuclear atrophy (Greenfield, 1963; Dunlap, 1927). There is secondary ventricular dilatation and gyral atrophy usually mainly frontal and around the Sylvian fissure. The corpus callosum may be thinned and the caudate and putamen (the striatum) are generally atrophic and stained brown. Opinions vary/

vary as to where the major atrophy occurs. Dunlap favours the head and anterior parts of the caudate nucleus and the putamen whereas Greenfield considers it to be the middle and posterior parts. There is no debate that the striatum is atrophic. According to Dunlap and Greenfield the cell loss is mainly of the small cells although Denny Brown disputes this (1962). Astroglial proliferation is generally marked giving rise to a non-neuronal hypercellularity.

Changes may also be observed in the pallidum and subthalamic nuclei, the thalamus, red nucleus, substantia nigra each or all of which can be either normal or suffer severe cellular depletion.

Generally the cortex is atrophic and the brain smaller than in normal controls (Dunlap). There is generalised cortical neuronal depletion being most marked in layers 3, 5 and 6. Usually the lepto meninges are thickened. (Greenfield, McLaren, Jelgersma, McCaughey, Dunlap all loc cit).

Pathophysiology:/

Pathophysiology:

Misunderstanding of the pathology of the disease vitiated much of the early physiological interpretations as to the functional abnormality causing Huntington's disease. In the light of present knowledge we can reject some of these early conclusions. In the light of present neurophysiological ignorance we must admit that current concepts on the nature of involuntary movements are more speculation than certainty.

Early interpretations of the choreic process were directed towards the explanation of the apparent paradox of increased motor activity resulting from neuronal loss. (Hughlings Jackson, 1869). Dementia could be rationalised in that diminution in intellect was paralleled by cortical neuronal depletion but the excess motor activity was more difficult to explain. Study of the motor cortex duly led to the observation of cell loss. Lannois and Paviot (1908) explained the observed hypermobility in Huntington's chorea by claiming that the motor cortical lesion was more irritative than destructive/

destructive. Hughlings Jackson (1869) had earlier postulated a vascular basis for chorea. He observed that microscopic embolisation occurred in the brain capillaries and smaller blood vessels in the basal ganglia of a case of typhoid who had bilateral chorea. From this he postulated that a negative pressure distal to the embolus was the stimulus to opening of collateral blood vessels with resultant hyperaemia. This hyperaemia led to increased excitation of the gangliar neurones and hence, chorea. If embolisation was extensive and continuously occurring then eventually tissue loss would occur and loss of function would be the result. His localisation of the causal process was accurate but his hypothesis was not. Initially, apart from Harbinson (loc cit), Huntington's chorea was considered mainly to affect the cerebral cortex by most investigators. Anton (1896) had demonstrated the importance of the basal ganglia in disorders of movement by the pathological finding in his case of congenital double athetosis. Jelgersma (1908) re-iterated this in his study of Parkinson's disease and chronic chorea. He emphasized the magnitude of the cell loss from the caudate and helped re-direct the attention of neurologists to the basal ganglia. Wilson (1912) confirmed their importance by/

by his description of hepato-lenticular degeneration.

These observations provided the basis for clinical, experimental and pathological investigation of the role of the basal ganglia in the genesis of involuntary movement. Current hypotheses as expounded by Kinneir Wilson (1954) Denny Brown (1962) and Purdon Martin (1960, 1967) are heavily indebted to the original observations and philosophy of the regulation of the nervous system of Hughlings Jackson.

Current theories on the basal ganglia i.e. the striatum and pallidum is that they are concerned with the maintenance of control of posture. Involuntary movements result when the basal ganglia or their fibre systems are damaged so that disintegration of motor function occurs. Such movements represent an intermediate stage between normality and fixity of posture. If the disease process is progressive or the gangliar lesion extensive then the involuntary movement will be replaced by fixity of posture, the result of complete as opposed to/

to partial disintegration of control of motor activity.

Two syndromes are theoretically distinguishable, the striatal and the pallidal, but generally disease processes are diffuse consequently the "pure" syndrome is rarely seen. The striatal syndrome includes those disorders characterised by more or less athetoid movements progressing to hemiplegic dystonia. The pallidal includes those disorders of which parkinsonian tremor is a feature and progress to dystonia in flexion. Huntington's chorea is one of the disorders included in the striatal syndrome.

The functional roles and relationships of the basal and brain stem ganglia with each other and the rest of the central nervous system are a matter of conjecture. Various theories on such matters have been postulated. Most are based on the premise that different levels of integration exist that interact to effect controls of posture and movement and the ganglia function at an intermediate level. Each level provides a natural balanced system/

system of movement. With increase in complexity of the system the range of motor activity is increased and there is re-representation of function at a higher degree of sophistication at successively higher levels of integration. These levels can be conveniently divided into: the mid brain subthalamic and cerebellar - concerned with body contact righting reflexes; the cortical - concerned with voluntary movement; and the basal gangliar, at which specialised involuntary movement is co-ordinated in relation to environmental stimuli. For normal function each level is dependent on the integrity of those less sophisticated and to some extent suppresses them. Loss of a higher level of integration results in the appearance of the more elementary and less well adapted level of control.

This concept of the nervous system conforms with current neurophysiological theory. It is impossible to confirm or refute with available methodology but it provides a working hypothesis and a rationale for neurosurgical intervention in disorders of posture or movement.

At/

At present neurosurgery can only offer cell or fibre destruction as therapy for the disorder. Conditions arising from imbalance between normal and abnormal components of the basal gangliar system can only be treated by what amounts, effectively to destruction of normal ganglia. Thus reduction in function in one is paralleled by the loss of function in the other. The disordered level of integration is elided. Normality can never be achieved as a result but functional improvement is to be expected.

If the disorder in Huntington's chorea was confined to basal ganglia then such procedures, once improved, could afford a reasonable degree of function to sufferers. However, the extent of the neuronal loss in the cerebrum ensures that such procedures would be no more than palliative.

Aetiology:

Huntington recognised the hereditary nature of the disease. He also anticipated Mendel's segregating units/

units indirectly by postulating, that the children of a sufferer faced two possibilities. They could either develop and transmit the disease or remain free of not transmitting it/ it to their descendants. He emphasised the novelty of this form of inheritance indicating that it differed from the common inherited disease such as tuberculosis or syphilis. In such disorders a generation might be observed to be spared but ultimately it would reappear in the family. This was the logical consequence of belief in the theory of blending inheritance which was current at that time. Thus, none were considered to be spared the morbific inheritance in a family but some were fortuitously spared the disease only to have it reappear in their children or grandchildren. Huntington categorically refutes this occurring in hereditary chorea. His assertion is, that once the line is free of disease, it will never recur in subsequent generations. Rediscovery of Mendel's laws provided scientific justification for the validity of this observation. Jellife (1908) was the first to state that the disease appeared to conform to a Mendelian dominant pattern of inheritance.

The/

The cellular lesion:

Awareness of the process of Mendelian inheritance re-orientated ideas on the aetiology of the disease. Two alternative theories were held. One was that the defect was an inherent structural defect of either the cell or its immediate environment whose cumulative effects led to the development of the disease. The other view was that some environmental factor acted by chance on an hereditarily predisposed terrain. (Lannois Paviot, 1908). The latter view was necessary to accommodate the misconception of blending inheritance. With the advent of mendelism such accommodation was superfluous and the former theory was, and still is, favoured. Apart from its conformity with Mendelism its ready acceptance was a function of the possession of a strong determinative ethos by the Mendelian gene. The tacit assumption now held is that Huntington's chorea is the end result of cell dysfunction. This dysfunction is considered to be the result of enzyme abnormality of structure or function secondary to some irregularity of structure, activation or interpretation of one or many chromosomal genes.

What/

What cell is fundamentally at fault is not known. The main susceptible cell appears to be the small neurone in the caudate nucleus but larger neurones are also affected. It may be that some abnormality exists in the small cells resulting in their premature senescence. However, it is equally possible that other cells may so alter the environment of the neurones that their survival is limited. If the blood supply to neurones is curtailed then they die no matter how "normal" they are.

Huntington's chorea is observed when a specific pattern of cell loss occurs. Only the more gross characteristics of this pattern are known, that the cells are mainly of one type and lost from particular ganglia and cortical layers. The detailed chronology, topography, and functional effects of cell loss have not been elucidated. This elucidation awaits refinements of neuro-anatomical and physiological methodology or information as to intra-cellular regulation and the biochemical lesion occurring in Huntington's disease.

Biochemical/

Biochemical Aspects:

Various investigators have examined the brain and blood of Huntington's choreics in attempts to elucidate the biochemical pathogenesis. Striatal syndromes have provided leads. Manganese poisoning can give choreiathetoid syndromes. Wilson's disease results from abnormal copper metabolism. The concentrations of heavy metal ions have been examined in choreic brains. Intracellular magnesium and calcium metabolism have been studied. (Bruyn, 1966; Kenyon, 1963).

Urinary end products of indoxyl and catecholamines and amino acids have been investigated. (Oliphant, 1960; Cowie, 1962; Curzon, 1963; Cumings and Kremer, 1967). Side effects of drugs have also indicated lines along which productive biochemical investigation can be directed. Reserpine was observed as producing Parkinsonism as a side effect. Investigation of this led to an appreciation of the possible importance of dopamine in the regulation of function in the basal ganglia (Calne, 1968).

It is now recognised that at least two neuropharmacologic fibre systems converge on the striatum. These are the cholinergic excitatory fibres converging on the caudate nucleus from several regions (MacLennan and York, 1966), and the dopaminergic inhibitory fibres ascending from the substantia nigra. Therefore release of acetylcholine leads to excitation and of dopamine to inhibition of neurones in the caudate nucleus. (MacLennan and York, 1966, 1967). This degree of understanding has led to the use of dopamine precursors being used in attempts to improve Parkinsonism (Cotzias, 1967; Godwin Austen et al, 1969) as a pathologic feature of Parkinsonism is the depletion of dopamine in the striatum (Hornykiewicz, cit Calne, 1968). Massive does of L. Dopa (dihydroxyphenylalanine, a dopamine precursor) have been given with marked clinical improvement in some cases of Parkinsonism (Calne, 1969). The assumption is that the striatal concentration of dopamine is restored to a level at which the caudate nucleus is inhibited to a degree approaching neurophysiological normality. Overdose results in the appearance of chorea (Cotzias, loc cit) also phenothiazines can produce either Parkinsonism or choreic dystonic syndromes (Hunter and Thorneycroft/

Thorneycroft, 1964) and such drugs are known to interfere with dopamine metabolism.

As techniques for neurobiochemical investigation appear they are applied in attempts to determine the biochemical lesion. Study is generally confined to established cases of chorea. They may be the least suitable material for elucidation of the genesis of the choreic process because the clinical phenomena probably succeed the initial, crucial, upset in physiology that condemns the cell. Because the condition is gradual we assume that the biochemical lesion is characterised with the same insidiousness. However, this chronology is only one of numerous possibilities. Instead of neurones steadily and mysteriously deteriorating with advancing age the process may be a stepwise progression. A specific environmental challenge, or series of challenges, may be necessary to initiate the abnormality that results in cell death and that pattern of cell loss whose end result is Huntington's chorea.

History/

History of social and genetic investigation:

Initial impetus to investigation of the disease was the interest aroused by its novelty and striking clinical features. Momentum of research was maintained by the development of eugenics promoting interest in inherited disease. Early studies were confined to clinical symptomatology in single or a few families with post mortem reports where available. Application of mendelian genetic principles to pedigrees indicated its inheritance according to a mendelian dominant pattern. Pedigree studies were also used to try to trace that miserable remote ancestor who introduced the affliction into the family.

The logical extension of intra-family studies was interfamilial comparisons of all observable features of the disease. These comparisons were made possible by regional surveys which also provided information on the prevalence of the condition and the burdens it placed on society. Lyon (1860) mentioned the social stigma of the disease militating against marriage into affected/

affected families. Putnam (1904) considered its social repercussions in detail. He advocated eugenic measures such as prohibition of marriage and procreation to choreic individuals.

Davenport and Muncey (1916) considered the more general social aspects in the first large survey ever ventured on Huntington's disease. They investigated the condition in the New England and Middle States of the U.S.A. Their main conclusions were that the disease was a social disaster, that the 962 choreics in the survey were sired by only six progemitors, and that the clinical features of the disease varied between families. This last assumption led them to conclude that different sub-types of the disease occurred and bred true. Appraisal of their technique of study reveals that such a conclusion was untenable. They selected cases in each family conforming to each subtype but did not describe each syndrome observed in every member of that family. Such selection vitiates the hypothesis. Also, their work was necessarily inexhaustive because of the time expended and sources of information used on the survey/

survey.

Although there are similarities in course and features of the disease between relatives it is difficult to quantify a syndrome. Davenport applied the term biotype to his sub-types of disease. Biotype means genetic identicality. To attribute similarities in clinical features solely to similarity of genetic endowment is unjustifiable oversimplification. The syndrome is observed in phenotypes and each phenotype is the result of environmental action upon the genotype. In human studies we can only observe phenotypes, and family members have similar ante-natal and post-natal environments. Therefore to ascribe intra familial resemblances solely to genotypes is inaccurate as well as presumptuous.

Panse (1942), in the next major survey, was more enlightened as to environmental effects. He considered that examination of large kindreds and the variations in disease patterns between the constituent family/

family lines would give a measure of detectable environmental modification of expression of the same genetic abnormality. This assumes that genomic alterations, other than in these abnormal genes occurring in Huntington's disease, have no effect upon the disease, i.e. that no modifying genes exist. Such an assumption, of necessity, is based on ignorance. However it is unnecessary. When a gene is being operated the residual genome can be considered as a component of the intra cellular environment affecting that gene. Panse's attitude can be justified in the light of this broad concept of environment.

His survey was the most detailed and extensive ever engineered. It was started in the Rhineland just before the Second World War. Legislation enacted under the Rassenhygien programme probably facilitated his search for cases but may also have led to concealment of illness or family history. Panse was aware of the possible genetic heterogeneity of his material. He tried to ensure homogeneity by careful selection of classical cases as his/

his probands - phenotypic selection for genetic homogeneity. He was also aware that this selection may have led to his rejection of cases bearing the genetic diathesis who were clinically atypical or asymptomatic, i.e. in genetic parlance, examples of incomplete penetrance.

The survey provided further confirmation of the Mendelian dominant pattern of inheritance as established by earlier studies notably those of Bell (1934) and Sjogren (1935). It provided important information on the clinical features and social importance of the disease.

In Britain such surveys have been sporadic and less extensive (Spillane and Phillips, 1936 ; Minski and Guttmann, 1938; Bickford and Ellison, 1953; Lyon, 1962, Bolt, 1970). The one of most import in terms of suggestions for improved management is that of Pleydell (1954-55). Extensive studies have been confined to the U.S.A. and Germany. The most recent and important is that of Reed and Chandler (1958, 1959). This was undertaken to obtain demographic/

demographic and clinical data on the disease in Michigan and to compare the fertility of choreics with that of the general population. One of the stimuli to their investigation was the report on a sample of two of Reed and Palm (1951) that choreics were more fertile than the general population. It has also been generally observed that cases of Huntington's chorea appear only to arise in pre-existing kindreds rather than de novo from genetic mutation. Reed and Chandler indicated that the logical outcome of increased fertility in choreics was that they would come to replace the present normal population. Equating the disease with an abnormal gene they considered that the replacement of a normal allele by a "deleterious" one was an undesirable and new biological phenomenon. It is discounted by their calculations that choreics on average have less children than the general population. Moreover their calculations assume genetic homogeneity of the disease population even though they state that statistical evidence indicates that more than one genetic locus is concerned with the production of chorea. They also make the assumption, that phenotype is synonymous with genotype.

Genetic Aspects:

Observation of genotypes is necessarily indirect, conclusions on it being inferential drawn from observations of the phenotype. Environmental action on the genotype leads to the development of the observable phenotype. Once fertilisation has occurred then the genotype is fixed (apart from rare intracellular accidents) and unique but environment is constantly varying. The limits of environmental variability are defined by what the organism can survive. Each phenotype results from variable environmental influences acting upon a fixed genotype and this must be considered when observing phenotype variations. Theoretically environment must be specified before conclusions can be drawn about genes. What constitutes an undesirable gene in one environment may be favourable in another. If Huntington's chorea is genetically determined, environments are conceivable in which the gene abnormality's effects can be minimised so that its possession confers no disadvantage. In the Messalian society chorea was a positive advantage (Gregoire, 1829), as Messalians grimaced constantly to ward off devils.

Some/

Some facts on the heredity of Huntington's disease are known. It is inherited. The mode of inheritance has frequently been demonstrated to follow a Mendelian dominant pattern. These observations provide the foundations for the assumption that it results from the possession of abnormal chromosomal genetic material. What number of genes or loci are involved is not known. Elucidation of differing biochemical lesions and linkage studies may clarify this aspect of its inheritance. Current techniques available for determining genetic homogeneity are applicable only to experimental animals (Pontecorvo, 1959).

It is assumed currently that abnormality probably occurs at more than one chromosomal locus in the disease (Reed and Chandler loc cit). Justification for this is provided by the spectrum of syndromes included by the term chronic progressive chorea. Conclusions on the genotype are drawn from observation of the phenotype.

Clinical/

Clinical Aspects:

The common concept of the disease is of a chorea of insidious onset but inexorable progression that first appears in adulthood and is accompanied by a personality disorder and increasing dementia. However there is a vast range of variability in clinical disease. Each abnormality of motor and psychiatric behaviour can predominate, appear early or late, or independently. Age of onset ranges from infancy to the senium. The range of clinical variability is paralleled by the spectrum of neuropathological changes observed. There has been no correlation possible between neuropathology and early clinical symptomatology. No method is available to determine who bears the diathesis prior to its clinical appearance consequently no study has been possible of pre-clinical choreics. Comparative studies of variations in clinical disease patterns and neuropathology between individuals are impossible because neither have been quantified.

Social/

Social Aspects:

The inter-relationships of disease, the family and society are of fundamental importance in study of the disease. They govern all investigation into the condition and their study can be of immediate benefit to choreics and families at risk. If its impact on the family is evaluated, a programme can be designed to minimise the distress engendered by the condition. Such studies also can provide a measure of environmental variation and correlation may be possible between environment and phenotype. This may provide a basis for disease prevention or palliation by revealing what environmental factors affect the course of disease.

From a practical viewpoint this must be the philosophy behind investigations of human heredity. Environment can be altered but the genome is fixed and inaccessible to manipulation. It is valuable to be so aware of patterns in inheritance that advice on procreation can be given. However, control of its processes can only be effected by modifying the environment.

The/

The environment of a gene is all that is external to it. This can be subdivided into: what, on a practical basis at present, is modifiable and what is not, within the limits of viability. The concept of genome and environment interacting to provide phenotype is a relic of determinism. Conceptualisation of the genome's independence from environment was artificial and was valuable only in that it specified the normal behaviour of a set of cell constituents. However, the genome never exists independent of the cell and, to be expressed, requires the temporal and physical environment it provides.

At present there is no method of directional alteration of genome and it must be considered as a non-modifiable environmental factor of any constituent gene. Molecular genetic engineering has been postulated in which a segment of the genome may be physically modified, tailoring it to produce a specific phenotype (Sonneborn, 1965). There is a dearth of knowledge of the intra genome genetic inter-relationships and environmental operation of the genome that would be necessary for precision/

precision in genetic engineering. The acquisition of such knowledge would make the process unnecessary as the appropriate environmental alteration would obviate any "deleterious" effects of possession or absence of specific genes. The ability to modify environments at present is an empiric process. To obtain an understanding of how it can be effected directionally, work must be from the general to the particular abstracting principles along which efforts may be productively directed. Study of the social aspects of Huntington's chorea affords the prospect of a start in this direction.

AIMS OF THE STUDY

The aims of the study can be summarised thus:

To ascertain the prevalence of Huntington's chorea in the South East region of Scotland and to register the families at risk;

To investigate some aspects of the social consequences of the disease;

To establish and maintain, an interest in the condition among the medical personnel in the region, and a supportive rapport with the families at risk; and

To make suggestions as to improving the detection of choreics and at risk families and the organising of research into the condition.

CHAPTER IV

METHOD OF INVESTIGATION

METHOD OF THE INVESTIGATION

In order to assess the prevalence of the condition one must first define the population to be investigated. This was decided as being that population living within the area served by the South East of Scotland Regional Hospital Board. The area includes the City of Edinburgh,and the Counties of Roxburgh, Selkirkshire, Berwickshire, Peebles, the Lothians and part of Fife containing a total population of 1,163, 877. (Scottish Hospital In - patient Statistics, for I966. Edinburgh, I968).

To ascertain all cases existing in a region is only possible if every member of that population be examined however a high percentage of current cases can be ascertained by consulting the medical personnel in the region considered likely to come in contact with or to treat sufferers from the disease and the records of institutions in which such patients will be treated. Because of the clinical variability of the disease, and the variability of home circumstances, it is probable that different types of institutions and forms of care will be available for patients. The main repository/

repository for such cases as required institutional care was thought to be the mental hospital, followed by the geriatric hospital and then the local authority home (partIII accommodation)*. It was felt that the best means of ascertaining cases would be contact with the medical practitioners in the region likely to encounter cases and a search of the records of all institutions in which there was a probability of cases being treated.

Consequently contact was made with the regional general practitioners, local authority medical staff, and the psychiatrists, neurologists and geriatricians of the mental and general hospitals in the region. Letters were sent to each family doctor in the region, informing them of our interest in the condition and desire to learn of cases in the region. Each local health authority medical officer of health was consulted as were the medical superintendents of the regional psychiatric hospitals. In addition the regional neurologists and geriatricians were approached. The end result was that permission was obtained to search the records of the regional mental hospitals/

* Accommodation provided under part III of the National Assistance Act 1948.

hospitals, the neurological clinics, and to visit the local authority part 3 accommodation. Geriatricians and local authority medical officers provided data on the cases that they had dealt with and were aware of.

Another potential source of information on cases was the Registrar General for Scotland in that certificates would be available on deaths specified as resulting from Huntington's chorea. Co-operation was obtained from the Registrar General and information was obtained on all deaths occurring from Huntington's chorea in Scotland during the period 1950 - 1963. The regional neuropathology centre also provided information on post mortems carried out on cases of Huntington's chorea.

This seeking of cases constituted the first phase of the investigation.

Search of the Records:

It was decided that the search be extended to cover/

cover as long a period as possible. As the disease has a variable age of onset, families bearing the diathesis could easily have no overt case at one point in time. Knowledge of such families is desirable so that they can be supervised over a long period and that the family doctor and the family involved can be adequately informed of the relevant risks. Thus records were searched as far back as possible in each hospital visited, although there were extreme differences in the adequacy of records between hospitals. Initially it was hoped that the inception of the Health Service might provide a suitable date to search back to under the delusion that, after this event, some standardisation of records would occur. Unfortunately this was not the case and as a result the period of search of records varied from hospital to hospital. All deaths with ascribed cause could be determined over the period from July 5, 1948 till July, 1967 and all current admissions with diagnoses were ascertained. However there were gaps in information in some institutions because of loss of case notes and inadequate history taking or poorly kept records. The initial operation in the search of an institution's records was the scrutiny of registers of admissions, discharges/

discharges, and deaths for cases of Huntington's chorea. Because of the difficulties encountered in diagnosis it was also decided to investigate cases diagnosed as of the pre-senile dementias and of idiopathic Parkinsonism, and all diagnoses of extra pyramidal motor disorder.

Wherever diagnostic indices were available they were used but unfortunately they were rare.

When admission and discharge registers were inadequate the entire collection of case notes dating from July 5, 1948 was examined to ascertain diagnoses, and thence cases. Whenever possible a résumé was made of the family history, and of clinical, pathological and hospitalisation data for each case of all the above conditions.

Other Sources of Information:

general practitioners were contacted and/

and invited to provide information. Geriatricians also provided what information they had as to past and present cases. Because of the variability in severity of the condition it was considered that some persons with Huntington's chorea, where personality disorder and dementia were minimal, could be accommodated in non-medical institutions such as local authority homes. With this in mind the medical officers of health for the local authorities in the region were consulted. They were asked for information on the presence or absence of choreics in local authority homes and permission was obtained to visit such institutions.

Once these sources of cases had been fully utilised the next phase of the investigation was the approaching of families at risk from the condition.

The Approach to the Family:

It was realised early in the investigation that knowledge of the disease was a potential psychiatric disaster/

disaster for individuals in at risk families. With this in mind it was decided to solicit as much pertinent advice as possible on the method and justification for approaching families. Again regional psychiatrists and neurologists and general practitioners were consulted. An informal conference was organised attended by interested medical practitioners.

In an attempt to establish contact with the general practitioners and doctors in the region interested in the condition it was considered that an informal conference would provide a means of doing so. Further, it would provide an opportunity for those interested to exchange ideas on relevant aspects of the disease. With these aims in mind an informal conference was arranged to which all general practitioners in the area, psychiatrists, neurologists and any other interested medical practitioner, was invited.

The format of the conference was that three brief papers were read on different facets of the disease and that these papers provided the impetus to subsequent general discussion by those attending. Dr. A.K.M. MacRae described the/

the clinical course of the condition and the problems encountered during the psychiatric management of the illness. I read a paper emphasising the variability of the condition, outlining its inheritance, and problems encountered in the social management of the condition. Dr. P.G. Gaskell then discussed the condition from the general practitioner's viewpoint introducing a former patient of his at risk from the disease who had been kind enough to co-operate. Dr. Gaskell used this case to illustrate the number of agencies, State and voluntary, involved in the care of a patient and family bearing the diathesis.

From the discussion following these papers it became apparent that although it was considered desirable by the majority present that patients and families be as fully informed as possible on the disease nevertheless there was a reluctance to inform all at risk of their chances of developing it. As only half the family members can be expected to develop chorea it was considered by some that it was unfair to worry unnecessarily persons who would escape the illness. However, the consensus of opinion was in favour of maximising the accurate information available to the family/

family and the presentation of such information to be related to the circumstances of the individual.

Discussion also brought to light the major importance of the family doctor in the management of the patient and the family involved and the need for a wide range of facilities in their care.

When specifically asked about the approach to families at risk it was considered that the best method would be through introduction by the family doctor. As only a minority of family doctors of potential interviewees were known this raised problems. The solution suggested was that letters be sent to individuals with whom interview was sought. These letters were to indicate only that the interviewer was seeking: co-operation in a medical research project, also the name of the recipient of each letter and his family doctor.

This/

This procedure was considered by the investigator as unlikely to produce a satisfactory response rate and a trial sample of fifty letters was sent. Replies were received to only eight of the letters, thus demonstrating the inadequacy of such a procedure. As a result the local medical committee of the Executive Council was contacted and at a meeting with them an alternative course of action was formulated. Intimation of the investigation was made in a newsletter circularised to all general practitioners. All those reluctant to have patients interviewed without their prior approval were invited to contact the investigator. When a family doctor was unknown before the interview, the interviewer would conclude the interview immediately if he learned that the family under study was on such a general practitioner's list. Hence one of the initial questions asked was the name of the family doctor of the interviewee.

However, the vast majority of family doctors were agreeable to being informed of such an interview after it had taken place. Consequently each general practitioner was notified as soon as possible after the event when an interview/

interview had been conducted.

The form of the interview was so arranged that the interviewer revealed nothing of the nature of the disease nor of its existence in the family to the interviewee unless asked by the family doctor or by the person concerned to do so (again provided the family doctor agreed). It was hoped that the interview would provide information on social and medical matters and was conducted in as minimally disturbing a way as possible. In addition it was hoped that the contact made with such families would be conducive to the maintenance of long term co-operation whether or not they knew of the disease. Consequent upon these aims it was necessary to present a minor aspect of the study as the main reason for the investigation. Justification for the approach and questioning was given by stating that the aim of the investigation was to find out what happens to a family when a member requires long term institutional care or suffers from a chronic disabling disease. Were the interviewees ignorant of the disease and/

and their situation then this was all the explanation given. For the better informed, explanation varied in detail according to the wishes of the general practitioner and the interviewee.

The families approached in the second phase of the investigation were those in the Lothians and Edinburgh who were known to be at risk from the condition. Because of migration and the interval between death and hospitalisation and the onset of this study some families were untraceable or family members were unavailable for personal interview. Wherever possible an attempt was made to interview personally each member of a family at risk.

Processing of Data:

The information sought was on social and medical matters and was entered on a working schedule to be coded at a later date and transferred to punch cards. Persons interviewed fell into three main categories: those affected with the disease; those at risk from the condition and those/

those not at risk. Those not at risk comprised the spouses of persons falling in the first two categories and along with controls, were compared with choreics and unaffected sibs in terms of education, occupation and some other factors. As at risk families are found mainly in the less skilled classes, and because of the range of ages in the choreic population, it was considered invalid to compare the fertility of choreics male and female, with that of the general population. Ideally a comparable control population matched for age, marital status, and social class, should have been drawn at random from the general population. However, because of limited resources and access to the population at large, it was decided to obtain our controls from the sibs of spouses of those at risk. As spouses tend to have similar ranges of intelligence and social backgrounds it was considered that the environments of risk free spouses and hence spouses sibs, would be similar to those experienced in families at risk from Huntington's chorea. Although this control population had a higher ratio of skilled to unskilled workers than the choreic nevertheless it was similar to it in age structure, marital status, and social class of origin (i.e. parental social class), and was considerably more comparable than the general population.

Each person on whom data was obtained was allocated a series/

series number unique to the individual. Every family was allocated a number also as was each sibship and position in that sibship. Consequently each individual in the series who belonged to each at risk family can be identified as to lineage and to sibship. In the event of both parents belonging to an at risk sibship further columns were to be used in which the maternal series number could have been entered but the paternal family will be taken as that of origin of the individual. This did not occur in this present series but could constitute a problem on expansion of the study. Selection of paternal as opposed to maternal lineage was arbitrary, influenced only by the fact that males do not change their name on marriage, and this might facilitate the tracing of pedigrees.

The Questions Asked:

Interviewing of all at risk individuals and spouses was undertaken by myself and the main categories of information sought were on the: education, occupational and reproductive history of the persons concerned. Additional information was obtained on clinical features of affected cases and the problems encountered by persons in families involved with the illness, what they knew about the illness and where they obtained what information they had. Clinical and other information was obtained from hospital and other records/

records.

Information was obtained by interview on a total of 396 individuals of whom 84 were or had been choreic. 153 were at risk from the disease, 77 were spouses of choreics or those at risk and 82 were controls. Information on the control population was obtained by two other interviewers who had been fully instructed as to the approach involved and the information desired.

This survey population was derived from 83 sibships in 39 families.

CHAPTER V

FINDINGS

FINDINGS

The information obtained can be subdivided into that concerned with the ascertainment of the cases; the quantifiable clinical features of the illness; the data on reproduction; on post scholastic education and employment. Tables are also given of numbers used in calculation of the inheritance of the illness and on the information persons concerned have about the disease. Clinical features of the illness are considered in more detail in the Discussion as are problems resulting from the illness.

Sources of information: Tables I to 5(a)

Table I shows the number of cases derived from each source used in the investigation. The major source of cases was the mental hospital providing information on 65.I% of all cases ascertained. As over 76% of cases die in such institutions (Table 4) it can be expected that approximately a further IO% of the total population will establish contact with the mental hospital. The next most prolific source of cases were death certificates. Although the sole source in seven cases, they provided a source of information second only to the mental hospital providing information on 5I cases. Neurological units and general practitioners also provided several cases but geriatricians, local authorities and survey of those at risk provided only a few.

Deficiencies in the records are probably reflected by the distribution of the numbers of cases admitted over the five year periods during the fifteen years from I950.

It/

It can be seen from Table 3 that the number of cases admitted in consecutive five year periods rises. The difference in numbers does not reach statistical significance.

Yet this rise is probably a real phenomenon resulting not from an increasing incidence of the disease, rather from decreasing deficiencies in records. More recent cases are more likely to be detected for two main reasons: records are better, and they are more likely to be admissions per case reflects the general changes in patient management that have occurred in the last fifteen years in mental hospitals. There has been a change in emphasis as a result of more enlightened legislation and therapeutic advances away from what was primarly custodial patient care towards effective social rhabilitation. Table 3(a) shows that numbers of admissions differ significantly in successive five year periods.

In table 4 the place of death of the patients is given. No statistically significant sex differences can be noted. 76% of deaths occur in mental hospitals. This/

This reflects the opinion that the major difficulties in management of patients are considered to be of a psychiatric nature and this will be discussed more fully later.

Table 5 shows the degree of hospital care of current cases. A statistically significant difference exists between the sexes.

No cases are at present resident in local authority part III accommodation and only three cases were ever there during the period of the survey.

TABLE 1 - CASES DETECTED BY SOURCES THROUGHOUT THE PERIOD JULY 1948 to JULY 1967
(PERCENTAGES EXPRESSED AS A FRACTION OF TOTAL CASES)
POST MORTEM SOURCES CITED ONLY WHEN SOLE SOURCE

	MENTAL HOSPITALS		NEUROLOGICAL UNIT		GENERAL PRACTITIONER		LOCAL AUTHORITY		GERIATRIC UNIT		POST MORTEM SOURCES		SURVEY		TRIPLE SOURCES i.e. MENTAL, NEUROLOGICAL AND G.P.	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
MENTAL HOSPITAL	81	49.4	7	4.3	5	3.0	2	1.2	1	0.6	7	4.3	17	10.2	11	6.7
NEUROLOGICAL UNIT	7		6	3.7	5	3.0	0	0	1	0.6						
GENERAL PRACTICE	5		5		12	7.3	0	0	1	0.6						
LOCAL AUTHORITY	2		0		0		3	1.8	0	0						
GERIATRIC	1		1		1				4	2.5						
TOTALS	108*	65.1	30*	18.3	35*	21.2	6	3.7	7	4.3	7	4.3	17	10.2	12	7.3

TRIPLE SOURCES i.e. MENTAL, LOCAL AUTHORITY AND G.P.

No.	%
1	0.6

KNOWN CASES: 81 FEMALES
83 MALES
TOTAL CASES: 164

* TOTALS ALSO INCLUDE CASES ASCERTAINED FROM THREE SOURCES

TABLE 2 - PERCENTAGE OF CASES BY SOURCES

	Number	Percent Total Cases
Single Source	130	79.3
Double Source	22	13.4
Triple Source	12	7.3
Totals	164	100

TABLE 3 - TABLE OF ADMISSIONS AND CASES BY YEAR OF LAST ADMISSION AND BY SEX

	PERIOD OF ADMISSION								
	1940 - 50	1951 - 55		1956 - 60		1961 - 65		TOTALS	
	Cases	Cases	Admissions	Cases	Admissions	Cases	Admissions	Cases	Admissions
MALE	12	8	11	13	17	14	24	47	52
FEMALE	10	12	13	10	13	20	27	52	53
TOTALS	22	20	24	23	30	34	51	99	105

TABLE 3a - TABLE OF ADMISSIONS (sexes pooled) for χ^2

	1951 - 55	1956 - 60	1961 - 65
NUMBERS OBSERVED (O)	24	30	51
NUMBERS EXPECTED (E)	35	35	35
$\frac{(O - E)^2}{E}$	3.457	0.714	7.314

$\chi^2_2 = 11.485$ χ^2_2 for p = 0.01 = 9.21 for p = .001 = 13.815

TABLE 4 - PLACE OF DEATH OF CHOREICS IN THE REGION DURING PERIOD JULY, 1948 to JULY, 1967

	MENTAL HOSPITAL	ACUTE HOSPITAL	GERIATRIC HOSPITAL	LOCAL AUTHORITY HOME	AT HOME	TOTALS
MALE	32	1	2	1	1	37
FEMALE	33	3	5	1	6	48
TOTALS	65	4	7	2	7	85

TABLE 4a - ABRIDGED TABLE OF PLACE OF DEATH FOR χ^2

	IN MENTAL HOSPITAL	ELSEWHERE	TOTALS
Males:			
Observed Numbers	32	5	37
Expected Numbers	28.3	8.7	
Females:			
Observed Numbers	33	15	48
Expected Numbers	33	11.3	
Totals Observed	65	20	85

$\chi^2 = 2.734$ χ^2 for p = 0.1 = 2.706

TABLE 5 - HOSPITALISATION STATUS OF LIVING CHOREICS IN THE REGION DURING PERIOD JULY 1967

	PERMANENTLY HOSPITALISED	INTERMITTENTLY HOSPITALISED	AT HOME	TOTALS
NUMBER OF LIVING MALES	11	7	27	45
NUMBER OF LIVING FEMALES	20	3	8	31
TOTALS	31	10	35	76

TABLE 5a - ABRIDGED TABLE FOR χ^2 of HOSPITAL STATUS

	MALES	FEMALES	TOTALS
RECEIVING HOSPITAL CARE:			
NUMBERS OBSERVED	18	28	38
NUMBERS EXPECTED	22.5	15.5	38
AT HOME:			
NUMBERS OBSERVED	27	8	38
NUMBERS EXPECTED	22.5	15.5	38
TOTALS OBSERVED	45	31	76

$\chi^2 = 7.316$ χ^2 for $p = 0.05 = 3.841$

$.01 > p > .005$

Clinical Features: Tables 6 to 9

Mean age of manifestation was ascertained for 123 cases and found to be 37. 83 years with a standard deviation of 10.11 years (Table 6). No significant difference in average age of onset was noted between the sexes although it was noted to be three years later in females than males, nor was there any significant difference in frequency distribution of age of onset (Table 6(a)). The range of age of onset was from fifteen to seventy four years, no cases being detected in children. One child aged eight was diagnosed as a possible Huntington's chorea with onset of symptoms aged five years but she left the region. Another child aged eleven has been tentatively diagnosed as Huntington's chorea but observation over a period of time will be necessary for firm diagnosis.

Duration of illness: because of difficulties in accurate assessment of age of onset the number of cases in which dur ation of illness is known is relatively small being only 69: 33 males and 36 females. The mean duration of illness was/

was found to be 14.75 years with a standard deviation of 5.75 years (Table 7). Variability was greater in the females than the males, more women having durations of illness less than ten years and more than twenty years than the men. However, comparisons of the frequency distributions, and the variance ratios shows that the level of probability of occurrence of such a difference by chance fails to reach a level of statistical significance (for grouped frequency distribution $\chi^2_3 = 7.33$ $0.1 > p > 0.05$, variance ratio $F^{35}_{32} = 1.445$, for $p = 0.05$, $F^{40}_{32} = 1.82$).

Age of Death: this was determined in 155 cases and the mean age of death of the choreic was found to be 56.3 years with a standard deviation of 10.8 years (Table 8). There were no significant differences in average age nor frequency distribution of age at death between the sexes.

None of these values are very different from those found in other surveys (Bell 1934; Panse 1942) Reed and Chandler (1958); with the exception of that of Lyon (1960) whose mean age of onset at 51.6 is the highest of any survey.

TABLE 6 - GROUPED FREQUENCY TABLE OF AGE OF MANIFESTATION OF DISEASE

	15 - 25 years	26 - 30 years	31 - 35 years	36 - 40 years	41 - 45 years	46 - 50 years	51 - 55 years	56 - 60 years	Over 60 years	Totals	Mean Age (years)	Standard Deviation (years)
NUMBER OF MALE PATIENTS	8	8	12	15	11	3	6	2	1	66	37.17	9.23
NUMBER OF FEMALE PATIENTS	2	10	8	13	6	9	3	4	2	57	40.33	10.86
TOTAL	10	18	20	28	17	12	9	6	3	123	38.63	10.11

Range: Male 15 years to 69 years

Female 19 years to 74 years

Numbers: Males 66

Females 57

Total cases 123

"t"$_{121}$ for difference between male and female mean age of onset is 0.947

0.4 > p > 0.3

TABLE 6a - ABRIDGED TABLE FOR χ^2

	⩽30 years	31 - 35 years	36 - 40 years	41 - 45 years	46 - 50 years	⩾50 years	Totals
MALES:							
OBSERVED NUMBER	16	12	15	11	3	9	66
EXPECTED NUMBER	19	10.7	15	9.1	6.4	9.7	65.9
FEMALES:							
OBSERVED NUMBER	12	8	13	6	9	9	57
EXPECTED NUMBER	(13)	9.3	13	7.9	5.6	8.3	57.1
TOTALS OBSERVED	28	20	28	17	12	18	123

$\chi^2_5 = 3.447$ $0.7 > p > 0.5$

TABLE 7 - GROUPED FREQUENCY TABLE OF DURATION OF ILLNESS

	1 - 5 years	6 - 10 years	11 - 15 years	16 - 20 years	21 - 25 years	Over 25 years	Totals	Mean Duration (years	Standard Deviation (years)
MALES	1	4	12	14	2	0	33	14.85	4.63
FEMALES	4	9	7	7	6	3	36	14.67	6.69
TOTALS	5	13	19	21	8	3	69	14.75	5.75

RANGE: Males 4 - 23 years

Females 2 - 32 years

Variance ratio $F_{32}^{35} = 1.445$

for p = 0.05 $F_{32}^{40} = 1.82$

TABLE 8 - GROUPED FREQUENCY TABLE OF AGE AT DEATH

	26 - 30 years	31 - 35 years	36 - 40 years	41 - 45 years	46 - 50 years	51 - 55 years	56 - 60 years	61 - 65 years	66 - 70 years	Over 70 years	Mean (years)	Standard Deviation (years)
MALES	1	1	2	5	9	15	15	6	4	7	56.1	11.1
FEMALES	0	3	4	5	14	13	16	16	12	6	56.4	10.7
TOTALS	1	4	6	10	23	28	31	22	16	14	56.3	10.8

Numbers: Males 66
Females 89
Totals 155

Range: Males 27-86 years
Females 31-84 years

't' variate for 153 degrees of freedom = 0.171

t_{120} for p = 0.9 = 0.126

TABLE 9 - ABRIDGED TABLE FOR χ^2

	≤ 45 years	46 - 50 years	51 - 55 years	56 - 60 years	61 - 65 years	65 - 70 years	Over 70 years	Totals
MALES:								
Observed Numbers	9	9	15	15	6	4	8	66
Expected Numbers	8.9	9.8	11.9	13.2	9.4	6.8	6	66
FEMALES:								
Observed Numbers	12	14	13	16	16	12	6	89
Expected Numbers	12.1	13.2	16.1	17.8	12.6	9.2	8	89
Total Observed	21	23	28	31	22	16	14	155

$\chi^2_6 = 5.354$ $\chi^2_6 = 0.5 = 5.348$

Information on Illness: Tables IO and II

In the second part of the investigation the amount of knowledge that the interviewer had on the condition dictated the nature of the interview. It was possible to determine what information the patient had on the illness and where he obtained it. From Table IO it can be seen that, of the 300 persons who could be expected to know about the disease, 27.7% had no information and IO.3% were either inaccurately or incompletely informed. No significant differences existed in amounts of information between choreics, their unaffected sibs or children and the spouses. It was considered that the patients were completely informed when they knew of the clinical features of the condition and that it was inherited. Only those who received information from medical practitioners or medical l terature could be expected to be accurately informed as to the possibility of themselves or their spouses or their children developing the disease. However such individuals were rare and even they could misinterpret accurate information in ways that suited them.

Sources/

Sources of information are given in Table 11 only the major sources of information being listed. Personal observation was the major source. Some degree of overlap occurred in categories between relatives and other sources as some individuals were informed from multiple sources (except those in the 'personal observation' group). Such overlapping was minimal occurring most frequently between those obtaining information from the literature and the general practitioner. For multiple sources the most informative was tabulated and this was generally a medical practitioner. However, doctors were the major source of information in only 22.5% of cases.

TABLE 10 - AMOUNT OF INFORMATION ON DISEASE ACCORDING TO CHOREIC STATUS AND RELATIONSHIP TO CHOREICS (sexes pooled)

	AT RISK				
	CHOREICS	NON-CHOREIC	SPOUSES	TOTALS	PERCENTAGE
ACCURATE COMPLETE INFORMATION	38	66	43	147	49.0
ACCURATE INCOMPLETE INFORMATION	1	8	3	12	4
INACCURATE INFORMATION	7	6	6	19	6.3
NO INFORMATION	19	39	25	83	27.7
UNKNOWN	19	20	0	29	12
TOTALS	84	I39	77	300	100

38% were incompletely informed

TABLE 11 - TABLE OF MAJOR SOURCE OF INFORMATION

	PERSONAL OBSERVATION	RELATIVES	LITERATURE	GENERAL PRACTITIONER	OTHER MEDICAL PRACTITIONERS	TOTALS
NUMBERS	104	25	9	18	22	178
PERCENTAGE	58.4	14.0	5.1	10.1	12.4	100

The Inheritance of the Condition: Table 12

The number of sibships in which individuals reached the age of fifty five before dying or manifesting the disease was twenty two. Table 12 shows the totals in these sibships and the numbers affected. Using (Haldanes (1938)) formula it would appear that the probability of inheriting the condition is 0.492 with a standard deviation of 0.063. This is close to the probability of 0.5 expected if mendelian dominant inheritance is followed and heterozygotes reproduce with risk free partners.

TABLE 12 - TABLE OF NUMBERS AFFECTED IN COMPLETED SIBSHIPS

Number of sibships	Total persons in all sibships	Number Affected
22	85	53

Using Haldane's (1938) formula the probability of developing the disease = p = 0.492 with standard deviation 0.063

Reproductive performance: Tables 13 - 17(b)

In consideration of selective survival or disadvantage of choreics the ultimate criterion by which this may be assessed is the reproductive efficiency of choreics compared with the general population. For males reproductive output is generally only measurable within marriage. Extra marital male reproduction is difficult to measure and if the male population were sexually active but disinclined to marry then their reproductive performances would be seriously underestimated. In this study only two conceptions were detected as sired illegitimately by a male choreic. Other measurable variables affecting reproductive performance are the probability of marriage and the age at marriage of the individual.

Numbers ever married: Table 13 shows the number and percentage of male and female choreics ever married or single. The figures were obtained for all the regional choreics combined with those obtained from death certificates for Scotland during the period 1950-63. No significant difference exists between the sexes, - 75% of males and 77.9% of females having ever married.

This/

This enlarged sample was not comparable with the control population as regional differences exist in the ratio of married to single persons (Census Scotland 1951 Vol. 3, ibid. 1961 General Volume) and also the age structure of the enlarged sample differed markedly from that of the controls.

Age at marriage: Table 14 shows age at marriage of 63 choreics for whom it was known and 72 controls. The numbers are small and show (Table 14a) that no significant differences exist between age of marriage of choreic males and females the mean age being 24.55 years for males and 23.08 years for females. Significant differences exist between ages at marriage of control males, mean age 25.34 years and females, mean age 21.3 years and between choreic females and control females. Because the numbers are small any conclusions drawn are of dubious worth but it does appear that choreic females marry at a later age than those not at risk and that there is no significant difference between age at marriage of choreics males and the controls.

Premarital wastage: The data in Table 15 were derived from the numbers of conceptions and losses for eighty seven choreics (54 males; 33 females), and eighty two risk free controls.

Pooling/

Pooling data on abortion and childhood death (under I5 years) estimation of x^2_3 for the Table gives a value of I.539 (0.7 p 0.5) indicating that no significant difference exists between groups II.43% of conceptions never reaching marriageable age. This again is probably an underestimate in that abortions may occur unnoticed or be forgotten more readily than live births.

Mean Fertility: In Table I6 the mean fertility is given for II4 choreics and eighty two controls. Although no great differences exist between any of the groups in Table I6, the most fertile is that of the female controls having an average of 2.86 children. As can be seen by consideration of the 't' variates obtained by comparing means (Table I6a) no statistically significant differences are found. This is in contrast with the findings of Reed and Chandler (I958, I959) which will be examined in detail later. For choreic males the mean fertility was calculated as 2.46, for choreic females 2.36, and pooled choreics 2.4I, children compared with 2.57 children for the controls.

Table I7 provides information on mean family size of choreics, controls and those unaffected yet at risk of/

of developing chorea. It can be seen that the males at risk had a significantly lower family size than all others however they are a much younger age group than the others containing the children as well as sibs of choreics. As there is a sex differential in age of marriage, (Census, Scotland 1951, Vol. 3, 1956 - ibid. 1961, General Volume 1966), though both males and females at risk have comparable mean ages and standard deviations (mean for males 39.3, females 40.2 years, standard deviation for males 17.4, for females 16.4 years) the earlier age of marriage of females is reflected in their greater mean family size. Comparisons in frequency distribution of family size have been made between sexes for choreics these being the groups where the major differences in distributions lay. No significant difference was detected the x^2_3 value for the abbreviated Table 17a yielding a probability of $0.5 > P > 0.3$. The major difference in mean family size also occurred between these groups and 't' variate gave a probability of $0.2 > P > 0.1$ which is within the level of statistical significance. It is thus apparent that no statistically significant differences exist between the sexes of choreics and controls and between choreics and controls (sexes pooled) in mean family size and frequency distribution of family size (Table 17b) the mean family size being/

being 3.11 children for choreics with a standard deviation of 2.15 children and of 3.18 children with a standard deviation of 2.77 children for controls. Both these values differ at a statistically significant level from the mean population completed fertility given by the Scottish Census (1956) of 2.52 however the age distribution of this sample differs from that of the Census population and it contains a preponderance of Social Classes III, IV and V who are more fertile than the mean population (Scottish Census ibid.).

There has been a substantial change in the number of children born to successive generations. This is demonstrable from Census data but also in this sample. Mean sibship size of choreics, those at risk, and those risk free were similar and pooled to give an overall sibship mean size of 5.9 (S.D. 3.1) children. Of the 89 married choreics who had children an average family size was 3.1 (S.D. 2.15) children which differs from that of their sibship of origin to a significance degree (t variate = 50.00 $p > 0.001$) even though the distribution of family size is skewed. Such striking changes in patterns of reproductive behaviour between successive generations appear to be a general phenomenon (Census/

(Census, Scotland, 1951, 1961). Reproductive efficiency is the ultimate index of selective advantage, yet it is demonstrably subject to social phenomena, viz, the increasing size of family with progress from Social Classes I - V, and (Census data loc cit) the decreasing size of family over recent generations. Hence selective advantage or disadvantage (as measured by reproductive performance) will tend to be a temporary phenomenon observable only in a specific cultural situation at a specific point in time

TABLE 13 - TABLE OF NUMBERS OF CHOREICS BY MARITAL STATUS AND SEX

	MALES		FEMALES		TOTALS	
	NUMBERS	PERCENT	NUMBERS	PERCENT	NUMBERS	PERCENT
MARRIED, WIDOWED OR DIVORCED	75	75	102	77.9	177	76.6
SINGLE	25	25	29	22.1	54	23.4
TOTALS	100		131		231	

χ^2 for differences between sexes = 0.124 $0.8 > P > 0.7$

TABLE 14 - TABLE OF AGE AT MARRIAGE BY SEX AND RISK STATUS

	CHOREIC MALES	CHOREIC FEMALES	MALE CONTROLS	FEMALE CONTROLS
NUMBER	38	25	35	37
MEAN AGE	24.55 years	23.08 years	25.54 years	21.3 years
STANDARD DEVIATION	3.82 years	4.0 years	5.83 years	3.2 years

TABLE 14a - TABLE FOR "t" VARIATES FOR DIFFERENCES BETWEEN MEAN AGES OF MARRIAGE

	BETWEEN SEXES (CHOREICS)	BETWEEN SEXES (CONTROLS)	BETWEEN MALES (CHOREICS/CONTROLS)	BETWEEN FEMALES (CHOREICS/CONTROLS)
"t" value	1.413	3.504	0.861	2.834
probability	$0.2 > p > 0.1$	0.001	$0.4 > p > 0.3$	$0.01 > p > 0.001$

TABLE 15 - TABLE OF CONCEPTIONS, ABORTIONS AND CHILDHOOD DEATHS IN FAMILIES BY RISK STATUS

	FAMILIES OF:				
	CHOREIC MALES	CHOREIC FEMALES	CONTROL MALES	CONTROL FEMALES	TOTALS
SURVIVING CONCEPTI	140	91	88	113	432
ABORTIONS	23	12	8	16	59
CHILDHOOD DEATHS	6	9	3	7	25
TOTALS	169	112	99	136	516

χ^2_3 value (summing abortions and childhood deaths) is 2.180 $0.7 > p > 0.5$

TABLE 16 - TABLE OF AVERAGE NUMBERS OF CHILDREN

	AFFECTED MALES	MALE CONTROLS	AFFECTED FEMALES	FEMALE CONTROLS	TOTAL AFFECTED	TOTAL CONTROLS
NUMBER IN SAMPLE	61	40	53	42	114	82
AVERAGE NUMBER OF CHILDREN	2.46	2.28	2.36	2.86	2.41	2.57
STANDARD DEVIATION	2.27	2.36	2.25	2.68	2.25	2.41

TABLE 16a - TABLE OF "t" VARIATE FOR DIFFERENCE BETWEEN MEANS

	BETWEEN SEXES (CONTROLS)	BETWEEN SEXES (AFFECTED)	BETWEEN MALE CONTROLS AND AFFECTED	BETWEEN FEMALE CONTROLS AND AFFECTED	BETWEEN TOTALS
"t" VARIATE	1.09	0.237	0.305	1.042	0.478
PROBABILITY	$0.3>p>0.2$	$0.9>p>0.8$	0.7	0.3	$0.7>p>0.6$

TABLE 17 - TABLE OF FREQUENCY DISTRIBUTION OF FAMILY SIZE BY RISK STATUS

RISK STATUS	NUMBER OF CHILDREN											TOTALS	MEAN FAMILY SIZE	STANDARD DEVIATION
	0	1	2	3	4	5	6	7	8	9	≥ 10			
MALE CHOREICS	3	4	12	6	6	7	6	1	0	0	1	46	3.43	2.10
FEMALE CHOREICS	7	8	8	7	5	5	1	3	1	1	0	45	2.78	2.19
ALL CHOREICS	10	12	20	13	11	12	7	4	1	1	1	91	3.11	2.15
MALE CONTROLS	8	3	5	9	3	4	1	2	0	0	1	36	2.97	2.67
FEMALE CONTROLS	7	2	7	7	3	4	3	4	0	0	1	38	3.37	2.76
ALL CONTROLS	15	5	12	16	6	8	4	6	0	0	2	74	3.81	2.71
MALES AT RISK	10	8	13	5	5	3	0	0	0	0	0	44	1.98	1.43
FEMALES AT RISK	8	11	15	16	8	2	1	1	0	1	1	64	2.63	2.47
ALL AT RISK	18	19	28	21	13	5	1	1	0	1	1	108	2.36	2.45
TOTALS OF FAMILY SIZE OVER ALL GROUPS	38	36	60	50	30	25	12	11	1	2	4	273	2.83	2.15

$'t'_{89}$ variate between male and female choreics is 1.438, p is $0.2 > p > 0.1$

TABLE 17a - ABBREVIATED TABLES OF FAMILY SIZE FOR χ^2 CALCULATION BETWEEN SEXES FOR CHOREICS

RISK STATUS	NUMBER OF CHILDREN				
	0 - 1	2 - 3	4 - 5	6 and over	Totals
MALE CHOREICS	7	18	13	8	46
FEMALE CHOREICS	15	15	10	5	45
TOTALS	22	33	23	13	91

$\chi^2_3 = 2.823$ $\quad 0.5 > P > 0.3$

TABLE 17b - ABBREVIATED TABLES OF FAMILY SIZE FOR χ^2 CALCULATION BETWEEN CHOREICS AND CONTROLS (SEXES POOLED)

RISK STATUS	NUMBER OF CHILDREN								
	0	1	2	3	4	5	6	≥7	Totals
CHOREICS	10	12	20	13	11	12	7	6	91
CONTROLS	15	5	12	16	6	8	4	8	74
TOTALS	25	17	32	29	17	20	11	14	165

$\chi^2_7 = 4.980$ $\quad 0.7 > P > 0.5$

Education: Tables 18 and 18a

It was impossible to obtain objective data on school performance of the individuals in the sample as the school records of children in the region are destroyed when the children reach the age of 21 years. Because of this the information obtained is subjective and subject to the inaccuracies of recall of the individual. It was felt that there was least scope for inaccuracy in the age at which they left school whether or not they obtained leaving certificates and whether or not they had any post scholastic education and these were the major questions asked. There were no significant differences between sexes or groups in school leaving age or age at completing further education, in the interviewed sample. The mean school leaving age for 83 choreics was 14.2 years, for 135 at risk non choreics was 14.6 years and for 158 persons not at risk was 14.3 years (Table 18). It was felt that the children of choreics might have to leave school earlier than the prescribed leaving age if an affected parent required nursing care or was unable to obtain an adequate income for the family. This happened in only sixteen of the 396 individuals on whom information was obtained occurring in seven of the 237 cases at risk or

suffering/

suffering from chorea and in nine of those not at risk indicating that the scholastic education of children of choreics was terminated prematurely no more frequently than that of their social peers.

Questioning individuals on whether or not they had obtained a leaving certificate from school and at what level may have obtained answers prompted more by pride than truth. In the younger age groups there was reluctance to admit to having obtained no certificates and this may have introduced a source of bias into assessment of what level of educational attainment was reached. However vanity is not the monopoly of any one group and so any differences be noted between groups may be real. Also there seemed little reluctance to state that no leaving certificates were obtained as 248 of 368 individuals (67.3%) on whom information was obtained stated that they had none. Because of the differences in age structure between the at risk non-choreics and other groups, comparisons between the former and the rest are of dubious validity. No significant difference exists between group numbers obtaining leaving or other certificates except between risk/

risk free males and females ($\chi^2 = 4.086$ $0.05 > p > 0.01$).

Differences are observable between males in post scholastic education and this is detailed in Table 18. Abbreviating the Table (18a) for comparisons of those that had or lacked post scholastic education it can be seen that significantly fewer choreic males received further education ($\chi^2 = 8.872$ $0.01 > p > 0.001$) This may be reflected by the 't' variate for the difference in mean years of education received between choreic and control males reaching a level of probable statistical significance ($t_{121} = 2.443$, $0.02 > p > 0.01$) however the distribution of years of education received is extremely skewed. It is probable that this difference is related to the occupational differences between the groups in that the control males tend to enter more skilled employment as can be seen from the Tables following.

TABLE 21 - NUMBERS CHANGING OCCUPATIONAL CATEGORIES BY RISK STATUS

	NON-CHOREICS	CHOREICS	CONTROLS	TOTAL
Never changed category	14	17	15	46
Changed once	32	26	39	97
Changed more than once	11	7	18	36
Total	57	50	72	179

$\chi^2_4 = 2.972$ $0.7 > P > 0.5$

TABLE 22 - TABLE OF DURATION OF WORKING LIFE AND UNEMPLOYMENT OF MEN IN SAMPLE BY RISK STATUS

STATUS	AT RISK UNAFFECTED	CHOREICS	CONTROLS
NUMBERS	57	52	74
AVERAGE WORKING LIFE	23.053 years	33.547 years	31.213 years
STANDARD DEVIATION	15.247 years	11.643 years	15.249 years
AVERAGE UNEMPLOYMENT	0.531 years	6.961 years	0.970 years
STANDARD DEVIATION	1.524 years	6.332 years	1.87 years
RATIO OF UNEMPLOYMENT TO WORKING LIFE	0.032	0.216	0.030
STANDARD DEVIATION	0.083	0.220	0.045

The more recent the admission the better was the likelihood of finding case notes except in cases undergoing specialised procedures for whom case notes were sometimes transferred out of central record offices to peripheral clinics. This was only a minor problem. However over the period of the survey one can assert that for the mental hospitals gross deficiencies exist in their records to an extent that known choreics are certain to have been missed. It is to be hoped that this will not be the case subsequently as all regional mental hospital admissions now have diagnostic data entered on a specific coding sheet which is returned to the Scottish Home and Health Department.

Other sources reveal that at least seven cases were missed in the search of mental hospital records and five cases in geriatric hospital records.

Deficiencies in reporting cases by General Practitioners:

Some general practitioners were extremely co-operative/

co-operative and had long memories. The furthest extent of recall of cases was to 1957 in the case of one doctor. However the majority of general practitioners providing information gave it on current cases or cases diagnosed or dying since 1960. An assessment of failure to report cases can be obtained by consideration of the numbers of known choreics living at home or admitted within the year previous to our first inquiry, i.e. since January 1965. It was felt that the problems created by choreics and their families should be of such a nature as to persist in the memory of general practitioners for at least a year. It was observed that only twenty two were reported of the forty cases either diagnosed and existing in the community or finally hospitalised since January 1965. Of the thirty one cases admitted during the period 1960-64 only seven were reported.

This degree of under-reporting could be attributed to three main causes: the reluctance of the general practitioner to co-operate; his failure to remember cases occurring more remotely in the past than a/

drug she developed choreic movements of her limbs. grimaces and masticatory movements. Her depression was at first little affected by the melleril and there did seem to be a mild intellectual impairment. At this time a possible diagnosis of Huntington's chorea was made. However, when the depression had lifted and the melleril was stopped the chorea disappeared. Hence a drug induced chorea is a much more likely diagnosis.

False positive diagnosis did not seem to occur in the presence of a known family history. It was more likely that alternative diagnoses be provided for, what in event proved to be, the early stages of Huntington's chorea. This occurred in four cases and in all of them the initial diagnosis was schizophrenia or schizoid reaction.

Mis-diagnosis occurred much more frequently in the case of Huntington's chorea than false positive diagnosis. Even though it could be mis-diagnosed with knowledge of the family history a major contributing factory to early mis-diagnosis was the lack of an adequate family history. This occurred/

occurred in twenty of the twenty six mis-diagnosed cases. The main reasons for absence of a family history were: it had not occurred previously in the family; the index case had insufficient information on one or other of his parents either because of their early death, or desertion or because he was illegitimate or brought up in an institution; there was deliberate concealment within the family or by those presenting as early cases of the disease. Ultimately the erroneous diagnosis was corrected but in some cases more than one mis-diagnosis was made during the course of the illness. Because the correct diagnosis was finally determined we can assess the initial error rate in diagnosis for recognised cases as being 20.8%. A much more difficult problem is the recognition of what percentage of undoubted choreics are never diagnosed as such. We found by retrospective investigation of the ascribed causes of death and clinical history, that during the surveyed period three such cases did occur. A more accurate assessment could be made if all deaths occurring in choreic sibships were investigated but this was outside the scope of this investigation. It is sufficient to know that a small percentage of cases of Huntington's chorea will/

sister's condition as being of the same aetiology as the patient this also demonstrated the wide range of clinical presentations possible. The patient herself was always intellectually well preserved in contrast with her dementing sister.

Case 9 - a married woman, denied all family history of mental illness although she had been brought up by a paternal aunt for unspecified reasons. Her mother died in Edinburgh Royal Infirmary when the patient was aged twenty-one. She was seen six years after the onset of symptoms which were increasing mental dullness and difficulty in walking. The neurologist found that there was degenerative disease of the cortex and basal ganglia with predominantly Parkinsonian symptoms, slight choreiform movements, and marked pre-senile dementia. In an absence of a family history a diagnosis of Jacob - Creuzfeldt disease was made. However when the case notes of the mother were obtained it was learned that she had been diagnosed as Parkinson's disease. She also had shown signs of cerebellar and cortical degeneration with psychotic symptoms before her death aged 40 years. The/

The mother's sister and father also had died of a similar illness. This information was provided by the patient's father who obviously concealed this knowledge from his daughter. Such behaviour is not uncommon and will be discussed more fully later. Whatever the reason it resulted in mis-diagnosis in both mother and daughter.

The cases that were diagnosed retrospectively numbered three during the period of the survey. Their histories follow.

Case 10 - a married woman she was the eldest of thirteen children. Her mother had died of Huntington's chorea but this information was only revealed subsequent to her death. Her illness started in her mid thirties with ataxia and clumsiness. It was steadily progressive so that eventually she was incapacitated enought to require her daughter to look after her. By this stage she had severe dysarthria and dysphagia and her family were well aware of the hereditary nature of her/

Although the numbers are small it can be seen that initial erroneous diagnosis is more likely in the absence of a family history and that psychiatric and neurological misdiagnoses were equally common. In cases with a positive family history, only psychiatric mis-diagnoses occurred, and mis-diagnoses was erroneous only in so far as it failed to identify the aetiology of the observed abnormal behaviour. It is obvious that in this condition an accurate family history is a major aid to correct diagnosis.

Obtaining a family history:

In view of the worth of a family history in facilitating diagnosis it is of value to discuss the reasons why family histories are not obtained and how the yield of family information may be improved. The basic causes of obtaining inadequate information are, either patient or kindred ignorance of the family history, or failure to communicate knowledge to the medical practitioner. There are practicable procedures which can overcome both types of difficulty.

Ignorance/

Ignorance of the family history:

If the patient is an only child and brought up in an institution then a family history may be impossible to obtain. This is less of a problem in diagnosis than that of the spuriously or really negative family history because the absence of a family history cannot be used as an argument against a diagnosis of Huntington's chorea. A truly negative family history can rarely be observed in this condition. However, knowledge that this possibility exists should be sufficient to deter the raising of the fact of a negative family history as a strong argument against clinical diagnosis. And even in large families in which only one inherits the condition (e.g. case 4) the question of paternity may be raised. Increased sexuality is a rare but nonetheless possible clinical feature of the condition and perhaps this might be a reason for the occurrence of isolated cases in families. Adultery is a much more common event than gene mutation and estimates of the mutation rate in Huntington's chorea are particularly low. (Reed and Neel, 1959).

In/

conceal information from the medical practitioner. It may be that their resistance to imparting information can be overcome by tactful and persistent questioning yet some individuals vehemently deny that there is any family history of the condition in spite of their certain knowledge to the contrary. They are few in number and on questioning them as to why they failed to provide such information as they knew they gave the reason that they felt questions on family matters represented an unjustifiable invasion on privacy. Whatever the reasons are for their unco-operativeness it is probable that such individuals would be more co-operative when visited at home rather than seen in a surgery or in a hospital.

It is possible to overcome difficulties in communication of all types if there are extra-familial sources of information on disease in the family in question for example, death certificates. This can be the case if adequate disease record linkage systems that can be consulted exist in the region. An alternative to this is the establishment of a regional and ultimately/

ultimately national, register, maintained in strict confidence, of all cases and families in which Huntington's chorea was diagnosed. This is possible for all areas in which surveys like the present one are undertaken.

It is also facilitated by the existence of a Scottish national network for the collection of data on hospital in-patients. Consequently it is to be hoped that no diagnosed cases will be missed from hospital sources.