

# 1

## Facts and figures about Huntington's disease

### ➔ Key points

- ◆ The first succinct description of the condition was given in 1872 by George Huntington.
- ◆ Approximately 1 person in 10,000 has Huntington's disease.
- ◆ Although Huntington's disease is rare, its genetic nature means it affects a large number of family members.
- ◆ It is difficult to date the onset of problems precisely, but in general the condition lasts for about 20 years.

Huntington's disease is a condition that affects the brain. Our brains contain millions of nerve cells, each one of which makes connections with many other nerve cells. We use our brains for thinking, planning, and remembering events, but the brain also controls a lot of processes automatically. The brain controls the movements of the body so that they are smooth and automatic. For example, when you wanted to pick up this book you were able to do so because your brain was able to co-ordinate a number of different functions without you giving each one conscious thought. We can consider some of the steps in this example: information from your eyes and where your hands were in relation to the book was co-ordinated; you could then smoothly move your arm so that your hand was close to the book; and you could use your fingers and thumb to pick up the book. All this movement was achieved without unbalancing the rest of your body.

The nerve cells in particular parts of the brain serve specific functions. In a person with Huntington's disease some nerve cells, in specific areas of the



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brain, die early. This produces a pattern of problems that allows doctors to make a diagnosis of Huntington's disease. We will consider this pattern of nerve cell loss in Chapter 9, but for the moment will continue with some of the more basic facts about Huntington's disease.

## The history of Huntington's disease

### Why is it called Huntington's disease?

Many medical conditions are named after a doctor who recognized and gave a clear description of the pattern of problems associated with that particular disorder. In our case Huntington's disease is named after an American doctor called George Huntington. Although George Huntington was not the first person to describe the condition, his was the first clear, succinct account. When other doctors then wanted to write about their patients they called the condition 'Huntington's chorea'. This now raises two questions.

### What is 'chorea' and why has the name been changed to Huntington's disease?

A lot of medical terms are derived from either the Greek or Latin languages. The word 'chorea' comes from the Greek word for dance. Nowadays, it is a word used to describe unwanted involuntary movements. Some involuntary movements are useful, such as breathing or blinking, but a patient with Huntington's disease has movements of the face, body, and limbs that are random and purposeless. I will describe the various types of movement problems in more detail in the next chapter, but for now it is enough to say that chorea is the most frequent movement problem seen in Huntington's disease. Chorea is not the only movement disorder that can be recognized, and as the emotional and behavioural aspects can be more of a difficulty for the patient and the family, the term 'Huntington's disease' has become fashionable in recent times. As with any fashion it takes time for the change to be widely adopted, so it is possible that you will still hear the term 'Huntington's chorea'.

### What was so remarkable about George Huntington's description?

George Huntington wrote a medical paper that was published in the Philadelphia-based *Medical and Surgical Reporter* in 1872. The title of the paper was 'On Chorea'. Huntington's disease is not the only cause of chorea, and at that time chorea was mostly commonly the result of a particular infection. Nowadays, we seldom see chorea due to infection, but that is another story. Most of George Huntington's paper was about the then most common cause of chorea. However, on the last page he described a hereditary form of chorea. His account of families with the hereditary form of chorea is





very succinct and accurate, and it enabled other doctors to separate this cause of chorea from the others.

It may be interesting to take a slight diversion and comment on why George Huntington was in a position to know so much about Huntington's disease at such a young age. George's forebears had migrated from England to the east coast of America. His father and grandfather practised medicine in an area of Long Island, New York, and looked after families with this condition. George first met someone with the condition at the age of eight, when he travelled on medical rounds with his father. George qualified as a doctor and wrote his paper soon afterwards, while still only 21 years old. He was able to draw on his father's experiences of the condition and the original manuscript contains notes made by his father.

### Other landmarks in the history of Huntington's disease

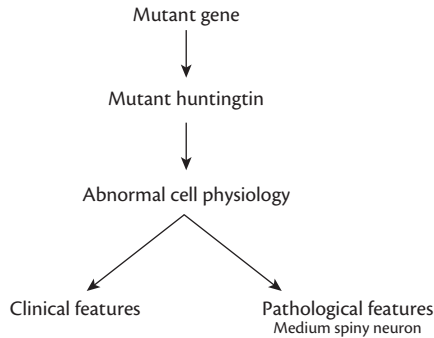
In the early part of the twentieth century there were relatively few publications on Huntington's disease, but the pattern of inheritance was confirmed. In addition, there were attempts to identify the number of patients in a given area, and some of the changes in the brain were documented. With time these studies became more sophisticated. The first book devoted to Huntington's disease was published by Michael Hayden in 1981. Although the book is based on his study of families with Huntington's disease in South Africa, it is clear that most of the natural history, basic genetics, and patterns of nerve cell damage in the brain have been well established.

Other notable landmarks include the foundation of the lay organization called the Committee to Combat Huntington's Disease, which was founded in the USA by Marjorie Guthrie in 1967. Her husband, the folk singer Woodie Guthrie, had died of the condition that year. The development of organizations for patients and families is described in more detail in Chapter 12.

The struggle to identify the problem with the gene that causes Huntington's disease covered the period from the 1980s to 1993 and will be described in Chapter 5. The identification of the genetic mistake has helped remove some uncertainties about the diagnosis and has allowed the development of reliable predictive tests, but was never an end in itself. The objective was, and remains, to understand Huntington's disease so that effective treatments may be developed to alter its natural history or delay its onset. Apart from humans, no other animal develops Huntington's disease. Once the gene that causes it was identified, an important landmark was its insertion into laboratory animals. There are a number of animal and cellular models of Huntington's disease. Our understanding of Huntington's disease is summarized in Figure 1.1.



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**Figure 1.1** Summary of our understanding of Huntington's disease. It is possible to tell a coherent story about the mistake in the gene which produces an abnormal protein. How this damages particular cells in the brain is still unclear. It is also possible to describe the clinical features seen in Huntington's disease and the changes that take place in the brain.

Genes are the instructions to make proteins. Knowledge of the Huntington's disease gene allowed the identification of the protein for which it is the code. The protein was called huntingtin. Abnormal huntingtin results in abnormal cellular processes; in turn, this leads to the clinical features that families and doctors recognize. Our knowledge of how these abnormal cellular processes leads to Huntington's disease is incomplete. A lot of progress has been made, but so far a treatment to alter the natural history is unavailable. For now, I want to concentrate on the numbers of people affected and some aspects of the natural history of the disease.

## How many people are affected?

In order to answer this question a doctor has to define a reasonable area, count the number of patients with Huntington's disease who were alive on a particular date, and compare that with the number of healthy people alive at the same time. This seems simple enough, but there are a number of problems with this type of study. Defining a reasonable area is important; if the area is too small then the result can be very misleading. If we take a row of houses that contain ten people and one person has Huntington's disease, then 1 person in 10 has Huntington's disease—but this answer is absurd. If the area is too large, then it may be difficult to identify all the patients with Huntington's disease. The early studies tended to underestimate the number of Huntington's disease patients. If we look at a number of studies of numbers of patients in the UK



that have been done in the last thirty years or so, then it is clear that results ranged between 4 and 10 patients with Huntington's disease for every 100,000 of the population. Some studies are more sophisticated than others so a convenient estimate would be 7–10 patients per 100,000. This means that in the UK, which has a population of approximately 60 million, there are about 4,200–6000 patients with Huntington's disease at any one time. It is now easy to see that Huntington's disease is a rare disorder, but if we count the carers and close relatives of a patient then many more people are affected by it. In addition, a patient has Huntington's disease for a very long period of time, so the condition represents a significant problem.

## Huntington's disease in various parts of the world

It is reasonable to ask if Huntington's disease occurs in all parts of the world and if different countries or continents have different numbers of Huntington's disease patients, and if so why? As we started with the UK it may be interesting to note that studies suggest very similar numbers of people are affected in European countries.

We can now go on to consider the English-speaking nations, since they were largely founded by migration from the UK and other parts of Europe. As might be expected, the number of people affected by Huntington's disease is again in the range of 4–10 per 100,000 in Canada, the USA, and Australia. It is also interesting to ask if Huntington's disease affects the native populations. This type of information is more difficult to gather. It may be that there are fewer cases among these peoples, but detailed studies have not been undertaken. Studies of numbers of patients with Huntington's disease have not been done in the Indian subcontinent; however, there has been a study of Huntington's disease among the immigrant population in the UK, which gave a result of 1.75 per 100,000. There are a number of reasons why this figure could be an underestimate, so it is reasonable to assume that Huntington's disease does occur in India and that if it were possible to do a systematic study, the numbers of people affected could be similar to that seen in Europe. Similarly, detailed studies have not been undertaken in other parts of Asia, but it has been well documented that there are fewer cases in Japan than in Europe.

Interesting things happen if relatively few people migrate to a sparsely populated part of the world. If one of the founders of that population has Huntington's disease and goes on to have a lot of descendants then the number of people affected with Huntington's disease can become unusually high. This has happened in Tasmania (Australia) and has also happened in an area of Venezuela.





One large family that lives around the shores of Lake Maracaibo in Venezuela has been particularly important in the search for the Huntington's disease gene. This story will be told in more detail in Chapter 5.

## When does Huntington's disease start?

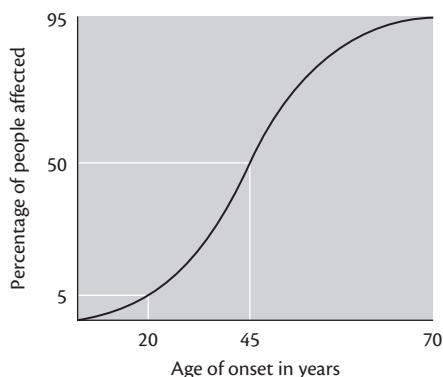
This question gives the impression that the age of onset of Huntington's disease can be documented accurately. This is not so. A person does not go to bed healthy and wake up the next day with Huntington's disease. Many people at risk for Huntington's disease have asked me to describe how Huntington's disease starts. On the face of it this is a reasonable question, but in fact it is difficult to give a clear answer. The problem is that some of the early features of Huntington's disease can occur in anyone. When doctors make a diagnosis of any condition they are effectively recognizing a pattern. The problem comes when a patient starts with mood changes or being less tidy than they once were. This can occur in anyone, and it is only possible to estimate that this was the start of Huntington's disease when more obvious signs, such as abnormal movements, occur later on.

Someone experienced in seeing patients with Huntington's disease may recognize small abnormal movements as chorea, especially if there is a family history. However, many patients will not see an experienced doctor at this time, and it may be some years before the patient and members of the family recognize that there is a problem and seek medical help. If the doctor then asks how long they have had a problem, the family have some difficulty in remembering the start because the condition comes on slowly. They may be able to give an estimate of the start, but it will not be accurate. For this reason, the onset of Huntington's disease is best described as insidious. As some of the very early changes can be non-specific, an experienced doctor who happens to see someone around this time may have some suspicions, but will want to examine the patient again to see if the signs persist and gradually worsen over time.

As we will see in Chapter 5, the identification of the gene has resulted in people at risk of developing Huntington's disease coming for predictive tests. As someone who offers predictive testing, I sometimes see people who have very minimal chorea and I am able to make a diagnosis much earlier than would have happened before these tests were available. In the past, the patient and family would have waited longer before seeing a doctor.

Despite these limitations, it has been possible to summarize the age of onset of patients in the form of a graph (Fig. 1.2). Over the years there have been a number of studies estimating the age of onset of Huntington's disease, but they all result in an S-shaped graph like this one. Given the shape of this graph,





**Figure 1.2** Age of onset curve for Huntington's disease. Huntington's disease can develop at almost any age but most people develop the condition between the ages of 35 and 55 years.

it is easy to work out that Huntington's disease can start at almost any age, but most people develop the condition between the ages of 35 and 55 years.

## How long does Huntington's disease last?

Again, this is a very simple question but one that is difficult to answer accurately. In a study of patients with Huntington's disease in a particular area it is possible to know precisely when an affected person died. The problem comes in trying to estimate when that person started to have Huntington's disease. As we saw in the last section, it is possible to ask the family to give an estimate but it will not be absolutely precise. A number of studies have accepted this limitation and estimated the duration of the disease. The results have varied but an average of 15–16 years is a reasonable estimate. Of course you have to remember that this is only an average, so some patients will have had the condition for a longer and some for a shorter time. Given the difficulties of families accurately dating the onset of the condition, I prefer to think of Huntington's disease as a condition which lasts around twenty years.

