A CLINICAL AND GENETIC STUDY IN MYOTONIC DYSTROPHY

Een klinisch en genetisch onderzoek bij dystrofia myotonica

PROEFSCHRIFT

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CHRISTIAAN JACOB HÖWELER
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PROMOTIECOMMISSIE:

Promotoren:
Prof.dr. A. Staal
Prof.dr. H.F.M. Busch

Overige leden:
Prof.dr. M.F. Niermeyer
Prof.dr. J.P.M. Geraedts

To the memory of my mother, Gerda Höweler - Oorthuys.

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CHAPTER I

INTRODUCTION

The genetic counselling for myotonic dystrophy patients appears to be relatively simple. The disease is transmitted as an autosomal dominant trait, and the patients risk of transmitting the abnormal gene to his children is 50%. However, many patients at the age at which genetic counselling is requested have only mild symptoms. Often there is only myotonia of the hands and mild weakness of the face and distal limbs. The patient may have a relative who is affected more severely, which causes anxiety for his own future and that of his children. Apart from the information on the genetic risk, he will have two other questions. Firstly: what does the future hold for him, what will be his own prognosis? Secondly: how severe will the disease be in a child if this will become affected?

There is no easy answer to these questions. The expression of the myotonic dystrophy gene is variable, both in age of onset as well as in the nature and severity of the signs and symptoms. In some patients the disease is benign, causing only a cataract at an elderly age. More often the disease starts around the age of twenty, and in the course of several decades the patient will be invalidated by muscle weakness and mental symptoms. Still many of these patients are able to lead a more or less independent life, to have a job and a family, until gradually their capabilities are limited by the increasing disability. However, if a child has congenital myotonic dystrophy his mental deficiency is often so severe that there is little chance of an independent life.

Thus, for the proper genetic counselling of myotonic dystrophy patients, one needs, apart from the determination of the genetic risk, information on:

1. The natural history of the disease and the prognosis in an individual patient.
2. The predictability of the severity of the disease in offspring inheriting the myotonic dystrophy gene.

The purpose of this study was to find an answer to these two questions. Literature data are summarised in chapters II and III. The families studied and the methods of examination are described in chapter IV. The results of the family study (chapter V), the study on the natural history (chapter VI), and on the severity of the disease in parent-child pairs (chapter VII) are given separately. The results will be discussed in chapter VIII and chapter IX gives a summary. Detailed information about the relatives who were examined is given in the two appendices.

CHAPTER II

THE NATURAL HISTORY OF MYOTONIC DYSTROPHY
A literature study

The natural history of myotonic dystrophy is rarely described. Most data on larger groups of patients were obtained in short term transversal studies, whereas myotonic dystrophy is a slowly progressive disease lasting for decades. The prognosis is then extrapolated by assuming that a patient with only mild symptoms will later be affected in a similar way as an elderly patient who is already severely ill. However, in a disease such as myotonic dystrophy with its greatly variable age of onset, nature and severity of symptoms and signs, this method is inappropriate. In the absence of well controlled studies, widely different views on the prognosis and natural history of myotonic dystrophy have been described.

Caughey (1963) stated that the disease usually advances steadily without remissions to complete invalidity and mental apathy. Few patients survive beyond the sixth decade. Merritt (1967) was more optimistic: the progression is usually slow and many of the patients live to an old age without becoming incapacitated. Occasionally they may become bedridden or confined to a bed-chair existence because of extensive muscular wasting.

Walton and Gardner-Medwin (1981) gave an intermediate picture: the course is one of steady deterioration. Most patients who present with muscular symptoms are severely disabled and unable to walk within 15 to 20 years of the onset. However, other patients may continue to walk with little disability throughout their lives.

Harper (1979) stated that the impression of severity depends to a large extent on the nature of the observer. The neurologist encounters myotonic dystrophy as a progressive disorder of adult life which may be extremely disabling in its later stage. The pediatrician encounters it as a disease of the newborn with respiratory distress, or as a disease of infants with developmental delay. The ophthalmologist sees the condition in later life presenting as cataracts, often with minimal muscle involvement. The medical geneticist will see a more complete picture of the overall pattern of the disease. Harper stresses that the variability of the disease is one of its main hallmarks.

Because of this variability it seemed impossible to give an accurate individual prognosis. In an individual patient some information may be gained from the previous course of the illness, since the speed of deterioration is rather constant. The degree of future invalidity might be estimated this way. Also the pattern of the disease in other family members offers a clue, but Harper cautioned that mild disease in one family member does not exclude severe disease in another.

Detailed data on the natural history of myotonic dystrophy can only be found in a few studies.

Thomasen (1948) studied the incidence of disability in 101 patients, and the correlation with the nature of the symptoms and the age of the patient. He estimated in 101 patients the degree of muscular dystrophy as expressed in the ability to work. In 26 patients the physical working ability was not reduced, in 36 patients mildly reduced, in 21 considerably reduced and in 18 severely reduced. A much higher proportion (61%) of patients was actually not working than was to be expected from their degree of muscular dystrophy. This was attributed to the accompanying deterioration of intellect and initiative. The reduction of the physical working ability differed in different age groups: 43% of the age group 15 - 60 years had reduced physical working ability with only 7% in those below 15 plus over 60. The degree of muscular dystrophy was almost equal in children and their parents, but in children initiative and intelligence were comparatively reduced.

Patients therefore of different age groups showed unexpected differences in the nature and severity of the symptoms. Thomasen did not correlate the age of the patient to the age of onset of the disease. Neither did he consider the duration of the disease in connection with nature and severity of the symptoms.

Dyken (1969) described, in a study of 197 patients, three basic clinical syndromes of myotonic dystrophy, differing for their age of onset. The mildest syndrome was always present in antecedents of typically affected patients. They characteristically had presenile cataracts with or without endocrine, somatic and muscular stigmata, which are usually related to the classical picture. The second syndrome represented individuals with typical muscular symptoms and other stigmata which are usually associated with the textbook description of the disease. The third syndrome, always found in the infants and children of typically affected parents, represented individuals with muscular symptoms which differed by way of early presentation (i.e. infantile hypotonia, facial diplegia, severe infantile feeding problems), congenital psychomotor and speech retardation, childhood behavioural problems, or with other congenital physical defects (talipes, arthrogryposis).

Thus, Dyken found three basic syndromes of myotonic dystrophy, related to the age of onset, and showing a changing pattern of systems involved. He does not mention if and how these syndromes change with a longer duration of the disease.

In congenital myotonic dystrophy the mental symptoms are more severe than in patients becoming affected later in life.

Dyken and Harper (1973) found a considerable lower (average 71) intelligence quotient (I.Q.) in 19 patients with congenital myotonic dystrophy, as compared to the average I.Q. of 100 in 10 patients with a later age of onset (transmitting parent without congenital stigmata). Harper (1975) confirmed the low average I.Q. (66.1) in 21 patients with congenital myotonic dystrophy. This mental retardation is present from birth, and is not progressive. Affected children have severe muscle weakness at birth, but this improves in the course of the first years. All 70 children surviving the neonatal period learned to walk. In late childhood and adolescence the 'adult' features of myotonic dystrophy appear. Harper (1979) stated that there is no evidence as to whether such

patients have a downhill course that is more, or less rapid than the disease with onset in adult life, but it seems improbable that they can look forward to a normal adult life.

O'Brien and Harper (1984) studied the natural history of myotonic dystrophy with an early onset over a longer period of time. They studied 71 patients with an onset below the age of 16 years; 40 patients had been followed for 10 years.

Forty six of the 71 patients had congenital myotonic dystrophy, most of whom (37) were between 10 and 30 years of age. Four patients died after the neonatal period at the ages of 4, 18, 19 and 22. Four patients were so severely disabled that their prognosis for life seemed poor. Of the 26 patients visiting school, only two were receiving a normal education and 24 a special education. Of the patients older than 18 only 2 were more or less independent: one was a housewife but coped poorly because of her mental handicap, and one was gainfully employed. Five patients had severe walking problems caused by talipes. Three patients had articulation defects interfering with communication. Only 8 patients had a cataract and only one had been operated upon.

If only a minority of the patients with congenital myotonic dystrophy have a bad prognosis for life, in general there is little chance of an independent life for them.

Data on the age of death in myotonic dystrophy are scarce. In the pre-war literature Bell (1947) found the average age of death to be 44.7 in 85 sibs suffering from myotonic dystrophy. Thomasen (1948) found an average age of 42.5 in 24 patients and Klein (1958) 50.6 in 92 patients. Harper (1979) suggested that the distribution of the age at death is probably considerably wider than is indicated by these figures.

Summary

The nature and severity of the symptoms of myotonic dystrophy appear to be so variable that the natural history of the disease is difficult to assess. Moreover, one easily gets a wrong impression of the natural history from transversal studies in selected groups of patients. Several authors indicated a correlation between the age of onset and the nature of the symptoms. Precise data however are scarce. The mental symptoms in patients with congenital myotonic dystrophy are definitely more severe than those in patients with a later age of onset. The severity of the symptoms is likely to be influenced by the duration of the disease; data on long term follow-up studies are rare, however.

Concrete questions for this study

The first question in the introduction - what is the natural history of myotonic dystrophy, and what is the prognosis in an individual patient - can now be specified as two concrete questions for this study:

1. Is there a correlation between the age of onset and the nature of the symptoms in myotonic dystrophy?
2. Do the nature and the severity of the symptoms change with increasing duration of the disease?

CHAPTER III

THE SEVERITY OF THE DISEASE IN SUCCESSIVE GENERATIONS - THE PROBLEM OF ANTICIPATION
A literature study

§ 1. Introduction

The risk of a patient with myotonic dystrophy of transmitting a severe form of the disease to his offspring is only rarely mentioned in the literature.

Grimm and Harper (1983) found different risks for the offspring of two groups of affected women: 20 - 35% for those who had a previous child with congenital myotonic dystrophy and 3 - 7% for those not having a previous child with this severe form of the disease.

Glanz and Fraser (1984) in a similar study found a similar difference in risk: 29 to 37% for women who had had a previous child with congenital myotonic dystrophy, and 6% for women who had not. They did not find indications for the exclusive occurrence of congenital myotonic dystrophy in particular families.

Harper (1979) estimated that women with myotonic dystrophy in general have a higher risk of having a severely affected child, and 20 to 25% of births will result in either a neonatal death or a severely affected child. The risk for severe childhood disease in the affected child of an affected man was found to be only 5.8% in a retrospective study.

The severity of a genetic disease may easily be estimated if the disease is constant in severity in all patients. The severity of myotonic dystrophy varies greatly however, so predictions on the degree of severity of this disease are complicated. However, older studies emphasize that the disease proceeds in a special and monotonous way from generation to generation (Fleischer, 1918; Ravin and Waring, 1939). Children in one family often show a remarkably similar picture, distinct from that of the diseased parent and parental sibs. Moreover, the age of onset of the disease in the children was always at an earlier age than that of the parents. This was named progressive inheritance: onset of the disease at an earlier age in successive generations (anticipation) and the increase of severity of disease in successive generations (potentiation). This might enable prediction of the severity of the disease in a following generation.

The authoritative geneticist Penrose (1948) dismissed anticipation as a biological phenomenon. He indicated how selection of families for study might create the false impression of anticipation. He presumed that the age of onset and the severity of myotonic dystrophy actually varied at random. If this is true one cannot predict the severity of the disease in the next generation. Subsequently geneticists rarely considered anticipation seriously (Myrianthopoulos, 1963; Bundey and Carter, 1970).

Others, especially clinicians, maintained that their frequent observation of anticipation in myotonic dystrophy families was real (Klein, 1958; Dyken, 1969; Pryse-Phillips et al, 1982).

This argument has been carrying on for many years. Yet the discussion is rarely serious, since most authors have preconceived points of view. Harper (1979) seems the only geneticist trying to reconcile the two points of view: 'Since Penrose's publication few arguments have been raised against it, particularly since no convincing explanation of how a gene could 'worsen' in successive generations was ever forthcoming, but the discovery of the almost exclusively maternal transmission of the severe infantile and congenital cases and the likely existence of a maternal environmental factor raised the question as to whether this might not provide a genuine biological basis for anticipation'. The question of anticipation being a real biological phenomenon or an artefact has consequences for genetic counselling as indicated above. Moreover, modern linkage studies will soon allow prenatal diagnosis of myotonic dystrophy (Shaw et al, 1985). The option of selective abortion will only be meaningful to parents, if they have a realistic idea about the expected severity of the disease in their offspring.

Therefore it seems worthwhile to re-examine the phenomenon anticipation. Before doing so, we traced back the history of the dispute from the literature, in order to find useful ways to study this phenomenon. The literature study is divided into three periods each marked by a monograph on myotonic dystrophy: of Bell (1947), Caughey and Myrianthopoulos (1963) and Harper (1979).

§ 2. **Anticipation discovered** (Fleischer to Bell)

In 1918 the Swiss ophthalmologist Fleischer described nine families suffering from myotonic dystrophy. His index patients had classical myotonic dystrophy with myotonia, muscle weakness and a cataract at an early age (25th -45th year). Several patients had a childless marriage, and those who did have children had many children dying at an early age. The parents of patients showed an increased incidence of presenile (50-70 year) cataract, but no muscular weakness. Among grandparents of his patients he often found a common senile cataract. He found common ancestors in the fourth or fifth generation of four families. He presumed that these common ancestors already carried the myotonic dystrophy gene, yet there was no history of cataract or muscular dystrophy in the generations before the grandparents. Fleischer concluded to a special pattern of transmission: the gene does not cause a disease in the first generations, then suddenly the disease appears in different branches of the family at the same genetic distance from the common ancestors. In a few generations one then observes a homologous (the same kind of symptoms) and homochronous (onset at the same age) disease with anticipation: in the first generation senile cataract, then presenile cataract with no muscle weakness, then early cataract with muscle weakness, then a generation with either children deceasing at an early age or no children at all. After this the disease would probably disappear from the family.

In 1922 Fleischer published an extensive five generation family- and clinical study with myotonic dystrophy only in the offspring of two of the eight

children of the ancestors. In the eldest generations of these two branches there was no indication of myotonic dystrophy in the family histories; age at death was late and there were large numbers of children with a low mortality rate. In the fifth and sixth generation mental deficiency became frequent with twice club-feet in mentally defective children. Similar 'degenerative' diseases were not found in the six unaffected branches of the family. He confirmed his earlier (1918) hypothesis on the pattern of inheritance.

Henke and Seeger (1927) restudied Fleischer's family. They confirmed his findings. In the affected generations the ratio of patients versus normals was approximately 1 to 1, which confirms dominant heredity. The theoretical explanation of anticipation was proposed. Some critics (Siemens and Lenz) had already speculated that anticipation could be an artefact, caused by the variable expression of a dominant gene, combined with selection during family studies. Henke and Seeger rejected this criticism since the gene expresses itself uniformly in the affected generations. They also rejected the theory that different genes or gene-combinations could cause anticipation. They explained anticipation by phenotypical induction, an exogenous influence of genetically altered body-cells on the myotonic dystrophy gene.

Meanwhile Vogt (1921) described the typical myotonic cataract enabling a distinction from senile cataract. On slit-lamp examination in the immature stage there are fine coloured opacities not causing visual complaints. He first observed this type of cataract in a myotonic dystrophy patient; in later cases patients turned out to have myotonic dystrophy, or affected myotonic dystrophy relatives. This type of cataract was apparently characteristic of myotonic dystrophy; if found in the absence of muscle weakness it should be seen as a 'forme fruste' of myotonic dystrophy. Later studies confirmed these data (Vos, 1936; Klein, 1958).

After Fleischer's description of the curious variant of dominant inheritance in myotonic dystrophy, several authors examined new families. Some used genealogical studies to link myotonic dystrophy families through common ancestors (Frey, 1923; Von Katzenstein-Sutro, 1938). No indications were found in the family histories of muscular disease in the generations preceding the first cataract generation. After that generation they found myotonic dystrophy patients with homologous and homochronous symptoms in several family branches: first a generation with senile cataract, then presenile cataract with mildly affected muscles, then juvenile cataract with severe myotonic dystrophy.

Others mainly studied the generations in which the disease appeared (Vos, 1936; Ravin and Waring, 1939). Anticipation was found in most families, without a history of disease in preceding generations.

Maas (1937) examined a large number of families. The segregation of the disease is not clear because he found a large group of relatives with dubious symptoms: slightly hollow temples, mild thenar atrophy and equivocal myotonia at percussion of the thenar. He thus found the remarkable percentages of 60% affected, 35% suspicious and 5% normal relatives.

Most studies agree on decreasing age of onset, change of symptoms and increasing severity of the disease in successive generations. The explanation of anticipation differed between various authors. Fleischer (1923) assumed dominant inheritance, the myotonic dystrophy gene being influenced exogenously by, for instance endocrine, derangements it had caused. Henke and Seeger (1927) supposed a similar mechanism. Vogt (1921) thought that several linked genes caused myotonic dystrophy, with different genes causing different symptoms. Waardenburg (1932) supposed one myotonic dystrophy gene with several ways of expression predetermined by the phenotypical structure of the individual. Kryschowa and Bajevskaja (1934) proposed other modifying genes besides the dominant myotonic dystrophy gene.

Ravin and Waring (1939) summarised the observations that led to the assumption that the transmission of the myotonic dystrophy gene differed from the regular dominant inheritance:

1. Parents and grandparents of patients from the first generation in which affected members were found, were either healthy or had only cataracts. This was also the case in families in which genealogical studies had revealed it to be most likely that these parents and grandparents carried the gene.
2. In all 58 affected parent-child pairs, collected from the literature, the age of onset in the child was lower than in the parent.
3. The disease was more severe in the children than in the transmitting parent.
4. Patients in the second and third generation with manifest myotonic dystrophy were affected so young and so severely that they usually did not have children and therefore did not transmit the gene.
5. In the two or three generations of a family in which the disease was found, myotonic dystrophy was diagnosed in 50% of the children of a carrier of the gene, and in both sexes. Therefore in these generations there was a dominant pattern of inheritance.

Bell's monograph of 1947 summarised pedigrees and descriptions of most previously published families. From the considerable group described by Maas (1937) she excluded all patiens not having clear myotonia. She was aware of differences between authors on the way of collecting family data, establishing age of onset, use of slit-lamp or not, etc. Because of the heterogeneity in the material, Bell calculated with reservations the correlation coefficient of ages of onset for pairs of sibs, cousins and parents-children. She concluded tentatively that indeed the ages of onset in the second generation are considerably lower than in the first generation of patients. Because selection might have been present in her material, she was reluctant to consider anticipation as proven. She concluded that in myotonic dystrophy being inherited as a dominant gene, this dominance is not typical in view of anticipation and the changing symptomatology in successive generations. She assumed that a factor in the plasm of the reproductive cell could play a part in this deflection of the normal dominant inheritance pattern.

Summarising: in the 20 years after Fleischer's description of anticipation in myotonic dystrophy families, this observation was confirmed by others, with widely varying interpretations, however.

§ 3. **Anticipation criticised** (Penrose to Myrianthopoulos)

In 1948 Penrose suggested that anticipation is an artefact caused by selection by clinicians studying a hereditary disease. They are more likely to study a family in which the disease occurs in several generations at the same time, than a family in which the disease occurs in only one generation at the time of examination. In this way those families are selected in which the grandparent is affected late, the parent during middle age and the child at an early age. The reverse situation, grandparent affected at an early age, parent during middle age and child late in life, cannot be observed within a period of sixty years, and is unlikely to be put on record. This bias may be intensified if the fertility of patients affected at an early age is diminished by the disease.

We will examine in detail how Penrose arrived at his conclusion and how he interpreted the observations of previous authors. The review of his article will be commented upon at intervals.

In the introduction Penrose stated that the anticipation phenomenon has often been described in the past. The concept is a traditional one. It was thought that various qualities like diabetes, mental illness could be reinforced in succeeding generations. Penrose stated that this anticipation was due to selective examination of families instead of being a biological phenomenon. Careful analysis usually indicated faults in the interpretation of progressive degeneration, yet the belief in it persisted. In myotonic dystrophy however anticipation seemed to appear in a more marked degree than in other diseases. Bell's complete description of the present state of knowledge on myotonic dystrophy made possible a critical discussion on the meaning of the anticipation phenomenon and its significance.

The other authors on myotonic dystrophy who introduced the concept of anticipation (Fleischer, Henke and Seeger, Ravin) were not mentioned. Beside Bell's review Penrose only referred to the somewhat confusing study of Maas (1937).

Penrose then stated that the degree of severity of myotonic dystrophy is not easily subjected to measurement, whilst ages of onset can conveniently be used for calculations. He cited the correlation coefficient of ages of onset as calculated by Bell, in parent-child pairs and pairs of sibs, being respectively 0,32 and 0,66. Therefore sib pairs showed more similarity in ages of onset than parent-child pairs.

The other aspects of anticipation were not discussed: the increasing severity in later generations, and the absence of disease in preceding generations.

Penrose then mentioned the need for a genetic theory to cover these different correlation coefficients and other peculiarities found in the pedigrees of myotonic dystrophy. Anticipation was not observed in experiments performed by animal or plant geneticists. Therefore it seemed wise to examine whether the circumstances characteristic of human genetic investigations could

have given rise to the appearance of anticipation. He presented the following possible 'causes' of anticipation:

1. Selection of affected parents with late onset of the disease. When a disease has had an early onset the patient's fertility may be diminished and he will be excluded from being a parent.
2. Selection of affected offspring in whom the onset of the disease is early, since only severely affected patients will be seen by physicians.
3. Selection of cases with simultaneous onset in parents and offspring. By far the most powerful type of selection, arising from the fact that investigations cover only limited periods of time. The complementary pairs in which the child is affected 25 years later in life than the parents, might be just as frequent in the general population. The distance between the onset ages will then be 50 to 60 years, and thus these complementary pairs will not be recorded.
4. Weakness of real correlation of onset ages in parents and offspring.
5. General variability in age of onset. The absolute quantity of anticipation is controlled by the total variability of the age of onset.

To illustrate this last point Penrose compared the 'anticipation index' of myotonic dystrophy to that of other diseases: the more the variation in age of onset between parents and offspring, the higher the anticipation index. As evidence, he presented the 51 parent-child pairs collected by Bell, in a table arranged per age of onset. All pairs were represented in that part of the table where the age of onset in the child preceded that in the parent by 20 to 40 years. Thus the disease arose more or less simultaneously in parents and their offspring. Pairs in that part of the table, where children became affected 40 or more years later than their parents, were lacking. Penrose now concluded that as many pedigrees probably had been missed as had been recorded, and called this 'perhaps not an unreasonable assumption'.

This assumption is in fact the core of Penrose's hypothesis. He stated that his assumption is perhaps not unreasonable and further assumed that these complementary pairs do exist. However, previous family studies should easily have detected complementary pairs. They would consist of a member of the oldest examined generation with late onset age and the transmitting parent with earlier onset age. Fig. 1 illustrates data that could have been possible, had these complementary pairs existed.

Several authors have unsuccessfully sought for 'alternative complementary pairs' as illustrated in the left top-block (Fleischer, 1918, 1922; Frey, 1923; Von Katzenstein-Sutro, 1938). Still a disease like myotonic dystrophy, lasting for years and easy to recognise from family portraits is unlikely to be forgotten by the children of a patient. The absence of these complementary pairs is a valid observation and one of the very keystones of the anticipation theory.

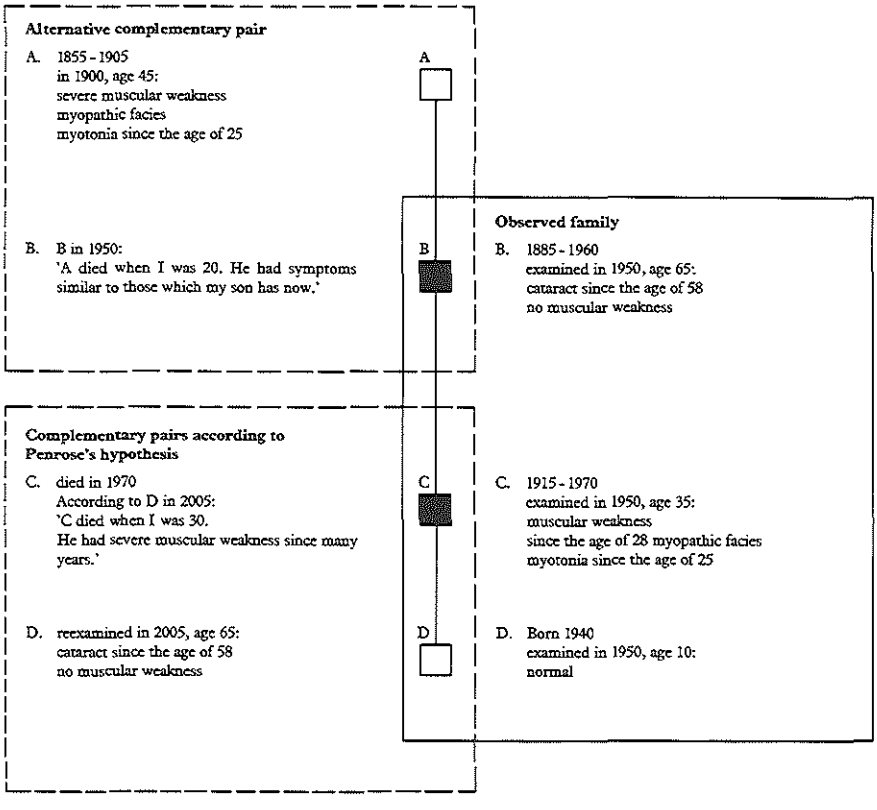


Fig. 1.
Fictitious family with future and past complementary parent-child pairs. The right block with the uninterrupted line illustrates a frequently observed situation. The left lower block illustrates a complementary pair according to Penrose's hypothesis. The left top block illustrates an alternative complementary pair that one should be able to find if Penrose's hypothesis is valid.

Penrose proposed multiple alleles to the myotonic dystrophy gene to explain the strong variability in the age of onset between parents and offspring. A late onset and mild form of myotonic dystrophy could be caused by the combined effect of the myotonic dystrophy gene and one allele; an early onset of a severe form of myotonic dystrophy could be caused by the combined effect of the myotonic dystrophy gene with another allele.

Conclusions on Penrose's paper:

It seems Penrose was opiniated about anticipation. He gave his own opinion on anticipation being an archaic genetic concept, and used Bell's literature review to illustrate his view. He neglected other clinical studies on the observation of anticipation in myotonic dystrophy. He introduced the hypothesis that complementary parent-child pairs may occur as frequently as anticipating parent-child pairs, without testing this hypothesis according to observations in the literature. Thus, Penrose's hypothesis that complementary parent-child pairs might exist, forms a challenge to search for them. However, there is no reason to simply adopt his view on anticipation.

Between 1945 and 1960 several large family studies in myotonic dystrophy were done in different countries. In Denmark Thomasen described 21 families, in The Netherlands De Jong described 11 families, in Northern Ireland Lynas described 13 families and in Switzerland Klein described 100 families.

Thomasen (1948) described 21 families containing 101 myotonic dystrophy patients and 17 cases with only a cataract. Three families showed 3 generations, 11 families 2 and 7 families 1 generation affected. In a precise clinical study (including slit-lamp examination) 46% of first degree relatives were found to be affected.

Thomasen did not mention Penrose's paper. Antedating of onset ages and potentiation of the clinical picture were found, particularly an increasing severity of mental symptoms in later generations. In successive generations the characteristic series of clinical pictures, from senile or presenile cataract to infertile myotonic dystrophy patients, were found. The decreasing fertility in the last generations was proposed as a possible cause for selection giving the impression of anticipation. He emphasized that anticipation needed additional evidence from studies of larger numbers of families. His own study did not contain sufficient three or more generation-families to confirm the hypothesis of anticipation.

Thomasen did not find families in which a myotonic dystrophy patient with late onset and a minor degree of severity had had a parent or grandparent with an early onset and severe degree of the disease. He did careful family histories, including studies of family portraits looking for relatives with a myopathic facies. In all cases suspected of myotonic dystrophy the diagnosis could be verified whenever possible, indicating that it was reliably established that late onset patients never have early onset (grand-)parents.

De Jong (1955) described 45 patients from 11 families. He did not give the ages of onset, but the clinical data showed in the younger generation nearly always a more severe disease, frequently with mental symptoms. De Jong took the sequence of cataract, mild myotonic dystrophy and severe myotonic dystrophy in successive generations as an established fact. He did not discuss Penrose's selection hypothesis.

De Jong gathered historical and genealogical data from the generations

preceding that of the index case. There was no indication for severe myotonic dystrophy in any of the ancestors.

Lynas (1957) studied 13 myotonic dystrophy families with 55 patients of which she examined 30 personally. Like Penrose she tried to calculate correlations of age of onset in parent-child pairs and sibling pairs with myotonic dystrophy. In recording the age of onset, she accepted the first subjective symptom given by the affected person, but also calculated for each patient the onset for different modes of onset: myotonia, cataract, baldness and muscular atrophy. She then calculated correlations of age of onset in parent-offspring pairs and sibling pairs for 3 categories of onset groups separately: all onsets combined, cataract only, and all onsets but cataract, respectively. The correlations found differed per category of onset group, which made them difficult to compare with the correlations calculated by Penrose. Lynas reached the cryptic conclusion that anticipation either is, or is not expressed in correlation differences of the onset ages of parent-offspring pairs and sib pairs, depending upon which symptom is taken as being the onset of the disease.

From Lynas' study one may conclude that it is important to define the age of onset as well as the symptoms at onset carefully in a family study.

Klein (1958) published the largest family study on myotonic dystrophy: 600 family members out of 100 families were examined, 319 people were affected. The slit-lamp was used extensively. Klein tried to reach a complete ascertainment of myotonic dystrophy in Switzerland to avoid selection of patients. His 121 index patients were referred by neurologists, ophthalmologists and psychiatric institutions. The history of deceased relatives and the genealogy of the families were included.

Anticipation was definitely found in families with multiple generations affected. The average age of onset in the older generation was 50.5 and in the younger 27.4. A changing pattern of symptoms as described by Fleischer was found: usually a first generation with senile cataract, next presenile cataract with or without mild myotonic dystrophy, then severe myotonic dystrophy with mental disturbances. Klein could not explain anticipation by selection mechanisms as Penrose had proposed. He did not select families in which the disease occurred in several generations at the same time, but he examined the families of all index patients. Furthermore he did not select severe cases because many index patients were referred by ophthalmologists. In the preceding generations complementary pairs were not found: there are no late onset patients with a severely affected onset parent in the detailed family descriptions. Klein concluded that myotonic dystrophy is transmitted as a dominant trait with anticipation and potentiation.

In 1963 the monograph 'Dystrophia myotonica and related disorders' by Caughey and Myrianthopoulos was published. Myrianthopoulos gave a review of the genetic aspects, mainly based on literature data of Thomasen, Klein, and Lynas. Myrianthopoulos stated that all the evidence points to autosomal

dominant inheritance with complete or almost complete penetrance. On anticipation he adopted Penrose's view: 'There is no evidence that anticipation is a phenomenon of direct biological significance and it can be adequately explained on the basis of the manner in which families with the particular trait are selected'. He assumed that complementary parent-child pairs occur as often as anticipating parent-child pairs. He thought that he had found evidence for the existence of complementary pairs in the families of Vos, Maas, Ravin and Klein. They describe myotonic dystrophy patients with muscle weakness who have children with only a cataract. Myrianthopoulos observed a similar family. He concluded that these children were affected less severely than the parent, and thus these parent-child pairs were complementary pairs.

This does not seem to be a correct conclusion. It is possible that at a certain moment in time the symptoms of a child who has been affected at an early age are milder than the symptoms of a parent affected at a later age. This does not make them a complementary pair, since the onset of the disease is still earlier in the child than in the parent, and the child will probably have more severe symptoms when reaching the age which the parent is at this moment in time.

Summarising: from 1947 to 1962 anticipation has been observed in most clinical studies. The geneticists Penrose and Myrianthopoulos rejected anticipation mainly on theoretical grounds. However, some of the observed phenomena are explained either unsatisfactorily by them, or not at all.

§ 4. **Anticipation nearly forgotten** (Myrianthopoulos to Harper)

Since 1962 the anticipation phenomenon has only rarely been mentioned in the literature on myotonic dystrophy. Genetic studies were focused on three new aspects which attracted attention: congenital myotonic dystrophy with the remarkably exclusive maternal transmission, the linkage of the secretor and myotonic dystrophy genes, and the heterozygote detection.

The clinical picture of congenital or neonatal myotonic dystrophy had not been recognised as such until 1960. The recognition of this syndrome was important, because it showed the variability of the clinical expression of myotonic dystrophy, as influenced by the sex of the transmitting parent.

Vanier (1960) first recognised that children who had myotonia and muscle weakness before the age of ten, had often shown neonatal hypotonia, sucking and swallowing problems, respiratory distress and stiff joints. This clinical picture was later extensively documented by Dyken and Harper (1973) and Harper (1975). When more neonatal intensive care units were opened, this diagnosis was also made in neonates whose respiratory insufficiency was so severe that they would have died without respiratory support (Aicardi et al, 1974; Sarnat et al, 1976; Pearse and Höweler, 1979). Sarnat and Silbert (1976) showed that probably many of the neonatal symptoms are caused by intrauterine maturation-retardation of the muscles. The high infant mortality in the last generations of myotonic dystrophy families, which had been reported previously (Fleischer, 1918; Thomasen, 1948; Klein, 1958) could now be

explained. Harper and Dyken (1972) found that children with congenital myotonic dystrophy always inherited the gene from the mother. They assumed that the most likely cause for this 'maternal effect' was a toxic or hormonal factor in the intrauterine environment. This factor did not affect children not carrying the gene of the same mother: they were born healthy. Furthermore the toxic factor did not affect children with the abnormal gene, transmitted by the father. So congenital myotonic dystrophy only developed when an affected mother gave birth to a child carrying the myotonic dystrophy gene. However, mothers with myotonic dystrophy could also have children who were normal at birth, but later developed classical myotonic dystrophy. The nature of this supposed toxic factor has not yet been identified.

We shall now continue the views on anticipation during this period.

Harper (1972) examined 392 individuals from 48 myotonic dystrophy families and found 167 affected individuals. He used the slit-lamp in most cases. The purpose of this study was to investigate the linkage between the myotonic dystrophy gene and genes of the secretor and lutheran factors. Anticipation was seen in a number of families: 'the question is not that this pattern of events occurs, but whether some unusual genetic mechanism is required to explain it'. He mentioned the combination of biasing factors which may favour anticipating parent-child pairs to be detected rather than the reverse pairs. His study could not resolve this question, because of his heterogeneous ascertainment of families.

After some hesitation Harper adopted Penrose's view: if one can find a different explanation for the observed anticipation, the phenomenon does not necessarily represent a deviation of the regular dominant pattern of heredity. Thus he reversed the problem like Penrose had done, by making the occurrence of anticipation conditional on its explanation. However, the question is not as to whether or not anticipation can be explained. One possibility is that anticipation occurs in every family and thus is inherent to the genetics of myotonic dystrophy. The other possibility is that anticipation occurs only sporadically and accidentally, because of bias in ascertainment.

Harper studied both large and small families. In the families described anticipation seems present whenever more generations had been examined. Many sibships however, were not examined completely and the age of onset was not always mentioned.

Bundey and Carter (1970) examined 124 relatives of 38 index patients with myotonic dystrophy. They concluded to dominant inheritance with great variability in severity and age of onset. The mean age of onset of the 19 secondary cases was considerably lower (17.0 years) than the age of onset of index cases (27.3 years). Bundey and Carter stated that this illustrates 2 points: firstly the diagnosis is made earlier when a relative is already known to suffer from myotonic dystrophy; secondly an observer will detect in a selected family only early onset cases and will miss later onset cases in the younger generation.

These two facts partially account for the supposed 'anticipation', together with the fact that early onset cases will not reproduce.
In a later study Bundey and Carter (1972) compared the age at onset in sib pairs and parent-offspring pairs. A rather large number of patients was not able to give the accurate data on this and was eliminated from the study. Thus 12 out of the 23 parents of index patients and 3 out of the 25 sibs of index patients were eliminated. In the remaining patients a correlation coefficient of ages of onset of 0.81 for sib pairs and 0.80 for parent-offspring pairs was established. The high correlation of age of onset in pairs of sibs and pairs of parent-offspring suggested more than one type of mutant gene: one causing an onset at infancy, one causing an onset between 20 and 60 years of age, and possibly a third gene causing an onset between the ages of 4 and 25.

Bundey and Carter thus closely adhered to Penrose's view. They did find a lower onset age in the younger generation, but assumed selection as a cause. They calculated the correlations of onset ages as Penrose had done; many patients had to be excluded which limits the value of their data. As Penrose did, the extreme variability of the disease is ascribed to genetic heterogeneity.

Schubert et al (1980) examined 97 individuals from 18 families. They found 53 affected individuals, 36 of whom were in the parental and 17 in the filial generation. A mean age of onset of 14 years was found in the filial generation; in the parental generation it was always higher. They assumed that anticipation, which appeared in their study, in reality was a statistical artefact, partially caused by a difference between subjective and objective ages of onset which favours a later age of onset in the parental generation, and in part by a decreased fertility in patients with early onset myotonic dystrophy.

Pryse-Phillips et al (1982) examined a large pedigree in Canada, consisting of 112 individuals. They found 32 individuals to be definitely affected, 53 normals and 27 individuals having a 'partial syndrome', defined as patients with signs other than clinical or electromyographic myotonia. They found a transmission rate of definite myotonic dystrophy from father to surviving child of 60% and from mother to surviving child of 48%. Where it was assumed that children who had died at birth or in early infancy had carried the myotonic dystrophy gene, the transmission rate for female parents became 63%. Anticipation occurred in this family. As the expected number of affected offspring had already appeared (transmission rates being over 50%), they assumed that there was little chance of members of generation IV carrying the gene but not expressing it. They concluded anticipation is a true biological, although not necessarily genetic, phenomenon.

Harper (1979) summarised the evidence for regular autosomal dominant inheritance and the absence of 'skipped generations' in pedigrees with the disease. In most studies less than the expected 50% of first degree relatives are affected indicating non-penetrance. Genetic heterogeneity as proposed by

Bundey and Carter (1972) was thought as less likely, mainly because linkage studies gave no evidence for multiple loci. In his opinion the disorder is a single genetic and biochemical entity with an extraordinary clinical variation within a family, notably between generations, which is as yet difficult to explain. Both genetic and environmental factors may contribute to this variability. The nature of anticipation is unresolved as to whether it represents a true biological phenomenon or results from biases in recording this type of families. A convincing explanation of how 'a gene could worsen' in successive generations has not been offered. However, the discovery of the almost exclusive maternal transmission of neonatal myotonic dystrophy and the likely existence of a maternal environmental factor raised the question as to whether this might not provide a genuine biological basis for anticipation. He concluded that anticipation in myotonic dystrophy can be satisfactorily explained on the basis of a situation in which both bias and a true biological factor are acting.

Summarising: between 1962 and 1979 the anticipation phenomenon was rarely discussed seriously. After Myrianthopoulos the geneticists Bundey and Harper also adopted Penrose's hypothesis that anticipation is an artefact, without much further discussion.
After the recognition of the exclusive maternal transmission of congenital myotonic dystrophy, which could not be explained by regular autosomal dominant inheritance, the discussion was reopened. Pryse-Phillips et al had no place left in their family for complementary pairs and expressed doubts on Penrose's selection hypothesis. Schubert did observe anticipation but explained it as an artefact. In 1979 Harper reconsidered if there is a biological basis for anticipation, although there was no suitable genetic explanation for the 'worsening of a gene' in successive generations.

§ 5. Conclusion and concrete questions for this study

Myotonic dystrophy is transmitted as an autosomal dominant trait, although there are some deviations from the regular transmission pattern:

a. The onset of myotonic dystrophy occurs usually at an earlier age in a child than in the transmitting parent. It is not clear if this is the case in all instances.
b. The severity of symptoms and signs increases with decreasing age of onset. This change takes place slowly and is difficult to express in concrete figures. The increasing severity of symptoms and signs, together with the decreasing age of onset, produce a monotonous pattern of symptoms and signs in successive generations of families.
c. A full clinical picture of a severe degree was never described in parents of patients with late onset and a mild form of myotonic dystrophy.
d. Congenital myotonic dystrophy is transmitted exclusively by the mother.

The phenomena a, b and c together are generally called anticipation. The obvious question is: are the four related? Secondly the frequency of occurrence

of a, b and c is to be established. If they are always present, anticipation would seem inherent to the transmission of the myotonic dystrophy gene.

Penrose did not believe that anticipation is a genetic mechanism. He proposed as an explanation for this phenomenon that it is caused by selection during family studies. In the preceding literature study some arguments have been raised against Penrose's article. Essential to Penrose's hypothesis is that complementary pairs should exist that cancel out the anticipating pairs. Anticipating parent-child pairs have been observed frequently, so complementary pairs should also occur frequently. However, complementary parent-child pairs have never been described in clinical studies. Even if these can not be found at present, they should be able to be found in the future or the past. If complementary pairs appear in the future the penetrance of the disease should be incomplete in the families studied. If there have been complementary pairs in the past, it should be possible to detect them during a careful family history. One could state that the hypothesis, that anticipation is inherent to the transmission of the myotonic dystrophy gene, should only be rejected if these complementary pairs are found frequently. Unfortunately Penrose's hypothesis has been prematurely accepted and has not been tested. So the peculiar situation has developed that the phenomenon of anticipation, although it was observed over and over again, was seen by most authors as an artefact and was not subjected to further studies.

Thus it seems worthwile to study the phenomenon of anticipation anew. A number of families will have to be examined carefully and as completely as possible, and preferably followed during many years.

Concrete questions for this study

The preceding literature study also made clear which concrete questions can be formulated for this study:

1. How frequently has a child with myotonic dystrophy an earlier age of onset than the transmitting parent?
2. How frequently has a child with myotonic dystrophy a more severe form of the disease than the transmitting parent?
3. Is the penetrance of myotonic dystrophy incomplete so that many complementary pairs can be expected to be found in the future?
4. Have there been complementary pairs in the past which can be detected retrospectively?
5. Is the fertility of myotonic dystrophy patients affected to such a degree, that only patients with a late age of onset are able to have children, and complementary pairs can not come into existence?

CHAPTER IV

PATIENTS, FAMILIES AND METHODS

§ 1. Introduction

A number of myotonic dystrophy families was examined for this study. From the literature study the following conditions were selected, to be fulfilled in order to obtain data adequate for the purpose of this study:

a. The selection mechanisms that might cause anticipation as an artefact had to be avoided as much as possible. The index patients should not form a selected group by way of either age, age of onset, or degree of severity of the disease. For the comparison of age of onset and severity of symptoms of parents and offspring, the index patient should be eliminated.
b. To calculate the penetrance of the disease the families had to be examined as completely as possible, with methods sufficiently accurate to detect symptom free heterozygotes.
c. Data on the parents of patients in the oldest examined generation had to be acquired in order to detect the transmitting parent and estimate the age of onset, if they had been affected.
d. The age of onset of the disease had to be defined exactly and to be determined as reliably as possible.
e. The degree of severity of the disease had to be measured in such a way, that different patients could be compared.

This chapter will describe successively which families were chosen, which methods were used to diagnose the disease and in which way the acquired data were analysed.

§ 2. Patients and families

Two approaches to prevent selection were possible:

a. The examination of large families with many affected relatives apart from the index patient, and preferably with more than one generation of affected individuals. In this way many parent-offspring pairs could be found in which the index patient did not participate.
b. The examination of the families of all patients that were presented within a certain period of time, provided that the place of presentation in itself would not cause selection of a special kind of patients.

The original plan was to use both approaches simultaneously. In the department of Neurology, Academic Hospital Dijkzigt, Rotterdam, 51 myotonic dystrophy patients were seen between 1970 and 1977. They were referred by several departments: neurology, child neurology, the neurological consultants of other departments of the hospital, of the Rotterdam Ophthalmological Hospital, and of the department of neonatology of the Sophia Children's Hospital, Rotterdam. Table I presents this preliminary group of index patients per age group. It shows a large variation of ages.

total	0	>0-9	10-19	20-29	30-39	40-49	50-59	60-69	70 & older	age in jears
51	3	4	2	11	12	9	6	4	0	number

Table I: Preliminary index patients 1970 - 1977 in age groups.

Soon it appeared to be impossible to use both approaches a and b simultaneously, for the following reasons:

1. More index patients were presented than we had expected; this number exceeded facilities for extensive family studies.
2. Some index patients had many relatives living far from Rotterdam, who were unwilling or unable to cooperate. Also some relatives of families in Rotterdam did not wish to cooperate.
3. In some cases approach b. prohibited approach a. because many relatives had died. In these families we could not examine complete family branches.

Considering the fact that these arguments made a systematic approach via method b. impossible we choose accordingly to opt to work for approach a. This implied that we had to choose families, thus introducing selection, but we considered that with approach a. we could avoid bias of ascertainment more effectively than with approach b. Families with many members willing to cooperate, and who lived in or near Rotterdam, were chosen. Furthermore, only those families with at least 3 patients in at least 2 generations were selected. The families were selected in 2 phases.

Selection phase I: a family history was obtained of each index patient. The patient was asked where his near relatives lived and which relatives had died. At this moment it was already obvious that some families were not suitable for this study. The relatives of 11 index patients lived too far from Rotterdam. Of one index patient both parents and grandparents had died, as well as several sibs.

Selection phase II: pedigrees were made of the remaining 39 index patients. The names of parents and grandparents were registered, as well as the names of sibs and their children. If patients could not supply these data themselves we applied for them at the registry office. All names and addresses were filed. We added the names of the patients who were examined by Junge (1966) in Rotterdam. In case identical names were found in families of different index patients, the genealogical study was extended to find the common ancestor of both families. If a common ancestor was found we assumed that this ancestor transmitted the gene to both families and the 2 families were joined in one pedigree. In this way we were able to make some large pedigrees with more than one index patient. The genealogy of other families could not be extended and remained smaller.

In this phase we had to exclude the families of 17 other index patients. Ten patients had many relatives living too far from Rotterdam. In 2 cases many relatives refused to cooperate. Parents and grandparents of one index patient had died and other living relatives could not be traced. The relatives of 4 index

patients were not examined because the study was terminated. As a result of the genealogical connection between different families with one pedigree we finally had 14 families with 22 index patients.

In brief: from the 51 preliminary index patients, 22 were chosen for the study in the following way:

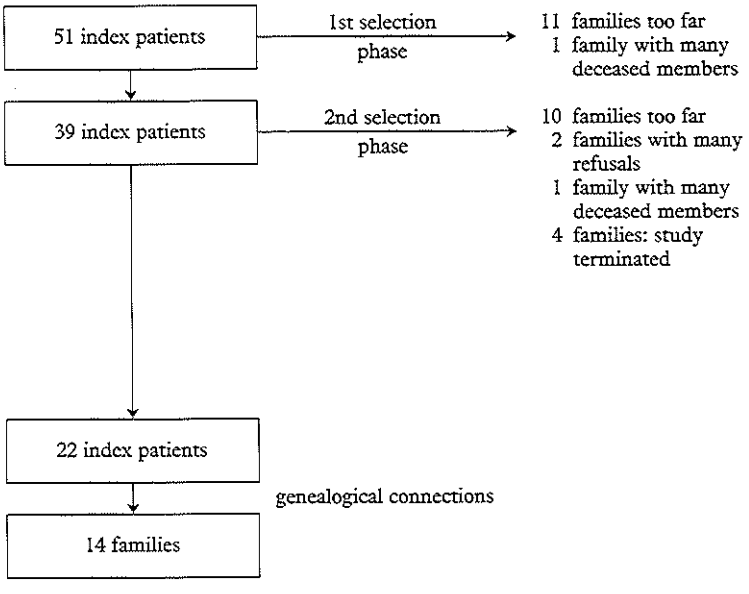


Table II shows the definite index patients per gender and age. Males and females are equally represented, and there was a fairly comprehensive range of age groups. Only the age group 10-19 has not been represented and a relatively large number of index patients are found in the age group 30-39.

total	0	>0-9	10-19	20-29	30-39	40-49	50-59	60-69	70 and over	age in years
11	0	2	0	4	2	0	2	1	0	male
11	3	0	0	1	5	1	0	1	0	female

Table II: Definite index patients per gender and age.

The 22 index patients were referred by the following departments: neurology (11), child neurology (2), other departments of the Academic Hospital (4), Ophthalmological Hospital (2) and neonatology department of the Children's Hospital (3).

decade of age of onset	0	1	2	3	4	5	6	7
number of index patients	4	0	6	6	2	0	3	0

Table III: Index patienst per age of onset measured in decades.

Table III shows the index patients per age of onset, measured in decades (see later). Most of the index patients have an age of onset in the second or third decade. Patients with an early and late onset of the disease are well represented, the first and fifth decade are not represented. One proband did not herself suffer from myotonic dystrophy, so she is not included in this table, resulting in the total of index patients in this table being 21.

In the study of a family the index patient and his near relatives were examined first. Next we examined the branches of the family where we expected to find myotonic dystrophy as indicated by the family history. We soon gave up attempts to examine other branches of the family, since the willingness to cooperate diminished the more distant the relationship was to an affected relative. Children of relatives, found to be normal at examination, were not examined. Home visits were offered when hospital out-patient studies were refused. Thirty relatives were examined that way, half of them with a portable slit-lamp. Electromyography was only done in the hospital.

Medical records were obtained on deceased relatives. In 6 patients the disease had been diagnosed and documented by a neurologist or an ophthalmologist. These patients were included in the study and data concerning age and symptoms at onset were supplied by close relatives. Data on 4 living relatives, living far away, were supplied by the attending neurologist. All together 264 relatives were examined.

§ 3. Methods

Purpose and type of the examination were explained to the relatives beforehand by letter or telephone. We offered the possibility of leaving out certain parts of the examination. All cooperating relatives agreed to the clinical and slit-lamp examination, some of them omitted the EMG. With children younger than 6 we did not propose an EMG examination.

In most cases myotonic dystrophy can be diagnosed with certainty by a physical examination: when active or percussion myotonia is found together with muscle weakness distributed characteristically for this disease. Bundey and Carter (1970) and Polgar et al (1972) demonstrated that electromyography and slit-lamp examination of the eyelens enables a diagnosis of the disease in a number of relatives who do not have symptoms and signs on clinical examination. At this moment the combination of these 3 methods in diagnosing myotonic dystrophy appears to be most effective. Since we wanted to examine as many family members as possible, time-consuming or discomforting procedures were omitted in order not to discourage relatives from cooperating.

For this reason we refrained from collecting data on other signs of myotonic dystrophy by means of ECG, bloodtests or pulmonary function tests. The three diagnostic methods used will be described in detail, as well as the determination of the age of onset and the severity of symptoms and signs.

A. Clinical examination

History

We used a standardised form, with categories for the usual symptoms and signs which may occur in myotonic dystrophy, such as myotonia, muscle weakness, articulation and swallowing problems etc. We also recorded a general history covering systematic symptoms, previous illnesses, developmental milestones, education, occupation and a family history. If a patient reported symptoms characteristic for myotonic dystrophy we asked as precisely as possible for the age at which he noticed these symptoms for the first time. This presented the problem as to which symptoms could be accepted as characteristic for the disease. In this variable disorder one may distinguish four characteristic onset patterns which can be recognised from historical data. These four symptoms were used as indicators for the onset of the disease:

1. Painless muscular cramp caused by myotonia, usually of the hands.
2. Weakness of the muscle systems of face, pharynx, neck and distal limbs.
3. Progressive deterioration of sight caused by a cataract.
4. The syndrome of congenital myotonic dystrophy, comprising respiratory distress, swallowing problems, hypotonia and stiff joints, in a child whose mother has myotonic dystrophy.

Other symptoms such as loss of hair, bowel complaints, irregular menses, mental inertia, were regarded as too unspecific to accept as symptoms marking the onset, since they occur frequently in normal people as well, or do not clearly indicate a change of function.

A second problem was the time scale for establishing the age of onset. A number of patients could not exactly recall the year in which a certain symptom had begun, especially when the disease had already been present for many years. In a preliminary study (Busch and Höweler, 1975) it appeared to be possible to determine the onset of a symptom in all patients within a range of several years, f.e. between the 10th and 20th year of age, especially by following milestones such as school years, marriage, birth of children, whilst searching for the onset of the symptom. To avoid having to exclude patients, we therefore chose for a wider range to determine the age of onset, namely the decade. Thus, patients who either gave the onset of a symptom exactly at their 14th year or between the ages 10 and 20 were classified for their age of onset in the 2nd decade. This meant that we had to sacrifice some accuracy in a number of patients, but we did not have to exclude patients.

When the onset of a symptom was given at a decade transition, f.i. 'around my 20th year of age', we asked the patient to choose or asked close relatives for additional information. Congenital myotonic dystrophy was classified as onset

in decade 0 in order to distinguish these patients from patients with a juvenile age of onset without neonatal symptoms.

In symptomfree patients the following rules were adhered to: if abnormalities were found during the physical examination (f.i. clinical myotonia or muscle weakness), the age at examination was considered as the age of onset; if only subclinical abnormalities were found (electromyographic myotonia only, or myotonic cataracts without impaired visual acuity) the age at examination plus 5 years was considered to be the age of onset. Here we followed Bundey and Carter (1972) who determined the age of onset of heterozygotes with subclinical abnormalities in the same way, with the explanation that lenticular changes have been noted to precede neurological disease by 6 years (Klein, 1958).

Physical examination

A general and neurological examination was done in all relatives examined in the hospital. We looked especially for active and percussion myotonia of the hands. Muscle weakness was noted in the British Medical Research Council (BMRC) scale of 0 - 5, the tendon reflexes of the limbs were examined and we looked for abnormalities in the articulation and walking patterns.

In patients seen at home we performed a limited neurological examination, still the data necessary to diagnose myotonic dystrophy could be obtained by examining articulation, face, neck and distal limbs.

B. Electromyography (EMG)

Electromyography was performed with a standard electromyograph (Disa) and concentric needle electrodes. Myotonia was exclusively sought for, in order to cause as little discomfort as possible. Usually only the abductor pollicis brevis muscle was examined, but sometimes also the extensor digitorum communis muscle of the forearm. Myotonic discharges were diagnosed if spontaneous electrical discharges with the characteristic waxing and waning of frequency and amplitude were seen or heard. In patients with obvious clinical myotonia, EMG examination was often not performed. On the other hand efforts were made to perform EMG in those relatives in whom clinical and slit-lamp examinations had revealed no abnormalities.

C. Slit-lamp Examination

For slit-lamp examination in the hospital a standard fixed slit-lamp (Haag-Streit) was used. A high resolution portable slit-lamp (Kowa) was used in 14 of the 30 relatives examined at home. Mydriatics were not administered, as the examination was performed in a dark room. A diagnosis of myotonic cataract was made if, in the anterior or posterior cortex, fine white dustlike opacities were found interspersed with a sufficient number of iridescent coloured

opacities (Junge, 1966). Since no quantitative criteria appear to exist we arbitrarily took a number of ten coloured opacities as a minimum for diagnosis. If a smaller number of coloured opacities, or only white opacities were observed, myotonic cataract was not diagnosed. Fleischer's star-shaped polar cataract and mature white or grey cataracts were not accepted as myotonic cataracts, unless coloured opacities were also present.

D. Criteria for the diagnosis myotonic dystrophy.

The diagnosis myotonic dystrophy was made if one or more of the following characteristics were established:

a) Clinical or electromyographical myotonia.
b) Muscle weakness in those groups of muscles characteristically affected by myotonic dystrophy; equivocal signs, such as mild atrophy of temporal or hand muscles, were disregarded if they occurred in isolation.
c) Myotonic cataract.
d) The syndrome of congenital myotonic dystrophy in neonates, provided that the mother was affected by myotonic dystrophy.

In one family (fam. P, appendix I) myotonia congenita was found in some relatives. For this study these patients were counted as normal. In this family myotonic dystrophy was only diagnosed if, apart from myotonia, other signs were present.

§ 4. Diagnostic sensitivities of the various methods

Not all relatives were studied by each of the three examination methods. In patients showing myotonia and muscle weakness, myotonic dystrophy could be reliably diagnosed without use of the slit-lamp and EMG. To distinguish normals from symptomfree heterozygotes we did need all 3 methods. Therefore we calculated how often each examination had been used for the diagnosis myotonic dystrophy or normal. Furthermore the results of each of the 3 methods was traced separately.

Table IV gives the number of individuals diagnosed as affected, normal and equivocal, with the methods applied.

	methods					
diagnosis	clin. ex. slitlamp EMG	clin. ex. slitlamp	clin. ex. EMG	clin. ex.	diagnosis from reports	total
affected	79 (50%)	26 (20%)	4 (3%)	16 (12%)	8 (6%)	133
normal	102 (80%)	14 (11%)	1 (1%)	8 (6%)	2 (2%)	127
equivocal	4 (100%)					4
total	185	40	5	24	10	264

Table IV: Diagnosis and methods applied in 264 individuals.

Whenever the relatives were found to be normal on clinical examination, efforts to complete the examination were made. In 80% slit-lamp as well as EMG examination was applied, and in another 11% slit-lamp examination was performed. In spite of the application of all 3 methods, 4 family members were diagnosed as equivocal. Three of them had only white opacities or only a few coloured opacities on slit-lamp examination (H-IV-1, L-IV-3 and L-V-13) and one had non-specific clinical abnormalities (absence of Achilles' tendon reflexes in D-III-2).
The number of complete examinations was smaller in the affected individuals (59%). Electromyography was omitted in patients who were afraid of the procedure, when clinical myotonia was present. Eight patients had had cataract operations, so that slit-lamp examination could not be performed. EMG examination was performed upon 4 of them. In more than 80% of the affected individuals the clinical diagnosis was confirmed by either slit-lamp or EMG examination. The results of clinical examination, slit-lamp examination and EMG will be briefly discussed separately.

Clinical examination

Of the 133 affected relatives, 125 were examined personally. In 8 cases the diagnosis was reported by a neurologist or an ophthalmologist. Of the 125 personally examined affected individuals 90 had clinical myotonia plus muscular weakness, 14 had only weakness, and in 8 myotonia was the only clinical abnormality found. Thirteen (10%) affected relatives had no muscular abnormalities. By slit-lamp and EMG in 8 of them both myotonic cataracts and electromyographic myotonia were present, in 3 only myotonic cataracts and in 2 only electromyographic myotonia were found.

Slit-lamp examination was performed upon 105 of the affected individuals. Myotonic cataracts were found in 62 of them (59%). Table V shows the findings of slit-lamp examination per age group.

age groups	<10 y	10-29	30-49	>50	total
myotonic cataracts	0	16	25	21	62
normal or non-specific lense abnormalities	9	19	12	3	43

Table V: Myotonic cataracts found in affected individuals in different age groups.

Myotonic cataracts were not found in subjects below the age of 10. Between the age of 10 and 30 the incidence rose to 46%, above the age of 50 to 87%. Thus slit-lamp examination was the most effective method for diagnosis in the older age groups.

Electromography was performed on 83 of the affected individuals. Myotonic discharges were found in 78 of them (94%). Table VI shows the results of the EMG examination per age group.

age groups	<10 y	10-29	30-49	>50	total
electromyographic myotonia present	6	26	28	18	78
electromyographic myotonia absent	0	1	0	4	5

Table VI: Electromyographic myotonia found in affected individuals in different age groups.

Myotonic discharges were found in nearly all examined affected relatives between the age of 6 and 50 (EMG was only rarely performed in children younger than 6). In the older age group electromyographic myotonia was absent in 18% of the affected individuals. Thus, EMG examination was the most effective method for diagnosis amongst younger age groups, when slit-lamp examination often is negative.

§ 5. Severity and duration of the disease

In chapter II two questions were raised concerning the relation between the age of onset and the nature and severity of symptoms and signs, and

concerning the influence of the duration of the disease on the symptoms and signs. We had to find a way to measure the severity of a number of symptoms and signs of myotonic dystrophy, to be able to compare groups of patients with similar age of onset and duration of the disease. We chose four symptoms to monitor the severity of the disease: cataract, muscle weakness, mental symptoms and myotonia, being the most frequently occurring symptoms and signs. Muscle weakness and mental symptoms largely determine the degree of disability in patients (Thomasen, 1948) and cataract and myotonia are the primary symptoms at the onset of the disease. We made an ordinal scale with 4 points for each of these 4 symptoms (see table VII).

symptoms and signs	criteria for scoring	scoring rate
cataract	- none	0
	- slitlamp cataract with normal visual acuity (>8/10)	1
	- cataract with decreased visual acuity	2
	- operated or mature cataract	3
muscular weakness	- none	0
	- mild, non-invalidating (BMRC: 4)	1
	- moderately invalidating or abnormal gait	2
	- severely invalidating	3
mental symptoms	- none	0
	- inertness, mild hypersomnia, with intelligence appearing normal	1
	- invalidating inertness or hypersomnia	2
	- mental retardation	3
myotonia	- none	0
	- electromyographic myotonia	1
	- clinical myotonia	2
	- severe, invalidating myotonia	3

Table VII: Severity score of symptoms and signs in myotonic dystrophy patients

This ordinal scale was developed because standards for these symptoms do not exist. Thus the scale only indicates an increasing severity with increase of the scoring rate.
The different scores in cataract are well defined. The height of the score and the severity of the complaints of a patient are well correlated.

For muscle weakness the scoring rates of 0 and 1 are clearly defined. We used rate 2 if a patient was obviously hindered by weakness of the muscles of arms and legs, but still could function well. Usually this concerned an abnormal gait, caused by weakness of the foot extensors. Scoring rate 3 was used in the case of impaired walking ability or hand function.

The mental symptoms were the most difficult to define, since the symptoms are not homogeneous and are not yet described systematically (Bird et al, 1983). At first we measured the intelligence quotient (I.Q.) in a number of

patients. However, the inertness of the patients so strongly influenced the result that the measured I.Q. often did not appear to correspond with the intelligence as estimated on clinical observation. Therefore we opted for a clinical estimation. The limits between rate 0, 1 and 2 with increasing inertness and hypersomnia were determined by the symptoms of the patient, his relatives and our own impression. Rate 3 was used for overt mental retardation as proven by the patient's attendance of a special school.

Myotonia is usually not progressive. Scoring rates 0, 1 and 2 indicate whether myotonia was either not, subclinically or clinically present. Rate 3 was only used when a patient stated that he was severely hindered by myotonia on using his hands.

After the examination the degree of severity of each of the four symptoms was recorded. Two groups of patients were excluded. Firstly the 8 patients whom we did not examine personally, and secondly the 7 children with congenital myotonic dystrophy, who had not yet reached the age of 5. In congenital myotonic dystrophy most symptoms improve in the first few years, to be replaced in later years by the adult features of the disease. The symptoms and signs in the first years differ so much from the symptoms and signs in later stages of the disease, that comparison is not relevant.

The patients were classified according to their corresponding ages of onset. These groups were again divided into groups with corresponding duration of the disease. The duration was counted in decades and calculated from the beginning of the decade at age of onset. For instance: a patient with an age of onset of the disease of 15, examined in his 38th year was classified as: age of onset in the second decade, duration of the disease 3 decades. The results of the comparison of the nature and severity of the symptoms and signs will be presented in chapter VI.

§ 6. The study of parent-child pairs with myotonic dystrophy

The research questions on anticipation (chapter III) concerned the comparison of the age of onset and the severity of symptoms in parent-child pairs, the penetrance of the disease, the search for complementary pairs in retrospect and the influence of the age of onset on the fertility of the patients.
The age of onset in pairs of affected parents and children was compared, excluding parent-child pairs in which an index patient was involved.
The severity of three symptoms was also compared in index free parent-child pairs.
The penetrance of the disease was examined by calculating the percentage of affected individuals in the examined sibships and generations.
During the family history we systematically asked patients from the oldest generation examined for data about the occurrence of muscle weakness and other myotonic dystrophy symptoms in their parents and grandparents.
The fertility of myotonic dystrophy patients was calculated per decade of onset group. The results of this part of the study will be presented in chapter VII.

CHAPTER V.

RESULTS: THE FAMILY STUDY

In this chapter the general results of the family study are presented.

Fourteen families have been examined. Seven families are derived from one index patient. Five families consist of several branches, each with its own index patient, and linked by genealogical studies (families A, F, G, N and P). A further two families consist of one main branch, supplemented by a small second branch indicating a common ancestor (families H and L). Altogether 264 individuals have been examined, 133 of these have been found to have myotonic dystrophy, 127 to be normal, and in 4 individuals the diagnosis was dubious. Of the affected individuals 72 are male and 61 female.

The families are presented in pedigrees A - P. For each myotonic dystrophy patient the decade of onset is given. Each family is briefly described. The individuals examined are described in detail in appendix I.

From the pedigrees it is seen that the onset age of the disease decreases in successive generations. This decrease does not run parallel in each branch of a family (see chapter VII). From the brief description of the families it appears that the clinical picture of the disease gradually changes by a lower age of onset (chapter VI and VII). It is also clear that the occurrence of a severe degree of myotonic dystrophy was not recorded in parents of patients with a late onset and mild disease (chapter VII).

In the 14 families we found 13 patients with congenital myotonic dystrophy. Furthermore the medical records on 12 perinatally deceased children allowed the conclusion that they probably were affected. In all these cases the mother was the transmitting parent.

LEGENDS

male, myotonic dystrophy, onset in the 6th decade


female, normal


deceased


normal, children not examined

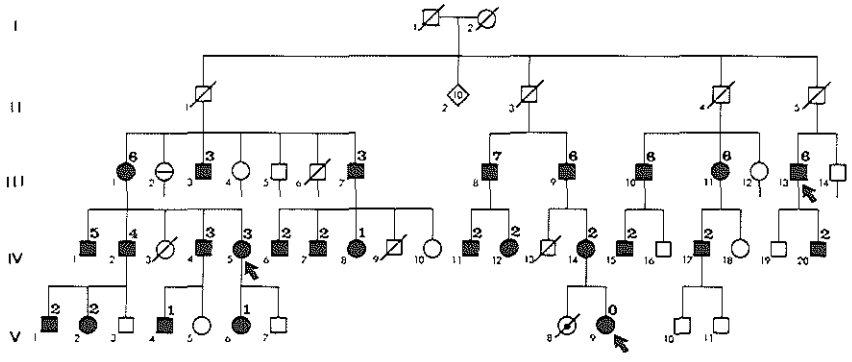

perinatal death after gestation > 7 months, medical reports suggestive of congenital myotonic dystrophy

diagnosis of myotonic dystrophy dubious


not examined

3 sibs, not examined


index patient



Summary of family A

In 4 branches of family A a total of 39 relatives were examined. Myotonic dystrophy was found in 26, 13 were normal and 6 first degree relatives were not examined (5 of these had died). The occurrence of a muscular or invalidating disease in generation I or II was not known to the members of generation III.

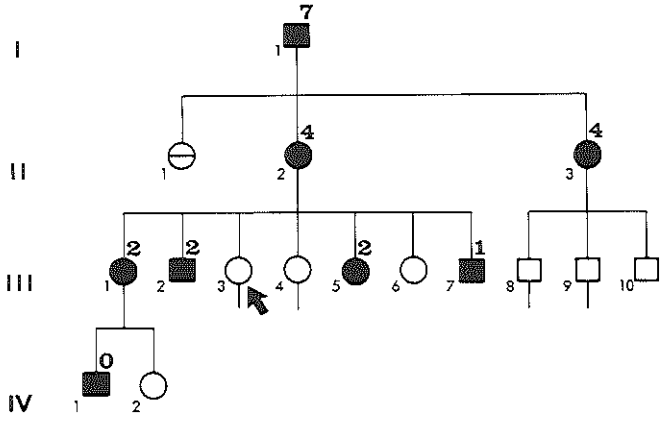
In *generation I* either I-1 or I-2 probably carried the gene. A cataract at a late age in I-2, but no invalidating disease was reported. The ages at death were 80 and 86 years respectively, which indicates that the disease would have been subclinical or very mild in the affected one.

The same applies to *generation II*: ages at death are 70 or over, in all 4 individuals who transmitted the gene. Senile cataracts were documented in II-1, II-3 and II-5, but there is no history of muscular disease.

In *generation III* severe myotonic dystrophy occurred in III-3 and III-7, with young adult onset and progressive muscular symptoms and death at the ages of 58 and 49 years. Both had mental symptoms in later stages of the disease. The other patients in generation III were mildly affected with presenile cataracts (subclinical in III-8, III-9 and III-11) and mild muscular symptoms of late onset (in III-1 and III-13). Mental symptoms were not seen.

In *generation IV* a large variety of ages of onset and of severity of the disease was seen. The affected children of III-7 had either an onset in childhood or as young adults, with predominant mental symptoms. IV-7 died suddenly at the age of 26, and his brother IV-9 was reportedly symptomatic before he died suddenly at the age of 15. The children of III-1 had late adult or young adult onset and muscular symptoms dominated. The other patients in generation IV (IV-11, IV-12, IV-14, IV-15, IV-17 and IV-20) had early adult onset and all had similar, still mild, muscular disease and mild mental symptoms.

In *generation V*, V-9 had congenital myotonic dystrophy, and her sister V-8 most probably died of the same disease. The other patients in generation V had childhood or young adult onset with mild to moderate mental symptoms and mild muscular symptoms.



Summary of family B

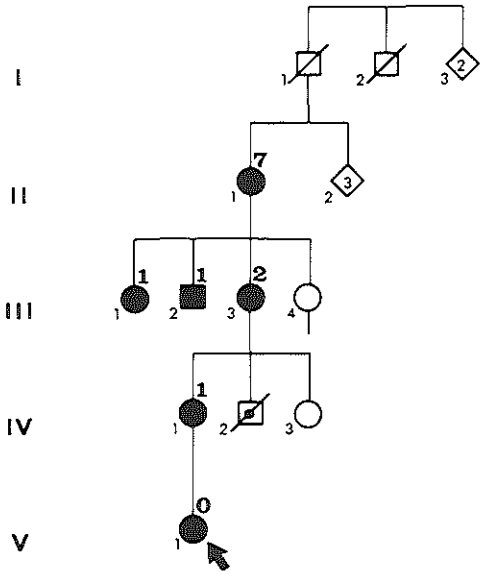
In this family 15 relatives were examined in generations I to IV, 8 had myotonic dystrophy, 7 were normal, 1 was not examined.
The proband in family B was not affected; she asked counselling because she was afraid her son might have the same disease as her brothers and sisters.

Generation I: I-1 had no history of muscular disease before his death at the age of 75. Myotonic cataracts were documented at the age of 68.

Generation II: II-2 and II-3 had already a family when their first muscular symptoms appeared. When examined 23 years after onset II-2 was severely disabled and inert, but her intelligence appeared to be normal. II-3 was moderately disabled and also appeared to be of normal intelligence.

In *generation III*, in all 4 patients the muscular symptoms had started during or before puberty. All four attended special schools for the retarded, whereas their healthy sibs were of normal intelligence. Mental symptoms were most severe in III-7 who already had myotonia in the first decade. At the time of examination all four had mild to moderate muscular symptoms.

In *generation IV* the only patient, IV-1, had congenital involvement and was mentally retarded.



Summary of family C

In family C eight relatives were examined in generations II to V, 6 were found to have myotonic dystrophy, 2 were normal and 4 were not examined (one of them had died).

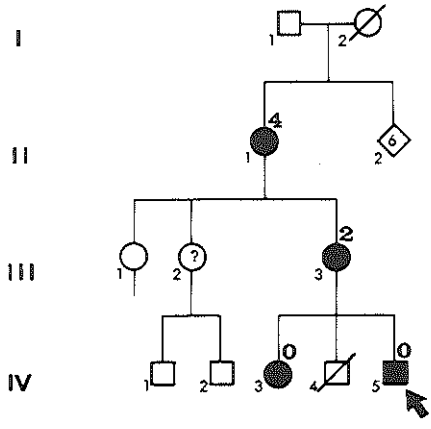
Generation I: I-1 was reported by his daughter as not having muscular weakness or cataracts before his death at age 59. His brother I-2 however had a disease similar to myotonic dystrophy.

In *generation II* only II-1 was examined and senile myotonic cataracts and percussion myotonia were found.

In *generation III*, III-3 had early adult onset of myotonia with mild muscle weakness at the age of 42. III-1 and III-2 reported the onset of myotonia already in childhood, they had prominent muscular symptoms without mental signs other than inertness.

In *generation IV*, IV-1 had onset during childhood with early dysarthria and mental retardation as prominent symptoms. Her brother, IV-2, probably died of neonatal myotonic dystrophy.

In *generation V*, V-1 died of severe neonatal myotonic dystrophy.



Summary family D

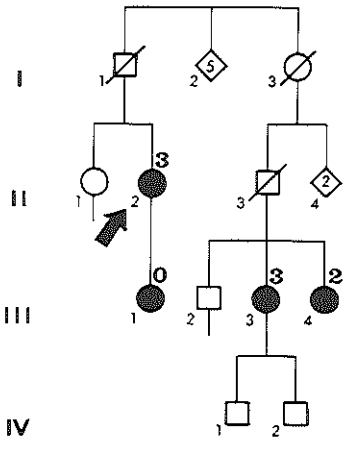
In family D nine relatives were examined in generations I to IV, 4 were found to have myotonic dystrophy, 4 were normal and 1 was classed as dubious because of mild neurological signs.

In *generation I*, I-1 had senile non-diagnostic cataracts at the age of 83. His wife had died at the age of 35 of post-partum thrombosis.

In *generation II*, II-1 had had presenile cataract, mild muscle weakness and a sudden death at the age of 56. Her sibs could not be examined.

In *generation III*, III-3 had mild muscle weakness and no mental symptoms.

In *generation IV*, IV-3 and IV-5 had congenital myotonic dystrophy with mental retardation plus mild or severe muscular signs. Their brother died immediately after birth and may have been affected, but medical data were not available. IV-1 and IV-2 were examined, because their mother had absent ankle jerks as the only sign. IV-1 had only minimal lenticular opacities.



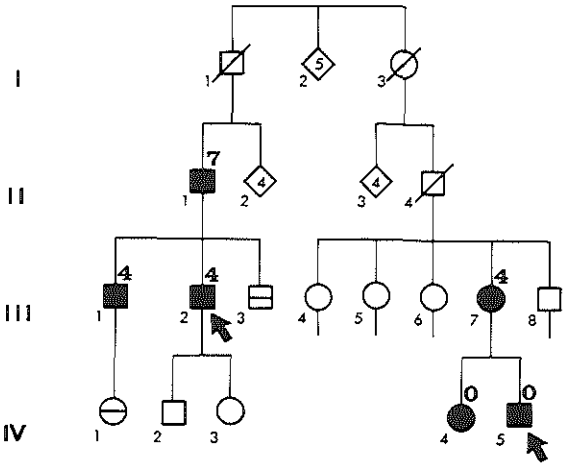
Summary of family E

In family E eight relatives in 2 branches were examined in generations II to IV, 4 had myotonic dystrophy and 4 were normal.

In *generation I*, I-1 and I-3 must have carried the abnormal gene. The ages of death were 68 and 73 years. No muscular disease or cataracts were reported.

In *generation II*, II-2 had moderately severe muscular, and mild mental signs. In II-3 no muscular disease was known before his sudden death at the age of 45.

In *generation III*, III-3 and III-4 had mild muscle weakness with notably early heart disease in III-3. III-1 had congenital myotonic dystrophy with mental retardation.



Summary of family F

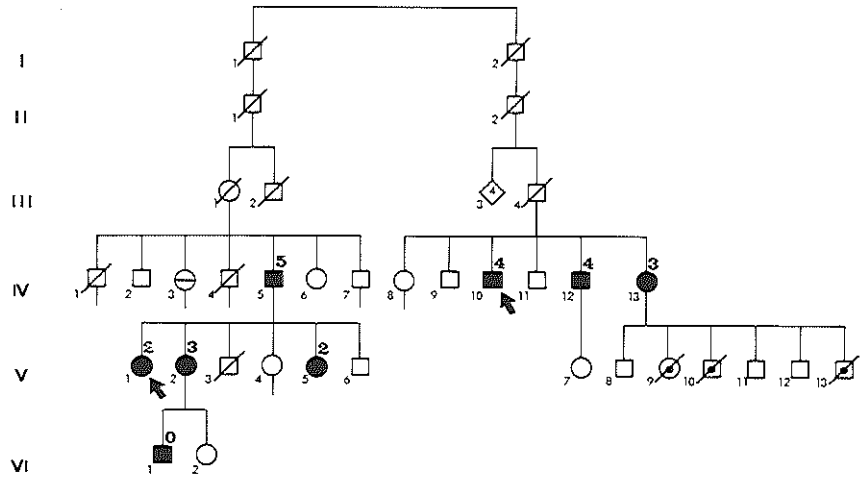
In 2 branches of family F twelve relatives were examined, 6 had myotonic dystrophy and 6 were normal.

In *generation I*, I-1 and I-3, who must have carried the abnormal gene, died aged 70 and 68 respectively; they had no history of invalidating disease or cataracts.

In *generation II*, II-1 had senile onset myotonic dystrophy with a cataract as the only sign. II-4 was not known to have had muscular disease, he died aged 58 of renal failure.

In *generation III*, III-1 and III-2 had mild muscular weakness without mental signs. III-7 had two children with congenital myotonic dystrophy but showed no signs at all when IV-4 was 7 years; however, one year later the diagnosis in III-7 could be made.

Generation IV: in IV-2 the disease was also suspected because he was slow and slightly built, but a diagnosis could not be made. IV-4 and IV-5 had congenital myotonic dystrophy with mental retardation.



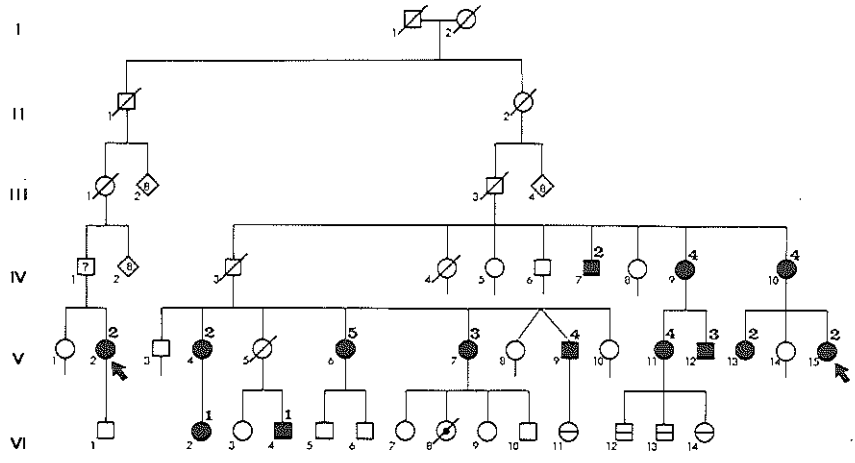
Summary of family G

In this family two branches were examined, having common ancestors born before 1800. In the two branches 21 relatives were examined in the generations IV to VI, 8 were found affected, 13 were normal. In neither of the two branches was an invalidating disease known before generation IV.

In *generation IV*, IV-5 had presenile cataracts as the only sign. IV-10, IV-12 and IV-13 had late adult onset and a duration of the disease over 25 years, with severe muscle weakness as the prominent symptom, however without ever noticing cramps in their hands; active myotonia could not be observed.

In *generation V*, V-1, V-2 and V-5 had young adult onset of the disease with mild muscle weakness and mild mental retardation in V-1. The 3 children of IV-13 who died of neonatal asphyxia were - in retrospect - probably affected by congenital myotonic dystrophy. The early death of these children combined with the reduced fertility of IV-10 and IV-12 limited the disease to one generation in this branch of the family.

In *generation VI*, VI-1 had congenital myotonic dystrophy with mental retardation as the prominent symptom.



Summary of family H

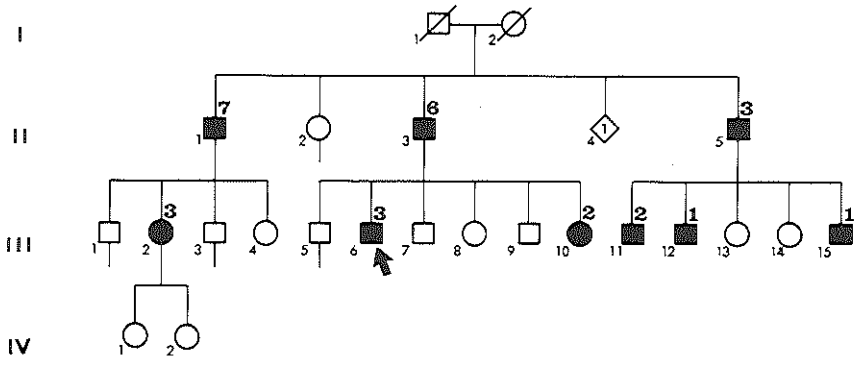
Family H consisted of one large branch, with a small second branch suggesting that the ancestors in generation II and III have carried the abnormal gene. Thirty relatives were examined in generations IV to VI, 14 were found to be affected, 15 were normal.

No invalidating disease was reported in *generations II and III*. In generation II the age of death of II-1 was 77, and in II-2 not known. In generation III the age of death of III-1 was 84, of III-3 it was 79; he reportedly had senile cataracts.

In *generation IV* a remarkable variation was seen in the ages of onset and in the severity of symptoms. In IV-1 no symptoms of myotonic dystrophy were present at the age of 71, although he must have carried the gene. IV-7 had early adult onset of the disease, IV-9 and IV-10 had late adult onset. IV-7 had progressive and severe muscle weakness, while IV-9 did not show any progression of symptoms during a period of 28 years.

In *generation V* the difference in the age at onset between V-4 and V-6 may be inaccurate: on examination both had similar mild muscular abnormalities. V-11 had the same decade of onset as her mother.

Generation VI was incompletely examined, since some parents objected to examination of their children. Two childhood cases were found, one with mild and one with severe mental signs. VI-8 was a still-born child with poly-hydramnios, suggesting congenital myotonic dystrophy.



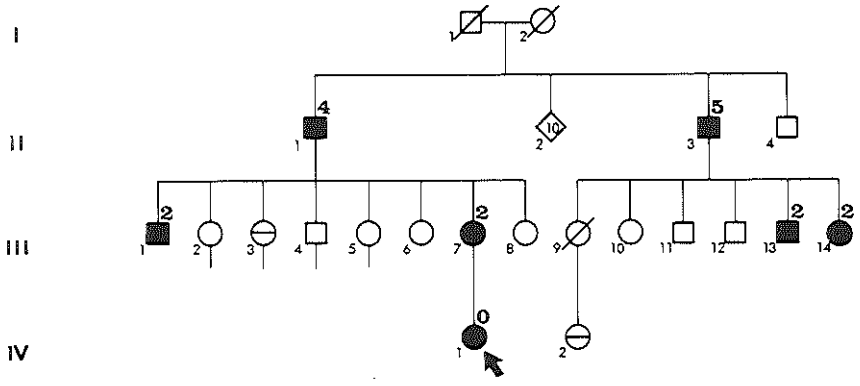
Summary of family J

Twenty-one relatives were examined in generations II to IV, 9 had myotonic dystrophy and 12 were normal.

No invalidating disease was known of in *generation I*. The ages of death were 86 and 84. I-1 was known to have had cataracts.

In *generation II* the two eldest brothers had late onset of myotonic dystrophy with cataracts and no muscular weakness, while the youngest brother had young adult onset with severe muscle weakness.

In *generation III* the affected children of II-1 and II-2 had young adult onset with mainly muscle symptoms; of the affected children of II-5, two had childhood onset and all were incapacitated more by mental than by muscular symptoms.



Summary of family K

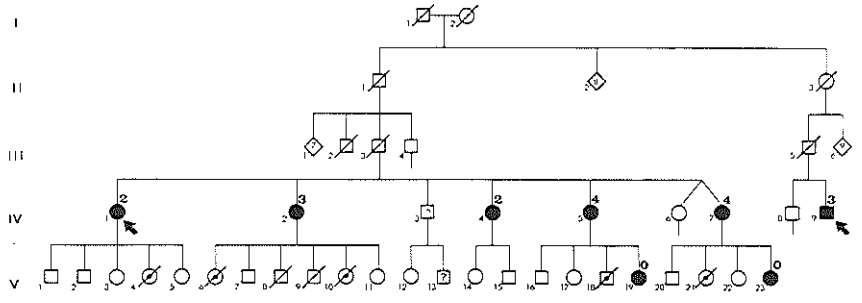
Sixteen relatives were examined in two branches of this family, 7 were found to have myotonic dystrophy, 9 were normal.

In *generation I* the ages of death were 67 and 77, no muscular disease or cataracts had been reported.

Generation II was not examined completely. II-1 and II-3 had late adult onset of myotonic dystrophy with moderately severe muscle weakness and mental inertness in a late stage of the disease.

In *generation III* all 4 patients had their first symptoms in the second decade, III-13 and III-14 possibly had an earlier onset in the first decade. III-7 had only mild muscular symptoms and had no mental signs, whereas III-1, III-13 and III-14 were alle mentally retarded. III-13 also had kernicterus as a neonate. III-9 suddenly died aged 21 and probably had had myotonic dystrophy.

In *generation IV* the only identified patient had congenital myotonic dystrophy.



Summary of family L

In family L a total of 26 relatives were examined, 23 of them in the main branch. A small second branch indicated that the ancestors in generation II and III must have carried the abnormal gene. Myotonic dystrophy was diagnosed in only 8 relatives, 16 were found to be normal and in two the diagnosis was dubious.

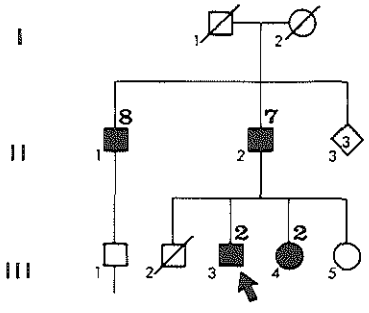
In *generation I* the ages of death were 64 and 66.

In *generation II* the ages of death were 47 and 73, no muscular disease or cataracts were known.

In *generation III*, III-3 died aged 48 of a brain tumour and was reported to have had muscular signs. In III-5 a cataract was recorded. III-2 probably had had myotonic dystrophy with onset in the third decade.

In *generation IV* the age of onset varied between the second and fourth decade, with similar mild to moderate muscular weakness and mental signs. An exception was IV-3, suspected of having myotonic dystrophy at the age of 42, who may have a later onset.

In *generation V* from a total of 21 children of 5 mothers having myotonic dystrophy, 12 were found to be normal, 2 had severe congenital myotonic dystrophy and 7 had perinatal death of unknown cause; medical data in four showed polyhydramnios suggesting congenital myotonic dystrophy.



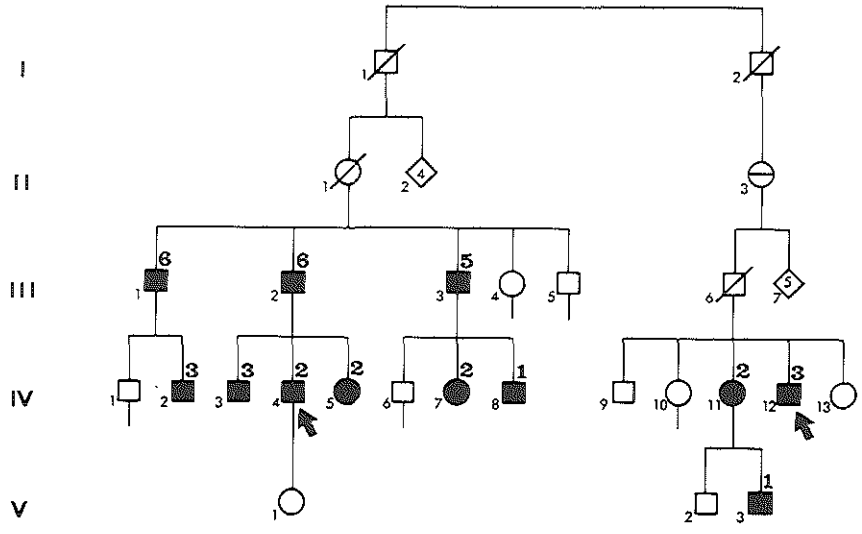
Summary of family M

Six relatives were examined, 4 had myotonic dystrophy and 2 were normal.

In *generation I* no muscular disease was known, the ages of death were 66 and 90.

In *generation II* late onset and mild myotonic dystrophy were found in II-1 and II-2.

In *generation III*, III-3 and III-4 had early adult onset of myotonic dystrophy, both were invalidated because of mental inertia and muscle weakness.



Summary of family N

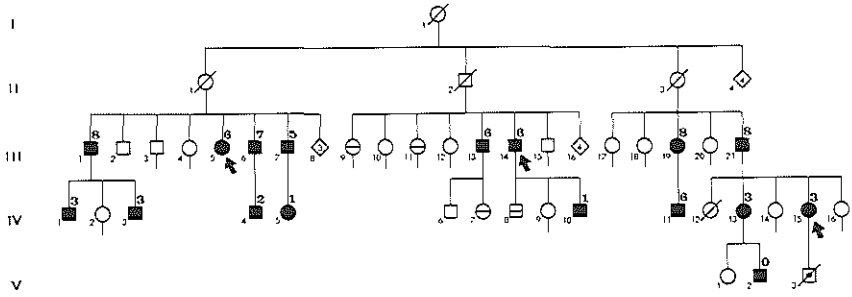
In family N twenty one relatives were examined in 2 branches, 12 had myotonic dystrophy, 9 were normal. Type A haemophilia also occurred in this family, transmitted as a regular X-linked recessive trait.

In *generations I and II* no invalidating disease similar to myotonic dystrophy was reported. The age of death of I-2 was 70. II-1 was operated upon for cataracts aged 65 and was reported to have had difficulty walking in old age.

In *generation III* senile onset of myotonic dystrophy was found in III-1 and III-2, with cataracts and no muscle weakness. III-3 had had late adult onset and had muscle weakness as well as mental signs. III-6 was not known to have muscle weakness when he suddenly died aged 57.

In *generation IV* most patients had early adult onset with myotonia and muscular and mental signs which were still mild. In IV-7 and IV-8 the first complaint was nasal speech. IV-7 had myotonic dystrophy and Turner's syndrome.

In *generation V*, V-3 had childhood onset with mental retardation and indistinct speech as the first symptoms.



Summary family P

Family P (identical with the families S + ST in Höweler et al, 1980) comprised three branches, each with a separate index patient. Thirty two relatives were examined, myotonic dystrophy was found in 17, and 15 were normal. Examination of the second branch was very incomplete. In the third branch, in addition to myotonic dystrophy, myotonia congenita was also found. For this study these latter patients were counted as normals.

In *generation I*, I-1 probably carried the abnormal gene because her brother's offspring also had myotonic dystrophy. She died aged 80. One of her parents must have transmitted the gene, their ages of death were 78 and 74.

In *generation II*, II-1 reportedly had cataracts. II-1, II-2 and II-3 died at ages 77, 71 and 76, and none had had muscular weakness.

In *generation III* only 17 of the 26 persons could be examined, 8 of these had myotonic dystrophy. In III-19 diagnostic changes were only observed during repeated examinations at the ages of 69 and 73. Senile onset was also found in III-1, III-6 and III-21. Three others had an onset in the sixth decade and the duration of their disease was sufficient to allow the development of moderate muscular weakness. In III-7 there was late adult onset and moderately severe muscle weakness; he died suddenly, three days after anaesthesia for a cataract operation.

In *generation IV*, 13 out of the 16 persons have been examined, 8 of these had myotonic dystrophy. Early adult age of onset was found in 5 cases and childhood age of onset in 2 cases. Muscle weakness was more severe in generation IV than in their parents, most patients also showed mental inertness and two had early cataract operations (aged 31 and 45). In IV-11 the age of onset was much later; aged 47 myotonic dystrophy could not be diagnosed, but when aged 51 he had diagnostic myotonic cataracts.

In *generation V*, V-2 had congenital myotonic dystrophy. V-3 died shortly after birth and in retrospect he probably also had congenital myotonic dystrophy.

CHAPTER VI

THE NATURAL HISTORY OF MYOTONIC DYSTROPHY

a) Introduction

The natural history of myotonic dystrophy has rarely been studied systematically. Accordingly, different opinions on the prognosis of the disease were given (see chapter II). There appears to be a correlation between the age of onset of the disease and the nature of the symptoms and signs. The mental symptoms for example are more severe in patients affected from birth, than in patients with a later age of onset. The degree of severity after a longer duration of the disease in patients with the same age of onset has only been studied for congenital myotonic dystrophy.

In chapter II two concrete questions were formulated for this study:

1. Is there a correlation between the age of onset and the nature of the symptoms in myotonic dystrophy?
2. Do the nature and the severity of the symptoms change with increasing duration of the disease?

In chapter IV it has been described how the age of onset as well as the duration of the disease of each patient were determined in units of decades. All examined patients were classified in groups with the same decade of onset and the same decade of duration of the disease.

To measure the severity of the disease we chose four symptoms as parameters: cataract, muscular weakness, mental symptoms and myotonia. The severity of these symptoms can not be measured in figures. Therefore we made a four points ordinal scale for each of these four symptoms. The degree of severity of each symptom in a patient was expressed by this scale. Children under five years old were excluded from this comparative study, because the symptoms of congenital myotonic dystrophy may improve in the first years. Therefore the results of this study only apply to patients over 5 years old.

The symptoms and signs found in each patient are described in detail in appendix I. The degree of severity of 115 patients, investigated for the four symptoms is summarised in appendix II. Since most groups of patients with the same age of onset and duration of the disease contained only a few patients, the nine age of onset groups were concentrated into four larger groups: childhood onset (age of onset up to 10), early adult onset (10-30), late adult onset (30-50) and senile onset (over 50).

In this chapter we shall analyse the severity of each symptom in the four age of onset groups, successively for a duration of the disease of one, two and three decades. This will be carried out with the use of histograms. The differences that occur within each age of onset group will be studied, as well as the variability among the patients of each group. In this way we may be able to obtain information about the possible existence of distinct syndromes for different ages of onset.

b) Severity of the symptoms and signs in different age at onset groups, affected during one decade.

b-1. Cataract

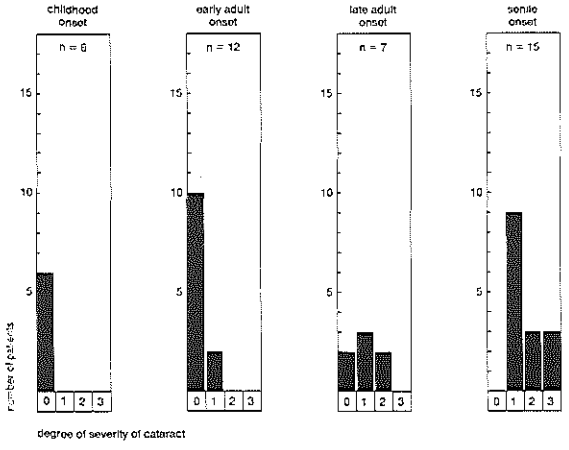


Figure 2. Severity of cataract in different age at onset groups, affected during one decade.

In the childhood onset group cataracts were not found; in the early adult onset group the majority of the patients did not have a cataract, a minority had subclinical cataracts. In the late adult onset group equal numbers of patients were found to have no cataracts, subclinical cataracts and moderately severe cataracts. In the senile onset group cataracts always appeared; in a majority of the patients subclinically, and in equal numbers in a moderate or severe degree.

b-2. Muscular weakness

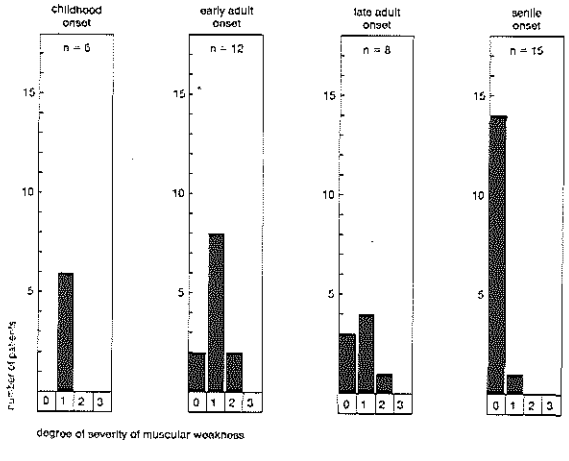


Figure 3. Severity of muscular weakness in different age at onset groups, affected during one decade.

In the childhood onset group all patients had mild muscular weakness. In the early adult onset group most patients had mild muscular weakness, while few had moderate muscular weakness and few had none. In the late adult onset group half of the patients showed mild muscular weakness, some had none and one had a moderate degree of muscular weakness. In the senile onset group muscular weakness was not seen, except in one patient with mild weakness.

b-3. Mental symptoms

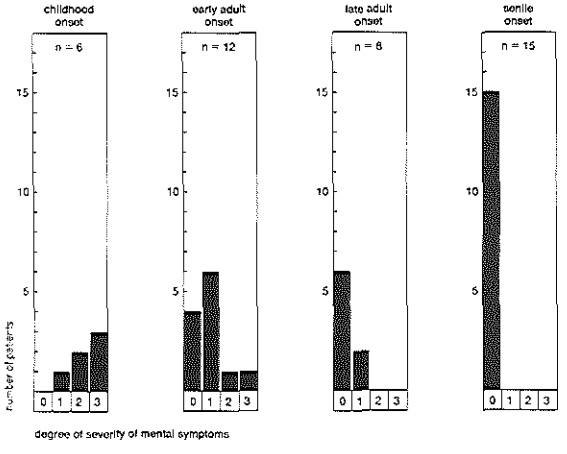


Figure 4. Severity of mental symptoms in different age at onset groups, affected during one decade.

In the childhood onset group mental symptoms were always present. The degree of severity differed, half of the children showed a severe degree. In the early adult onset group half of the patients had mild mental symptoms and part of them none. More severe mental symptoms are only found sporadically. In the late adult onset group few patients presented mild mental symptoms. In the senile onset group no mental symptoms were found.

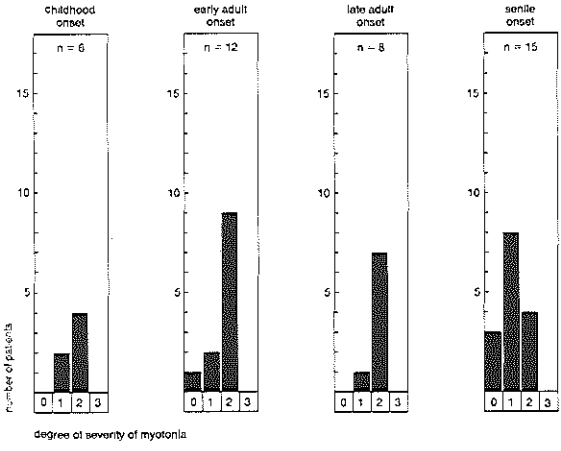


Figure 5. Severity of myotonia in different age at onset groups, affected during one decade.

In the childhood onset group myotonia was always found, either electromyographically or clinically. In the early adult onset group myotonia was nearly always found, in a majority clinically. In the late adult onset group all patients were found to have myotonia, nearly always clinically. In the senile onset group myotonia was found electromyographically more often than clinically, but 20% of the patients did not have myotonia.

b-5. Summary of the severity of symptoms and signs of different age at onset groups, affected during one decade.

Different patterns of severity were found in three of the four symptoms in three of the four age of onset groups. Myotonia, either electromyographical or clinical, was present in nearly all patients in all age of onset groups.

— With onset in childhood no cataracts, always mild muscular weakness and always mild to severe mental symptoms were found.
— With onset in early adulthood cataracts were rarely found and most patients had mild muscular weakness. Mild mental symptoms were found in half of the patients, one third had none.
— With senile onset cataracts were always found, muscular weakness rarely and mental symptoms were not found.

In the group of patients with onset in late adulthood the degree of severity of cataract and muscular weakness varied greatly. A separate syndrome did not appear to exist.

c) Severity of the symptoms and signs in different age at onset groups, affected during two decades.

c-1. Cataract

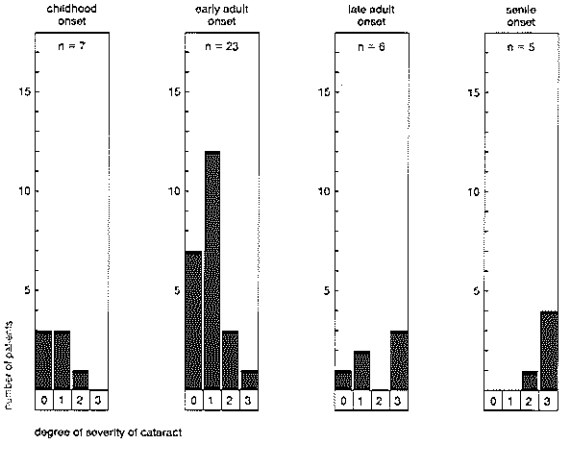


Figure 6. Severity of cataract in different age at onset groups, affected during two decades.

In the childhood onset group most patients had either no or subclinical cataracts. Only one case of a cataract with decreased visual acuity was seen. In the early adult onset group a majority had either no or subclinical cataracts, a few patients had cataracts with decreased visual acuity. In the late adult onset group some patients had either no or subclinical cataracts and some mature or operated cataracts. In the senile onset group all patients were found to have cataracts with decreased visual acuity. Most of them had been operated upon.

c-2. Muscular weakness

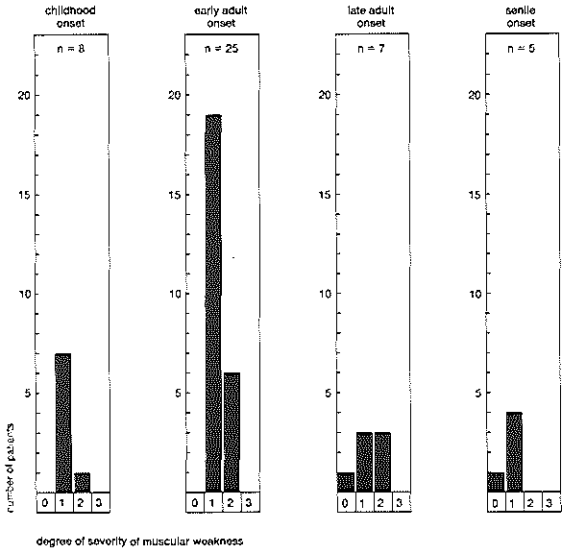


Figure 7. Severity of muscular weakness in different age at onset groups, affected during two decades.

In the childhood onset group most patients had mild muscular weakness, moderate weakness was seen once. In the early adult onset group the majority showed mild, a minority moderately severe weakness. In the late adult onset group one patient did not have muscular weakness and equal numbers of patients had mild and moderate muscular weakness. In the senile onset group most patients had mild muscular weakness.

c-3. Mental symptoms

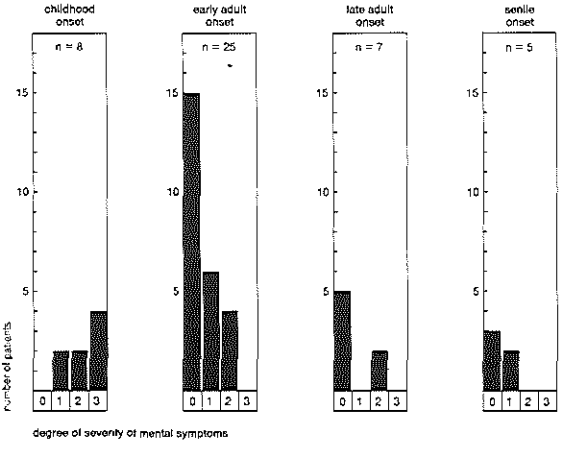


Figure 8. Severity of mental symptoms in different age at onset groups, affected during two decades.

The childhood onset patients all presented with mental symptoms, in half of them to a severe degree. In the early adult onset group only a minority had mild or moderate mental symptoms. In the late adult onset group a few had moderate mental symptoms. In the senile onset group either mild mental symptoms were found or none at all.

c-4. Myotonia

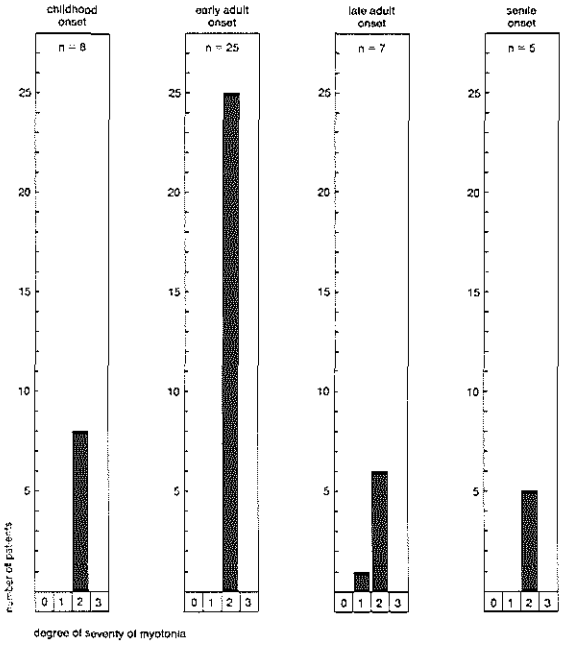


Figure 9. Severity of myotonia in different age at onset groups, affected during two decades.

All patients except one, in all age of onset groups, showed clinical myotonia.

c-5. Summary of the severity of symptoms and signs of different age at onset groups, affected during two decades.

Where the disease had covered two decades the patterns of symptoms were not as clearly different as those with a short duration of the disease. The symptom myotonia was present in all patients and did not contribute to the distinction of the syndromes. The other three symptoms however, still showed different patterns in the groups of childhood, early adult and senile onset of the disease. These syndromes were less clearly distinct by differences in nature of symptoms, because many patients had more symptoms and therefore a more 'complete' clinical picture of myotonic dystrophy. However, the syndromes were still distinct by the differences in severity of the symptoms in three of the four age of onset groups.

— Where onset occurred in childhood over half of the patients had cataracts,

usually subclinical. Most patients had mild muscular weakness and all had mild to severe mental symptoms.

— Where onset occurred in early adulthood most patients presented with cataracts, mainly subclinical. All patients had muscular weakness, most of them mild, a quarter moderate. The appearance of mental symptoms varied greatly, over half of the patients did not have mental symptoms, a quarter in a mild degree and the others in a moderate degree.

— Where senile onset occurred the degree of cataract was almost always severe, muscular weakness mild and mental symptoms were absent or mild.

In the group of patients with late adult onset the degree of severity of the symptoms varied so much that a special syndrome did not appear to exist.

d) Severity of the symptoms and signs in different age of onset groups, affected during three decades.

d-1. Cataract

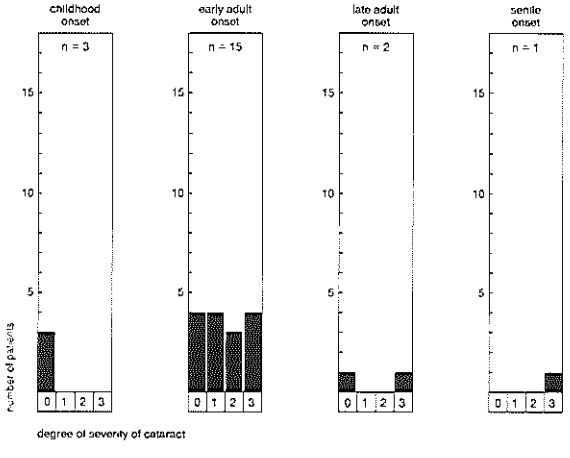


Figure 10. Severity of cataract in different age at onset groups, affected during three decades.

The groups of patients with childhood, late adult and senile onset are too small for conclusions to be drawn. In the early adult onset group nearly equal numbers of patients were found in the four degrees of severity.

d-2. Muscular weakness

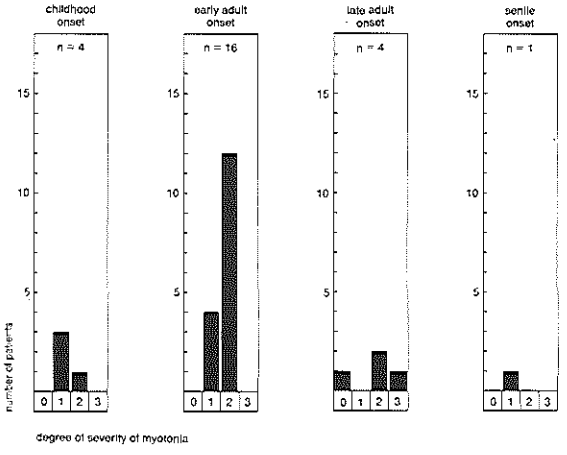


Figure 11. Severity of muscular weakness in different age at onset groups, affected during three decades.

In the early adult onset group muscular weakness was found to be moderately severe in most patients. It was never found to be severely invalidating or totally absent.

d-3. Mental symptoms

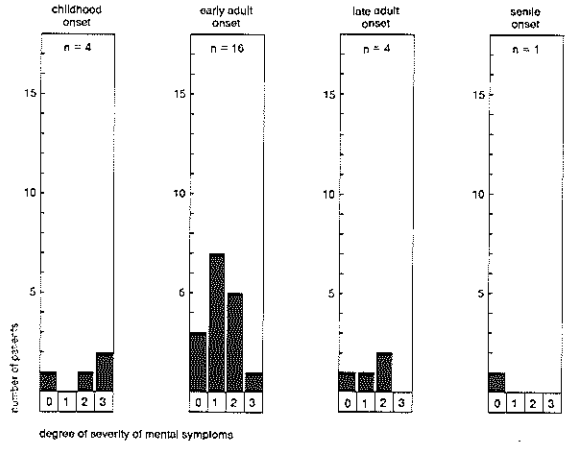


Figure 12. Severity of mental symptoms in different age at onset groups, affected during three decades.

The variety in the early adult onset group was larger than by a shorter duration of the disease. Most patients showed mildly to moderately severe mental symptoms.

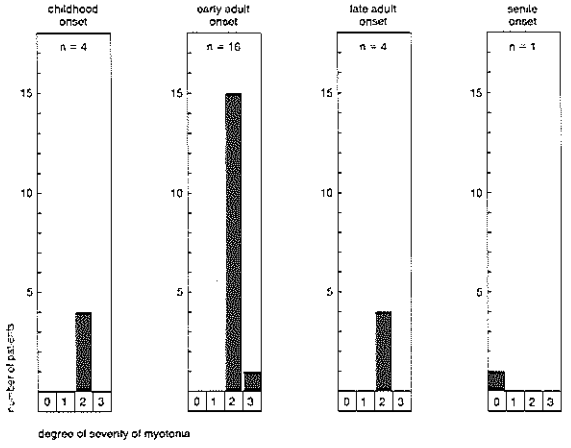


Figure 13. Severity of myotonia in different age at onset groups, affected during three decades.

Nearly all patients had clinical myotonia.

d-5. Summary of the severity of symptoms and signs of different age at onset groups, affected during three decades.

The childhood, late adult and senile onset groups of patients were too small to draw conclusions from the differences in the severity of the symptoms. With early adult onset the severity of cataract and mental symptoms showed more variation after three decades than with shorter duration of the disease. Furthermore, the number of patients with a moderately severe cataract, muscular weakness and mental symptoms increased after three decades. Myotonia was not found to be more severe after three decades than after a shorter duration of the disease.

e) Summary

The analysis of the nature and severity of four symptoms, in different age at onset groups and increasing duration of the disease, showed that three myotonic dystrophy syndromes may be distinguished: childhood onset ($>$ 10 years), early adult onset (10-30 years) and senile onset ($<$ 50 years) myotonic dystrophy. The late adult onset group (30-50 years) did not show a specific pattern.

Three symptoms appeared to be important for the differentiation: cataract, muscular weakness and mental symptoms. Myotonia was present in most patients in all groups and did not contribute to the differentiation.

The three syndromes were clearly distinguishable after one decade of disease, by differences in severity and nature of the symptoms in the different age of onset groups. With a disease duration of two decades many patients had developed more symptoms and showed a more "complete" clinical picture. Differentiation of the three syndromes however, was still possible by analysing

the severity of the three symptoms. The number of patients in three of the four age at onset groups, affected during three decades, was too small to enable meaningful conclusions. The early adult onset group at three decades duration could only be compared with the same onset group at a shorter stage in the disease. The patients in this group showed a greater variation in severity of symptoms in three decades, than with a shorter duration of the disease, and some of the patients had more severe symptoms.
The three distinct syndromes can be outlined as follows:

1. Myotonic dystrophy with onset in childhood (< 10 years) causes no cataract in the first decade of the disease. Some of the patients develop cataracts in the second decade of the disease. The muscular weakness is mild in the first decade (between the fifth and tenth year of age, when the muscular weakness of the neonatal period has lessened), and remains so in the second decade. The mental symptoms are already severe to moderately severe in the first decade and do not improve. Therefore myotonic dystrophy with onset in childhood is mainly characterised by mental symptoms, with mild muscular weakness and sometimes cataracts as secondary symptoms. Since the mental symptoms are rather severe from the beginning this syndrome is disabling from the early stages.
2. Myotonic dystrophy with early adult onset (10-30 years) causes only occasionally a subclinical cataract in the first decade of the disease. In the second decade most patients have a subclinical cataract and in the third decade a cataract may be either absent, mild, moderately severe or severe. Muscular weakness is usually mild in the first and second decade, but moderately invalidating in the third decade. Mental symptoms are usually absent or mild in the first two decades and mild to moderately severe in the third decade. Thus the prime symptom of early adult onset myotonic dystrophy appears to be muscular weakness. This muscular weakness may become disabling late in the disease, and may then be complicated by mild to moderately severe mental symptoms and also by cataracts in most of the patients. An important difference between this syndrome and myotonic dystrophy with onset in childhood is that the disability occurs later in the disease and is conditioned to a smaller degree by mental symptoms.
3. Myotonic dystrophy with senile onset (> 50 years) always causes cataracts early in the disease with decreasing visual acuity already in the 2nd decade. Muscular weakness occurs mildly in the 2nd decade of the disease, while only part of the patients show mild mental symptoms in the 2nd decade. Thus myotonic dystrophy with senile onset is mainly characterised by cataracts which soon give clinical symptoms, while mild muscular weakness and mild mental symptoms may be secondary symptoms late in the disease. Since cataracts can be treated sufficiently, senile onset myotonic dystrophy is hardly disabling.

This outline of the three syndromes is probably applicable to most of the patients. Within the age of onset groups there is still variation in severity of the

symptoms, which seems to increase with longer duration of the disease. Possibly the speed of progression of the disease varies from patient to patient within these groups. It seems evident that the distinction between the three syndromes is a relative one, and that gradual transitions exist between them. With an age of onset at 10 years old a patient will show symptoms between the childhood and the early adult onset syndrome. Possibly the variation of symptoms seen in the late adult onset group (30-50 years) has been caused by a similar transition between the early adult and senile onset syndromes. Still the distinction of the syndromes may be useful for the determination of the prognosis for a patient.

The symptom myotonia did not contribute to the differentiation of the three syndromes. It still is one of the characteristic symptoms of myotonic dystrophy, and it is an important symptom for the distinction of the disease from other diseases.

CHAPTER VII

RESULTS: THE STUDY OF PARENT-CHILD PAIRS

§ a Introduction

The prediction of the severity of the disease in children of patients with myotonic dystrophy is influenced by the existence or non-existence of anticipation (chapter III). We also traced back the confusion about this phenomenon in the past 40 years. At the end of the literature study 5 concrete questions were formulated:

1. How frequently has a child with myotonic dystrophy an earlier age of onset than the transmitting parent?
2. How frequently has a child with myotonic dystrophy a more severe form of the disease than the transmitting parent?
3. Is the penetrance of myotonic dystrophy incomplete, so that many complementary pairs can be expected to be found in the future?
4. Have there been complementary pairs in the past which can be detected retrospectively?
5. Is the fertility of myotonic dystrophy patients affected to such a degree, that only patients with a late age of onset are able to have children, and complementary pairs can not come into existence?

This chapter gives data on these points from our family material.

§ b The age of onset of myotonic dystrophy in parent-child pairs.

In the pedigrees in chapter V the ages of onset of the patients show that in all but one case the onset in the child is one or more decades earlier than in the transmitting parent.

The only exception is parent-child pair H-IV-9/H-V-11; both parent and child gave a history of onset in the fourth decade. We had doubts however, as to whether the age of onset of H-IV-9 was possibly stated too early, since she did not show any signs other than myotonia at the time of examination, which was 27 years after the onset she gave for this symptom.

In some families anticipation of the ages of onset does not run parallel in different branches. In family A the children of A-III-7 presented ages of onset in the same decades as the grandchildren of his sister A-III-1. Similarly in family C there are patients with ages of onset in the first decade in generation III as well as in generation IV.

Table VIII presents the differences in ages of onset in parent-child pairs per family. The parent-child pairs not involving an index patient are presented separately. The mean difference in ages of onset of parent and child is given in decades, as well as the range of the differences in ages of onset.

			indexfree parent-child pairs		
family	total number of parent-child pairs	number of indexfree pairs	sum of differences of ages of onset	mean differences of ages of onset	range of differences
A	18	14	38	2.7	1-5
B	7	7	17	2.4	2-3
C	5	4	16	4.0	1-6
D	3	2	4	2.0	—
E	1	0	—	—	—
F	4	2	7	3.5	3-4
G	4	3	8	2.6	2-3
H	5	4	4	1.0	0-2
J	6	5	13	2.6	1-4
K	5	4	10	2.5	2-3
L	2	2	8	4.0	—
M	2	1	5	5.0	—
N	7	6	18	3.0	1-4
P	9	7	29	4.1	2-5
total	78	61	177	2.9	0-6

Table VIII: Differences in ages of onset of myotonic dystrophy in decades in parent-child pairs per family.

After exclusion of index cases, there were 61 parent-child pairs; in 60 of those (98%) the child had an earlier age at onset than the transmitting parent. The mean difference in ages of onset of the 61 parent-child pairs was 2.9 decades, ranging between 0 and 6 decades. A great range was sometimes seen within one family, f.i. in family C from 1 to 6 decades.

Subsequently the influence of the gender of the parent or the child was studied. In table IX the differences in ages of onset are divided according to the gender of parents and children. In this table the index patients have been included, because there were as many male as female index patients (see table II).

	number of pairs	mean differences of ages of onset in decades	sum of differences of ages of onset in decades	range
father - son	24	3.20	77	1-5
father - daughter	19	3.47	66	2-5
mother-son	15	2.60	39	1-6
mother-daughter	20	2.45	49	0-6

Table IX: Affected parent-child pairs and mean differences of ages of onset in decades, per gender.

The difference in ages of onset appeared to be greater when the father was the transmitting parent, than when the mother transmitted the disease. On applying the median test with X^2 the difference between pairs with a transmitting father and pairs with a transmitting mother appeared to be very significant with a confidence limit < 0.01 .

The gender of the parent thus appeared to influence the difference of the ages of onset. However, this is not the only influence, since the range of the differences is wide for both genders.

§ c The severity of myotonic dystrophy in parent-child pairs.

The severity of a disease like myotonic dystrophy in parent-child pairs is more difficult to compare than its age of onset, because a parent and a child often present with different signs and symptoms. One can not compare the severity of the disease of a patient with only cataracts to the severity of the disease in a patient with only muscular weakness. Therefore we compared separately the severity of the individual symptoms cataract, muscular weakness and mental symptoms.

A second problem was that the severity of these features, measured according to the criteria in table VII, was not recorded in standard measures but in an ordinal scale. Therefore we could only examine whether a symptom in a parent was more severe, equally severe, or less severe, in comparison with that symptom in the child.

Only indexfree parent-child pairs were used for the comparison of the severity of the disease. Patients who were not examined personally were also eliminated, because the criteria in table VII contained subjective measures. Children with congenital myotonic dystrophy under the age of five were also eliminated, because their symptoms could still improve in the first years (see chapter VI).

In this way 50 parent-child pairs were available for study. In 9 pairs the severity of cataracts could not be compared, because either the parent or the child did not have a slit-lamp examination. The results are given in table X.

proportional severity	cataract	muscular weakness	mental symptoms
parent > child	27	9	3
parent = child	12	21	21
parent < child	2	20	26

Table X: Proportional severity of 3 symptoms in parent-child pairs.

In most parent-child pairs the severity of cataract was higher in the parent than in the child, in 12 pairs it was similar. In 7 of these pairs neither the parent nor the child had cataracts. In two pairs the severity of cataracts was higher in the child than in the parent: H-V-4/H-VI-2 and P-III-21/P-IV-13.

In less than half of the pairs (40%) the severity of muscular weakness was higher in the child than in the parent. In a similar percentage of pairs the severity of muscular weakness was identical. In only three of these pairs neither parent nor child had muscular weakness. In 9 parent child-pairs the weakness was more severe in the parent: A-III-1/A-IV-1, A-IV-2/A-V-2, B-II-2/B-III-5, B-II-2/B-III-7, J-II-5/J-III-11, J-II-5/J-III-12, J-II-5/J-III-15, N-III-3/N-IV-7 and N-III-3/ N-IV-8.

Mental symptoms were more severe in children in 52% of the pairs. In 21 pairs they were identical. However, in most of these pairs (16) neither parent nor child had mental symptoms at all. In 3 parent-child pairs the degree of severity of mental symptoms was higher in the parent: K-II-3/K-III-14, N-III-3/N-IV-7 and N-III-3/N-IV-8.

The comparison of the severity of myotonic dystrophy in parent-child pairs is complex. The group of parent-child pairs is heterogeneous according to the age of onset of the disease, and the onset of the disease in parent and child does not always take place at the same moment in time. Therefore the duration of the disease can be different in parent and child at the time of examination. This influences the degree of severity of the symptoms as is seen in chapter VI.

It is difficult to draw conclusions from these data. Yet in general one could say that the comparison of the degree of severity of parent-child pairs shows that:

— cataracts are usually more severe in the parent than in the child
— muscular weakness is as frequently more severe in the child, as equally severe in parent and child. However, in a considerable number of pairs the muscular weakness is more severe in the parent.
— mental symptoms, if present, are usually more severe in the child than in the parent.

§ d The penetrance of the myotonic dystrophy gene

Penrose assumed that in the future so many complementary parent-child pairs will appear that these will evenly match the anticipating pairs and so cancel out the anticipation phenomenon. If this is true one should find an incomplete penetrance of the myotonic dystrophy gene during a family study.

The penetrance of a gene is complete when all persons carrying that gene can actually be detected. Myotonic dystrophy is an autosomal dominantly transmitted disease, so the penetrance is complete when 50% of the children of gene carriers show signs of the disease.

Calculating the penetrance of the disease only makes sense if all descendants of a gene carrier are examined. In our 14 families some generations or sibships could only be partially examined, since some individuals had died or

did not wish to be examined. We therefore only calculated the penetrance in those generations and sibships where 50% or more of the family members had been examined. The index patients were eliminated from the calculations. Family members who presented equivocal abnormalities were considered to be normal. The deceased or not examined family members were not counted and we assumed that this group (38 individuals = 13%) did not influence the calculations. Table XI shows the calculated penetrance in the 14 families studied.

family	myotonic dystrophy	myotonic dystrophy excluding indices	normal or ?	deceased or not examined	penetrance	not calculated generations or sibships (<50% examined)
A	26	23	13	6	64%	gen. I and II
B	7	7	7	1	50%	gen. I
C	5	4	2	1	67%	gen. I and II
D	3	2	4	1	33%	gen. I and II
E	4	3	4	0	43%	gen. I and II and sibship II_3 - II_4
F	5	3	6	1	33%	gen. I and II and sibship IV_1
G	8	6	13	7	31%	gen. I, II and III
H	14	12	15	4	44%	gen. I, II and III and sibship IV_1 - IV_2, VI_{11} and VI_{12} - VI_{14}
J	9	8	12	4	40%	gen. I
K	5	4	8	2	33%	gen. I and II and sibship IV_2
L	8	6	15	3	29%	gen. I, II and III and sibship V_6 - V_{11}
M	2	1	2	1	33%	gen.I and II
N	12	10	9	0	53%	gen. I and II and sibship III_6 - III_7
P	15	13	12	7	52%	gen. I and II and sibship III_9 - III_{16}
total	123	102	122	38	46%	

Table XI: Penetrance of myotonic dystrophy per family.

The calculated percentage of patients in the 14 families combined was 46%. Thus the penetrance of the myotonic dystrophy gene was almost complete. However, there were large differences in the percentages of patients in the different families. In family A and C we found a high percentage of patients, 64% and 67%. In the families B, E, H, J, N and P the percentage of patients was between 40% and 50%. A percentage of patients below 35% was found in the families D, F, G, K, L and M. In family G and family L a higher percentage of patients would have been found, if the children who had probably died of congenital myotonic dystrophy would have been included in the calculations (41% and 39%).

Only in 4 families, D, F, K and M, the penetrance was incomplete. One may expect that in a number of individuals in whom no signs of myotonic dystrophy were found, the gene will still be expressed. These four families however are relatively small, implying that the number of individuals, who will still be found to be affected in the future, is small.

Since the penetrance in the total of the 14 families was almost complete, it is not to be expected that a sufficient number of complementary pairs will appear in the future to cancel out the anticipation phenomenon observed in these families.

§ e Complementary pairs in retrospect

If complementary pairs had existed in the past, one should be able to find them retrospectively. These pairs would consist of patients of the oldest examined generation with a late age of onset and their transmitting parents, who would have had an earlier age of onset and a more severe disease. It is to be expected that children would remember the characteristic features of the disease of their parent (see fig. 1).

In this study we collected historical data on the parents who transmitted the disease to the members of the oldest examined generation. Twenty five individuals must have transmitted the abnormal gene to the different branches of the families. In 20 cases the transmitting parent could be detected by the genealogical data. In 4 families this was not possible, so we collected data on both parents. Data on the parents of patient B-I-1 were not available.

Table XII presents the collected information on these transmitting or potentially transmitting parents. Two of them were still living and were examined. Myotonic dystrophy was not diagnosed. One (H-IV-1) is likely as the transmitter of the gene as the genealogical connection indicated. Yet at the age of 71 years he only showed non-specific lenticular opacities.

transmitting parent	age at examination or age at death	description of symptoms by their children	presumptive diagnosis
A.II.1	80	cataract operation aged 78, no muscular weakness	senile onset myotonic dystrophy
A.II.3	92	cataract since age 80, no muscular weakness	senile onset myotonic dystrophy
A.II.4	70	no cataract or muscular weakness	no clinical myotonic dystrophy
A.II.5	80	cataract operation aged 67, no muscular weakness	senile onset myotonic dystrophy
C.I.1	59	no cataract or muscular weakness, sudden death	no clinical myotonic dystrophy
D.I.1	83	at examination nonspecific lenticular opacities, no muscular weakness	no clinical myotonic dystrophy
D.I.2	35	died of postpartum thrombosis, no muscular weakness	no clinical myotonic dystrophy
E.I.1	68	no cataract or muscular weakness, died of diabetes	no clinical myotonic dystrophy
E.II.3	45	no cataract or muscular weakness, sudden death	no clinical myotonic dystrophy
F.I.1	70	no cataract or muscular weakness, died of war injuries	no clinical myotonic dystrophy
F.I.3	68	no cataract or muscular weakness	no clinical myotonic dystrophy
G.III.1	46	no cataract or muscular weakness, died of galbladder disease	no clinical myotonic dystrophy
G.III.4	56	no cataract or muscular weakness, died of a stroke	no clinical myotonic dystrophy
H.IV.1	71	at examination nonspecific lenticular opacities, no muscular weakness	no clinical myotonic dystrophy
H.III.3	79	cataract operation aged 68, no muscular weakness	senile onset myotonic dystrophy
J.I.1	86	cataract since age 80, no muscular weakness	senile onset myotonic dystrophy
J.I.2	84	no cataract or muscular weakness	no clinical myotonic dystrophy
K.I.1	67	no cataract or muscular weakness, died of bladder disease	no clinical myotonic dystrophy
K.I.2	77	no cataract or muscular weakness	no clinical myotonic dystrophy
L.III.3	48	cramps in hands and muscular weakness, died of glioblastoma	late adult onset myotonic dystrophy
L.III.5	51	cataract aged 48, no muscular weakness, sudden death	late adult onset myotonic dystrophy
M.I.1	66	no cataract or muscular weakness	no clinical myotonic dystrophy
M.I.2	90	nno cataract or muscular weakness	no clinical myotonic dystrophy
N.II.1	75	cataract operation aged 65, later walking problems	senile onset myotonic dystrophy
N.III.6	57	no cataract or muscular disease, sudden death	no clinical myotonic dystrophy
P.II.1	77	cataract operation aged 55, rheumatism since age 64	senile onset myotonic dystrophy
P.II.2	71	no cataract or muscular weakness	no clinical myotonic dystrophy
P.II.3	76	no cataract or muscular weakness	no clinical myotonic dystrophy

Table XII: Data on the not examined transmitting parents.

Fourteen parents died after the age of 70, 8 parents died of causes that did not seem to be related to myotonic dystrophy and 4 parents died suddenly, possibly of a heart disease related to myotonic dystrophy. Based on the description of the symptoms according to their children we presumed the following diagnoses:

— 19 parents probably did not have clinically myotonic dystrophy.

— 7 parents probably had senile myotonic dystrophy with cataracts as the only or main sign. Only two had had difficulties in walking since the age of 64 years.

— 2 parents probably had myotonic dystrophy with late adult onset. A cataract was diagnosed in L-III-5, he did not have muscular weakness. He suddenly died aged 51. His age of onset was estimated in the 5th decade. His son had myotonic dystrophy with onset in the 3rd decade. Therefore the onset of the disease of L-III-5 was probably at a later age than the onset of the disease in his son. L-III-3 died of a glioblastoma aged 48. His widow and children told us that he had had the same strange cramps in his hands as his children had, but they were not able to say since what age. They had not observed muscular weakness. His age of onset was presumed in the 5th decade. The onset of the disease in his children was in the 2nd, 3rd and 4th decade. Therefore the onset of the disease in L-III-3 was probably at a later age than the onset in his children.

In these 14 families we did not find a deceased transmitting parent with signs of myotonic dystrophy with onset at an earlier age than his children, which means that we did not find complementary pairs which have existed in the past.

Historical data on the grandparents of the oldest examined generation are still more difficult to assess than those of the parents. If complementary pairs had existed, one would expect that some of these grandparents would have had muscular weakness. Some grandchildren would probably remember this, either from their own experience or through stories from their parents.

We also collected historical data on the 11 transmitting grandparents of the oldest examined generation, indicated as transmitters of the gene according to genealogical connections. None of them was known with cataracts or to be disabled by muscular weakness. Six of these grandparents died aged over 70 years. So there were no indications for myotonic dystrophy in the transmitting grandparents.

During the family history two patients of the oldest examined generation reported a disease resembling myotonic dystrophy in a deceased uncle. The age of onset of the disease of these uncles was presumed earlier than their own age of onset (C-I-2: before the 6th decade and C-II-1: 7th decade; L-III-2: 3rd decade and L-IV-5: 4th decade). Since these patients are not parent and child, they do not form complementary pairs. A similar situation was found in family A where the anticipation of the age of onset did not run parallel in different branches of the family (see § b, A-IV-1 with his uncle A-III-3).

One might suppose that new mutations occurred in the oldest examined generations. However, the genealogical data often revealed connections with other branches of the families, indicating the probable heterozygotes in the family. Furthermore the occurrence of cataracts was reported in 8 parents of patients in the oldest examined generation, suggesting they were heterozygotes. In one probable heterozygote (H-IV-1) myotonic dystrophy could not be diagnosed at the age of 71. One may conclude that in the 9 families where the transmitting parent was indicated by genealogical data (families A, C, E, F, G, H, L, N and P) the myotonic dystrophy gene probably was already present in the parents of the oldest examined generation.

§ f The fertility of myotonic dystrophy patients

Anticipation might also occur, if the disease would affect the fertility of the patients in such a way that only patients with a late onset age would have children, and patients with an earlier onset age would be infertile. In that case anticipation would become a secondary effect of the infertility.

We studied the fertility of patients in the 14 families, grouped per decade of age of onset. Since testicular atrophy is frequently found in affected men, the fertility was also calculated for each gender. The results are given in table XIII. For comparison we also calculated the fertility of the normal brothers and sisters of the patients.

Onset decade	all patients		males		females	
	n	mean number of children	n	mean number of children	n	mean number of children
0	0	---	0	---	0	---
1	7	0.13	4	0.00	3	0.33
2	31	0.80	12	0.25	19	1.15
3	22	1.81	12	1.00	10	2.80
4	16	2.93	7	2.28	9	3.44
5	6	3.00	5	3.20	1	2.
6	12	2.41	9	2.44	3	2.33
7	7	3.00	6	2.83	1	4.
8	4	2.50	3	3.00	1	1.
total	105	1.82	58	1.63	47	2.06
normal sibs	84	1.75	39	1.48	45	1.97

Table XIII: Number of children of myotonic dystrophy patients over 20, per onset decade and per gender. Children deceased in the perinatal period, after a gestation of > 28 weeks, are included.

The fertility of the patients of all age of onset groups together was slightly higher than the fertility of the normal sibs. The patients with an age of onset over 20 years (3rd to 8th decade) had still higher fertility than the normal sibs. However, male patients with onset in the 3rd decade had reduced fertility compared to the female patients. With onset in the 2nd decade, both genders together had considerably lower fertility than the normal sibs, mainly because of a strongly diminished fertility in the male patients. Female patients with onset below 10 years had nearly zero fertility. However, many of these were still young at the time of examination and may not yet have completed their families, in contrast to the patients with a later onset age.

The question now arises as to whether this diminished fertility may have caused the anticipation in these families. Assuming a normal fertility of 1.48 (mean fertility of normal brothers), the male patients with an onset in the first, second and third decade would have had a further 25.72 children if their fertility had been normal ($4 \times 1.48 + 12 \times (1.48 - 0.25) + 12 \times (1.48 - 1.00)$).

Assuming a normal female fertility of 1.97, the female patients with an onset in the first and second decade would have had a further 20.50 children if their fertility had been normal. Thus, with a normal fertility another 46.22 children would have been born in these families, half of whom (23.11) would have carried the abnormal gene. If anticipation is an artefact, the age of onset is variable at random and only a limited number of these 23.11 children would have had a late onset. But even if all would have had a late onset and thus would form complementary pairs with their parents, there would be only 23 complementary pairs, far below the 60 anticipating pairs observed in the study.

These data show strongly reduced fertility only in patients with a very early onset of the disease. This effect appears to be too small to have caused anticipation. The fertility of male patients with onset between 10 and 30 years old was found to be considerably lower than in female patients with similar age at onset.

§ g Summary

Anticipation of the ages of onset of myotonic dystrophy was found in 98% of 61 parent-child pairs of 14 families. The severity of the disease was compared in 50 parent-child pairs. This was complicated by methodological problems. In general, cataracts are usually more severe in the parent, muscular weakness is varying in severity between the parent and the child and mental symptoms are usually more severe in the child.

The possibility of the future existence of complementary pairs was studied. The penetrance of the myotonic dystrophy gene appeared to be almost complete in the 14 families. It is unlikely, therefore, that sufficient complementary pairs will appear in the future to cancel out entirely the observed anticipation.

The family history did not reveal myotonic dystrophy with an earlier onset in deceased transmitting parents of patients from the oldest examined generation. Thus, also in retrospect we did not find complementary pairs.

Possible differences in fertility between patients with a late and with an early age of onset were studied. A markedly diminished fertility was only found amongst affected females with onset in the first decade, and in males with an onset in the first and second decade. The effect of the difference of fertility between early and late onset patients was shown to be too small to cause the observed anticipation phenomenon.

CHAPTER VIII

DISCUSSION

§ 1. Introduction

The aim of this study was to obtain additional information on two questions in the genetic counselling of myotonic dystrophy patients:

1. What is the natural history of the disease and what is the prognosis in an individual patient?
2. Is it possible to predict the severity of the disease in descendants inheriting the myotonic dystrophy gene?

In chapters II and III the literature on these two questions was reviewed and concrete questions for this study were formulated. The results were analysed in chapters VI and VII.

In this chapter the results will be discussed and an attempt will be made to answer the two above mentioned questions.

§ 2. The natural history of myotonic dystrophy

2.1 The nature and the severity of four symptoms of myotonic dystrophy were studied in four groups of patients with different ages of onset, as well after a short as after a longer duration of the disease.

Three myotonic dystrophy syndromes could be distinguished, determined by the age of onset: childhood, early adult and senile onset myotonic dystrophy. Three symptoms proved to be important for the distinction of these syndromes: cataracts, muscular weakness and mental symptoms.

Differentiation between these syndromes is most clear early in the disease, since at that stage the nature of the symptoms differed per syndrome. Later in the disease the three syndromes showed a more 'complete' clinical picture of myotonic dystrophy. However, the individual syndromes could still be distinguished because the severity of the predominant symptoms still differed per syndrome. With childhood onset of the disease the mental symptoms appeared to be the predominating feature, and muscular weakness and cataracts were of less importance. With early adult onset muscular weakness appeared to be the main symptom, while varying degrees of mental symptoms and cataracts may complicate the disease in its later stages. With senile onset cataracts were the main symptom and muscular weakness and mental symptoms were late and usually mild symptoms.

These three myotonic dystrophy syndromes correspond well with the three syndromes described by Dyken (1969). Dyken outlined the syndromes from his clinical experience with a large number of patients. The results of this study confirmed the validity of his observations and provide more detailed documentation of the differences between the syndromes. The influence of the duration of the disease on the three syndromes also became more clear.

In later stages of the disease the syndromes differ in two ways from the syndromes in the early stage: more 'secondary' symptoms appear, completing

the clinical picture of myotonic dystrophy, and the variation in severity of the symptoms appears to increase within the age of onset groups. These two phenomena together cause the impression of extreme variability of symptoms between patients, and conceal the influence of the age of onset on the nature and the severity of the symptoms. Harper (1979) stated that the variability of myotonic dystrophy is one of its hallmarks, and that this makes an accurate prognosis impossible. The results of this study indicate that the distinction of the three syndromes may give at least some indication for a prognosis (see 2.3).

2.2 A number of methodical problems limit the value of this study.

We only studied four symptoms of myotonic dystrophy. These symptoms were chosen because they are frequently present and were considered to be prime symptoms of the disease. However, other symptoms may also be important, particularly cardiac, respiratory, gastro-intestinal and uterine problems and testicular atrophy. These symptoms are less frequent. Furthermore it was practically impossible to collect detailed information on all these symptoms in a large group of patients. In individual patients however, these symptoms may be so prominent, that they influence the ability more than the four symptoms studied (see for instance E-III-3).

The scoring system for the severity of the four symptoms was not very exact. We had no standards to measure the degree of severity and had to use an ordinal scale. The limits of the scoring rates could not always be defined exactly.

Classifying the severity of cataracts did not cause problems; the only limiting factor is that the most severe degree of cataract, a mature or operated cataract, occurred quite early in the disease. This makes the scale less suitable to compare patients with a longer duration of the disease.

For muscular weakness the limits between the different degrees of severity are not as well defined. BMRC grade 4 gives a wide variation of the degree of muscular strength. Furthermore the difference between grade 3 and 4 can only be measured for limb muscles and not for facial and pharyngeal muscles. Thus moderately severe muscular weakness was only measured in limb muscles.

Mental symptoms were most difficult to graduate for severity. Measuring the I.Q. of patients gave only limited information because of the inertness of many patients. Therefore we decided to use the clinical impression obtained from the patient, his relatives and our own opinion. This estimate therefore was relatively subjective. All patients were examined by the same person, which may decrease part of the objections, but the scale we used is less suitable for comparative studies by others. Furthermore the same examiner also runs the risk of being biased in favour of the theory he prefers.

The groups of patients with equal ages of onset and duration of the disease were often very small. It is doubtful whether the measured severity of the symptoms in the smaller groups has a general validity, especially when the scores within the group were very variable as frequently was the case with a longer duration of the disease. With a duration of the disease of three decades only the early adult onset group was large enough to consider. A duration of the

disease of four decades was only found in five patients and a duration of five decades only in one patient (see appendix II).

A prognosis is not complete without an estimation of the life expectancy. In this short term study the life expectancy could not be studied. A prospective study over a longer period of time would be necessary.
We collected data on 14 deceased affected family members, (A-III-3, A-III-7, A-IV-7, A-IV-9, B-I-7, D-II-4, G-IV-12, G-V-3, H-IV-7, H-V-5, K-II-1, K-III-9, L-IV-1, P-III-7, see appendix I). The causes of death were variable: sudden death (6), respiratory complications (3), stroke (2), traumatic dens fracture (1) and sudden death briefly after anaesthesia (2).

The age at death varied between 15 and 75 years of age, after one to five decades of illness. Furthermore, two children with congenital myotonic dystrophy died shortly after birth. Medical data on 12 other neonatal deaths indicated congenital myotonic dystrophy as a probable cause.

The age at death in myotonic dystrophy is probably extremely variable (Harper, 1979), and is determined mostly by complications of the disease. Yet the life expectancy for childhood and early adult onset cases is probably reduced.

2.3 Conclusion: The prognosis of myotonic dystrophy for an individual patient.

By distinguishing the three different syndromes of myotonic dystrophy it seems possible to give some indication for a prognosis on the disability of an individual patient.

In the childhood onset type of the disease the mental symptoms are rather severe from the beginning, causing this syndrome to be already disabling in an early stage. This also was shown in the study of O'Brien and Harper (1984) who found limited possibilities for an independent life with early age of onset of the disease.

In the early adult onset type the prognosis is more favourable. Disability occurs later in the disease and is conditioned more by muscular weakness than by mental symptoms. Patients can enjoy an independent life much longer and the independence can be supported by medical and social facilities.

The senile onset form carries a favourable prognosis: cataracts can be adequately treated. Mild muscular weakness and mild mental symptoms are secondary symptoms occurring late in the disease without causing much disability.

Thus Harper's statement (1979) that the severity of myotonic dystrophy is too variable to give a prognosis, is only partially valid. Caughey's opinion (1963) that the disease usually advances steadily to complete invalidism and mental apathy is too pessimistic. This probably only applies to a small part of the patients and then only after a long duration of the disease. The prognosis given by Merritt (1967) and Walton and Gardner-Medwin (1981) mainly considers muscular weakness, and not the mental symptoms.

The natural history and the prognosis of the different myotonic dystrophy syndromes may become clarified by studying larger groups of patients matched

for disease-duration and type of myotonic dystrophy. Also better methods to measure and classify the mental symptoms and signs of myotonic dystrophy should be developed.

§ 3. The severity of the disease on transmission of the gene

3.1 In this study we examined how frequently anticipation of the ages of onset of myotonic dystrophy occurred in index free parent-child pairs in 14 families. We made an attempt to compare the severity of the disease in parent-child pairs. We searched for complementary pairs, whether they can be expected to appear in the future, and whether they have existed in the past. At last we examined whether a diminished fertility in patients with an early onset of the disease might be the cause of complementary pairs not coming into existence.

Anticipation of the ages of onset of the disease was found in 98% of the 61 index free parent-child pairs. This finding agrees with previous clinical studies that compared onset ages in parent-child pairs (Fleischer, 1922; Henke and Seeger, 1927; Ravin and Waring, 1939; Thomasen, 1948; Klein, 1958; Bundey and Carter, 1970; Schubert et al, 1980; Pryse-Phillips et al, 1982). These studies often concern small families, and the index patient was usually included in the calculations. Therefore doubts remained as to whether bias produced by the index patients might have caused selection of anticipating parent-child pairs. This study concerned larger families with so many parent-child pairs that the index patients could be excluded. Still anticipation of the ages of onset was found in nearly all parent-child pairs. Thus, the anticipation phenomenon was not caused by bias produced by the index patients.

The difference in ages of onset was found to be significantly greater in pairs with a transmitting father than in pairs with a transmitting mother. An explanation for this finding is difficult to give as long as the cause of the anticipation phenomenon is not known. One is inclined to assume a relation with the exclusively maternal transmission of congenital myotonic dystrophy. This also is an as yet unexplained phenomenon related to the gender of the transmitting parent.

The comparison of the severity of the disease in parent-child pairs appeared to be difficult because of methodological problems. Only a general conclusion could be drawn as to the fact that cataracts are usually more severe in the parent, muscular weakness is varying in severity between the parent and the child, and mental symptoms are usually more severe in the child. Many previous authors stated that the signs and symptoms of myotonic dystrophy are more severe in the children than in the transmitting parent (Fleischer, 1918; Ravin and Waring, 1939; Thomasen, 1948; De Jong, 1955; Klein, 1958). This statement was based on the impression of the severity on clinical examination. The gradual change of symptoms and signs with decreasing age of onset made it difficult to express the increasing severity in concrete figures. In this study the severity of the disease also appeared to increase in succeeding generations (see chapter V) and with an earlier age at onset (see chapter VI). However, as in previous studies, this increasing severity was difficult to measure in parent-

child pairs. Assuming however that mental symptoms are more invalidating than muscular weakness, and muscular weakness is more invalidating than cataracts, one may conclude that myotonic dystrophy is usually more severe in the child than in the transmitting parent.

The penetrance of the myotonic dystrophy gene in this study was almost complete in the 14 families combined. This is in agreement with Pryse-Phillips et al (1982) who found anticipation of ages of onset in one very large family with complete penetrance of the gene. It thus seems unlikely that in the future a sufficient number of complementary parent-child pairs will appear to cancel out the anticipation phenomenon observed in these families. It would mean that in these 14 families 60 children of myotonic dystrophy patients, who had no symptoms at the time of examination during this study, will still contract the disease at a later age. The percentage of patients in the families would then be far beyond the expected 50%.

The collected data on the deceased transmitting parents in these families indicated that none of the patients with a late onset of the disease had a parent with a muscular disease with an earlier age of onset. This finding was analogous to that of other clinical studies where systematic inquiries were made concerning the deceased parents of the oldest examined generation (Fleischer, 1922; Henke and Seeger, 1927; Ravin and Waring, 1939; Thomasen, 1948; De Jong, 1955; Klein, 1958). Thus complementary parent-child pairs in retrospect have not been found in the more than 150 families of whom data have been collected on the deceased transmitting parents. One may thus assume that these 'alternative' complementary parent-child pairs (see fig. 1) do not exist, and that the age of onset of myotonic dystrophy does not vary at random.

A strongly diminished fertility was only found in the group of patients with a very early onset of the disease: in women with onset in the first decade, and in men with onset in the first and second decade. With a later age of onset of the disease the fertility was diminished only moderately (in women with an age of onset in the second decade and in men with an age of onset in the third decade), or was found to be normal. It therefore seems improbable that the observed anticipation is caused by the fact that only patients with a late onset of the disease can have offspring, as was suggested by Thomasen (1948) and Penrose (1948).

From the data obtained in these 14 families the conclusion seems justified that the observed anticipation is not an artefact, but a true biological phenomenon inherent to the transmission of myotonic dystrophy. The complementary pairs, assumed by Penrose, were neither found in this study nor in previous studies, and they probably do not exist.

Grimm and Harper (1983) and Glanz and Fraser (1984) found a remarkable difference in the risk of offspring having congenital myotonic dystrophy for women who had a previous child with congenital myotonic dystrophy and women who did not yet have a child with this severe form of the disease. If one accepts anticipation in myotonic dystrophy, then this difference may be explained. The group of women who did not yet have a child with

congenital myotonic dystrophy probably included more women with a later onset of the disease, than the group of women, who already had a child with congenital myotonic dystrophy. Therefore the risk of having a child with congenital myotonic dystrophy will be higher in the last group.

Harper and Dyken (1972) found that congenital myotonic dystrophy is transmitted exclusively via the mother. They assumed the existence of an intrauterine toxic factor as the cause of this exclusively maternal transmission. The nature of this toxic influence has not yet been found. Harper and Dyken (1972) did not find a difference in fertility between men and women with myotonic dystrophy. They studied, however, the fertility of patients of all age of onset groups combined.

In the present study we also found little difference in fertility between affected men and women, when patients of all ages of onset combined were compared. Yet in patients with an age of onset in the second and third decade the fertility in men was decreased in comparison with the fertility in women. The difference in fertility in these age of onset groups, combined with the anticipation phenomenon, may also explain the exclusively maternal transmission in congenital myotonic dystrophy. The combined effect may be the cause of myotonic dystrophy in women being transmitted one generation further than in men.

3.2 Some methods used in this study may raise questions. One may wonder whether these 14 families form a selected group of families. The 22 index patients of these 14 families were chosen from a group of 51 index patients seen in Rotterdam between 1970 and 1977 (see chapter IV). The original plan was to avoid selection by examining the families of all index patients presented within this period. This appeared to be practically impossible.The 14 studied families were mainly chosen because most of the members lived in or near Rotterdam. Some other families were eliminated, because too many members refused to cooperate, or too many members had died. These reasons for eliminiation do not appear to be sources of selection of anticipating parent-child pairs.

The question remains as to whether anticipation also appeared in the families of the 29 eliminated index patients. This question is difficult to answer, since we examined only some members of these families, and in some of the families we did not even examine the index patient ourselves.

We calculated the difference of age of onset in those parent-child pairs with myotonic dystrophy in these 29 families who had been examined. In 9 cases both the parent and the child had been examined. In another 6 cases only one of them had been examined, but the age of onset of the other one could be estimated from the data provided by the examined patient. In all 15 cases the age of onset of the child was earlier than the age of onset of the transmitting parent. So anticipation of the ages of onset of the disease also occurred in those eliminated families of whom data were available.

Questions may arise as to whether the determination of the age of onset was reliable. Some authors (Bethlem, 1955; Lynas, 1957; Schubert et al, 1980) state

that it is not possible to determine the age of onset of myotonic dystrophy reliably on the basis of historical data. We considered that this is only true when the measure in which the age of onset is expressed is too specific, and when the symptoms marking the onset of the disease are not exactly defined. For this reason we chose a wider measure to determine the age of onset: the decade. Only occasional patients found difficulty fixing the onset of a symptom at a certain decade. Only four symptoms or symptom patterns were used to mark the onset of the disease. These symptoms cause an obvious change of function and patients were well able to remember their onset.

Another question may be as to whether the age of onset of the disease of patients with different onset symptoms can be compared. For instance, can one compare the age of onset of a patient with a cataract with the age of onset of a patient with myotonia as onset symptom? We considered this as possible in the present study. The onset symptom may differ in different patients, but after a longer duration of the disease most patients developed the other main symptoms of myotonic dystrophy as well (see chapter VI).

In my opinion the methods used in this study are sufficiently reliable to draw the conclusion that the anticipation of ages of onset of the disease found is a true biological phenomenon, and that the families studied were not selected for this phenomenon.

For genetic counselling the question is important as to whether anticipation appears in every myotonic dystrophy family or not. From the literature study it emerged that anticipation was observed in all studies where the age of onset in parent-child pairs was compared, although the phenomenon was seen as an artefact by some of the authors. This study showed that the existence of Penrose's complementary pairs is improbable. Thus, as long as the frequent existence of complementary pairs is not reported, one may assume that anticipation appears in all myotonic dystrophy families.

It is not yet possible to explain how a gene can 'worsen' in successive generations, since little is known about the factors influencing the expression of genes. However the recent localisation of the myotonic dystrophy gene on chromosome 19 opens options for further studies at the DNA-level to obtain insight into molecular interactions that influence the expression of the myotonic dystrophy gene. The results of this study may inspire such further studies.

3.3 Consequences for genetic counselling

The conclusion of the present study is that anticipation is a real phenomenon inherent to the transmission of myotonic dystrophy, although the cause of the phenomenon is still not clear. The consequence for genetic counselling is that patients with myotonic dystrophy may be informed that their affected children are likely to have a more severe form of the disease than they have themselves, with onset at an earlier age. This is also true for patients only having mild symptoms.

Genetic counselling is usually requested by patients between 15 and 35

years old, having early adult onset of myotonic dystrophy. If they transmit the gene to a child, the risk of having a child with congenital myotonic dystrophy is high in the cases where the transmitter is a woman, but the risk of having a child with early onset myotonic dystrophy is also high in the cases where the man is the transmitter. The disease will then give rise to early disability, mainly caused by mental symptoms. In my opinion this depressing conclusion does not only apply to women, who already have a child with congenital myotonic dystrophy, like Grimm and Harper (1983) and Glanz and Fraser (1984) stated, but to all patients with an age of onset of the disease in the first, second and possibly also in the third decade.

CHAPTER IX

SUMMARY

This thesis presents a clinical and genetic study of 14 families with myotonic dystrophy.

Chapter I describes the clinical problem which prompted this study: the only information that can be given to a patient with myotonic dystrophy, when asking for genetic counselling, is that the risk for transmission of the disease to his offspring is 50%. The other 2 questions which are often raised are difficult to answer:

1. What is the risk for this individual patient of becoming disabled?
2. How severe will the disease be in the case of a child being affected?

In chapter II the literature on the natural history of myotonic dystrophy is reviewed. The nature and the severity of symptoms and signs vary so much in different patients that it is difficult to assess the natural history of the disease. A different prognosis is therefore given by different authors, varying from poor to reasonably favourable. One author stated that it is not possible to give a prognosis for an individual patient.

Several authors observed a correlation between the age of onset and the nature of the symptoms. The severity of the symptoms and signs can also be expected to be related to the duration of the disease. In only one study the nature and the severity of the symptoms and signs were studied over a longer period of time in a group of patients with similar age of onset of the disease.

The literature study led to two concrete questions with relation to this part of the study:

1. Is there a correlation between the age of onset and the nature of the symptoms in myotonic dystrophy?
2. Do the nature and the severity of the symptoms change with increasing duration of the disease?

In chapter III the literature on the severity of the disease after transmission of the abnormal gene is reviewed. Little appeared to be known concerning the risk of a patient transmitting a severe form of the disease to his offspring. A mother already having a child with congenital myotonic dystrophy is known to have a higher risk of getting a second child with this severe degree of the disease than a patient who had not as yet a child with congenital myotonic dystrophy.

Whether the severity of the disease after transmission of the gene is variable at random or not, appeared to be related to the question as to whether anticipation in myotonic dystrophy - an earlier age of onset and a more severe disease in successive generations - is a real phenomenon or an artefact. If anticipation is inherent to the transmission of myotonic dystrophy, a child

inheriting the gene will have a more severe degree of the disease than the transmitting parent. If anticipation is an artefact one may expect the severity of the disease after transmission of the gene to be variable at random. The course of the dispute was traced which concerned anticipation being a real phenomenon or an artefact caused by the study of selected families. It appeared that Penrose in fact had only proposed a hypothesis in his article which has played such a dominant role in the discussion: in about 50 years a sufficient number of complementary parent-child pairs will appear to cancel out the observed phenomenon of anticipation. This hypothesis has never been confirmed and such complementary pairs have never been described. Penrose himself did not make clear that he had proposed a hypothesis and many authors accepted his hypothesis as a proven fact. The phenomenon anticipation has since rarely been studied and complementary pairs have not been searched for. To study the anticipation phenomenon five questions were formulated:

1. How frequently has a child with myotonic dystrophy an earlier age of onset that the transmitting parent?
2. How frequently has a child with myotonic dystrophy a more severe form of the disease than the transmitting parent?
3. Is the penetrance of myotonic dystrophy incomplete, so that many complementary pairs can be expected to be found in the future?
4. Have there been complementary pairs in the past which can be detected retrospectively?
5. Is the fertility of myotonic dystrophy patients affected to such a degree, that only patients with a late age of onset are able to have children and complementary pairs can not come into existence?

Chapter IV describes the families chosen for this study, the methods used to examine the relatives and to analyse the collected data.

Selection of biased parent-child pairs was avoided by examining large families with many branches. In this way it was possible to exclude the parent-child pairs including an index patient. Thus only index free parent-child pairs were involved in the comparison of onset ages. The age of onset of the patients was determined from the history in a uniform way. Four features causing an obvious change of function were chosen as signs marking the onset of the disease: myotonia, muscular weakness, deterioration of sight caused by cataracts, and the syndrome of congenital myotonic dystrophy. The age of onset was measured in decades.

To obtain a complete detection of the heterozygotes the relatives were examined in 3 ways, whenever possible: a clinical examination, electromyography, and a slit-lamp examination.

The degree of severity of the disease was measured in an ordinal scale with four points for each of the four symptoms cataract, muscular weakness, mental symptoms and myotonia.

During the family history patients in the oldest examined generation were asked for data about the occurring of characteristic features of myotonic dystrophy in their parents and grandparents.

In chapter V the general results of the family study are presented. Of the examined 264 family members 133 were found to have myotonic dystrophy, 127 to be normal and in 4 individuals the diagnosis was dubious. The pedigrees of the 14 families are presented with a short description of each family.

In chapter VI the results of the study of natural history of myotonic dystrophy are analysed. The nature and severity of the symptoms were compared in 4 groups of patients with corresponding ages of onset, and with a short and a longer duration of the disease. Three different syndromes could be distinguished, determined by the age of onset: myotonic dystrophy with onset in childhood, with early adult onset and with senile onset. Three symptoms appeared to be important for the distinction of the syndromes: cataract, muscular weakness and mental symptoms.

Myotonic dystrophy with onset in childhood is mainly characterised by mental symptoms, with muscular weakness and sometimes cataract as secondary symptoms. The syndrome is already disabling at an early stage and the chances for an independent life are small. In myotonic dystrophy with early adult onset the main symptom is muscular weakness, mental symptoms and cataracts of varying degrees becoming important in later stages of the disease. Disability occurs later in the disease and is more characterised by muscular weakness than by mental symptoms. Myotonic dystrophy with senile onset is mainly characterised by cataracts, while muscular weakness and mental symptoms may develop in a mild form late in the disease. Since cataracts can be treated adequately this syndrome is hardly disabling.

In chapter VII the results of the study of the parent-child pairs are analysed.

Anticipation of the ages of onset was found in 98% of the 61 index free parent-child pairs.

The study of the severity of the disease in parent-child pairs was complicated by methodological problems. Only a general conclusion could be drawn as to the fact that cataracts are usually more severe in the parent, muscular weakness is varying in severity between the parent and the child, and mental symptoms are usually more severe in the child.

The penetrance of the myotonic dystrophy gene was almost complete in the 14 families combined. It seems therefore unlikely that in the future a sufficient number of complementary pairs will appear to cancel out the observed anticipation phenomenon.

In the family history no indications were found which pointed to the fact that deceased transmitting parents had myotonic dystrophy with an age of onset earlier than that of their children. Thus, also in retrospect complementary pairs were not found.

A strongly diminished fertility was found only among the affected female patients with onset of the disease in the first decade and in affected male patients with an onset of the disease in the first and second decade. It seems therefore

unlikely that the observed anticipation is caused by a selective difference in fertility between patients with onset at a later age opposed to patients with onset at an early adult age.

In chapter VIII the results are discussed and compared to the data known from the literature. Also the methodological problems are discussed which may have influenced the results of this study. At last an attempt is made to answer the two questions which prompted this study. It is not yet possible to give a detailed prognosis for an individual patient. However, the distinction between the three myotonic dystrophy syndromes determined by the age of onset makes it possible to predict the expected disability for an individual patient in general. The prognosis is poor for patients with childhood onset of the disease, more favourable with early adult onset and good with senile onset.

One may assume that the anticipation phenomenon is inherent to the transmission of myotonic dystrophy and that it occurs in all myotonic dystrophy families, as long as the frequent occurrence of complementary pairs has not been proved. This means that patients with a childhood or early adult onset of the disease have a high risk of transmitting a severe form of the disease to their offspring. This applies to male as well as to female patients.

SAMENVATTING

Dit proefschrift bevat een klinisch en genetisch onderzoek van 14 families met dystrofia myotonica.

In hoofdstuk I wordt het klinische probleem beschreven dat de aanleiding vormde tot dit onderzoek. Wanneer een patiënt met dystrofia myotonica genetisch advies vraagt, kan men voorspellen hoe groot de kans is op overdracht van de ziekte aan zijn kinderen. De adviesvrager stelt echter veelal nog twee vragen, die niet gemakkelijk te beantwoorden zijn:

1. Hoe groot is de kans op invaliditeit voor de patiënt zelf?
2. Hoe ernstig zal de ziekte van het kind zijn als de ziekte wordt overgedragen?

In hoofdstuk II wordt besproken wat er in de literatuur bekend is over het natuurlijk verloop van dystrofia myotonica. Het bleek dat de aard en de ernst van de symptomen zo sterk variëren van patiënt tot patiënt dat het natuurlijk verloop van de ziekte moeilijk te beoordelen is. De prognose van de ziekte wordt door verschillende auteurs dan ook zeer verschillend beoordeeld, variërend van slecht tot redelijk goed. Ook wordt gesteld dat een prognose voor een individuele patiënt niet gegeven kan worden.

In enkele studies werd een relatie gevonden tussen de aard van de symptomen en de ziektebeginleeftijd. Verder werd verondersteld dat de ernst van de ziekte ook beinvloed wordt door de ziekteduur. Het bleek dat slechts in één studie gedurende langere tijd de aard en de ernst van de symptomen

onderzocht is bij een groep patiënten met een zelfde ziektebeginleeftijd. Naar aanleiding van dit literatuuronderzoek werden twee concrete vragen voor dit onderdeel van het onderzoek geformuleerd:

a. Is er een verband tussen ziektebeginleeftijd en de aard van de verschijnselen bij dystrofia myotonica?
b. Veranderen de aard en de ernst van de ziekteverschijnselen bij een langere ziekteduur?

In hoofdstuk III wordt de literatuur besproken betreffende de ernst van de ziekte na overdracht van het abnormale gen. Het bleek dat slechts weinig bekend is over het risico voor een kind een ernstige vorm van dystrofia myotonica te krijgen, wanneer het de ziekte van een van zijn ouders erft. Wel is bekend dat een moeder van een kind met congenitale dystrofia myotonica een veel grotere kans heeft een tweede kind met deze ernstige vorm van de ziekte te krijgen, dan een patiente die niet eerder een kind met congenitale dystrofia myotonica heeft gehad.

De vraag of de ernst van de ziekte in een volgende generatie willekeurig variabel is of niet, bleek samen te hangen met het al of niet optreden van anticipatie in dystrofia myotonica families: een jonger ziektebegin en een ernstiger ziekte in opeenvolgende generaties. Als anticipatie inherent is aan de overdracht van dystrofia myotonica zal een kind dat het gen erft, altijd een ernstiger ziekte krijgen dan de overdragende ouder. Als anticipatie slechts een schijneffect is zou men verwachten dat de ernst van de ziekte na overdracht willekeurig variabel is. De discussie in de literatuur over de vraag of anticipatie werkelijkheid is of slechts een drogbeeld, veroorzaakt door onderzoek van geselecteerde families, werd gevolgd. Hierbij bleek dat Penrose in zijn artikel, dat zo'n grote rol speelde in de discussie, in feite een hypothese naar voren bracht: er zouden in de toekomst voldoende complementaire ouder-kind paren ontstaan om het geobserveerde verschijnsel anticipatie op te heffen. Deze complementaire ouder-kind paren zouden pas zo'n 50 jaar na het vinden van de anticiperende ouder-kind paren gevonden kunnen worden. Deze hypothese is nooit bevestigd en complementaire ouder-kind paren blijken ook nooit te zijn beschreven. In het artikel van Penrose (1948) bleef onduidelijk dat een hypothese werd beschreven en veel onderzoekers beschouwden de hypothese als een bewezen feit. Het verschijnsel anticipatie is daarom nauwelijks verder onderzocht en naar het voorkomen van complementaire paren is niet gezocht.

Vijf concrete vragen werden geformuleerd om het verschijnsel anticipatie te onderzoeken:

1. Hoe frequent is de beginleeftijd van dystrofia myotonica bij het kind lager dan bij de overdragende ouder?
2. Hoe frequent is de ziekte bij kinderen met dystrofia myotonica ernstiger dan bij de overdragende ouder?
3. Is de penetrantie van dystrofia myotonica in de families incompleet, zodat men in de toekomst nog veel complementaire paren kan verwachten?
4. Zijn er in het verleden complementaire paren geweest en zijn deze

retrospectief te vinden?

5. Wordt de fertiliteit van dystrofia myotonica patiënten zo sterk beinvloed door de ziekte dat uitsluitend patiënten met een laat ziektebegin kinderen krijgen en complementaire paren daarom niet gevormd kunnen worden?

In hoofdstuk IV worden de families beschreven die gekozen werden voor dit onderzoek, alsmede de methoden waarmee de familieleden werden onderzocht en de wijze waarop de resultaten werden geanalyseerd.

Selectie van een bepaald type ouder-kind paren werd vermeden door grote families te onderzoeken met zoveel mogelijk zijtakken. Op deze wijze konden alle ouder-kind paren waarbij de indexpatient betrokken was uitgesloten worden bij de berekeningen, zodat alleen indexvrije ouder-kind paren betrokken waren bij de vergelijking van de ziektebeginleeftijd en de ziekte-ernst.

De beginleeftijd van patiënten werd anamnestisch vastgesteld op een zo uniform mogelijke wijze. Vier symptomen die een duidelijke functieverandering veroorzaken werden gebruikt als markering van het ziektebegin, namelijk spierzwakte, myotonie, visusdaling door cataract en het syndroom van congenitale dystrofia myotonica. De beginleeftijd werd bij alle patiënten in decaden gemeten.

Om een volledige detectie van heterozygoten te bereiken, werden de familieleden zoveel mogelijk zowel klinisch-neurologisch als electromyografisch als met de spleetlamp onderzocht.

De ziekte-ernst werd gemeten met een vierpunts rangorde schaal voor de vier symptomen cataract, spierzwakte, mentale verschijnselen en myotonie. Op deze wijze kon de ziekte-ernst bij verschillende patiënten vergeleken worden. Bij patiënten uit de oudste onderzochte generatie werd een systematische familie-anamnese afgenomen met de vraag of kenmerkende symptomen van dystrofia myotonica bij hun ouders aanwezig waren geweest.

In hoofdstuk V worden de algemene resultaten van het familie-onderzoek gepresenteerd. In totaal werden 264 familieleden onderzocht. Hiervan hadden 133 dystrofia myotonica, 127 hadden geen afwijkingen en bij vier familieleden bestond er twijfel over de diagnose. De stambomen van de 14 families worden gepresenteerd samen met een korte beschrijving van elke familie.

In hoofdstuk VI worden de resultaten geanalyseerd van het onderzoek naar het natuurlijk verloop van dystrofia myotonica. Onderzocht werd in hoeverre de aard en de ernst van vier symptomen verschilden bij vier groepen patiënten met overeenkomende ziektebeginleeftijd, zowel bij een korte als bij een langere ziekteduur. Drie dystrofia myotonica syndromen, bepaald door de beginleeftijd, bleken van elkaar te onderscheiden te kunnen worden: dystrofia myotonica met ziektebegin op kinderleeftijd, met ziektebegin op jong volwassen leeftijd en met ziektebegin op oudere leeftijd. Drie symptomen bleken belangrijk voor het onderscheiden van deze syndromen, namelijk cataract, spierzwakte en mentale verschijnselen.

Bij dystrofia myotonica met ziektebegin op kinderleeftijd bleken de mentale verschijnselen op de voorgrond te staan en waren spierzwakte en cataract bijsymptomen. Dit ziektebeeld leidt al vroeg tot invaliditeit en de kans op een onafhankelijk bestaan is klein.

Bij dystrofia myotonica met ziektebegin op jong volwassen leeftijd bleek spierzwakte het hoofdsymptoom, en werden mentale verschijnselen en cataract in wisselende ernst pas later belangrijk. Invaliditeit treedt veel later in de ziekte op en wordt sterker bepaald door spierzwakte dan door mentale verschijnselen. Een onafhankelijk leven is voor deze patiënten veel langer mogelijk en de validiteit kan ondersteund worden door medische en sociale voorzieningen.

Bij dystrofia myotonica met ziektebegin op oudere leeftijd bleek cataract het hoofdsymptoom te zijn en waren spierzwakte en mentale verschijnselen milde en late bijverschijnselen. De prognose is goed omdat het cataract goed behandeld kan worden.

In hoofdstuk VII worden de resultaten geanalyseerd van het onderzoek van de ouder-kind paren. Anticipatie van de ziektebeginleeftijd werd gevonden bij 98% van de 61 indexvrije ouder-kind paren.

Het onderzoek naar de ziekte-ernst bij ouder-kind paren werd belemmerd door methodologische problemen. Er konden alleen zeer globale conclusies worden getrokken: cataract is meestal ernstiger bij de ouder, spierzwakte wisselend ernstiger bij ouder en kind, en mentale verschijnselen zijn meestal ernstiger bij het kind.

De penetrantie van het dystrofia myotonica gen bleek in de 14 families gezamenlijk bijna compleet, zodat het onwaarschijnlijk is dat in de toekomst voldoende complementaire ouder-kind paren zullen ontstaan om het gevonden anticipatie effect op te heffen. In de familie-anamnese werden geen overleden overdragende ouders gevonden met klachten passend bij dystrofia myotonica met een ziektebegin op jongere leeftijd dan hun kinderen. Complementaire paren werden dus ook retrospectief niet gevonden.

Een sterk verminderde fertiliteit van dystrofia myotonica patiënten werd alleen gevonden in de groep vrouwelijke patiënten met een ziektebegin in de eerste decade en in de groep mannelijke patienten met een ziektebegin in de eerste en tweede decade. De gevonden anticipatie lijkt niet veroorzaakt te zijn door een selectief fertiliteitsverschil tussen patiënten met ziektebegin op oudere leeftijd en patiënten met ziektebegin op jong volwassen leeftijd.

In hoofdstuk VIII worden de resultaten bediscussieerd en vergeleken met de gegevens die in de literatuur bekend zijn. Tevens worden de methodische problemen besproken die de resultaten van dit onderzoek beinvloed kunnen hebben. Tenslotte wordt een poging gedaan om een antwoord te geven op de twee vragen die de aanleiding waren voor dit onderzoek.

Het is nog niet mogelijk een exacte prognose te geven voor een individuele patiënt. Wel geeft de onderscheiding van drie dystrofia myotonica syndromen de mogelijkheid de te verwachten invaliditeit voor een individuele patiënt in

grote lijnen aan te geven. De prognose is slecht bij een ziektebegin op kinderleeftijd, gunstiger bij een ziektebegin op jong volwassen leeftijd en goed bij een ziektebegin op oudere leeftijd.

Zolang het frequent voorkomen van complementaire paren niet is aangetoond, mag men aannemen dat anticipatie inherent is aan de overdracht van dystrofia myotonica en optreedt in alle dystrofia myotonica families. Dit betekent dat patiënten met een ziektebegin op kinderleeftijd of jong volwassen leeftijd een grote kans hebben om een ernstige vorm van de ziekte aan hun kinderen over te dragen. Dit geldt zowel voor mannelijke als voor vrouwelijke patiënten.

APPENDIX I:

THE EXAMINED RELATIVES OF THE 14 FAMILIES

cat = cataract, my = myotonia, we = weakness, me = mental symptoms

Family A

The first index patient, IV-5, consulted an ophthalmologist for failing vision at the age of 32. Myotonic cataracts were found and she was subsequently referred.
She noticed cramps and weakness of her hands at the age of 25. At 32 she was running her own household and appeared to be of normal intelligence. She had facial and distal arm weakness, with indistinct speech and myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 3 - my 2 - we 2 - me 0.

The second index patient, III-13, consulted the neurologist for weakness of his hands at the age of 56. Myotonia was found at EMG examination and his name was subsequently recognized as being the same as IV-5's mother's name. As an amateur juggler he noticed an 'unwilling index finger' at 50 years of age and some years later all fingers became weak. He never noticed cramps. At 56 he was still working and appeared of normal intelligence. He had weakness of facial, neck and distal limb muscles. Clinical myotonia was not found.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 6th decade.
Severity score: cat 1 - my 1 - we 1 - me 0.

The third index patient, V-9, was admitted to the neonatal intensive care unit for postpartum asphyxia. The pediatrician diagnosed neonatal myotonic dystrophy on the clinical picture, which was confirmed by diagnosing myotonic dystrophy in the mother. The mother's name was recognized as being that of family A. At te age of 10 days she had severe general hypotonia and muscle weakness, a tent-shaped mouth and atrophic arms and legs; she had to be ventilated for 19 days (case 4, Pearse and Höweler, 1979).
Slit-lamp examination and EMG were not performed.
At 7 months her motor development was moderately delayed.
Myotonic dystrophy, congenital involvement, onset decade 0.

I-1 Died aged 80; was reported by his grandson, III-5, to have been a healthy policeman.

I-2 Died aged 86; was reported by her grandson to have had cataracts.

II-1 Died aged 80; was operated upon for cataracts aged 78, the ophthalmologist diagnosed mature senile cataracts. Was reported by his children to have been a healthy and active man who had been able to jump from the floor onto a table at the age of 70.

II-2 Ten sibs; 8 had died, aged 36, 2, 82, 52, 80, 70, 71; the age of death of one sib was not known. Two were still alive, aged 77 and 79, but were not examined. No invalidating disease was known to their nephews and nieces. Of 3 of these 10 sibs a child was fully examined and found to be normal and the family history of these branches was not suspect for myotonic dystrophy.

II-3 Died aged 92; he had cataracts from the age of 80, but was not operated upon; the ophthalmologist diagnosed senile cortical and nuclear cataracts. He was reported by his sons to have been otherwise healthy.

II-4 Died aged 70 from cancer. No cataract or muscular disease was known to his children.

II-5 Died aged 80; was operated upon for cataracts at the age of 67. The ophthalmologist diagnosed posterior cortical cataracts. No muscular disease was known to his sons, he could still do a handstand at the age of 75.

III-1 Was operated upon for cataracts at the age of 53, the ophthalmologist diagnosed a mature left catataract and the beginning of a posterior cortical right cataract. From the age of 60 she had noticed weakness of her hands when carrying weights, she had never noticed cramps. At 70 she had mild weakness of her hands and of the foot extensors, no clinical myotonia.
EMG: normal.
Myotonic dystrophy, onset 6th decade.
Severity score: cat 3 - my o - we 1 - me 0.

III-2 Not examined.

III-3 Died suddenly when aged 58; had severe myotonic dystrophy; spent his last years in a wheelchair and was reported to have been slow and inactive. His widow said that cramps and weakness had started after the age of 20, he was prematurely discharged from military service for this reason. At 49 he was found, by a neurologist, to have a myopathic facies, indistinct speech, severe general muscle atrophy, and a stepping gait.
Myotonic discharges were recorded on the EMG.
Myotonic dystrophy, onset 3rd decade.

III-4 Aged 64, full examination normal.

III-5 Aged 61, full examination normal.

III-6 Died suddenly aged 53, was reported by a son to have been healthy before his death.

III-7 Died of pneumonia aged 49; he had severe myotonic dystrophy, but could still walk at that time. When aged 27 he had still been accepted as a military volonteer, but his former wife said he had had cramps and weakness of his hands when he married at the age of 28. At 36 myotonic dystrophy was diagnosed by a neurologist. Weakness of facial, sternomastoid and arm muscles was found, with percussion myotonia of the thenar.
Mytonic dystrophy, onset 3rd decade.

III-8 Aged 59, no symptoms or signs.
Slit-lamp: myotonic cataracts with normal visual acuity.
EMG: myotonic discharges.
Mytonic dystrophy, onset 7th decade (age + 5 years).
Severity score: cat 1 - my 1 - we 0 - me 0.

III-9 Aged 55, no symptoms. Myotonia was found on percussion of the thenar, no muscle weakness.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 6th decade.
Severity score: cat 1 - my 2 - we 0 - me 0.

III-10 Was examined in Oslo (Prof. R. Nyberg-Hansen) when he heard of this family study. He had no symptoms. At 58 he had a myopathic facies, mildly atrophic masseters and a nasal voice.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 6th decade.

III-11 Aged 56, no symptoms. Myotonia was found on percussion of the thenar, no muscle weakness. Slit-lamp: myotonic cataracts.
EMG: mytonic discharges.
Myotonic dystrophy, onset 6th decade.
Severity score: cat 1 - my 2 - we 0 - me 0.

III-12 Aged 47, no symptoms or signs.
Slit-lamp: non specific white lenticular opacities.
EMG: normal.
Her only child was fully examined and found to be normal.

III-13 Second index patient, see above.

III-14 Aged 46, full examination normal.

IV-1 Aged 48, had no symptoms. Myotonia was found on percussion of the thenars. No muscle weakness.
Slit-lamp: coloured opacities too few for a diagnosis.
EMG: myotonic discharges.
Myotonic dystrophy, onset 5th decade.
Severity score: cat 0 - my 2 - we 0 - me 0.

IV-2 Noticed difficulty in extending his fingers in cold water at the age of 30. At 45 he held a full-time job and appeared to be of normal intelligence. He had mild weakness of eye closure, hands and forearms, with myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 4th decade.
Severity score: cat 1 - my 2 - we 1 - me 0.

IV-3 Died aged 2 years, cause unknown.

IV-4 Difficulty in opening his fist was noticed by his wife before they were married, at about the age of 25. He completed his military service. At 38 he was fully employed. His intelligence appeared normal. He had mild weakness of face and hand muscles, with indistinct speech and myotonia of grip.
Slit-lamp: coloured opacities too few for a diagnosis.
EMG: myotonic discharges.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 0 - my 2 - we 1 - me 0.

IV-5 First index patient, see above.

IV-6 Difficulty in opening a fist was noticed by a stepmother at their first encounter, when he was 16. He was slow and repeated 3 classes in primary school. His mother reported he had been a normal baby. At 25 he worked in a sheltered workshop and appeared slow, he had mild weakness of facial, neck and hand muscles with myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade (possibly 1st).
Severity score: cat 1 - my 2 - we 1 - me 1.

IV-7 Cramps in hands and difficulties when chewing and swallowing were noticed by a stepmother at their first encounter, at the age of 15. His mother reported he had been a normal baby. At 24 he worked in a sheltered workshop, appeared slow and was reported to have severe hypersomnia. He had mild weakness of facial, neck and hand muscles, with indistinct speech and myotonia of grip.
Slit-lamp: normal lenses.
EMG: myotonic discharges.
He died suddenly at the age of 26, postmortem examination showed no cause of death.
Myotonic dystrophy, onset 2nd decade (possibly 1st).
Severity score: cat 0 - my 2 - we 1 - me 2.

IV-8 Her mother said she was very quiet as a baby, but not floppy, and she had no feeding problems. Cramps in her hands were noticed by her stepmother at their first encounter, when she was 5 years old. She was mentally retarded and attended a special school, later also hypersomnia developed. At 23 she was married, but could not run her household well. She was mentally retarded and slow, and had mild weakness of facial and hand muscles, with indistinct speech and myotonia of grip.
Slit-lamp: coloured opacities too few for a diagnosis.
EMG: not performed.
Myotonic dystrophy, onset 1st decade.
Severity score: cat 0 - my 2 - we 1 - me 3.

IV-9 Died suddenly at school at the age of 15. Was reported by his stepmother to have had a stepping gait and cramps of his hands.

IV-10 Aged 20, normal neurological and slit-lamp examination.
EMG not performed.

IV-11 Noticed difficulty opening a fist during sports at the age of 16. At 21 he kept an administrative job but appeared slow. He had mild facial weakness and myotonia of grip.
Slit-lamp: normal lenses.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 0 - my 2 - we 1 - me 1.

IV-12 Noticed cramps in her hands and tongue at the age of 17. At 20 she worked as a telephone operator and appeared of normal intelligence. She had mild facial, jaw and neck weakness and myotonia of grip.
Slit-lamp: normal lenses.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 0 - my 2 - we 1 - me 1.

IV-13 Died at the age of 2 days, according to his father of cerebral haemorrhage, caused by obstructed labour.

IV-14 Noticed difficulty opening a fist at the age of 18. Her father reported she had been a lively child, but she became inactive around the age of 12. At 27 she ran her own household and appeared of normal intelligence. She had mild weakness of facial, jaw and neck muscles, with indistinct speech and myotonia of grip.
Slit-lamp: coloured opacities too few for a diagnosis.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 0 - my 2 - we 1 - me 1.

IV-15 Was examined in Oslo (Prof. R. Nyberg-Hansen) when he heard of this family study. Noticed stiffness in his hands and a nasal speech a few years before examination. At 20 he had weakness of facial, masseter, sternomastoid and triceps muscles with nasal speech and myotonia of the hands.
Slit-lamp: some changes in the lens which were not typical of myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.

IV-16 Aged 17, was also examined in Oslo: no symptoms or signs.
Slit-lamp and EMG not performed.

IV-17 Noticed inability to open a fist quickly during his work as a mechanic at the age of 15, when he also became irritatingly slow and inactive according to his sister. At 30 he had to give up his work in a storehouse because he was too slow. He had mild weakness of facial, jaw and neck muscles, with absent arm reflexes and myotonia of grip.
Slit-lamp: coloured opacities too few for a diagnosis.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 0 - my 2 - we 1 - me 2.

IV-18 Aged 28, full examination normal.

IV-19 Aged 22, full examination normal.

IV-20 Noticed inability to extend his fingers quickly when he was 15. He attended special schools from the age of 10. At 15 he also appeared slow but not retarded. He had weak eye closure and myotonia of grip.
Slit-lamp: coloured opacities too few for a diagnosis.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 0 - my 2 - we 1 - me 1.

V-1 Has difficulty opening his fists and sometimes cramps in tongue, but does not know since when. At 19 he worked in a shop and appeared slow; he had mild weakness of facial and distal limb muscles with indistinct speech and myotonia of grip.
Slit-lamp: normal lenses.
EMG: myotonic discharges.

Myotonic dystrophy, onset 2nd decade.
Severity score: cat 0 - my 2 - we 1- me 1.

V-2 Aged 10, had no symptoms apart from frequent vomiting diagnosed as repeated stomach retention. She had difficulties keeping up in primary school and repeated one class. She appeared slow and had weak eye closure.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 0 - my 1 - we 0 - me 1.

V-3 Aged 4, no symptoms apart from chronic constipation. Was an active child with normal motor performance, no weakness or myotonia were found.
Slit-lamp: normal lenses.
EMG: normal.

V-4 Noticed stiff hands some weeks before examination at the age of 9. Had difficulties keeping up in primary school and repeated one class. At 9 she was slender and appeared slow. Weak eye closure was the only sign.
Slit-lamp: normal lenses.
EMG: myotonic discharges.
Myotonic dystrophy, onset 1st decade.
Severity score: cat 0 - my 1 - we 1 - me 1.

V-5 Aged 7, full examination normal.

V-6 Attended a special school because she was too slow. Her mother said she was a normal baby and her motor development had been normal. At 9 she had weak eye closure and a myopathic facies.
Slit-lamp: normal.
EMG: Myotonic discharges.
Myotonic dystrophy, onset 1st decade.
Severity score: cat 0 - my 2 - we 1 - me 2.

V-7 Full examination was normal at the age of 5 and again at the age of 10.

V-8 Died shortly after premature birth. The gynaecologist reported gestation was 33 weeks, complicated by polyhydramnios of 2500 cc. She did not start to breathe, although the heart action was normal and she was noted to be hypotonic. The birth weight was 1720 gram. No diagnosis was made, the routine postmortum examination was normal.

V-9 Third index patient, see above.

V-10 Aged 6, was an active child, no symptoms or signs.
Slit-lamp: normal lenses.
EMG: not performed.

V-11 Aged 2, was an active child with normal motor performance, no symptoms or signs.
Slit-lamp and EMG not performed.

Family B

The eye symptoms of this family have been reported by Junge (1966, pedigree G). Several patients of this family were examined at their homes and EMG and slit-lamp examination could not be performed.

The index case was III-3. She had no symptoms, but worried about whether her son, who was slow in motor development, might have the same muscular disease as her brothers and sisters. She said Junge had examined her family in 1964. She was 27 years old and was normal at full examination. Her son had no signs of myotonic dystrophy on examination, but slit-lamp and EMG examination were not performed.

I-1 Died at the age of 75 of a stroke. At 68 myotonic cataracts were diagnosed by Junge in the course of a family investigation. At the age of 69 he was operated upon for these. His

daughters reported he never had muscle weakness or cramps and he had been an active man.
Myotonic dystrophy, onset 7th decade.

II-1 Not examined, lived abroad.

II-2 Noticed difficulty opening her fists after her 5th pregnancy at the age of 31. Later she developed progressive weakness of arms and legs with hypersomnia and inactivity. At 54 she was slow, but appeared of normal intelligence. She could still walk with support and needed full time help to run her household. She had moderate weakness of facial, neck and proximal limb muscles and severe distal limb weakness with myotonia of grip. Cataracts were seen on ophthalmoscopy. Slit-lamp and EMG were not performed. Junge diagnosed myotonic cataracts at the age of 42.
Myotonic dystrophy, onset 4th decade.
Severity score: cat ? - my 2 - we 2 - me 2.

II-3 Noticed cramps of her hands at the age of about 35. Was operated upon for cataracts when aged 40 and 44. A 51 she appeared inactive but of normal intelligence. She ran her own household. She had mild weakness of facial, neck and distal limb muscles with indistinct speech and myotonia of grip.
EMG: myotonic discharges.
Myotonic dystrophy, onset 4th decade.
Severity score: cat 3 - my 2 - we 2 - me 1.

III-1 First noticed cramps at the age of 13 when writing at school. She attended primary school until the age of 10 and later a special school for retarded children. At 31 she was slow and complained of hypersomnia, she needed a daily help to run her household. She had mild weakness of facial, neck and distal arm muscles and moderate weakness of foot extension with a stepping gait. Her speech was indistinct and she had myotonia of grip. Slit-lamp and EMG were not performed.
Junge diagnosed a beginning myotonic cataract at the age of 19.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat ? - my 2 - we 2- me 2.

III-2 Noticed cramps and weakness of his hands during gymnastics at school when he was 12. Attended a special school for retarded children. At 29 he worked in a sheltered workshop and was not married. He had mild weakness of facial, neck and distal arm muscles and moderate weakness of foot extension, with myotonia of grip. Cataracts were seen on ophthalmoscopy.
Slit-lamp and EMG were not performed.
Junge found no cataracts at the age of 16.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat ? - my 2 - we 2 - me 2.

III-3 Index case, see above.

III-4 At the age of 26, no symptoms or signs on examination at her home.
Slit-lamp and EMG were not performed.

III-5 First noticed cramps in her hands during gymnastics at school at the age of 14. Attended a special school for retarded children from the age of 6, where she learned to read, write and cook. At 23 she worked in a sheltered workshop. She appeared to be inert. She had mild weakness of facial, neck and distal limb muscles with myotonia of grip and indistinct speech.
Slit-lamp and EMG were not performed. Junge found no cataracts at the age of 11.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat ? - my 2 - we 1 - me 2.

III-6 At the age of 19, full examination normal.

III-7 Was admitted into a home for retarded children at the age of 4. His mother noticed he had difficulty opening a fist during childhood, but reported no symptoms in the neonatal period. At 18 he could not read or write, was very slow and hypersomniacal. He had mild weakness of facial, neck and distal limb muscles with myotonia of grip and indistinct speech.

Slit-lamp and EMG were not performed.
Junge found no cataracts at the age of 5, but reported clinical myotonia.
Myotonic dystrophy, onset 1st decade.
Severity score: cat ? - my 2 - we 1 - me 3.

III-8 At the age of 31, full examination normal.

III-9 At the age of 28, normal neurological and slit-lamp examination.
EMG not performed.

III-10 At the age of 23, traumatic cervical cord lesion, no signs of myotonic dystrophy.
Slit-lamp normal, EMG not performed.

IV-1 His mother reported he had respiratory and feeding problems during the neonatal period. He was a lazy baby and his motor development was delayed. Speech was always indistinct and he attended a special school for retarded children. At 11 he had a tent-shaped mouth, weakness of facial, neck and foot extension muscles and myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, congenital involvement, decade 0.
Severity score: cat 2 - my 2 - we 2 - me 3.

IV-2 At the age of 3 an active child with normal motor performance.
Neurological and EMG examination normal.
Slit-lamp not performed.

Family C

The index patient, V-1, was admitted to the neonatal intensive care unit for severe neonatal myotonic dystrophy. The diagnosis was made by the pediatrician on the clinical picture: she had severe hypotonia, bilateral talipes equinovarus, facial diplegia and no respiratory activity at all. After 3 days of artificial ventilation she died (case III, Pearse and Höweler, 1979). At postmortem examination a subcapsular haematoma of the liver and agenesis of the corpus callosum were found. slit-lamp and EMG were not performed. Myotonic dystrophy, congenital involvement, onset decade 0.

I-1 A sculptor, died suddenly at the age of 59. His daughter, II-1, reported he had no invalidating disease or cataracts and he had been able to work until his death.

I-2 Died suddenly at the age of about 55. II-1 reported that he probably had the same disease as III-1, 2 and 3, because he had similar difficulties in walking and buttoning his coat. He was married but had no children. A photograph taken at the age of about 40 shows his early frontal balding but no myopathic facies.

I-3 Two sibs, no data.

II-1 Was operated upon for right-sided cataract at the age of 71, her visual acuity had diminished two years before the operation. At 71 the vision of the left eye was also declining, she had no other symptoms and was running her own household. She had percussion myotonia of the thenars and mild sternomastoid atrophy.
Slit-lamp: left myotonic cataract.
EMG: not performed.
Myotonic dystrophy, onset 7th decade.
Severity score: cat 3 - my 2 - we 0 - me 0.

II-2 Three sibs, not examined, one was known to II-1 to have myotonic dystrophy.

III-1 First noticed cramps in her hands on opening a door at the age of 8; after the age of 40 she started to fall frequently. At 48 she was married without children and was running her own household. She appeared slow and had indistinct speech. She had mild weakness of facial, neck and distal limb muscles with myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: not performed.

Myotonic dystrophy, onset 1st decade.
Severity score: cat ? - my 2 - we 2 - me 1.

III-2 Noticed cramps in his hands on making a fist at the age of 7. After the age of 30 walking became difficult, but he could sustain a full-time administrative post until the age of 45. He was married without children. At 47 he still had a part time administrative job. He appeared slow but of normal intelligence. He had weak facial and neck muscles and moderate distal limb weakness.
Slit-lamp: Myotonic cataracts.
EMG: not performed.
Myotonic dystrophy, onset 1st decade.
Severity score: cat ? - my 2 - we 2 - me 1.

III-3 First noticed cramps in her hands when playing the piano at the age of 17. Muscle weakness started 10 years later. At 42 she appeared alert and of normal intelligence and could run her own household. She had mild weakness of facial, neck and distal limb muscles, with myotonia of grip.
Slit-lamp: coloured opacities too few for a diagnosis.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 0 - my 2 - we 2 - me 0.

III-4 At 38 no symptoms or signs.
Slit-lamp normal, EMG not performed.

IV-1 Was a normal baby with normal motor development, but attended a special school for retarded children from the age of 4. Remembered having cramps in her hands at school at the age of 6; she attended speech lessons when she was 8. At 21 she appeared to be mentally retarded but could run her own household. She had weakness of facial, jaw and neck muscles and weak foot extension, with indistinct speech and myotonia of grip.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonic dystrophy, onset 1st decade.
Severity score: cat 0 - my 2 - we 2 - me 3.

IV-2 Died after birth of unexplained asphyxia. The gynaecologist reported him as appearing normal and he had a normal heart action. There was polyhydramnios from the 29th week of pregnancy and several times 3 to 4 liter excessive amniotic fluid had been removed. In retrospect this baby probably had congenital myotonic dystrophy.

IV-3 At the age of 14, full examination normal.

V-1 Index patient, see above.

Family D

The index patient, IV-5, was referred to the children's neurology department for psychomotor retardation at the age of 2 years and myotonic dystrophy was diagnosed on the clinical picture and the recognition of myotonic hands in the mother. At birth he had been floppy and was admitted to a hospital for insufficient respiration and feeding problems. The gynaecologist reported polyhydramnios of 12000 cc. At 2 years he could not role, sit or stand. He was hypotonic with head lag and the legs in frog position. He had facial diplegia, general muscle weakness and absent tendon jerks.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonic dystrophy, congenital involvement, onset decade 0.

I-1 At 83, no symptoms or signs apart from diminished visual acuity.
Slit-lamp: non-diagnostic white lenticular opacities.
EMG: normal.

I-2 Died at the age of 35 of postpartum thrombosis.

II-1 Noticed difficulty opening her fists during a flood at the age of 34. Was operated upon for cataracts when aged 48 and 49. At 55 she could run her own household. She appeared active and of normal intelligence. She had mild weakness of facial and hand muscles and myotonia of grip. She died suddenly at the age of 56.
EMG not performed.
Myotonic dystrophy, onset 4th decade.
Severity score: cat 3 - my 2 - we 1 - me 0.

II-2 Six sibs, not examined. II-1 reported one of them had muscle weakness and cramps in his hands.

III-1 At 38, full examination normal.

III-2 Aged 36. No symptoms; absent ankle jerks. slit-lamp and EMG normal.
Conclusion: equivocal diagnosis; the absent ankle jerks may be an early sign of myotonic dystrophy, but they are not sufficient for a diagnosis.

III-3 First noticed cramps in her hands when washing in cold water at the age of 13. At 29 she could run her own household and appeared active and of normal intelligence. She had mild facial and neck weakness with myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: not performed.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 1 - my 2 - we 1 - me 0.

IV-1 Aged 18. No symptoms or signs.
Slit-lamp: 3 coloured subcapsular opacities, too few for making a diagnosis.
EMG: normal.

IV-2 Aged 16, full examination normal.

IV-3 Was floppy at birth and had to be admitted to a hospital for respiratory and feeding problems for several weeks. Sat and walked late, speech had always been indistinct. At 9 she attended a special school for mentally retarded children. She had facial diplegia with a tent-shaped mouth, mild neck weakness and myotonia of grip.
Slit-lamp: normal. EMG not performed.
Myotonic dystrophy, congenital involvement, onset decade 0.
Severity score: cat 0 - my 2 - we 1 - me 3.

IV-4 Died shortly after birth at home, cause unknown, gestation and delivery were normal.

IV-5 Index patient, see above.

Family E

The index patient, II-2, was admitted to the medical department at the age of 47, for fatigue and constipation. Indistinct speech and difficult walking were noticed, and the consultant neurologist diagnosed myotonic dystrophy. At 23 she first noticed stiffness and weakness of her hands when making a fist and 20 years later walking became difficult. She discontinued her full-time administrative job at the age of 46 because of general fatigue. At 47 she could not run her household without help, but she appeared of normal intelligence. She had atrophy and weakness of facial, jaw, neck and distal limb muscles with myotonia of grip. Slit-lamp: coloured opacities too few for making a diagnosis.
EMG: myotonic discharges.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 0 - my 2 - we 2 - me 1.

I-1 Died at 68 of diabetes. No muscle symptoms or cataracts were known to his widow.

I-2 Five sibs, no data.

I-3 Died at 73 of heart disease, had no muscle symptoms or cataracts according to his grandchild.

II-1 At 51, full examination normal.

II-2 Index patient, see above.

II-3 Died suddenly at the age of 45, presumably of heart disease; according to his son he had been a strong and active man.

II-4 Two sibs, one died at 42 of cancer, the other was not examined.

III-1 Had respiratory problems after birth; had to be resuscitated after a normal delivery. Kept drinking very slowly for several months. Her motor development was normal, but she appeared mentally retarded when she was 4 and attended special schools. At 16 she had a tent-shaped mouth, weakness of facial, neck and distal limb muscles and percussion myotonia of the thenars.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonic dystrophy, onset decade 0, congenital involvement.
Severity score: cat 0 - my 2 - we 1 - me 3.

III-2 Aged 36, full examination normal.

III-3 Noticed inability opening a fist at the age of 22. Since the age of 28 she was repeatedly admitted for atrial fibrillation and congestive heart failure for which no cause was found. At 31 she managed her own household but appeared slow. She had weakness of eye closure and foot extension and myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 1 - my 2 - we 1 - me 1.

III-4 Noticed cramps in her hands when she was 21, but already at school her speech had been nasal. At 23 she worked as an enrolled nurse and appeared alert and of normal intelligence. She had weak eye closure, atrophy of temporals and sternomastoids, and myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 1 - my 2 - we 1 - me 0.

IV-1 Aged 16, full examination normal.

IV-2 Aged 14, full examination normal.

Family F

The first index patient, IV-5, was referred to the department of child neurology for psychomotor retardation. At birth he had had severe asphyxia and had been ventilated for 15 minutes. He had been floppy and had had feeding problems. His motor development was slow, he sat at the age of 14 months. At the age of 20 months he could stand but he could neither walk nor talk. On examination at 20 months he had facial diplegia, a tent-shaped drooping mouth, hyptonic limbs with normal muscle strength and normal tendon jerks.
Slit-lamp: normal.
EMG: myotonic discharges.
A diagnosis of congenital myotonic dystrophy was made by the child neurologist, onset decade 0.

The second index patient, III-2, was referred to the neurologist for weakness of his hands since the age of 34. He had never had cramps in his hands. At 36 he worked as a driver. He had mild weakness of facial and neck muscles, and moderate weakness of his hands and forearms. Myotonia was found on percussion of the thenars.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 4th decade.
Severity score: cat 2 - my 2 - we 2 - me 0.

I-1 Died at the age of 70 of septicaemia after a war injury; he also had diabetes. He had no invalidating disease or cataracts according to his son.

I-2 Five sibs, no data.

I-3 Died at the age of 68, cause unknown. No invalidating disease was reported.

II-1 At the age of 66, the visual acuity of his right eye had been diminished for a year because of a cataract. No other symptoms or signs.
Slit-lamp: left myotonic cataract, right mature grey cataract.
EMG: normal.
Myotonic dystrophy, onset 7th decade.
Severity score: cat 3 - my 0 - we 0 - me 0.

II-2 Four sibs; two died, two were not examined. No invalidating disease or cataracts reported by their brother.

II-3 Four sibs, two died, two were not examined. No invalidating disease or cataracts were reported by III-6.

II-4 Died at the age of 58 of renal failure, was reported by his widow to have been otherwise healthy.

III-1 Aged 39, had no symptoms and worked as a busdriver. On examination weak eye closure, atrophic temporals and sternomastoids and percussion myotonia of the thenars were found.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 4th decade.
Severity score: cat 1 - my 2 - we 1 - me 0.

III-2 Second index patient, see above.

III-3 Aged 32, not examined.

III-4 Aged 44, full examination normal, reported her three children as being healthy.

III-5 Aged 41, full examination normal, reported her two children as being healthy.

III-6 Aged 38, full examination normal. Reported her three children as being healthy.

III-7 Was first examined at the age of 32, when congenital myotonic dystrophy was diagnosed in her two children, the elder being 7. She had no symptoms or signs. EMG was normal and on slitlamp examination only one green subcapsular opacity was found, which was considered non-diagnostic. Her husband was also normal on full examination. When reexamined one year later slit-lamp examination showed many coloured opacities diagnostic for myotonic cataracts, and she had myotonic discharges on the EMG.
Myotonic dystrophy, onset 4th decade.
Severity score: cat 1 - my 1 - we 0 - me 0.

III-8 Aged 30, full examination normal.

IV-1 Not examined.

IV-2 Aged 11, was slow and slightly built, but no diagnostic symptoms or signs were found. Slit-lamp and EMG normal.

IV-3 Aged 7, normal on neurological and slit-lamp examination.
EMG not performed.

IV-4 Had had cyanotic attacks for several days after birth, feeding problems for several weeks, and had been hypotonic for several months. Her motor development had been slow and she always had an open drooping mouth. At 7 she attended a special school for retarded children. She had a tent-shaped mouth and weak eye closure, indistinct speech and weak foot extension. Her I.Q. was found to be 85.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonic dystrophy, onset decade 0, congenital involvement.
Severity score: cat 0 - my 1 - we 1 - me 3.

IV-5 First index patient, see above.

Family G

The first index patient, IV-10, was referred to the neurologist for difficulty in walking at the age of 58. Some years before his marriage, when aged 40, he started to fall frequently. His condition deteriorated and he had to give up his farm at the age of 45. He never had cramps in his hands. At 63 he still walked with a cane, and worked in a sheltered workshop. He had severe weakness of facial, neck and distal limb muscles. Grip or percussion myotonia could not be found.
Slit-lamp: right myotonic cataract, left mature diffuse cataract.
EMG: myotonic discharges.
Myotonic dystrophy, onset 4th decade.
Severity score: cat 2 - my 1 - we 3 - me 2.

The second index patient, V-1, was referred to the neurologist for stiff hands when aged 32. She first noticed this when hanging in swinging rings during gymnastics between the age of 12 and 14. She was prematurely born, weighing 1500 grams, and had always been slow. At 32 she had no job and was not married. She was slow and irritable; she had milk weakness of facial, neck and distal limb muscles and severe myotonia of grip. Slit-lamp: Myotonic cataracts. EMG: not performed. Myotonic dystrophy, onset 2nd decade. Severity score: cat 2 - my 3 - we 2 - me 2.

I-1 Born in 1799, age of death unknown.

I-2 Born in 1813, died at the age of 77.

II-1 Age of death unknown.

II-2 Died at the age of 79 of a stroke.

III-1 Died at 46 of galbladder disease. Her children reported her as not having muscular disease or cataracts.

III-2 Died at the age of 81, had no children.

III-3 Four sibs, no data.

III-4 Died at 56 of a stroke. His children reported he had had no invalidating disease or cataracts.

IV-1 Died at 67 of kidney disease.

IV-2 Aged 70, no symptoms or signs. Slit-lamp: non specifiec nuclear lens opacities.
EMG: normal.

IV-3 Not examined.

IV-4 Died suddenly at the age of 32, no further data.

IV-5 Was operated upon for cataracts at 46 and 48 respectively. When examined at 62 he had no other symptoms or signs.
EMG: myotonic discharges.
Myotonic dystrophy, onset 5th decade.
Severity score: cat 3 - my 1 - we 0 - me 0.

IV-6 Aged 60, no symptoms or signs.
Slit-lamp: non specific white lenticular opacities.
EMG: normal.

IV-7 Aged 56, full examination normal.

IV-8 Aged 65, no symptoms or signs. At slit-lamp examination a few green subcapsular opacities were seen. EMG normal.
Some doubts existed as to whether the lenticular opacities were senile or myotonic opacities. Therefore 5 of her 6 children were fully examined; they were found to be normal.
Conclusion: probably no heterozygote for myotonic dystrophy.

IV-9 Aged 64, full examination normal.

IV-10 First index patient, see above.

IV-11 Aged 61, full examination normal.

IV-12 Had already indistinct speech when married at the age of 26, but he was then still active in sports; weakness of arms and legs started at the age of 36 and gradually progressed. He never had stiff hands. He had protected work until the age of 57. At 58 he was very slow but his intelligence appeared normal. He could still walk a hundred meters. He had macroscopic cataracts, severe weakness of facial, neck and distal limb muscles and percussion myotonia of the thenars.
Slit-lamp and EMG not performed.
He died suddenly at the age of 59.
Myotonic dystrophy, onset 4th decade (possibly 3rd).
Severity score: cat ? - my 2 - we 3 - me 2.

IV-13 Began to fall frequently shortly after her marriage at the age of 26. The weakness of legs and arms progressed especially during pregnancies. At 54 she could only walk with support for 30 meters. She was slow and had hypersomnia, but could still run her household. She had severe weakness of facial, jaw and distal limb muscles, and also weakness of proximal leg muscles. Myotonia was found on percussion of the thenars.
Slit-lamp: coloured opacities too few for making a diagnosis.
EMG not performed.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 0 - my 2 - we 3 - me 1.

V-1 Second index patient, see above.

V-2 Noticed difficulty in opening a fist between the ages of 20 and 30. At the age of 31 she had mild weakness of face and neck muscles, nasal speech and myotonia on percussion of the thenars.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 1 - my 2 - we 1 - me 0.

V-3 Died at the age of 18 of acute staphylococcal pneumonia. His sister said he had had the same face and mental inertness as V-1.

V-4 Aged 28, full examination normal.

V-5 Noticed inability to open a fist when she was 14, and started to fall frequently at the age of 24. At 26 she had mild facial, neck and foot extension weakness, and myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 1 - my 2 - we 2 - me 0.

V-6 Aged 21, full examination normal.

V-7 Aged 31, full examination normal.

V-8 Aged 25, full examination normal.

V-9 Died 15 minutes after birth; did not breathe for unknown reason. The midwife reported polyhydramnios. In retrospect this baby probably had congenital myotonic dystrophy.

V-10 Died half an hour after birth. The gynaecologist reported that he did not breathe although the reason was unknown; his heart action was normal at birth. Birth weight 2080 grams; the membranes had ruptured at home. Postmortem examination did not reveal a cause of death.
In retrospect this baby may have had congenital myotonic dystrophy.

V-11 Aged 20, full examination normal.

V-12 Aged 18, full examination normal.

V-13 Died 18 hours after delivery by caesarian section for placenta praevia. The gynaecologist reported that he did not breathe well. Gestation 33 weeks, birth-weight 2400 grams, no hydramnios. Death was attributed to prematurity.

In retrospect this baby may have had congenital myotonic dystrophy.

VI-1 Had respiratory problems for several days and feeding problems for several months after birth; the motor development was delayed, he did not walk until the age of 3. When two years old, a left hemiparesis was diagnosed. At the age of 3 he was admitted to a home for mentally retarded children. At 9 he was a mentally retarded boy with indistinct speech and a tent-shaped drooping mouth. He had weakness of facial, neck and hand muscles, and a pyramidal paresis of the left leg. Myotonia could be elicited on percussion of the thenars.
Slit-lamp: normal.
EMG: not performed.
Myotonic dystrophy, onset decade 0, congenital involvement.
Severity score: cat 0 - my 2 - we 1 - me 3.

VI-2 Aged 6, no symptoms or signs.
Slit-lamp normal, EMG not performed.

Family H

The first index patient, V-15, was referred to the neurologist for weakness of her hands. She noticed difficulty opening a fist at the age of 15. Weakness started 5 years later. At 29 she was married and was running her own household. She had mild weakness of eye closure, neck flexion and foot extension, and moderate weakness of hand muscles with myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 2 - my 2 - we 2 - me 0.

The second index patient, V-2, was referred to the neurological department for weakness of her hands and indistinct speech. Her grandmother"s name was recognized as being the same as that of II-2. She first noticed cramps when shaking hands at the age of 16. Indistinct speech was noticed when she was 21, and gradually her hands became weak. At 38 she was married and capable of running her household. She had mild weakness of eye closure, hand muscles and foot extensors, atrophic temporals and sternomastoids, indistinct speech and myotonia of grip. Slit-lamp: coloured opacities too few for making a diagnosis.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 0 - my 2 - we 1 - me 0.

I-1 Born 1819, age of death not known.

I-2 Born 1824, age of death not known.

II-1 Died at the age of 77.

II-2 Age of death not known.

III-1 Died at the age of 84, did not have an invalidating disease or cataract, according to his son.

III-2 Eight sibs, no data.

III-3 Died at 79 of a stroke. Was operated upon for cataracts when about 68, no muscular disease was known to his children.

III-4 Eight sibs, no data.

IV-1 No symptoms or signs at 71.
Slit-lamp: coloured opacities too few for making a diagnosis.
EMG: normal.
No diagnosis could be made. His wife was normal on full examination.

IV-2 Of his 8 brothers and sisters no one was known to have cataracts or a muscular disease.

IV-3 Died at 56 of cancer. According to his children he had no muscular disease or cataracts.

IV-4 Died at 70 of cancer. Had no invalidating disease, but several of her 12 children living abroad were known to have myotonic dystrophy.

IV-5 Aged 69, full examination normal.

IV-6 Aged 68, full examination normal.

IV-7 Noticed cramps in his hands, jaw muscles, tongue and eye muscles at the age of 14. Was admitted to a neurological department at the age of 23, and weakness of facial, jaw, hand and arm muscles was found, with active and percussion myotonia of forearm muscles. A diagnosis of myotonic dystrophy was made.
Slit-lamp: no cataracts.
EMG: not performed.
According to his brother his condition progressed gradually with increasing muscle weakness necessitating a wheelchair at the age of 48, increasing slowness and hypersomnia, diarrhoea, baldness and cataracts. He died at the age of 53. Myotonic dystrophy, onset 2nd decade.

IV-8 Aged 62, full examination normal.

IV-9 Noticed difficulty opening her fists when washing in cold water at the age of 33. She also had cramps in her lips when talking. Her condition did not deteriorate. She was admitted at the age of 60 for heart arrhythmia; at 61 she had percussion myotonia of the thenars but no muscular weakness was found, apart from weak left foot extension which had remained after a lumbar disk hernia. Slit-lamp: coloured opacities too few for a diagnosis.
EMG: myotonic discharges.
Myotonic dystrophy, onset 4th decade.
Severity score: cat 0 - my 2 - we 0 - me 0.

IV-10 Noticed cramps in her hands at the age of 36. Weakness of hands and difficulty walking appeared after the age of 50. She was operated upon for cataract at the age of 53. At 56 she was capable of running her household. She had mild weakness of facial, jaw and neck muscles, and moderate weakness of distal limb muscles.
Slit-lamp: left myotonic cataract.
EMG: not performed.
Myotonic dystrophy, onset 4th decade.
Severity score: cat 3 - my 2 - we 2 - me 0.

V-1 Aged 43, full examination normal.

V-2 Second index patient, see above.

V-3 Aged 45, full examination normal.

V-4 Noticed stiffness of her hands at domestic science school at the age of 15, when washing in cold water. She did not notice muscle weakness, but frequently sprained her ankles. At 44 she was well capable of running her household. She had atrophic temporals and sternomastoids, and weakness of eye closure, neck flexion and foot extension.
Slit-lamp: coloured opacities too few for making a diagnosis.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 0 - my 2 - we 1 - me 0.

V-5 Died suddenly at the age of 37, the night after having a hysterectomy. She was not known to have myotonic dystrophy, but her widower said she already had cramps in her hands and indistinct speech before she married at 26.

V-6 Noticed cramps in her hands during cold weather at the age of 41, and at the same time she could not raise her hands when lying down. At 42 she had atrophic temporals and sternomastoids and mild weakness of facial, neck and distal limb muscles, with percussion myotonia of the thenars.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 5th decade, possibly 4th.

Severity score: cat 1 - my 2 - we 1 - me 0.

V-7 First noticed cramps in her hands after carrying weights and washing in cold water at the age of 23. Weakness appeared in the left hand when she was 39. At 41 she was well capable of running her household. She had weakness of facial, neck and left hand muscles and atrophic temporals, sternomastoids and forearms, with myotonia of grip.
Slit-lamp: coloured opacities too few for making a diagnosis.
EMG: myotonic discharges.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 0 - my 2 - we 1 - me 0.

V-8 Aged 40, full examination normal.

V-9 Noticed cramps in his hands in cold weather at the age of 35. Two years later he started to fall frequently. At 40 he still coped with his work as a carpenter. He had mild weakness of facial, neck and distal limb muscles, and moderate weakness of proximal muscles of arms and legs! Myotonia was found in his hand muscles.
Slit-lamp: myotonic cataracts.
EMG: not performed.
Myotonic dystrophy, onset 4th decade.
Severity score: cat 1 - my 2 - we 2 - me 0.

V-10 Aged 37, full examination normal.

V-11 Noticed stiffness of tongue, jaw muscles and upper lip during talking, laughing and swallowing, at the age of 33. At 33 she had thin sternomastoids, percussion myotonia of the thenars and weak ankle jerks.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonic dystrophy, onset 4th decade.
Severity score: cat 0 - my 2 - we 0 - me 0.

V-12 Noticed cramps in his hands when carrying heavy weights at the age of 26. At 27 he had thin sternomastoids and active myotonia of upper lip and hand muscles.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 0 - my 2 - we 0 - me 0.

V-13 Noticed cramps in her hands in cold weather at the age of approximately 15. Noticed leg weakness when she was 33. At 34 she was capable of running her own household. She had weakness of facial, neck and distal limb muscles and myotonia on percussion of the thenars.
Slit-lamp: myotonic cataracts.
EMG: not performed.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 2 - my 2 - we 2 - me 0.

V-14 Aged 32, full examination normal.

V-15 First index patient, see above.

VI-1 Aged 6, no symptoms or signs on examination.
Slit-lamp: normal.
EMG: not performed.

VI-2 Developed nasal speech after tonsillectomy when aged 5, having previously had normal speech. Has always been a slow child, but attended primary school and domestic science school. First noticed cramps in her hands when she was 14. At 19 she worked as an enrolled nurse. She was a quiet girl with weak facial and neck muscles, nasal speech, absent tendon jerks of the arms, and myotonia on percussion of the thenars.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 1st decade.
Severity score: cat 1 - my 2 - we 1 - me 1.

VI-3 Aged 16, full examination normal.

VI-4 Had indistinct nasal speech and an open mouth since childhood, but no symptoms were noted in the neonatal period. Mental retardation was noticed at nursery school and he attended special schools. Age not known when cramps in his hands began. At 15 he had a tent-shaped mouth, weak eye closure and neck flexors, and myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 1st decade.
Severity score: cat 1 - my 2 - we 1 - me 3.

VI-5 Aged 16, full examination normal.

VI-6 Aged 14, full examination normal.

VI-7 Aged 15, full examination normal.

VI-8 Still-born after 36 weeks' gestation. The mother said foetal movements were absent two weeks before delivery. Polyhydramnios of 4000 cc was documented by the gynaecologist. No cause was found at routine postmortem examination.
In retrospect this baby probably had congenital myotonic dystrophy.

VI-9 Aged 11, full examination normal.

VI-10 Aged 8. After a normal perinatal period and psychomotor development he became psychotic at the age of two, and now lives in a home for psychotic children. The neurologist reported he found no signs apart from mild hypotonia, and EMG examination was normal.

VI-11 Nine months old, not examined, normal neonatal period and motor development according to his father.

VI-12, 13 and 14 not examined.

Family J

The index patient, III-6, was referred to the neurological department at the age of 26 for difficulty in walking. At about the age of 20 his speech became indistinct and when he was 24 he first noticed cramps and weakness of his hands; a year later he started to stumble frequently. He was active in sports until the age of 16. At the age of 26 he was well capable of doing his work as a social worker. He had mild weakness of facial, jaw, neck and distal arm muscles, and moderate weakness of the foot extensors, with myotonia of grip.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonic dystrophy, onset 3rd decade, possibly 2nd.
Severity score: cat 0 - my 2 - we 2 - me 0.

I-1 Died at the age of 86, became blinded by cataracts after the age of 80. According to his sons he was otherwise healthy.

I-2 Died at the age of 84, reported as being healthy until old age.

II-1 Aged 60, no symptoms or signs.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 7th decade.
Severity score: cat 1 - my 1 - we 0 - me 0.

II-2 Aged 58, no symptoms or signs.
Slit-lamp: normal.
EMG: not performed.

II-3 Aged 53, no symptoms or signs.
Slit-lamp: myotonic cataracts.

EMG: normal.
Myotonic dystrophy, onset 6th decade.
Severity score: cat 1 - my 0 - we 0 - me 0.

II-4 Died at the age of 3 weeks of spina bifida.

II-5 Started to stumble shortly after completing his military service at the age of 22. His condition gradually deteriorated, he had to stop work as a mechanic when he was 42. At 47 he could still walk unsupported for 20 minutes, but could not drink out of a cup without help. His intelligence appeared normal. He had mild weakness of facial and neck muscles, moderate proximal and severe distal limb weakness, with myotonia on percussion of the thenars.
Slit-lamp: myotonic cataracts.
EMG: not performed.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 1 - my 2 - we 2 - me 1.

III-1 Aged 29, full examination normal.

III-2 Started to have nasal speech approximately at the age of 20, no other symptoms. She worked as a secretary until her marriage. At 27 no other signs than nasal speech could be found.
Slit-lamp: myotonic cataracts.
EMG: normal.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 1 - my 0 - we 1 - me 0.

III-3 Aged 24, full examination normal.

III-4 Aged 17, full examination normal.

III-5 Aged 27, full examination normal.

III-6 Index patient, see above.

III-7 Aged 24, full examination normal.

III-8 Aged 20, full examination normal.

III-9 Aged 17, full examination normal.

III-10 Noticed difficulty stretching her fingers some months before examination. At 13 she was reported to be inactive, she attended a domestic science school after completing primary education. Se had atrophic temporals and mild facial weakness and myotonia of grip.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 0 - my 2 - we 1 - me 1.

III-11 Noticed cramps in his hands during gymnastics at school at the age of 14. Completed primary and technical school. At 23 he worked in a sheltered workshop and was single. He was quiet and slow, and had mild weakness of facial, neck and distal limb muscles, with myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 1 - my 2 - we 1 - me 1.

III-12 Had nasal and indistinct speech since childhood, for which he had palatal surgery when he was 10. He completed primary and technical school. Cramps in his hands were noticed at the age of 14. At 21 he worked in a sheltered workshop, he was too slow in other jobs. He had weakness of facial and neck muscles and atrophic temporals, sternomastoids and forearms, with myotonia of grip and indistinct speech.
Slit-lamp: coloured opacities too few for making a diagnosis.
EMG: myotonic discharges.
Myotonic dystrophy, onset 1st decade.

Severity score: cat 0 - my 2 - we 1 - me 2.

III-13 Aged 19, full examination normal.

III-14 Aged 18, full examination normal.

III-15 Was 9 when his brother's disease was diagnosed; his mother noticed that he frequently sprained his ankles, had hypersomnia and frequent diarrhoea. His general condition was reported to have improved after the age of 12. At 14 he attended a special school for retarded children. He had mild facial weakness and indistinct speech, absent tendon jerks of arms and ankles, and myotonia of grip.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonic dystrophy, onset 1st decade.
Severity score: cat 0 - my 2 - we 1 - me 1.

IV-1 Aged 21 months, no symptoms or signs, normal neonatal period and motor development. Slit-lamp and EMG not performed.

IV-2 Aged 2 months. No symptoms or signs. Normal neonatal period and motor development. Slit-lamp and EMG not performed.

Family K

The index patient, IV-1, was admitted to the neonatal intensive care unit for postnatal asphyxia shortly after birth. She had severe hypotonia, oedema, facial diplegia with a tent-schaped mouth and generalized weakness and atrophy of the limb muscles. Neonatal myotonic dystrophy was suspected by the child neurologist and diagnosed after examination of the mother. She gradually improved, but hypotonia of the legs was still present when she was 14 months old and her motor development was mildly retarded (case 2, Pearse and Höweler, 1979). Myotonic dystrophy, onset decade 0, congenital involvement.

I-1 Died at the age of 67 of bladder disease, no invalidating disease or cataracts according to his children.

I-2 Died at the age of 77, no invalidating disease or cataracts according to her children.

II-1 Was operated upon for cataracts at the ages of 38 and 50. His wife noticed, when he was about 47 years old, that his hands became weak and that he had difficulty walking; later he became slow and slept much during the day. At 67 he died of a neck fracture after falling down the stairs. During admission for this trauma, myotonic dystrophy was diagnosed by the neurologist. Apart from a spastic tetraparesis he had atrophic temporal and hand muscles ad myotonia on percussion of the thenars.
EMG was not performed.
Myotonic dystrophy, onset 4th decade.

II-2 Ten sibs were not examined: 3 had died, one of these was known to have had the same disease as II-1. Seven were alive, two of these were known to have the same muscular disease as II-1. These 3 myotonic dystrophy patients were all married but none had had children.

II-3 Noticed inability to open a fist quickly at the age of about 44, when working in a dairy factory with his hands in cold water. After the age of 50 his hands became weak, he became slow and slept frequently during the day. At 54 he had just given up work as a ditch cleaner. He had mild weakness of facial, neck and distal limb muscles, atrophic temporals and sternomastoids and myotonia on percussion of the thenars.
Slit-lamp: normal.
EMG: not performed.
Myotonic dystrophy, onset 5th decade.
Severity score: cat 0 - my 2 - we 1 - me 2.

II-4 Aged 48, full examination normal.

III-1 Started to have cramps, weakness of his hands and difficulty with walking when about 15 years of age. Had always been slow and attended special schools for retarded children

from the age of 8. His mother said he has been a normal baby and his motor development was normal. A left cataract was operated upon when he was 33. At 38 he worked in a sheltered workshop because of mental retardation. He had mild facial and moderate neck weakness, mild distal arm weakness and moderate weakness of the foot extensors with myotonia of grip.
Slit-lamp: right mature grey cataract.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 3 - my 2 - we 2 - me 3.

III-2 Aged 36, full examination normal.

III-3 Not examined.

III-4 Aged 31, full examination normal.

III-5 Aged 28, full examination normal.

III-6 Aged 26, full examination normal.

III-7 Noticed difficulty opening a fist during gymnastics when about 13. Was active in sports until the age of 22 and never noticed weakness. Worked as a secretary until her marriage at 22. At 23 she had weak eye closure and atrophic temporals and sternomastoids, absent tendon jerks of arms and ankles and myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 2 - my 2 - we 1 - me 0.

III-8 Aged 21, full examination normal.

III-9 Died suddenly at the age of 21, 5 weeks after the delivery of her first child. According to her mother she was always slow and attended special schools from the age of 6, and she had noticed her having cramps in her hands from the age of 16. She had had no neonatal signs. At postmortem examination myocarditis with hypoplastic adrenals were reported as the probable cause of death. A diagnosis of myotonic dystrophy was not made.

III-10 Aged 24, no symptoms or signs.
Slit-lamp: normal.
EMG: not performed.

III-11 Aged 22, no symptoms or signs.
Slit-lamp: normal.
EMG: not performed.

III-12 Aged 20, full examination normal.

III-13 Had neonatal kernicterus and has always been retarded and deaf and dumb. His mother noticed cramps in his hands at the age of 11, later he started to shuffle when walking. At 17 he attended a school for retarded children. He had facial weakness with a tent-shaped mouth. He could not speak, but produced nasal sounds and he had myotonia of grip. His knee and ankle yerks were clonic.
Slit-lamp: normal.
EMG: not performed.
Myotonic dystrophy, onset 2nd decade, possibly 1st.
Severity score: cat 0 - my 2 - we 1 - me 3.

III-14 Noticed cramps in her hands when aged 10. Was slow at school but completed primary school. At 15 she attended the domestic science school, she appeared slow. She had mild facial weakness and atrophic sternomastoids, with nasal speech and myotonia of grip.
Slit-lamp: normal.
EMG: not performed.
Myotonic dystrophy, onset 2nd decade, possibly 1st.
Severity score: cat 0 - my 2 - we 1 - me 1.

IV-1 Index patient, see above.

IV-2 Not examined.

Family L

The first index patient, IV-1, was referred to the neurology department for neck and distal limb weakness at the age of 38. She first had difficulty opening a fist at about the age of 10. Her condition slowly deteriorated. At 38 she tired so quickly that she could not run her household with 4 children without help. She had moderate weakness of facial, neck, and distal limb muscles with myotonia of grip. She also had diabetes, cardiomyopathy and hydronephrosis.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Her lenses were extracted when she was 40; she died of a stroke at the age of 43.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 3 - my 2 - we 2 - me 1.

The second index patient, IV-9, was referred to the neurologist for weakness of arms and legs. When shaking hands, he noticed cramps at the age of 21. Later his hands became weak and he started to fall frequently when he was 32. He had to give up his work as a salesman at the age of 33. At 33 he had mild weakness of face and neck, and moderate distal limb weakness, with myotonia of grip.
Slit-lamp: right myotonic cataract.
EMG: myotonic discharges.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 1 - my 2 - we 2 - me 0.

I-1 Died aged 64 of a stroke.

I-2 Died aged 66 of diabetes. Their grandson, III-4, reported them as not having any invalidating disease or cataracts.

II-1 Died aged 47 of a stroke. His son said he had been a strong man, bald, and a skilled carpenter.

II-2 Eight sibs, no data.

II-3 Died aged 73, was reported to have been invalidated by hip disease.

III-1 Of 7 sibs 6 died very young, no data known.

III-2 Died at the age of 44, one day after galbladder surgery. His widow said he had had difficulty opening his fists from the age of 25, but had good strength in his arms and legs. He had no children.

III-3 Died when 48 of a right temporal glioblastoma. His widow said he had had cramps in his hands similar to those of his daughters. Prior to brain surgery the neurologist found weakness of both arms and legs, more prominent of the left arm, but the diagnosis of myotonic dystrophy was not made.

III-4 Aged 66, no symptoms or signs. Slit-lamp and EMG not performed.

III-5 Died suddenly of heart disease at the age of 51. According to his son he was a healthy man before that. The ophthalmologist found a cataract when he was 48, but characteristics of myotonic cataract were not noticed.

III-6 Nine sibs, not examined.

IV-1 First index patient, see above.

IV-2 Noticed cramps in her hands while washing in cold water at the age of about 20. At the age of approximately 40 she started to stumble frequently and to tire quickly. At 43 she could run her own household, she appeared slow but of normal intelligence. She had atrophic temporals and facial weakness, weak foot extension, absent tendon reflexes and percussion myotonia of the thenars. She had also had diabetes for 4 years and atrial fibrillation.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 2 - my 2 - we 2 - me 1.

IV-3 Aged 42, no symptoms or signs. Slit-lamp: multiple fine white subcapsular opacities, no coloured opacities were seen.
EMG: normal.
No diagnosis could be made, but beginning myotonic cataracts were suspected; in his son myotonic cataracts were also suspected.

IV-4 Noticed inability to stretch her fingers after wringing out clothes at the age of 16. Gradually her hands got weaker and she started to stumble. At 39 she could run her own household, she was slow but appeared of normal intelligence. She had moderate weakness of facial and neck muscles, and mild weakness of distal limb muscles with percussion myotonia of the thenars.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 1 - my 2 - we 2 - me 1.

IV-5 Noticed difficulty opening a fist during her third pregnancy when she was 32. At 37 she could run her own household and had no symptoms. She had mild weakness of facial, neck and foot extension muscles, and percussion myotonia of the thenars.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 4th decade.
Severity score: cat 2 - my 2 - we 1 - me 1.

IV-6 Aged 32, full examination normal. Two of her 3 children were fully examined and found to be normal, the third had no symptoms or signs but was too small for slit-lamp and EMG.

IV-7 Twin sister of IV-6 but very dissimilar from early childhood. During her third pregnancy, when she was 31, she noticed cramps in her hands and in her legs when starting to walk. During her 4th pregnancy, when she was 33, she started to stumble. At 33 she could run her household with two children, she was slow but appeared of normal intelligence. She had atrophic temporals, sternomastoids and forearms, indistinct speech and mild weakness of facial, neck and foot extension muscles. Myotonia was found on percussion of the thenars. Cataracts were seen on ophthalmoscopy.
Slit-lamp and EMG were not performed.
Myotonic dystrophy, onset 4th decade, possibly 3rd.
Severity score: cat ? - my 2 - we 1 - me 1.

IV-8 Aged 38, full examination normal.

IV-9 Second index patient, see above.

V-1 Aged 19, full examination normal.

V-2 Aged 19, full examination normal.

V-3 Aged 16, full examination normal.

V-4 Died one hour after premature birth, birth weight 1600 grams. Enormous polyhydramnios was documented by the gynaecologist. The duration of the pregnancy was 32 weeks. Routine postmortem examination did not reveal a cause of death. The mother had a disturbed kidney function but normal glucose tolerance.
In retrospect this baby probably had congenital myotonic dystrophy.

V-5 Aged 8, full examination normal.

V-6 Died after premature birth. The gynaecologist reported that she made only few gasping respiratory movements, while the heart rate was slow and irregular. Polyhydramnios measured 5000 cc, the duration of the pregnancy was 34 weeks, birth weight 1970 grams. Postmortem examination showed thrombosis of the left renal vein continuing into the superior vena cava; haematomas in the wall of the ductus arteriosus and in thymus and pia mater were also seen, and local adrenal cytomegaly.
In retrospect she probably had congenital myotonic dystrophy.

V-7 Aged 12, had sometimes difficulty opening a fist. On examination no abnormalities were

found, apart from a slightly nasal voice.
Slit-lamp and EMG normal.
No diagnosis was made.

V-8 Died shortly after birth at home. The parents said she did not breathe because of thick secreta in the lungs, and resuscitation had failed. No further data.

V-9 Still-born after a nine months' pregnancy, no foetal movements were felt during the last 3 months of pregnancy. No further data.

V-10 Died shortly after a normal birth, having made only few weak respiratory movements while the heart beat was reported to be slow. Oedema of the child and polyhydramnios were noted by the gynaecologist. Postmortem examination showed thrombosis of renal veins and hypertrophic Langerhans islets.
In retrospect she probably had congenital myotonic dystrophy.

V-11 Aged 6, examination and slitlamp normal.
EMG not performed.

V-12 Aged 11, full examination normal.

V-13 Aged 8, no symptoms or signs.
Slit-lamp examination showed many fine white subcapsular opacities, and 6 red and green opacities were seen, too few to diagnose myotonic cataracts.
EMG was normal.
No diagnosis could be made, but beginning myotonic cataracts were suspected.

V-14 Aged 12, full examination normal.

V-15 Aged 11, full examination normal.

V-16 Aged 13, full examination normal.

V-17 Aged 11, full examination normal.

V-18 Died shortly after premature birth. The obstetrician reported that the Apgar score was 1. Birth weight 2280 grams, gestation 35 weeks, a polyhydramnios of 4200 cc was documented. The postmortem examination showed 30 cc intra-abdominal blood of unknown origin and meningeal bleeding. The mother had a normal glucose tolerance.
In retrospect he probably had congenital myotonic dystrophy.

V-19 Severe congenital myotonic dystrophy was diagnosed at birth by the pediatrician, because of severe hypotonia, insufficient respiration, facial diplegia with a tent-shaped mouth, generalized muscle atrophy and oedema (case 5, Pearse and Höweler, 1979). The mother was known to have myotonic dystrophy at the time of delivery. A polyhydramnios of 2700 cc was noted, the duration of the pregnancy was 30 weeks. She had to be ventilated for two months and her motor development was severely delayed at 6 months.
Slit-lamp and EMG not performed.
Myotonic dystrophy, onset decade 0, congenital involvement.

V-20 Aged 5, no symptoms or signs.
Slit-lamp and EMG not performed.

V-21 Died a few hours after premature birth. The obstetrician reported that polyhydramnios complicated the pregnancy, and that the gestation was 32 weeks. The birth weight was 1640 grams. The pediatrician reported the insufficient respiration and acidosis had not improved with oxygen by mask and bicarbonate infusion, and she died a few hours after birth. Prematurity was assumed to be the cause of death.
In retrospect this baby probably had congenital myotonic dystrophy.

V-22 Aged 2, no symptoms or signs.
Slit-lamp and EMG not performed.

V-23 Died 19 days old, having been ventilated without success since birth. Had severe hypotonia, facial diplegia, joint deformities, and did not breathe. Was delivered by caesarian section at 30 weeks' gestation because of abruptio placentae. The pregnancy had been complicated by polyhydramnios. Routine postmortem examination gave no

cause of death. A diagnosis of congenital myotonic dystrophy was made after death, when the mother was found to have myotonic dystrophy (case 1, Pearse and Höweler, 1979). Myotonic dystrophy, onset decade 0, congenital involvement.

Family M

The index patient, III-3, was referred when he was 28 to the neurology department for pain in the legs and muscle weakness. He first noticed muscle weakness of his hands when kneading dough as a baker at the age of 19, and he said he was rejected for military service for the same reason. His mother reported that he was slow as a child and repeated four classes in primary school. At 36 he was single and worked in a sheltered workshop. He was slow and had indistinct speech. He had atrophic temporals and sternomastoids, and moderate weakness of facial, neck and distal limb muscles, with myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: not performed.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 1 - my 2 - we 2 - me 2.

I-1 Died aged 66 of bladder disease. According to his son, II-2, he had not had muscular disease or cataracts.

I-2 Died aged 90, no known invalidating disease or cataracts.

II-1 At the age of 74, decreasing visual acuity was the only symptom or sign.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 8th decade.
Severity score: cat 2 - my 1 - we 0 - me 0.

II-2 The visual acuity had diminished since te age of 68. At 72 he had mild neck weakness, atrophic sternomastoids, and percussion myotonia of the thenars.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 7th decade.
Severity score: cat 3 - my 2 - we 1 - me 0.

II-3 Three children, died shortly after birth. No data.

III-1 Aged 48, full examination proved normal.

III-2 Died after premature birth, no more data.

III-3 Index patient, see above.

III-4 Noticed cramps in her hands when 14, and weakness of her hands during gymnastics at the age of 12. Her mother reported that she had been slow since the age of 6, and she had attended special schools. At 35 she was single. She had given up her work as a seamstress. She was slow and had indistinct speech, atrophic temporals and sternomastoids, and mild weakness of facial, neck and distal limbs muscles. Myotonia was found on percussion of the thenars.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade, possibly 1st.
Severity score: cat 1 - my 2 - we 1 - me 2.

III-5 Aged 24, full examination normal.

Family N

The first index patient, IV-4, was referred to the neurological department with stiff hands at the age of 24. He first noticed difficulty opening a fist when he was 20, but he already started to have a nasal speech when he was 13, which had not improved despite tonsillectomy and speech lessons. At 24 he worked as a roofer and appeared of normal intelligence. He had mild weakness of his face and neck muscles, indistinct speech and myotonia of grip.

Slit-lamp: myotonic cataracts.
EMG: not performed.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 1 - my 2 - we 1 - me 0.

The second index patient, IV-12, was referred to the neurological department for difficulty in walking at the age of 29. The name of his grandmother was recognized as being the same as IV-4's grandmother's. At 22 he had first noticed his hands as being weak, and some years later he also noticed cramps in his hands, and difficulty in walking developed. He had been an active football player until the age of 23. At 29 he was an unemployed bookkeeper. He appeared slow but of normal intelligence. He had mild weakness of facial and neck muscles, and moderate weakness of proximal as well as distal limb muscles, with myotonia of grip.
Slit-lamp: coloured opacities too few for making a diagnosis.
EMG: myotonic discharges.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 0 - my 2 - we 2 - me 1.

I-1 Born 1847, age of death unknown. III-1 reported him as having problems with bleeding, but he had not had any muscle weakness.

I-2 Born in 1850, died at 70, no further data.

II-1 Died at the age of 75. Her son, III-5, reported that she had been healthy until the age of 65, when she was operated upon for cataracts; later she also developed diabetes and began to shuffle.

II-2 Four sibs all died, ages of death not known. One had two grandchildren with documented myotonic dystrophy. III-1 reported that another sister had two sons with bleeding problems, and a third had been mentally retarded from early childhood.

II-3 Aged 88, not examined.

III-1 Aged 59, had no muscle symptoms, but complained that his visual acuity had decreased in the last few years. He had had problems with bleeding since childhood. The haematologist diagnosed haemophilia type A. He worked as an iron-smith and appeared to be of normal intelligence. He had no muscle weakness or myotonia.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 6th decade.
Severity score: cat 2 - my 1 - we 0 - me 0.

III-2 At the age of 55 he had no muscle symptoms apart from frequent choking. He had had bleeding problems since childhood and his right leg had been amputated following a motor accident. When he was 46 atrophy of the optic nerves was diagnosed and his visual acuity had gradually diminished further. Because of this he worked in a sheltered workshop, he appeared to be of normal intelligence. He had myotonia on percussion of the thenars as the only muscle sign.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 6th decade.
Severity score: cat 3 - my 2 - we 0 - me 0.

III-3 First noticed weakness of his hands after a motor accident when he was 48. His wife reported that the weakness gradually progressed, and he became slow and hypersomniacal. He had had bleeding problems since childhood. The haematologist diagnosed haemophilia type A. At 54 he still worked part-time as a tram conductor; he appeared slow but of normal intelligence. He had mild weakness of facial, neck and foot extension muscles, and severe distal arm weakness with motonia on percussion of the thenars.
Slit-lamp: not performed.
EMG: myotonic discharges.
Myotonic dystrophy, onset 5th decade.
Severity score: cat ? - my 2 - we 2 - me 2.

III-4 Aged 52, full examination normal. She reported that one of her sons was a haemophylliac.

III-5 Aged 47, full examination normal.

III-6 Died suddenly aged 57. His son, IV-12, reported he had not had cataracts or muscle weakness.

III-7 Five sibs, not examined. IV-12 reported that one uncle was a haemophylliac.

IV-1 Aged 33, full examination normal.

IV-2 First noticed difficulty opening a fist when he was 25. Two years later weakness of the hands developed. He was an active hiker until the age of 26, when he started to sprain his ankles regularly. At the age of 10 he changed from primary school to a special school because he was too slow. At 28 he could cope well with his factory work, he appeared slow but of normal intelligence. He had mild weakness of facial, neck and distal limb muscles, and myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: not performed.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 1 - my 2 - we 1 - me 2.

IV-3 First noticed inability to open a fist quickly shortly before the examination. He completed military service and was still an active football player. At 30 he worked as a roofer and appeared of normal intelligence. He had mild facial weakness and atrophic sternomastoids and forearms, with myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 1 - my 2 - we 1 - me 0.

IV-4 First index patient, see above.

IV-5 Had no symptoms at the age of 19. She worked as a domestic help and appeared of normal intelligence. She had mild weakness of face and neck muscles and dubious myotonia on percussion of the thenars.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 0 - my 1 - we 1 - me 0.

IV-6 Aged 27, no symptoms or signs.
Slit-lamp normal.
EMG: not performed.

IV-7 First noticed cramps in her hands at the age of 18, but she had already had nasal speech since she was 16. She had been a dwarf since childhood. The pediatrician who examined her at the age of 11 reported Turner's syndrome had been diagnosed because no Barr bodies were found in cheek scrapings and no drumsticks were seen in the leucocytes. The growth hormone level had been normal. She did not start to menstruate. At 24 she was married and could run her own household. She appeared of normal intelligence and measured 1.35 meters. She had mild weakness of facial, neck and distal limb muscles and myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: not performed.
Myotonic dystrophy, onset 2nd decade; also Turner's syndrome.
Severity score: cat 1 - my 2 - we 1 - me 0.

IV-8 Began to have nasal speech at the age of 9, for which he had speech lessons without success. Denied having other symptoms. Was an active football player until the age of 18. At 22 he had an administrative job, he appeared alert and of normal intelligence. He had atrophic temporals, sternomastoids, forearms and lower legs, and weakness of facial and neck muscles, with indistinct speech and myotonia of grip. Cataracts were seen on ophthalmoscopy.

Slit-lamp and EMG not performed.
Myotonic dystrophy, onset 1st decade.
Severity score: cat ? - my 2 - we 1 - me 0.

IV-9 Aged 39, full examination normal.

IV-10 Aged 32, full examination normal.

IV-11 First noticed inability to open a fist during gymnastics at the age of 16. Did not notice muscle weakness but said she tired quickly when doing domestic work. At 31 she could run her own household, she appeared alert and of normal intelligence. She had atrophic sternomastoids, mild facial weakness and myotonia of grip.
Slit-lamp: coloured opacities too few for a diagnosis.
EMG: myotonic discharges.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 0 - my 2 - we 1 - me 0.

IV-12 Second index patient, see above.

IV-13 Aged 28, full examination normal.

V-1 Aged 4, no symptoms or signs, an active child with normal psychomotor development.
Slit-lamp and EMG not performed.

V-2 Aged 12, full examination normal.

V-3 Had no symptoms during the perinatal period and had a normal motor development; he walked at the age of 14 months. When 2 years old, he started to talk, but speech had always been indistinct. Mental retardation and clumsy movements were noticed in nursery school when he was 4. At 6 he attended a special nursery school and appeared slow. He had mild facial weakness, indistinct nasal speech, and myotonia on percussion of thenars.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonic dystrophy onset 1st decade.
Severity score: cat 0 - my 2 - we 1 - me 2.

Family P

This family is identical with the families S (descendants of P-II-1, and P-II-2) plus ST (descendants of P-II-3) in Höweler et al, 1980.

The first index patient, IV-15, was referred to the neurological department with difficulty in walking when she was 30. After her first pregnancy at the age of 25, she began to tire quickly when walking and to drop things from her hands. Later she also noticed cramps in her hands. At 30 she held a full-time administrative job, she appeared alert and of normal intelligence. She had mild weakness of facial, neck and distal arm muscles and moderate weakness of distal leg muscles, with indistinct speech and myotonia of grip.
Slit-lamp: non-diagnostic white subcapsular opacities.
EMG: myotonic discharges.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 0 - my 2 - we 2 - me 0.

The second index patient, III-5, was referred to the neurological department for progressive muscle weakness at the age of 69. Weakness of one hand had started at the age of 59. She had been admitted at that time, but no diagnosis could be made and the EMG did not show myotonic discharges. The weakness progressed gradually and she started to fall frequently, and her speech became affected. At 69 she needed help to manage her household. She appeared slow, but when tested she had normal intelligence. She had mild weakness of facial and distal limb muscles, and myotonia on percussion of the thenars.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 6th decade.
Severity score: cat 2 - my 2 - we 1 - me 1.

The third index patient, III-14, was admitted to the ophthalmological department for a cataract operation when he was 61. He also had muscle weakness and the consultant neurologist diagnosed myotonic dystrophy. His name was recognized as being the same as that of III-5's mother. When about 54 he first noticed cramps in his hands in cold weather. Later his hands and legs became weak. At 64 he worked part-time as a flower-seller. He appeared slow but of normal intelligence. He had mild weakness of facial, neck and distal arm muscles, indistinct speech and myotonia of grip.
EMG: myotonic discharges.
Myotonic dystrophy, onset 6th decade.
Severity score: cat 3 - my 2 - we 1 - me 1.

I-1 Was born in 1840, died aged 80. No further data. Her brother was the grandfather of Junge's (1966) patient H-III-1. Her parents were born in 1811 and 1812 and died aged 78 and 74.

II-1 Died aged 77. Her son, III-2, reported that she had been operated upon for cataracts when she was about 55, and that she had been invalidated by painful rheumatic joints after the age of 64.

II-2 Died aged 71. His son, III-14, reported that he had not had cataracts or muscle weakness.

II-3 Died aged 76. Her daughter, III-18, reported that she had not had cataracts or muscle weakness.

II-4 Four sibs died aged 72, 81, 74 and age unknown (but over 77). One was reported by a son as having had cataracts, and his daughter had muscle weakness and cramps in her hands.

III-1 Was operated upon for bilateral cataracts at the age of 78. At 79 he had no muscle weakness, and on examination myotonia on percussion of the thenars was the only abnormal sign.
Slit-lamp and EMG not performed.
Myotonic dystrophy, onset 8th decade.
Severity score: cat 3 - my 2 - we 0 - me 0.

III-2 Aged 78, full examination normal.

III-3. Aged 75, full examination normal.

III-4 Aged 75, full examination normal.

III-5 Second index patient, see above.

III-6 Aged 69. Noticed difficulty in opening a fist when carrying a heavy bag a few years earlier. At 69 he still had a part-time administrative job, he appeared alert and of normal intelligence. He had no muscle weakness, and myotonia could not be elicited.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 7th decade.
Severity score: cat 2 - my 1 - we 0 - me 0.

III-7 Died suddenly 3 days after an operation for bilateral myotonic cataract, at the age of 56. His widow said he had had cramps and weakness since about the age of 50, and later also a stepping gait. He was seen by a neurologist at the age of 49, during the first admission of his sister, III-5, when weak and wasted thenars were documented, but myotonic dystrophy was not diagnosed. When he was 56 the ophthalmologist diagnosed typical cataracts. Prior to the operation under general anaesthesia a temporary pacemaker was inserted as a complete left and incomplete right bundle branch block were found on the ECG. He suddenly died 12 hours after removal of this pacemaker.
Myotonic dystrophy, onset 5th decade.

III-8 Three sibs, died aged 2 months, 9 months and 73 years. The latter died of stomach cancer, no muscle weakness or cataracts were known to his daughter.

III-9 Not examined.

III-10 Aged 74, full examination normal.

III-11 Not examined.

III-12 Aged 68, full examination normal.

III-13 First noticed cramps and weakness of his hands at the age of about 50. The weakness gradually progressed, but he could continue his work as a construction worker until the age of 62. At 66 he appeared slow but of normal intelligence. He had mild weakness of facial, neck and distal limb muscles, indistinct speech and myotonia of grip. Slit-lamp: right myotonic cataract, left mature grey cataract.
EMG: not performed.
Myotonic dystrophy, onset 6th decade.
Severity score: cat 3 - my 2 - we 1 - me 1.

III-14 Third index patient, see above.

III-15 Aged 60, no symptoms or signs.
Slit-lamp normal, EMG not performed.

III-16 Four sibs died aged 53 years, 3 months, 37 years and 51 years. No medical reports.

III-17 Had cramps in the muscles of her eyes, face, tongue, neck, arms and legs from early childhood, at its most severe during pregnancies and diminishing after the age of 50. At 72 she had myotonia of the eyelids and percussion myotonia of the thenars, but no weakness or wasting of muscles.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonia congenita.

III-18 Had cramps in the muscles of the eyes and eyelids, throat, arms and legs from early childhood, at its most severe between the ages of 15 and 30 and during pregnancies, diminishing after the age of 50. At 71 she had no clinical myotonia and no muscle weakness or muscle wasting.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonia congenita.

III-19 When first examined at the age of 69 she had no symptoms, and no muscle weakness or myotonia was found on examination. Slit-lamp: coloured opacities which were too few for a diagnosis.
EMG: normal.
On reexamination at the age of 70 she had no symptoms or signs, similar slit-lamp abnormalities were seen, but myotonic discharges were found on the EMG.
At 73 she had many coloured subcapsular opacities on slit-lamp examination, diagnostic for myotonic cataracts.
Myotonic dystrophy, onset 8th decade.
Severity score: cat 1 - my 1 - we 0 - me 0.

III-20 Had cramps in muscles of the eyelids, tongue, throat, neck, arms and legs since early childhood, at its most severe during pregnancies, and diminishing after the age of 40. At 68 she had no clinical myotonia and no muscle weakness or waisting.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonia congenita.

III-21 Aged 66, no symptoms or signs.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 8th decade.
Severity score: cat 1 - my 1 - we 0 - me 0.

IV-1 First noticed inability to open a fist at the age of 25, after completing military service. Gradually muscle weakness also developed and he had to give up his administrative job. He was operated upon for cataracts when he was 45 and 46. At 47 he worked in a sheltered workshop. He appeared slow but of normal intelligence. He had mild facial and neck weakness and moderate weakness of distal limb muscles, with indistinct speech and

myotonia of grip.
EMG: not performed.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 3 - my 2 - we 2 - me 1.

IV-2 Aged 44, full examination normal.

IV-3 Noticed cramps and weakness when he was 20 during military service, from which he was prematurely discharged. The weakness gradually progressed and he had to give up his administrative job. At 41 he worked in a sheltered workshop. He appeared slow but of normal intelligence. He had moderate weakness of facial and distal limb muscles, atrophic temporals and sternomastoids, and myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: not performed.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 3 - my 2 - we 2 - me 1.

IV-4 First noticed cramps in his hands at the age of 18 when carrying a heavy bag. Later his hands became weak and hypersomnia developed. At 69 he worked in a sheltered workshop. He appeared slow and mildly retarded. He had mild weakness of facial and distal arm muscles, indistinct speech and myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: not performed.
Myotonic dystrophy, onset 2nd decade.
Severity score: cat 1 - my 2 - we 1 - me 2.

IV-5 Started to have a nasal speech at the age of 8, speech lessons did not improve her condition. Cramps in her hands were noticed but the age was not recorded. She changed to a special school at the age of 8. At 16 she attended a domestic school, she appeared slow and mildly retarded. She had mild facial and distal arm weakness, indistinct speech and myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: not performed.
Myotonic dystrophy, onset 1st decade.
Severity score: cat 1 - my 2 - we 1 - me 2.

IV-6 Aged 35, full examination normal.

IV-7 Not examined.

IV-8 Not examined.

IV-9 Aged 38, full examination normal.

IV-10 First noticed cramps in his hands at the age of 6 when swimming. Was prematurely discharged from military service because he could not release the trigger. Later weakness of his hands developed. He was operated upon for cataracts at the age of 31 and 33. At 34 he worked in a sheltered workshop. He appeared slow but of normal intellligence. He had mild weakness of facial, neck and distal limb muscles, with myotonia of grip.
EMG not performed.
Myotonic dystrophy, onset 1st decade.
Severity score: cat 3 - my 2 - we 1 - me 1.

IV-11 At the age of 47 he had no symptoms or signs. He was a businessman, he appeared alert and of normal intelligence.
Slit-lamp: coloured opacities too few for making a diagnosis.
EMG: normal.
At the age of 51 he was reexamined; he still had no symptoms or signs; the EMG was normal, but on slit-lamp examination he had myotonic cataracts.
Myotonic dystrophy, onset 6th decade.
Severity score: cat 1 - my 0 - we 0 - me 0.

IV-12 Died at the age of 8 after being operated upon for acute bowel obstruction.

IV-13 First noticed cramps in her hands and jaw muscles when she was about 28. Gradually

mild weakness of the hands developed, but she could still play tennis. At 38 she could run her own household, she appeared alert and of normal intelligence. She had mild facial and distal arm weakness, atrophic sternomastoids and myotonia of grip.
Slit-lamp: myotonic cataracts.
EMG: myotonic discharges.
Myotonic dystrophy, onset 3rd decade.
Severity score: cat 2 - my 2 - we 1 - me 0.

IV-14 At the age of 36 she had no symptoms or signs.
Slit-lamp: non-specific white subcapsular opacities.
EMG: normal.
On reexamination at the age of 40 the same non-specific lenticular opacities were found, and EMG and neurological examination were again normal.

IV-15 First index patient, see above.

IV-16 Aged 29, full examination normal.

V-1 Aged 16, full examination normal.

V-2 Had difficulties breathing, sucking and swallowing during the first week after birth. Kept drinking very slowly for three months. The motor development was normal, but he was always slower than his sister and he had difficulty in keeping up in primary school. His speech had always been nasal and his hands weak. At 10 he was slow and had a tent-shaped mouth. He had weakness of facial and hand muscles, indistinct speech and myotonia on percussion of the thenars.
Slit-lamp: normal.
EMG: myotonic discharges.
Myotonic dystrophy, congenital involvement, onset decade 0.
Severity score: cat 0 - my 2 - we 1 - me 2.

V-3 Died shortly after birth. The gynaecologist reported that he was floppy and atrophic and did not start breathing, and after 20 minutes of assisted ventilation the heartbeat also stopped. His birth weight was 2500 grams, the gestation of 37 weeks had been complicated by hydramnios of 8000 cc. No cause of death was found on routine postmortem examination. In retrospect this baby probably had congenital myotonic dystrophy.

APPENDIX II

The degree of severity of 4 symptoms of myotonic dystrophy, using an ordinal scale of 0 - 1 - 2 - 3, and measured in 115 patients, is given in table XIV. The patients are classified in groups, according to the age of onset and the duration of the disease in decades. Each vertical series of numbers within a section denotes the scoring rate of one patient (cat = cataract, weak = muscular weakness, men = mental symptoms and signs, my = myotonia).

age of onset in decades							
8	cat weak men my	1321 0000 0000 1211					
7	cat weak men my	2131 0000 0000 1101		33 10 00 22			
6	cat weak men my	1321111 0000100 0000000 0210122		332 111 110 222	3 1 0 0		
5	cat weak men my	10 10 00 22		-03 210 220 221			
4	cat weak men my	-20121 110021 110000 222122		1331 2211 0000 2222	0-3- 0322 0212 2222	2 3 2 1	
3	cat weak men my	01010 21210 12000 22202		021101130 211211121 000000100 222222222	33210 22222 11111 22222	0 3 1 2	
2	cat weak men my	0000000 1111011 0131111 1222122		2111--0000111121 2211121111111111 0000221112120001 2222222222222222	011133202-0 11222221221 02211300222 22222222322	00 12 00 22	
1	cat weak men my	000 111 221 221		1011- 11111 21313 22222	-000 1121 0233 2222	3 1 1 2	— 22 11 22
0	cat weak men my	0-5 yrs	000 111 333 212	002 112 233 222			
		1		2	3	4	5

Table XIV Duration of the disease in decades.

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Mijn vrouw Marijke Jansen vertaalde de tekst in het Engels en liet, als beste kenner van mijn blinde vlekken, regelmatig haar licht schijnen over nog duistere passages.
Mw. J.E. Best corrigeerde de Engelse versie en wees ons een weekend lang de weg langs de voetangels en klemmen van het Engelse idioom.
Prof.dr. M.F. Niermeyer stroomlijnde de laatste versie.
Mijn zwager R.W. Sypkens doorzocht de tekst op spellingfouten.
Mw. J. Doornbosch heeft in de Rotterdamse fase veel secretarieel werk verricht en nuttige taalkundige adviezen gegeven.
Mw. T.A.M.J. van Lieshout typte met veel geduld verschillende versies van het manuscript en zorgde voor een nauwkeurige afwerking van de uiteindelijke tekst.
Mijn Maastrichtse collega's maakten het mogelijk regelmatig enkele weken achtereen aan dit proefschrift te werken door mijn gezondheidszorgtaak waar te nemen.

CURRICULUM VITAE

Chris Höweler werd in 1939 in Amsterdam geboren en bracht zijn kinderjaren door in Bandjermasin en in Soest. Hij bezocht het Amersfoorts Lyceum, waar hij in 1958 het gymnasium B examen aflegde. Hij studeerde geneeskunde aan de Rijksuniversiteit te Utrecht tot het doctoraal examen, en aan de Stichting Klinisch Hoger Onderwijs te Rotterdam tot het artsexamen in 1967.
Vervolgens was hij anderhalf jaar wissel-assistent in het St. Jozef Ziekenhuis te Gouda en bezocht de Tropencursus voor artsen te Amsterdam. Van 1969 tot 1972 werkte hij als algemeen arts in het Nguludi Hospital in Malawi.
Hierna begon hij zijn opleiding tot neuroloog in het Academisch Ziekenhuis Dijkzigt te Rotterdam (Prof.dr. A. Staal). Ook de aantekening Klinische Neurofysiologie werd daar behaald (Prof.dr. M. de Vlieger). De stage psychiatrie werd gedaan in het Psychiatrisch Ziekenhuis Bloemendaal te Den Haag (Dr. J.A. Schipper). De opleiding werd twee keer een jaar onderbroken om het in dit proefschrift beschreven onderzoek voor te bereiden en uit te voeren.
Sinds 1980 is hij als neuroloog verbonden aan de Rijksuniversiteit Limburg en het Academisch Ziekenhuis Maastricht.