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Congenital myotonic dystrophy in Britain

II. Genetic basis

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Harper, P. S. (1975). *Archives of Disease in Childhood*, **50**, 514. **Congenital myotonic dystrophy in Britain. II. Genetic basis.** Genetic analysis of 54 sibships containing 70 patients with congenital myotonic dystrophy has shown paternal transmission in only one case, the disorder being maternally transmitted in 51 sibships. No instance of new mutation was found. At least half the sibs were unaffected; 9 sibs were affected without definite congenital involvement. No evidence for genetic heterogeneity was found, most affected mothers having few or no symptoms. There was no disturbance of sex ratio for the affected grandparents, nor in the sibships of the affected parents. The genetic data from this study and from previous published reports support the clinical evidence that the congenital form of myotonic dystrophy results from a maternal intrauterine factor affecting those individuals carrying the myotonic dystrophy gene.

A clinical and genetic survey of all known cases of myotonic dystrophy presenting in early childhood in mainland Britain has been carried out from which 70 patients have been identified in whom onset appeared to be from the time of birth. The basis of the survey has been described in the preceding paper, and the clinical features in infancy and in the antenatal period have been discussed. This paper analyses the family data recorded as part of the study, with particular reference to the hypothesis that the congenital form of myotonic dystrophy may result from the interaction of an abnormal gene and a maternal intrauterine factor.

Method

Information was collected on all available relatives living and deceased, as well as on stillbirths and abortions. A particular effort was made to examine sibs and parents of affected individuals, whether or not known to be affected, and also the grandparental generation, when available. Pedigrees of the families are given in Fig. 1–3; the numbering of families and individuals corresponds to that in the text and tables of this and the preceding paper. Only those individuals with the congenital form are given a case number.

Results

Sibs. Table I gives details of the sibships of congenital myotonic dystrophy patients. Out of the total of 149 liveborn individuals, 79 are known to have myotonic dystrophy, 70 having the congenital form, of which 56 were propositi. The sex ratio of both affected and unaffected individuals does not differ significantly from equality, though an excess of males in the congenital nonpropositus group is present.

TABLE I

Data on sibships

	Total	Male	Female
Congenital cases			
Total	70	40	30
Propositi	56	27	29
Nonpropositi	14	12	2
Other affected sibs	9	5	4
Unaffected sibs	46	22	24
Neonatal deaths (1 sex uncertain)	24	10	13
Total liveborn	149	77	71

Twenty-eight of the 70 patients in this series belonged to sibships in which more than one member was affected with congenital myotonic dystrophy. In addition, 9 affected sibs were found in whom there was no clear evidence of congenital onset of the disease; this may be an underestimate since not all apparently unaffected sibs could be examined. Thus, while there is close concordance for the congenital form within a sibship, this is by

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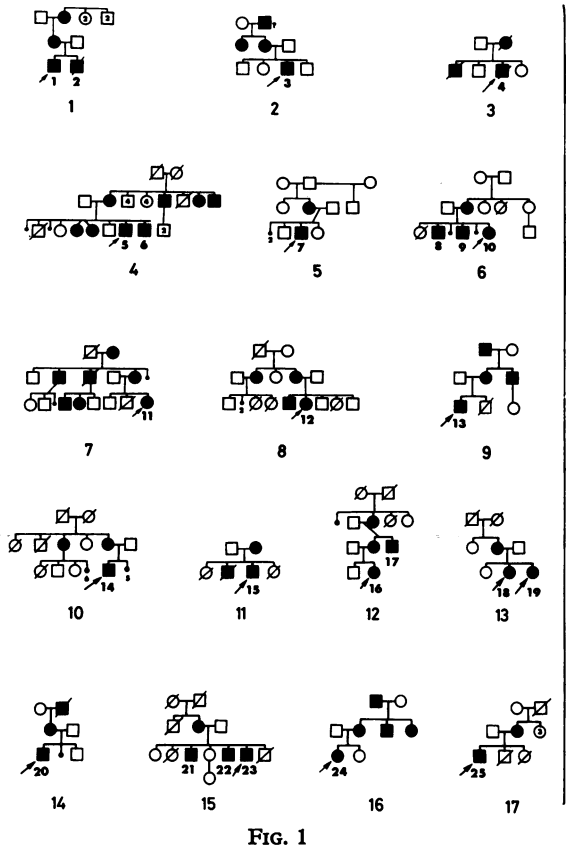

FIG. 1

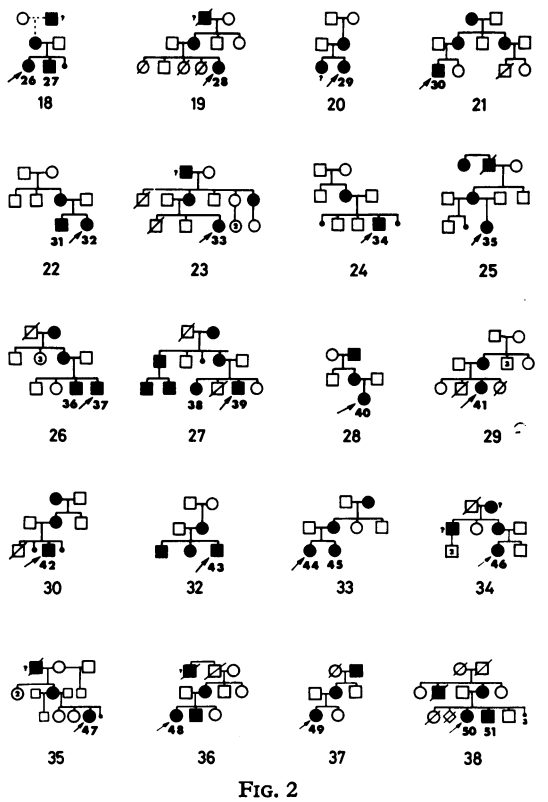

FIG. 2

FIGS. 1–3.—*Pedigrees of families of congenital myotonic dystrophy patients. Family and case numbers correspond to those in text and tables.* ■, ● *affected male, female; diagonal line represents deceased member;* ↗ *propositus.*

no means complete. The relatively young age of most apparently unaffected sibs leaves unanswered the question as to the proportion of these that might ultimately develop milder manifestations of the disease, though previous studies (Harper, 1973; Bundey, 1974) have suggested that this is small in those families where the disease occurs in childhood.

One discordant pair of dizygotic twins was encountered in the study (family 46), the co-twin being completely free from any signs of the disease, though only 7 years old at the time of examination. This suggests that the congenital disorder cannot be attributed to intrauterine enviromental factors alone.

Parental generation. A striking inequality is seen in the sex ratio of the affected parents (Table II). In 51 of the 54 sibships the mother was the affected parent, while in only one case was the father affected. No instance of a new mutation was recorded; in both cases recorded as 'uncertain' the mother had died young from another cause, the father being unaffected. The single offspring of an affected father was included with some hesitation and was not typical of the series. The diagnosis was made at 5 years, and there were no abnormalities in the pregnancy or neonatal period, but facial weakness was evident from a photograph taken at 2 years of age. The father was moderately disabled.

TABLE II

Sex of affected parent (54 sibships)

Mother	51
Father	1
Unknown	2

Data on the grandparental generation are shown in Table III. Though incomplete, they show no suggestion of the distorted sex ratio shown by the parental generation. Nor is there anything unusual

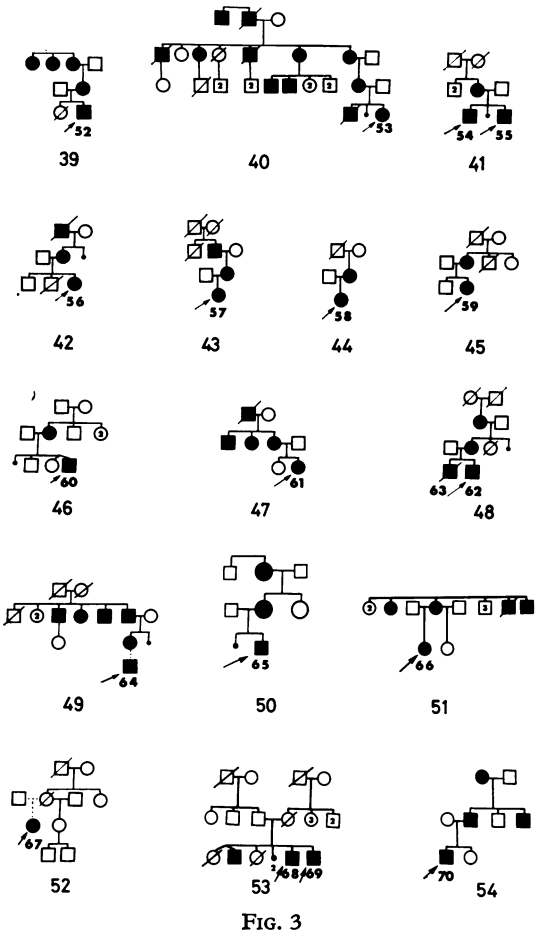

FIG. 3

in the sibships of the affected parents (Table IV), in particular no abnormality of the sex ratio; the deficiency of affected as compared with unaffected sibs is likely to reflect the young age of many of them, and the fact that not all were examined personally.

TABLE III

Affected grandparent (54 sibships)

Grandmother Definite (8) Probable (6)	14
Grandfather Definite (8) Probable (7)	15
Uncertain	25

The severity of disease in the affected parent was graded clinically as shown in Table V. It can be seen that 20 of the 54 parents were asymptomatic at the time of diagnosis of myotonic dystrophy in their child, while a further 14 had not sought medical attention for their symptoms. Age of onset in the affected parent was found to be an extremely unreliable criterion, and was not used in the grading. In those parents without symptoms it is possible that no abnormality would have been noted for some years had not a child with congenital myotonic dystrophy been born, while in cases with symptoms a minor degree of myotonia was sometimes remembered from adolescence even though no medical advice was sought till adult life.

No clear differences were found between the characteristics of the disease in the affected parent and those normally seen in myotonic dystrophy. Clinical myotonia was present in all cases, even when there was no complaint. Muscle weakness, where present, was generally slowly progressive. No history of symptoms of congenital onset was found in any of the parents. The mean maternal age for those cases having an affected mother is recorded in Table VI, together with the corre-

TABLE IV

Sibs of affected parent

	Male	Female	Total
All sibs	47	47	94
Affected sibs	12	8	20
Sibs dying in childhood	4	4	8
Abortions and stillbirths	0	0	5

TABLE V

Severity of parental disease and grade

	No.
Asymptomatic (1)	20
Minor symptoms, medical attention not sought (2)	14
Symptoms sufficient to require medical attention (3)	8
Moderately disabled (4)	5
Severely disabled (5)	1
Uncertain	4
Parent not identified	2
Total	54

TABLE VI

Parental age (age at birth of affected child)

	Present series	General population England and Wales (1965)
Mother	25·95 (SD 4·55)	26·71
Father	30·58 (SD 5·06)	29·65

TABLE VII

Birth rank of cases of congenital myotonic dystrophy

(Live births only included; unexplained neonatal deaths counted as unaffected)

Sibship size	Rank							Total
	1	2	3	4	5	6	7	
1	7							7
2	14	17						31
3	1	2	6					9
4	1	2	6	3				12
5		1	1	2	2			6
6								0
7			1		1	2	1	5
Total	23	22	14	5	3	2	1	70

sponding age for the unaffected fathers. Neither differs significantly from that of the normal population, data being taken for live legitimate births in England and Wales for the year 1965, the median year of birth for patients in this series (Registrar General, 1967).

The distribution of birth rank of affected cases is shown in Table VII. Comparison with the general population shows no significant differences, whether propositi alone, or all congenital cases are considered (Table VIII).

Discussion

Previous genetic studies of myotonic dystrophy (Bell, 1948; Thomasen, 1948; Klein, 1958) have clearly shown autosomal dominant inheritance, and these surveys, dealing principally with the disease in adult life, have not shown any distortion from the expected equality of sex ratio in the parental generation. The locus for myotonic dystrophy has been found to be on the same chromosome as those for the secretor and Lutheran blood group loci (Mohr, 1954, Renwick *et al.*, 1971; Harper *et al.*, 1972).

The inheritance of the congenital form contrasts sharply with this orthodox Mendelian situation. The tendency for the mother to be the affected parent was noted in the original description of myotonic dystrophy in infancy by Vanier (1960), and subsequent case reports have provided further evidence, though often containing cases with congenital onset along with others showing onset in later childhood. Table IX summarizes data collected from those published cases in which sufficient detail is given to establish whether or not congenital onset of the diseases was likely. Details are given in Table X. Two larger, and partially overlapping series, combined in Table IX (Harper and Dyken, 1972; Dyken and Harper, 1973) show similar results.

The results of the present study, taken in conjunction with previous reports, leave no doubt that the inheritance of congenital myotonic dystrophy is

TABLE VIII

Birth rank compared with general population

Birth rank	Livebirths England & Wales 1965		All congenital cases		Propositi only	
	No.	%	No.	%	No.	%
1	282 502	35·9	23	32·9	22	39·3
2	246 015	31·2	22	31·4	16	28·6
3	133 388	16·9	14	20·0	11	19·6
4	63 337	8·0	5	7·2	3	5·4
5	30 032	3·8	3	4·3	2	3·6
6	15 328	1·9	2	2·9	2	3·6
7	8 965	1·1	1	1·4	0	0
>7	9 184	1·2	0	0	0	0
Total	788 751	100	70	100	56	100

Note: χ^2 for all congenital cases = 0·66 (0·975 >P > 0·95) (4 degrees of freedom). χ^2 for propositi only = 3·43 (0·4> P >0·3) (3 degrees of freedom).

TABLE IX

Data from previous reports

	Collected case reports	USA study*	Total
Total cases	60	46	106
Male	30	27	57
Female	30	19	49
Total sibships	44	34	78
Affected parent			
Mother	39	28	67
Father	1	4	5
Unknown	4	2	6

*Combined data of Harper and Dyken (1972) and Dyken and Harper (1973).

anomalous. Neither autosomal dominant nor other modes of Mendelian inheritance are sufficient alone to explain the overwhelming proportion of patients in whom the mother is the affected parent. The hypothesis previously proposed (Harper and Dyken, 1972), that the congenital form of myotonic dystrophy results from a combination of an intrauterine environmental factor with the autosomal dominant gene for the more typical form of the disease, will be examined in the light of the new evidence and other possible explanations will be discussed.

Evidence favouring the action of a maternal intrauterine factor comes from several sources. (1) Clinical evidence is suggestive, though not in itself conclusive. The high incidence of talipes, hydramnios, and reduction of fetal movements suggests a prenatal onset, as discussed in the preceding paper; severity of hypotonia and other symptoms is usually greatest in the days immediately after birth, with subsequent improvement during the first decade until myotonia and other 'adult' features make their appearance. Mental retardation, when present, appears to date from birth, if not before. The clinical picture of severe symptoms at birth with subsequent improvement is compatible with a passively acting factor transferred *in utero*, and contrasts with some other disorders of prenatal onset, such as Werdnig-Hoffmann disease, where progressive deterioration continues after birth.

(2) Genetic evidence favouring a maternal environmental factor is the marked preponderance of cases in which the mother is the affected parent. In addition, no definite instance of a new mutation has been recorded in the present series, nor in any of the previous reports. Originally it was thought possible that this might reflect failure of diagnosis in the absence of an affected parent, but this now seems implausible in view of the large number of known cases and the increasing recognition of the clinical syndrome in infancy by paediatricians and neurologists.

(3) The deficiency of affected fathers, though striking, is not absolute, and it is of interest to examine more closely those cases in which the father is reported to be the affected parent. In the present series evidence of congenital onset in the only paternally transmitted case was tenuous; the case of Harper and Dyken (1972), also included in the fuller study of Dyken and Harper (1973), showed extremely severe mental retardation but no other congenital features; it is possible that another cause for the retardation was operating. In only one of the three other paternally transmitted cases of Dyken and Harper was the onset unequivocally congenital, talipes being present in this case.

It thus seems clear that when congenital involvement, as opposed to childhood onset of disease, is taken as the criterion, maternal trasmission is almost invariable, and that those instances where the disease appears in early childhood with previously normal development are likely to represent the extreme range of the 'adult' form, already well known to be highly variable in its age of onset and severity.

Alternative hypotheses must now be examined. Bundey and Carter (1972) have proposed that the abnormal sex ratio of affected parents can be explained by the existence of at least two genes for myotonic dystrophy, one of which produces early onset of disease and also results in relative infertility of the affected males, while in the later onset form fertility is little impaired in either sex. Since their criterion for 'early onset' is under 20 years of age, comparison with the category showing congenital onset is not simple; genetic heterogeneity has proved to be widespread in genetic disorders and is a plausible explanation for some of the phenotypic variability seen in myotonic dystrophy. That it cannot readily explain the present situation is evident from a number of facts:

The severity of the affected parent was found to be mild in most families of the present series (Table V). Though some mothers had minor symptoms of myotonia for many years, over one-half had sought no medical attention up to the time of birth of their severely affected child. The features of myotonic dystrophy in the parents were not notably different from the typical picture of the disease in adult life, with myotonia universally present, along with varying degrees of muscle weakness and wasting in the characteristic distribution; the clinical picture was in marked contrast to that in the affected children, where hypotonia was prominent and myotonia rarely evident till later childhood. Likewise the affected

TABLE X

Reported cases with congenital onset

Author	Case	Sex	Affected parent
Vanier (1960)	1	F	Mother
	2	M	Mother
	3	F	?
	4	M	Mother
	5	M	Mother
	6	F	Mother
Parker (1963)	D7	M	Father
	D15	M	Mother
	D16	M	
Dodge *et al.* (1965)	1	M	Mother
	2	F	
	4	F	Mother
	5	F	
	6	M	Mother
	9	M	Mother
Calderon (1966)	1	F	Mother
	2	F	Mother
Pruzanski (1966)	1	F	Mother
	2	F	?
Gordon and Hilson (1967)	1	M	Mother
Verger, Guillard, and Eschapasse (1967)	1	F	Mother
	2	M	
Watters and Williams (1967)	C-II-2	M	Mother
	F-II-1	F	Mother
	F-II-4	F	
	H-II-5	M	Mother
	H-II-8	M	
	H-III-1	F	Mother
	L-II-2	M	Mother
Giovanucci, Calabri, and Paoli (1969)	1	F	?
L'Hirondel *et al.* (1970)	1	M	Mother
Mundler (1970)	1	F	Mother
	2	M	
	3	F	Mother
	4	M	
	5	M	
	6	M	?
Bell and Smith (1972)	1	M	Mother
Serradell (1972)	1	F	Mother
Karpati *et al.* (1973)	1	M	Mother
	2	M	Mother
	3	F	Mother
	4	M	Mother
Zellweger and Ionasescu (1973)	D-II-1	F	Mother
	D-II-2	F	
	D-II-4	F	
	D-II-5	F	
Aicardi, Conti, and Goutières (1974)	1, 4, 5, 7, 10, 11	M	Mother (all 8 sibships)
	2, 3, 6, 8, 9, 12	F	

grandparents and sibs of the parents showed features of the adult form, with the exception of one brother with congenital onset (Case 17) whose mildly affected sister herself had a congenitally affected child.

Data on fertility of affected sibs in the present study are two few to permit detailed analysis, but Table IV shows that there is no obvious deficiency or mortality of males in the parental generation. The equality of sex ratio in the grandparental generation (Table III) is also against the existence of a separate genetic type of myotonic dystrophy producing differential fertility between the sexes.

The results of the present study thus provide no support for the existence of genetic heterogeneity in myotonic dystrophy and argue strongly against that being the cause of the congenital form.

X-linked inheritance is ruled out by the approximately equal sex ratio of the congenitally affected children, nor would an X-linked or autosomal modifying gene explain the situation. Thus, the only satisfactory explanation of the observed

facts remains the original hypothesis of a maternal environmental factor acting on the genetically predisposed individual.

Two further findings must be considered: the existence of a significant proportion of apparently normal sibs of congenitally affected patients, and the occurrence in the sibships of cases without clear congenital onset. If the proposed maternal factor acts only on the individual carrying the gene for myotonic dystrophy, half of the sibs would be expected to be normal. The observed proportion of affected sibs is less than half, though the exact figure is subject to error due to the considerable number of neonatal deaths, a proportion of which may have been affected. From the data in Table I, discounting propositi and counting twice those sibships with two propositi, the proportion of affected is 0·24 (counting neonatal deaths as unaffected) or 0·45 (counting neonatal deaths as affected). Whatever the exact proportion affected in this sibships, it is clear that not all offspring are, and thus the direct action of a maternal factor independent of genotype, such as appears to act in the offspring of phenylketonuric mothers, cannot fully explain the congenital onset of the disease. The finding that those cases observed long enough all eventually develop progressive features of adult myotonic dystrophy is further support for the presence of the gene as well as a maternal factor.

Among the 149 liveborn members of the sibships 9 individuals were found who were affected but who had no clear evidence of congenital involvement. Whether closer neonatal observation would have shown such features is uncertain, but the existence of such cases, together with the marked variation in severity of the disease in those congenitally affected, suggests that the maternal factor must be a graded one. Equally, not all women with myotonic dystrophy have children with congenital involvement. A prospective study of the offspring of unselected female compared with male patients would be valuable.

Final confirmation of the existence of the maternal factor can only come from its precise identification. Evidence regarding this will be presented in a future paper; it should be recognized that study of corresponding situations in man and other species has shown a variety of such maternal factors which may affect fetal development and interact with the fetal genome. Direct metabolic effects, immune reactions, and hereditary infections are all well established mechanisms for such maternally transmitted factors.

Direct transplacental effects of phenylalanine are thought to produce the damage seen in offspring of phenylketonuric mothers, while in the mouse a similar situation is seen for histidinaemia (Kacser, Bulfield, and Wallace, 1973; Bulfield and Kacser, 1974). The fetal-maternal interaction of Rhesus and ABO haemolytic disease of the newborn has an immunological basis, while a maternally transmitted infective agent, interacting with specific genotypes, is responsible for scrapie in sheep and mice (Dickinson and Meikle, 1971; Dickinson, Stamp, and Renwick, 1974). The 'killer' factors of *Paramecium* and yeasts, which also require the action of a nuclear gene, appear to be RNA viruses (Bevan, Herring, and Mitchell, 1973). Into which of these categories the maternal factor identified in congenital myotonic dystrophy will fall is unknown, and investigation is hindered by our ignorance of the basic biochemical defect in myotonic dystrophy as a whole. The existence of similar maternal factors in other human and nonhuman disorders makes it likely that maternal-fetal interactions play a larger role in genetic disease than has hitherto been realized.

This study would not have been possible without the help of many clinicians throughout Britain who allowed access to their patients and records. In addition I thank Professor Hubert Campbell for advice regarding birth rank analysis, and Drs. Sarah Bundey and Cedric Carter for stimulating discussion regarding some unresolved genetic questions in this disorder. The work was supported by the Muscular Dystrophy Group of Great Britain.

References

Aicardi, J., Conti, D., and Goutières, F. (1974). Les formes néonatales de la dystrophie myotonique de Steinhert. *Journal of the Neurological Sciences*, **22**, 149.

Bell, J. (1948). Dystrophia myotonica and allied diseases. *Treasury of Human Inheritance V*, p. 343. Cambridge University Press, London.

Bell, D. B., and Smith, D. W. (1972). Myotonic dystrophy in the neonate. *Journal of Pediatrics*, **81**, 83.

Bevan, E. A., Herring, A. J., and Mitchell, D. J. (1973). Preliminary characterization of two species of dsRNA in yeast and their relationship to the 'killer' character. *Nature*, **245**, 81.

Bulfield, G., and Kacser, H. (1974). Histidinaemia in mouse and man. *Archives of Disease in Childhood*, **49**, 545.

Bundey, S. (1974). Detection of heterozygotes for myotonic dystrophy. *Clinical Genetics*, **5**, 107.

Bundey, S., and Carter, C. O. (1972). Genetic heterogeneity for dystrophia myotonica. *Journal of Medical Genetics*, **9**, 311.

Calderon, R. (1966). Myotonic dystrophy: a neglected cause of mental retardation. *Journal of Pediatrics*, **68**, 423.

Dickinson, A. G., and Meikle, V. M. H. (1971). Host-genotype and agent effects in scrapie incubation: change in allelic interaction with different strains of agent. *Molecular and General Genetics*, **112**, 73.

Dickinson, A. G., Stamp, J. T., and Renwick, C. C. (1974). Maternal and lateral transmission of scrapie in sheep. *Journal of Comparative Pathology*, **84**, 19.

Dodge, P. R., Gamstorp, I., Byers, R. K., and Russell, P. (1965). Myotonic dystrophy in infancy and childhood. *Pediatrics*, **35**, 3.

Dyken, P. R., and Harper, P. S. (1973). Congenital dystrophia myotonica. *Neurology (Minneapolis)*, **23**, 465.

Gordon, N., and Hilson, D. (1967). Myotonic dystrophy: its occurrence in childhood. *British Journal of Clinical Practice*, **21**, 537.

Giovanucci, M. L., Calabri, G., and Paoli, A. (1969). Su di un caso di distrofia miotonica in una bambina con ritardo mentale. *Haematologica*, **54**, 849.

Harper, P. S. (1973). Pre-symptomatic detection and genetic counselling in myotonic dystrophy. *Clinical Genetics*, **4**, 134.

Harper, P. S., and Dyken, P. R. (1972). Early-onset dystrophia myotonica. Evidence supporting a maternal environmental factor. *Lancet*, **2**, 53.

Harper, P. S., Rivas, M. L., Bias, W. B., Hutchinson, J. R., Dyken, P. R., and McKusick, V. A. (1972). Genetic linkage confirmed between the locus for myotonic dystrophy and the ABH-secretion and Lutheran blood group loci. *American Journal of Human Genetics*, **24**, 310.

L'Hirondel, J., Guihard, J., Velot-Leroo, A., and Orange, C. R. (1970). La maladie de Steinert néonatale. *Semaine des Hôpitaux de Paris*, **46**, 1867.

Kacser, H., Bulfield, G., and Wallace, M. E. (1973). Histidinaemic mutant in the mouse. *Nature*, **244**, 77.

Karpati, G., Carpenter, S., Watters, G. V., Eisen, A. E., and Andermann, F. (1973). Infantile myotonic dystrophy. Histochemical and electron microscopic features in skeletal muscle. *Neurology (Minneapolis)*, **23**, 1066.

Klein, D. (1958). La dystrophie myotonique (Steinert) et la myotonie congéntale (Thomsen) en Suisse. *Journal of Génétique Humaine*, **7** (Suppl.).

Mohr, J. (1954). *A Study of Linkage in Man.* Munksgaard, Copenhagen.

Mundler, F. (1970). Formes néonatale et infantile précoce de la dystrophie myotonique. *Pédiatrie*, **25**, 865.

Parker, N. (1963). Dystrophia myotonica presenting as congenital facial diplegia. *Medical Journal of Australia*, **2**, 939.

Pruzanski, W. (1966). Variants of myotonic dystrophy in pre-adolescent life. *Brain*, **89**, 563.

Registrar General's Statistical Review of England and Wales for the Year 1965 (1967). H.M.S.O., London.

Renwick, J. H., Bundey, S. E., Ferguson-Smith, M. A., and Izatt, M. M. (1971). Confirmation of linkage of the loci for myotonic dystrophy and ABH secretion. *Journal of Medical Genetics*, **8**, 407.

Serradell, A. P. (1972). La enfermedad de Steinert neonatal. A proposite de una observacion. *Medicina Clinica*, **58**, 43.

Thomasen, E. (1948). *Myotonia.* Univeritetsforlaget i Aarhus.

Vanier, T. M. (1960). Dystrophia myotonica in childhood. *British Medical Journal*, **2**, 1284.

Verger, P., Guillard, J. M., and Eschapasse, P. (1967). La maladie de Steinert (myopathie myotonique) à debut précoce (dans la petite enfance). *Annales de Pediatrie*, **14**, 745.

Watters, G. B., and Williams, T. W. (1967). Early onset myotonic dystrophy. *Archives of Neurology (Chicago)*, **17**, 137.

Zellweger, H., and Ionasescu, V. (1973). Early onset of myotonic dystrophy in infants. *American Journal of Diseases of Children*, **125**, 601.

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