
The isometric force of arm and leg muscles was studied in five unrelated patients with recessive generalized myotonia (Becker). The symptom of myotonia was present mainly in the legs, whereas transient weakness was the prominent symptom in the arms. Tocainide improved both symptoms, although it improved the stiffness more than the weakness. A specimen of intact muscle fibers was excised from the external intercostal muscle of one of the patients. The resting potential of the fibers was normal, but on injection of depolarizing current the fibers responded with repetitive action potentials. In normal interstitial fluid the current-voltage relationship was N-shaped, with a region of negative slope between -70 and -55 mV. Replacement of chloride by an impermeant anion changed this relationship very little, suggesting an abnormally small chloride conductance. The potassium current through the inward-going rectifier was larger than normal. The force of tetanic contractions of a rested bundle was not sustained but fell quickly to a plateau that increased with repeated stimulation. The relaxation of a rested tetanus was slow and accompanied by spontaneous electrical activity. In subsequent contractions the relaxation became faster and electrical after-activity decreased. However at 23°C the speed of relaxation was always high despite a large amount of electrical after-activity. The electrical instability of the membrane and the transient weakness can be explained on the basis of the N-shaped membrane characteristic.

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TRANSIENT WEAKNESS AND ALTERED MEMBRANE CHARACTERISTIC IN RECESSIVE GENERALIZED MYOTONIA (BECKER)

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About 30 years ago, Becker^{3,4} discovered a form of myotonic disease that was clinically similar to myotonia congenita (Thomsen) but genetically different. The new type was characterized by autosomal recessive inheritance, whereas the mode of inheritance in Thomsen's disease is dominant. Initially, Becker called the new disease The Reces-

sive Form of Myotonia Congenita,⁴ although it is not congenital but usually has its onset in the second half of the first decade of life or later. He later coined the term Recessive Generalized Myotonia^{5,6} to stress that the recessive form usually affects all skeletal muscles, whereas in Thomsen's disease the myotonia may be limited to the leg muscles, the limb muscles, or rarely to the leg and eye muscles.⁵ Recessive generalized myotonia seems to be more common than dominant myotonia congenita, but it should be kept in mind that relatively more patients with recessive myotonia may come to medical notice because they tend to be more severely affected than patients with Thomsen's disease.

Clinically, the prominent symptom of recessive generalized myotonia is a transient stiffening of the muscles that occurs when the muscles are used after a period of rest. Quite often another symptom contributes seriously to the impairment of proper movements in these patients, namely a transient weakness that replaces the stiffness.^{2,8,16,20,22}

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It is now widely accepted that the basis of the myotonic stiffness is electrical instability of the muscle fiber membrane.²⁵ Bryant⁹ was the first to recognize that a similar instability is produced in normal muscle fiber membranes when the chloride conductance is reduced. Indeed, a smaller than normal chloride conductance was shown to be the basis of the stiffness in goats with myotonia congenita.⁹ Lipicky and Bryant¹⁹ determined the membrane component conductances in myotonia patients and found that four out of six patients had a smaller than normal chloride conductance. The study was later extended,¹⁸ and a reduced membrane conductance was reported for nine cases altogether. The two earlier cases with normal membrane conductance are as yet unexplained, and since, unfortunately, the genetic classification of all these cases is unknown, there is the possibility that the pathomechanism of myotonia is different in the two forms with different inheritance. This uncertainty is one reason for the present study. EMG recording from the abductor digiti V during repetitive ulnar nerve stimulation showed that, as the force decreases, the action potential becomes very small, although it does not disappear as in myasthenia gravis.²² Elucidation of the pathogenesis of myotonic weakness is the other reason for this study.

PATIENTS AND METHODS

Five unrelated patients with generalized myotonia were clinically investigated (see Table 1). Four of these cases were sporadic; in one case the proband's sister also had the disease. In all cases the parents were said to be without myotonic symptoms. The patients remembered the beginning

of the disease between age 6 and 13, and in the following 5 years the symptoms became worse.

All patients had remarkably strongly developed thigh and calf muscles and, in contrast, normal or even underdeveloped arm muscles. The lid-lag phenomenon was always present, and percussion myotonia could be shown in all muscles. Muscle stiffness was obvious during climbing stairs but was barely noticeable after a handshake. The force of the hand and arm muscles was low when the muscles were rested, and it turned normal in repeated contractions. Other than that the neurological investigation showed no abnormalities. In no case was there a suspicion of myotonic dystrophy, nor was a cataract detected. The EMGs showed short myotonic runs and normal motor unit potentials.

The isometric force of the m. biceps, m. quadriceps, and the finger flexors was tested at room temperature by asking the patients to exert a series of maximal jerks or long-lasting (5–18 seconds) maximal voluntary pulls on appropriate force transducers.^{13,29} Tocainide (Xylotocan, Astra, Wedel/Holstein, FRG) was administered at doses given in the Results section.

Patient 2 gave informed consent to having a biopsy taken from his external intercostal muscle. The project was approved by the Ethics Commission of the Technical University of Munich and was carried out in accordance with the Helsinki convention. The biopsy was performed under general anesthesia without muscle relaxants. The muscle specimen was kept in synthetic ("Bretag's") interstitial solution⁷ at room temperature for dissection into small bundles (~ 500 fibers) and storage. For the determination of the membrane pa-

Table 1. List of patients with recessive generalized myotonia entering the clinical study (in decreasing order of severity of symptoms).

Case	Age	Sex	Family history	Age at which symptoms were first experienced	Creatine kinase* (units/L)	Time needed for climbing 9 steps (seconds)†	
						Rested	Fifth consecutive attempt
1	36	M	Sporadic	12	175	30 (10.4)	6.4 (4.3)
2	16	M	Sporadic	12	145	25 (7.1)	4.2 (3.4)
3	45	M	Sporadic	6	116	16 (9.4)‡	4.7
4	22	M	Sister affected	13	52	10 (3.8)	2.5 (2.0)
5	22	F	Sporadic	9	41	18 (5.0)	3.4 (2.8)

*Normal values are <70 units/L for females and <80 units/L for males.

†Figures in brackets give times after tocainide treatment.

‡Plasma level of drug slightly below therapeutic concentration at time of test.

rameters and the contraction properties, a bundle was placed in a shallow, temperature-controlled chamber kept at 37°C. Excitability characteristics were determined as described earlier.¹⁴ Voltage-clamp experiments were performed according to the three-microelectrode method of Adrian and Marshall as described before.^{17,26} For contraction experiments one end of the bundle was fastened to a quasiisometric semiconductor force transducer (Akers, Horton, Norway). Tetanic stimuli were delivered via two silver wires running along the sides of the bundle ("transverse field stimulation"). Stimulus frequency, duration, and amplitude were varied as mentioned in the Results section. Extracellular recording of the muscle activity was made via two platinum wires placed on the surface of the muscle bundle. Other details of the set-up related to contraction experiments have already been reported.²³

CLINICAL RESULTS

Transient Weakness. In all patients the symptom of myotonic weakness was easily demonstrable with the isometric force transducers. As an example, Fig. 1 shows brief jerks (A) and 5 second contractions (B) exerted with the finger flexors by patient 3 whose affection was moderate (see Table 1). The experiment was carried out in the morning when the patient was completely rested; therefore the force at the beginning was typically small (trace A). During the series of jerks, the force amplitude decreased for 5 consecutive contractions and then increased to its normal full amplitude within the next 70 contractions (about 1 minute). A short (8 second) interruption of the series did not reintroduce the weakness. The series of long-lasting contractions (trace B) was carried out 15 minutes later. It shows another typical aspect of the transient weakness. The finger flexors are still somewhat "warmed up," so that the maximal force amplitude is reached in the first (although not in the second) contraction. However, the force is not sustained for the requested 5 seconds but quickly falls to a low level that gradually increases with repeated contractions. Sometimes the rest force slightly recovered after the initial fall, but usually it attained a plateau after a few seconds.

In patients 1 and 2, who were the most heavily affected, the time course of the transient weakness usually had an extra feature illustrated in the diagrams of Fig. 2A and B. When the muscle was completely rested, the first contraction was very low in amplitude, then there was an increase in

force during the following 2 contractions, then a decrease again during the next 3–5 contractions, and finally a slow increase that led to a plateau within the next 5–10 contractions.

Effect of Tocainide on Transient Weakness. Series of lower-arm jerks were investigated before, 3 days after, and 6 weeks after tocainide therapy. All patients responded very well to the medication with a decrease of the weakness. Figure 2B shows for one of the two most severely affected patients that even when the muscle was rested for 60 minutes, under medication the first contraction was high, almost twice the plateau value in the unmedicated state. The duration of the following transient weakness was shortened, and the ensuing final force was much higher than in the unmedicated case, but the minimum force during the transient weakness was never improved. Unfortunately, tocainide did not improve the level of the rest force in long-lasting contractions either. Experiments carried out with patient 2 after 10 weeks of treatment showed this very clearly (Fig.

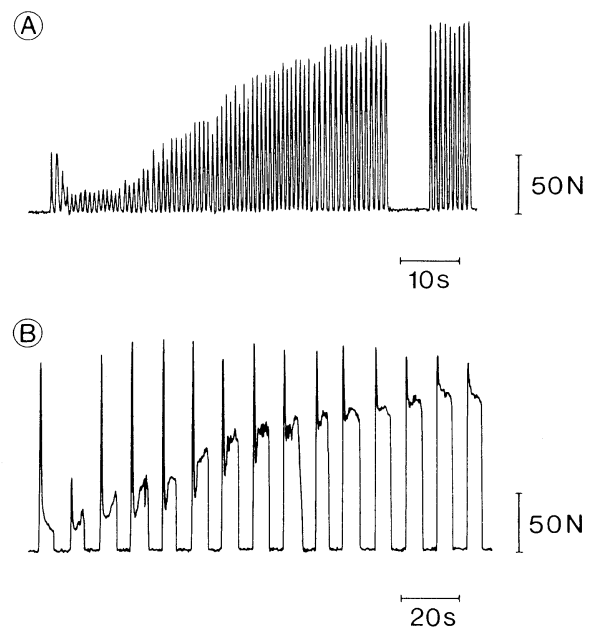


FIGURE 1. Recordings of isometric force of flexor digitorum from patient 3. **(A)** Series of voluntary brief maximal contractions. Force is low at the beginning probably because the muscle was completely rested. Transient weakness very pronounced. A voluntary pause of 8 seconds has no influence on the force. Note slight myotonia in contractions 2 and 3. **(B)** Series of voluntary long-lasting (5 second) maximal contractions recorded 15 minutes after series A. Throughout each contraction, force is not sustained but drops to a plateau after an initial spike. The plateau increases with repeated muscle activation.

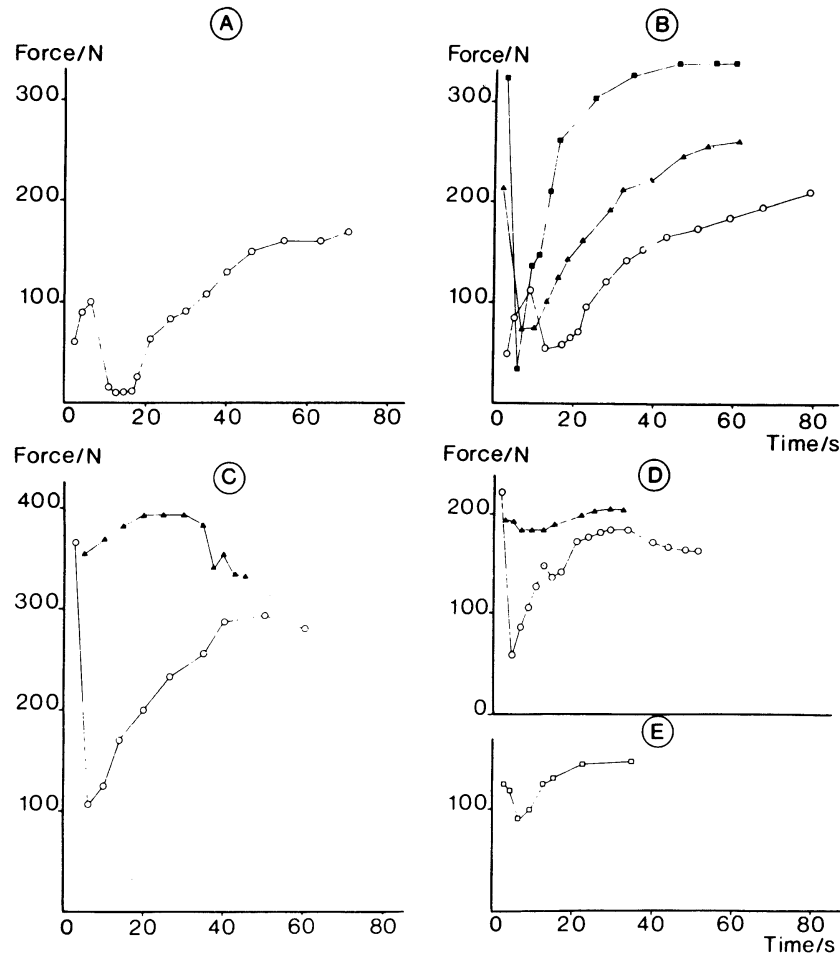


FIGURE 2. Maximal force in series of voluntary brief contractions performed by four patients with generalized myotonia. **(A)** Patient 1, m. biceps after 60 min of rest. **(B)** Patient 2, m. biceps, effect of 6×400 mg/day tocainide; all series after 30 minutes of rest. Circles, before therapy; triangles, day 3 of treatment; squares, after 10 weeks. **(C)** Patient 4, m. biceps after 30 minutes of rest. Circles, before therapy; triangles, after 3×400 mg/day tocainide. **(D)** Patient 5, m. biceps, after 30 minutes of rest. Circles, before therapy; triangles, after 3×400 mg/day tocainide. **(E)** Patient 5, m. quadriceps, after 60 minutes of rest, unmedicated.

3). These experiments illustrate another feature of the weakness present with and without medication. The low force plateau could not be increased by prolonging the contraction to as much as 20 seconds. The amplitude of the plateau rather depended in a complicated way on the recent history of the muscle. If the time interval to the foregoing contraction was decreased, the plateau becomes lower, and vice versa (Fig. 3). Yet, after 6 weeks of treatment with 6×400 mg per day, the subjective judgement of this patient was that the stiffness had completely gone and the weakness was only "a bit there." He did not complain about any side effects. Patient 1, whose impediment was the severest of all patients, showed a similar improvement with daily 3×400 mg tocainide, but on day

4 and 5 of treatment he complained about dizziness, headache, and depressive mood, so that the test was stopped. Patients 4 and 5 were treated with 3×400 mg tocainide per day, and since they were only mildly affected, the result was very satisfactory (Fig. 2C and D). These patients did not complain about any side effects; in fact, they felt much better, mainly because their walking was so much improved. This is also owing to the fact that myotonic weakness was as a rule far less pronounced in the legs (Fig. 2E) than in the arms (Fig. 2D, open circles, from patient 5 before medication).

Myotonic Stiffness. Slowed relaxation was usually not detectable in the finger flexors and in the

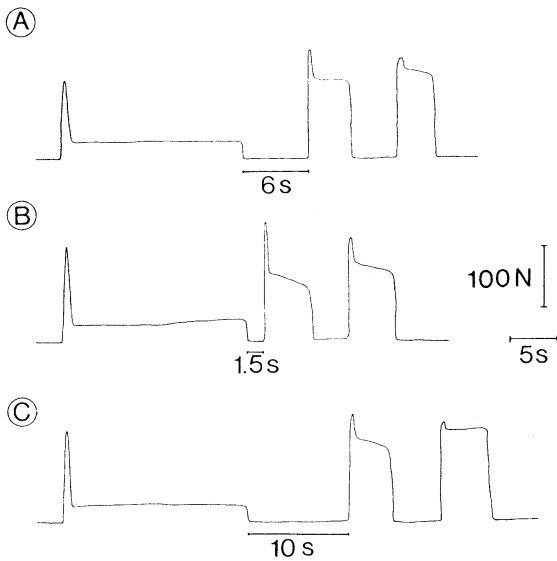


FIGURE 3. Dependence of the sustained forces of flexor digitorum on the history of voluntary activation. Patient 2, medicated with tocainide for 10 weeks, 10 minutes of rest between records **A**, **B**, and **C**. Even during attempts lasting 20 seconds, the patient is not able to increase his plateau force, but a short pause leads to an increased plateau. (**A**) Pause 6 seconds, (**B**) pause 1.5 seconds, (**C**) pause 10 seconds.

m. biceps except for the second and third contraction of a series where it was barely conspicuous (Fig. 1A). This was different in the leg muscles, where myotonia was demonstrable in all patients (cf. Fig. 4A). The myotonia was completely abolished in all patients by the administration of 3×400 mg tocainide (Fig. 4B). This treatment led in all cases to a normalization of the time required to climb nine steps (see Table 1).

IN VITRO RESULTS

Electrophysiological Measurements. The biopsy was carried out before the patient had been set on therapy and was without any complication. The resting potential of the fibers was -81.8 ± 4.4 mV (SD, $n = 21$), i.e., not significantly different from the -83.7 ± 4 mV of normal fibers.¹⁴ The parameters of 51 action potentials measured at threshold were as follows: electrical threshold 51.0 ± 42 mV, overshoot $+7.1 \pm 7.2$ mV, and latency 64.4 ± 42 msec. In comparison with normal muscle fibers,¹⁴ these figures display the greater variability characteristic for myotonia. The only parameter that is significantly different is the very long latency. In contrast to normal fibers,¹⁴ the fibers from the patient responded to long-lasting depolarizing pulses with multiple spikes, even if

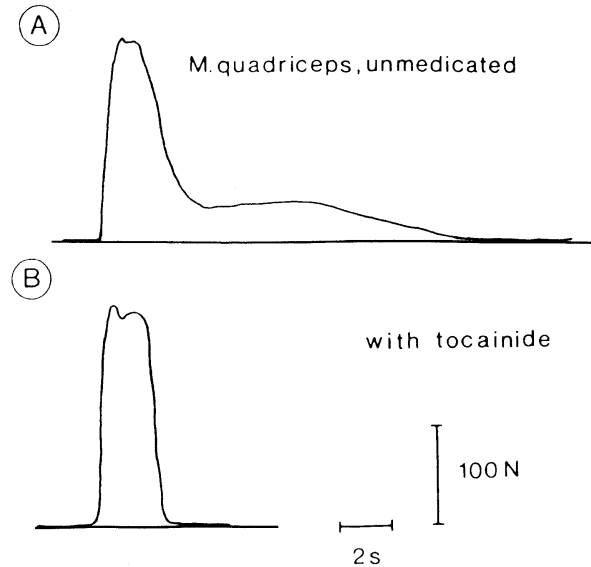


FIGURE 4. Isometric force recorded from the m. quadriceps of patient 5 during maximal voluntary contractions lasting 2 seconds. (**A**) Before treatment myotonia is pronounced; (**B**) after 10 weeks of 3×400 mg/day tocainide the relaxation is normal.

the stimulus was just above threshold (Fig. 5A and B). Raising the current amplitude to 2–3 times rheobase resulted in multiple spikes, and often the spiking continued for some time after the current injection (Fig. 5C and D).

The resting potential did not significantly change (-79.7 ± 4.5 , $n = 21$) when we added 0.3 mg/L tetrodotoxin (TTX) to the bathing solution to prevent the generation of action potentials during voltage clamp pulses. The membrane currents recorded during depolarizing voltage clamp pulses reached steady levels after about 15 msec as in normal fibers, but the amplitudes of these steady levels were abnormally small when the clamp potential was between -70 and -50 mV. As a consequence, a region of negative slope was apparent in this range of the relationship between current density and voltage. This is illustrated in Fig. 6, where the filled squares represent the mean results obtained from 16 fibers from the patient. The heavy line represents the current-voltage relationship of normal fibers for comparison.¹⁵ The error bars denoting the standard deviation of the membrane current density at -60 mV show that the difference between myotonic and normal fibers is highly significant. Since both curves were recorded in the presence of TTX, it is unlikely that the negative slope for the myotonic fibers is caused by the flow of an abnormal so-

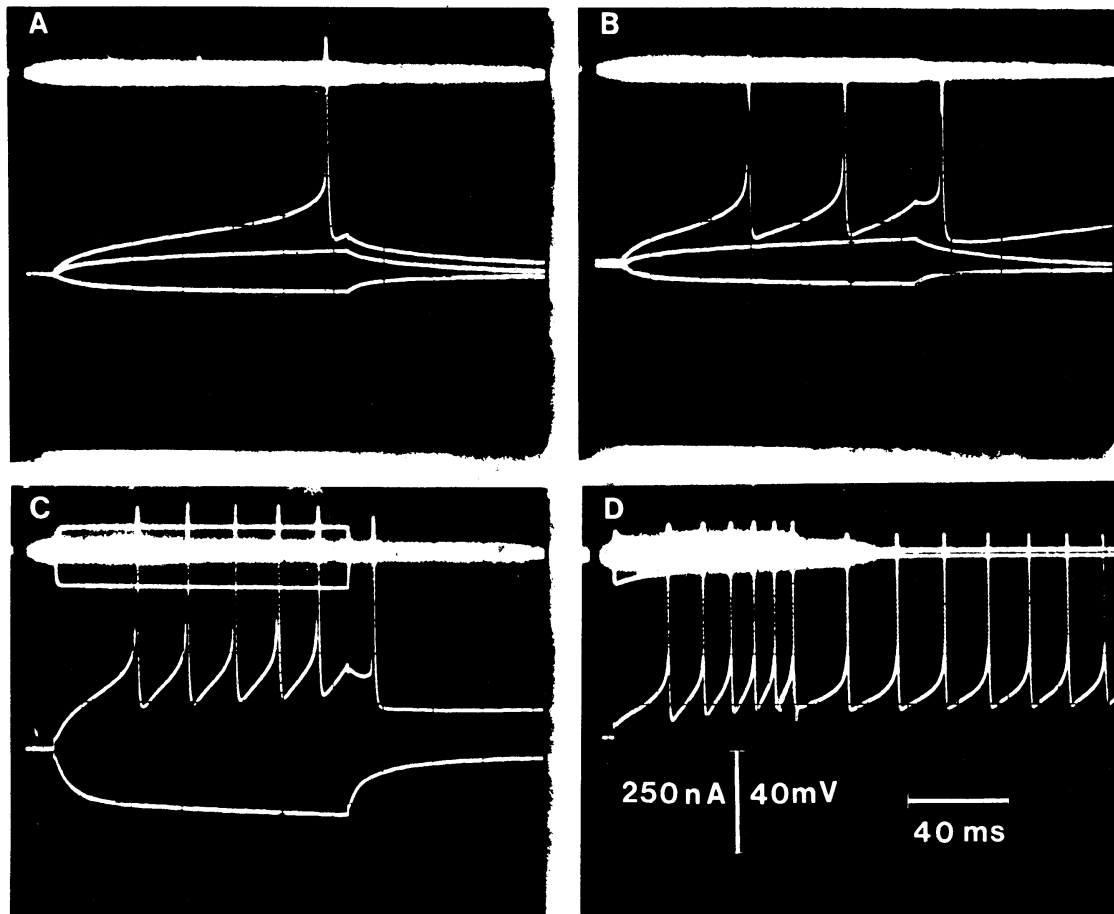


FIGURE 5. Intracellular action potentials recorded in vitro from external intercostal muscle fibers biopsied from patient 2. Intracellular current pulses lasting 120 msec (upper traces) in **A**, **B**, and **C** are given both in hyperpolarizing and depolarizing direction for better illustration of potential deviation in the absence of spikes. In each frame the position of the upper trace also denotes zero potential; the resting potential is about -80 mV. (**A**) Single spike at threshold; (**B**) multiple spikes with stimulating current just above threshold; (**C**, **D**) spontaneous spiking following current injection at 2–3 times rheobase.

dium current. We also made a few measurements in the absence of TTX. Because of fiber twitching these measurements covered only the potential range negative to -65 mV, where they gave similar results to those obtained in the presence of TTX (not illustrated).

To estimate the chloride component of the membrane current, we measured current density-voltage relationships in chloride-free solution (containing 0.3 mg/L TTX). The resting potential in this solution was -80.1 ± 2.8 mV ($n = 10$). The filled circles in Fig. 6 show the averaged data obtained with 8 fibers from the patient. In the potential range from -100 to -50 mV, the curves recorded in the absence and presence of extracellular chloride did not differ very much. This suggests that in the fibers from the myotonia patient the chloride current is very small indeed.

The membrane resistance of these fibers at rest is given by the slope of these curves at -80 mV. For the 16 fibers bathed in normal (TTX-containing) Bretag's solution, the mean value was $8400 \Omega\text{cm}^2$, which is 1.4 times higher than the $5970 \Omega\text{cm}^2$ of normal fibers.¹⁴ We also determined the membrane resistance in this solution after the bundle was cooled to 23°C . The mean value of 3 fibers was $12,400 \Omega\text{cm}^2$, about 1.5 times more than at 37°C . The Q_{10} of 1.2 calculated from these values is very similar to the Q_{10} found for normal fibers.¹⁴

The mean membrane resistance of the 8 fibers bathed in chloride-free solution at 37°C was $14,030 \Omega\text{cm}^2$, i.e., much lower than the $24,210 \Omega\text{cm}^2$ measured in normal fibers.¹⁴ Since potassium is the only ionic species likely to carry current in this condition, these results indicate that in

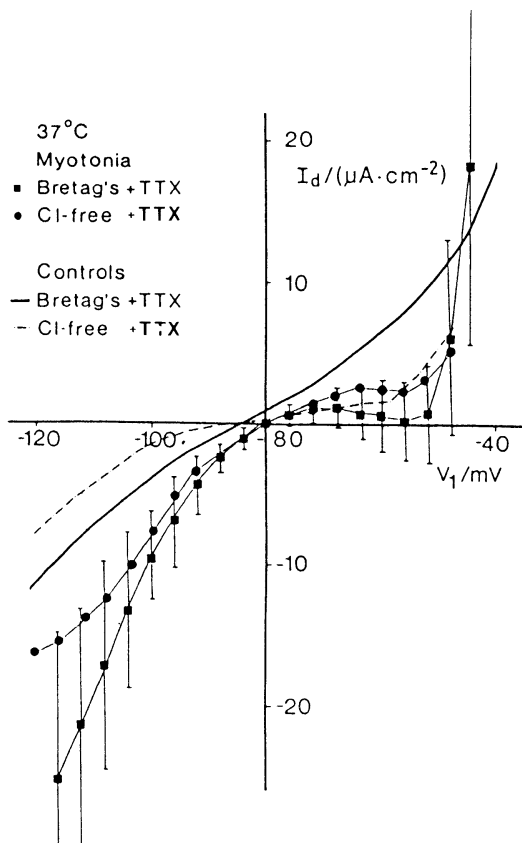


FIGURE 6. Current-voltage relationships of intercostal muscle fibers. Mean results from fibers from patient 2 in normal synthetic interstitial fluid (squares, $n = 16$) and in chloride-free solution (circles, $n = 8$). Controls in normal (heavy line) and in chloride-free solution (thin line) taken from Kwieciński et al.¹⁵ All solutions contained 0.3 mg/L tetrodotoxin (TTX) to prevent fiber twitching.

the fibers from the patient the chloride conductance was remarkably low and, perhaps as a compensation, the potassium conductance (at the resting potential) was increased by a factor of 1.7.

Contraction Measurements. With all bundles from the myotonia patient we had the puzzling experience that it was difficult to choose the right set of stimulus parameters so that a 20 or 50 Hz tetanus of a rested bundle was sustained for a second or so. With the pulse parameters found appropriate for normal fibers (0.2 msec duration, 50 V amplitude), the force rose quickly to a peak and then immediately dropped to a plateau somewhere between 20 and 90% of the peak value (Fig. 7A). Only the last stimulus of the train was able to trigger a second full peak of contraction, independently of the number of pulses in the

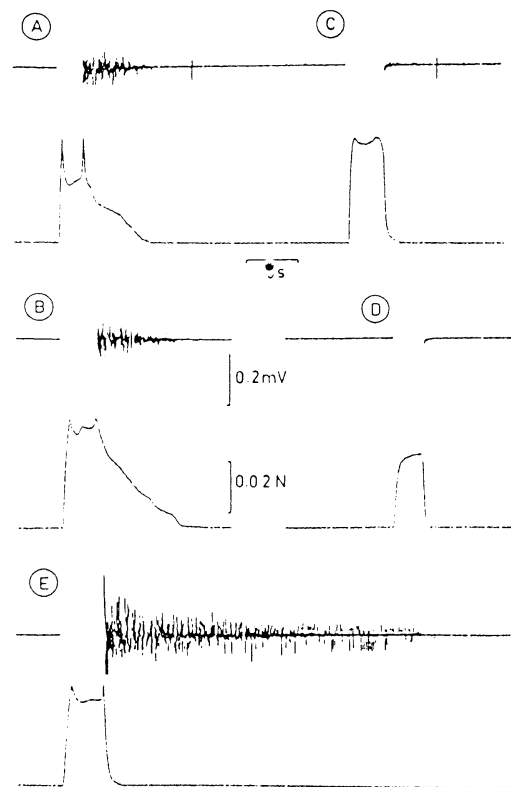


FIGURE 7. Mechanograms (lower traces) and electromyograms (upper traces) recorded from a fiber bundle of patient 2 at 37°C. (A, B) Contractions after a longer (>5 minute) period of rest; (C) is 13 seconds after A; (D) 30 seconds after B. The stimulus conditions for the single pulses in the 20 Hz trains were 50 V amplitude and 0.2 msec duration in A and C and 30 V amplitude and 0.1 msec in B and D. (E) Recorded from the same bundle, but at 23°C; stimulating pulses 20 V, 0.2 msec. During stimulation the EMG trace is blanked.

train. The relaxation following this second peak was usually very much slowed, and the accompanying EMG showed a large amount of after-activity that could account for the slow decay of force. When the pulse duration and/or the pulse amplitude were decreased, the force amplitude of the plateau was increased (Fig. 7B), and vice versa. The peaks at the beginning and the end of the tetanus were rather unaffected by the stimulus parameters provided these were suprathreshold but not too supramaximal.

When a bundle was stimulated with two identical trains at an interval of 5–30 seconds, the second tetanus was always much better sustained than the first one, so that the plateau force was often close to 100% throughout stimulation (Fig. 7C). The relaxation was then much more normal than after the first train, and correspondingly the

after-activity was decreased. However, a tetanus with a normal shape (a fast rise of force, a plateau with a small upward creep, and a fast relaxation) only occurred when the pulses were so short (0.1 msec) and small (20 V) that the force did not rise to its full amplitude (Fig. 7D).

Measurements at Low Temperature. When we cooled one of the bundles to 22°C and investigated tetanic contractions, we repeatedly obtained the surprising result illustrated in Fig. 7E. Although the electrical after-activity of rested-state as well as of follow-up contractions was high, the speed of relaxation was always fast. In other words, we found a pronounced electrical myotonia in the cold, but it did not produce any mechanical myotonia. The resting potential determined at 23°C was -83 ± 3.6 mV ($n = 28$).

DISCUSSION

The clinical results show that the transient weakness is a very distinct symptom of recessive generalized myotonia. Particularly in the muscles of the upper and lower arm, the transient weakness was a far greater impediment for the patients than the myotonia. By contrast, in the leg muscles the myotonia was the predominant symptom. This is why myotonia is most readily detected with the stair test.

Tocainide was very effective in abolishing the myotonic stiffness^{24,28} but only moderately effective in abolishing the weakness. Albeit during brief contractions the duration of the period of weakness was shortened, during long-lasting contractions tocainide seemed almost without any effect on the weakness. As an antiarrhythmic agent, tocainide affects mainly the fast sodium current, which did not seem abnormal in these muscles. This might explain the drug's lower effectiveness in myotonia than in paramyotonia.¹³ Nevertheless, tocainide and the closely related mexiletine are, in our experience, the drugs of choice to alleviate myotonic symptoms.

Perhaps the most important result of this study is the finding that in recessive generalized myotonia the chloride conductance is smaller than normal. This means that the pathogenesis of muscle stiffness in this disease is similar to that in myotonia congenita of humans¹² and goats.¹¹ The repetitive discharges in human recessive generalized myotonia are almost indistinguishable from those recorded from goats with dominant myotonia congenita.¹ The N-shape of the current density-voltage relationship may provide an answer to

the question of why Lipicky and Bryant¹⁹ obtained variable (and mostly highly increased) values for the membrane resistance in intercostal fibers from myotonia patients. The early determinations were done without voltage clamping at resting potentials that were usually lower than ours, i.e., in a potential range where a slight depolarization causes a large increase of the membrane resistance.

Measurement of the whole current-voltage relationship provides a much better understanding of the pathogenesis of myotonia than mere determinations of the component conductances at the resting potential. Comparing the curves in Fig. 6, we suggest the following interpretation. The chloride current is missing in the fibers from the patient, and this is in part compensated for by an increased flow of potassium current through the channels of the inward-going rectifier that operates in the potential range negative to -70 mV. These two abnormalities lead to the observed N-shape of the characteristic curve for the myotonic membrane with a nearly normal shape (conductance) at the resting potential and a negative slope around -65 mV. For an exact analysis of the events during physiologic activation of a myotonic muscle, it would be necessary to know the dynamic current-voltage relations for de- and repolarization and the changes these curves undergo as a consequence of activity. But the available information permits some speculations. When the muscle is activated after rest, it seems that during the repolarization phase of the early action potentials there is a high probability for the membrane potential to fail to return to its normal resting value. For example, when the repolarization has reached -75 mV, the potential could return to the normal resting value of -80 mV, but it could also decrease again towards -55 mV. When this depolarization occurs so slowly that no action potential is triggered, the membrane potential could remain at -55 mV for quite some time. A fiber with such a low resting potential would be inexcitable, and the symptom of transient weakness would be explained by this alternative. On the other hand, when the depolarization after incomplete repolarization occurs fast enough to activate the excitatory sodium current, another action potential would follow, and this cycle could repeat itself as long as the characteristic curve retains its region of negative slope. This alternative would thus result in myotonic runs that seem to occur preferentially at the end of voluntary activation. Some secondary process might slowly straighten

the characteristic curve toward the normal shape, thus terminating the myotonic run and causing "warm-up" for the next few minutes or so.

The *in vitro* mechanograms of the myotonic bundles showed many similarities with the mechanograms recorded from the patients. Under both conditions the initial peak was rather constant, and the level of the plateau showed the same dependence on the stimulation history. Therefore, we have little doubt that the abnormalities have a common origin. This supports the earlier hypothesis²² that the transient weakness is not caused by failure of the neuromuscular transmission but by a failure residing further down in the chain of events leading to muscle contraction. Since the full force was attained only at the beginning and at the very end of the tetanus *in vitro*, it is obvious that the development of excitation in these fibers must be so slow that each response within the train is negatively affected by the subsequent stimulus. With the electrode arrangement used here, the applied current that enters and leaves the fiber should have about the same density.²⁷ Therefore, it depends mainly on the slope of the current-voltage relationship whether the depolarizing or the hyperpolarizing effect of the current prevails. When the curve is bent towards the voltage axis, as is the case in the pa-

tient's fibers at the resting potential, the net result of current flow is depolarization, the effect desired for stimulation. When the curve bends away from the voltage axis, as is the case at -65 mV, the net result *during* the flow of current is hyperpolarization. When the stimulus is over, the fiber might slowly depolarize far enough to reach the threshold for an action potential. We suggest that in cases such as those illustrated in Fig. 7, this depolarization took longer than the interval between stimuli, so that excitation was prevented—in some of the fibers—until the last stimulus.

Our *in vitro* experiments in the cold confirm earlier results in myotonia patients that the muscle stiffness is alleviated in the cold.²¹ The finding of electrical myotonia without mechanical myotonia in the cold leads us to question the generally accepted opinion that the muscle stiffness in myotonia is totally caused by the electrical after-activity. It seems that in the case of Fig. 7E spontaneous activity in a few fibers produces a rather dense pattern, at the same time generating relatively little force. On the other hand, the spontaneous activity in the case of Fig. 7A can hardly account for the slowed relaxation. A similar disproportionality has been reported by Bryant¹⁰ for muscle from neonatal myotonic goat both *in situ* and *in vitro*.

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