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 -56 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.
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. 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 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 abidance 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>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Family history</th>
<th>Age at which symptoms were first experienced</th>
<th>Creatine kinase* (units/L)</th>
<th>Time needed for climbing 9 steps (seconds)†</th>
<th>Rested</th>
<th>Fifth consecutive attempt</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>M</td>
<td>Sporadic</td>
<td>12</td>
<td>175</td>
<td>30 (10.4)</td>
<td>6.4 (4.3)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>M</td>
<td>Sporadic</td>
<td>12</td>
<td>145</td>
<td>25 (7.1)</td>
<td>4.2 (3.4)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>M</td>
<td>Sporadic</td>
<td>6</td>
<td>116</td>
<td>16 (9.4)‡</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>M</td>
<td>Sister affected</td>
<td>13</td>
<td>52</td>
<td>10 (3.8)</td>
<td>2.5 (2.0)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>F</td>
<td>Sporadic</td>
<td>9</td>
<td>41</td>
<td>18 (5.0)</td>
<td>3.4 (2.8)</td>
<td></td>
</tr>
</tbody>
</table>

*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 therapeutical 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. Voltage-clamp experiments were performed according to the three-microelectrode method of Adrian and Marshall as described before. For contraction experiments one end of the bundle was fastened to a quasisometric 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.

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](https://example.com/figure1.png)
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 x 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 x 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 x 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
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. 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-

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. The parameters of 51 action potentials measured at threshold were as follows: electrical threshold 51.0 ± 42 mV, overshoot +7.1 ± 7.2 mV, and latency 64.4 ± 42 msec. In comparison with normal muscle fibers, 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, the fibers from the patient responded to long-lasting depolarizing pulses with multiple spikes, even if 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).

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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 Ωcm², which is 1.4 times higher than the 5970 Ωcm² of normal fibers. 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 Ωcm², about 1.5 times more than at 37°C. The Q₁₀ of 1.2 calculated from these values is very similar to the Q₁₀ found for normal fibers.

The mean membrane resistance of the 8 fibers bathed in chloride-free solution at 37°C was 14,030 Ωcm², i.e., much lower than the 24,210 Ωcm² measured in normal fibers. 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 Kwiecinski et al.\(^\text{15}\) 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 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

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.
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 investi-
gated tetanic contractions, we repeatedly obtained
the surprising result illustrated in Fig. 7E. Al-
though 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 myo-
tonia in the cold, but it did not produce any me-
chanical myotonia. The resting potential deter-
mined at 23°C was \(-83 \pm 3.6 \text{ mV} (n = 28)\).

DISCUSSION

The clinical results show that the transient weak-
ness is a very distinct symptom of recessive gen-
eralized 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 myo-
tonia was the predominant symptom. This is why
myotonia is most readily detected with the stair

Tocainide was very effective in abolishing the
myotonic stiffness\(^2^4,2^5\) but only moderately effect-
in abolishing the weakness. Albeit during
brief contractions the duration of the period of
weakness was shortened, during long-lasting con-
tractions tocainide seemed almost without any ef-
fect 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.\(^3^9\) Neverthe-
less, tocainide and the closely related mexiletine
are, in our experience, the drugs of choice to alle-
viate 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 mus-
cle stiffness in this disease is similar to that in
myotonia congenita of humans\(^1^2\) and goats.\(^1^1\) The
repetitive discharges in human recessive gener-
alized myotonia are almost indistinguishable from
those recorded from goats with dominant myoto-
nia congenita.\(^1\) The N-shape of the current densi-
ty-voltage relationship may provide an answer to

the question of why Lipicky and Bryant\(^1^9\) ob-
tained variable (and mostly highly increased) val-
ues for the membrane resistance in intercostal
fibers from myotonia patients. The early determi-
nations were done without voltage clamping at
resting potentials that were usually lower than
ours, i.e., in a potential range where a slight depo-
larization causes a large increase of the membrane
resistance.

Measurement of the whole current-voltage rela-
tionship provides a much better understanding
of the pathogenesis of myotonia than mere deter-
ninations of the component conductances at the
resting potential. Comparing the curves in Fig. 6,
we suggest the following interpretation. The chlo-
ride current is missing in the fibers from the pa-
tient, and this is in part compensated for by an
increased flow of potassium current through the
channels of the inward-going rectifier that oper-
ates in the potential range negative to \(-70 \text{ mV}\).
These two abnormalities lead to the observed N-
shape of the characteristic curve for the myotonic
membrane with a nearly normal shape (conduc-
tance) at the resting potential and a negative slope
around \(-65 \text{ mV}\). For an exact analysis of the
events during physiologic activation of a myotonic
muscle, it would be necessary to know the dy-
namic current-voltage relations for de- and repo-
larization and the changes these curves undergo
as a consequence of activity. But the available in-
formation permits some speculations. When the
muscle is activated after rest, it seems that during
the repolarization phase of the early action poten-
tials there is a high probability for the membrane
potential to fail to return to its normal resting val-
ue. For example, when the repolarization has
reached \(-75 \text{ mV}\), the potential could return to
the normal resting value of \(-80 \text{ mV}\), but it could
also decrease again towards \(-55 \text{ mV}\). When this
depolarization occurs so slowly that no action po-
tential is triggered, the membrane potential could
remain at \(-55 \text{ mV}\) for quite some time. A fiber
with such a low resting potential would be inexci-
table, and the symptom of transient weakness
would be explained by this alternative. On the
other hand, when the depolarization after incom-
plete repolarization occurs fast enough to activate
the excitatory sodium current, another action po-
tential would follow, and this cycle could repeat it-
self 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 hypothesis \(^{22}\) 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 patient'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 Bryant \(^{10}\) for muscle from neonatal myotonic goat both in situ and in vitro.

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