

To investigate the pathomechanism of paramyotonic stiffness, the mechanogram of isometric finger force and the electromyogram of the flexor digitorum muscle were simultaneously recorded in five unrelated paramyotonia congenita patients. Cooling of the forearm provoked "spontaneous" electrical activity, but the accompanying force was <5% of the maximal voluntary isometric contraction amplitude. The relaxation of maximal voluntary contractions executed in the cold had a normal first phase and a very slow second phase. The force amplitude at the beginning of the slow phase was up to 80% of the maximal contraction amplitude; the duration of the slow phase was up to several minutes. It was concluded that the slowed muscle relaxation is more important as a factor contributing to paramyotonic stiffness than spontaneous force generation. Involuntary electrical activity recorded during the slow relaxation phase was too low to account for the force. Intercostal muscle biopsies obtained from four patients showed similar phases of slow relaxation when stimulated to give isometric twitches or tetani in the cold. Extracellular recording with electrodes designed to pick up all activity from the small bundles clearly showed that the slow relaxation phase was not caused by spontaneous action potentials. One possible explanation for the slowed relaxation is a long-lasting depolarization-induced contracture of the muscle fibers following activation in the cold.

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## MUSCLE STIFFNESS AND ELECTRICAL ACTIVITY IN PARAMYOTONIA CONGENITA

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Involuntary electrical and mechanical after-activity following muscle activation have been shown to be responsible for the muscle stiffness in myotonia congenita.<sup>4,8</sup> Involuntary electrical activity is also a feature detectable in the electromyogram (EMG) of patients with paramyotonia congenita, which is another hereditary disease characterized by the symptom of muscle stiffness.

Several investigators<sup>2,5,16,19</sup> have questioned the idea that involuntary electrical activity is the cause of paramyotonic stiffness. Their doubts were based on the dissociation between the intensities of electrical activity and the stiffness observed in vivo, e.g., during simultaneous recording of the EMG from the long finger flexors and of the passive resistance to hand opening.<sup>5</sup> However, many muscles act on the metacarpophalangeal and interphalangeal joints, so that one can hardly be sure that the electrical activity recorded from one muscle is representative of the total involuntary activity in all the muscles involved in the production of the stiffness. This uncertainty does not exist in a simultaneous in vitro measurement of electrical activity and force of a small muscle bundle dissected intact from a paramyotonia patient. In the present work we report such experiments that lead us to the conclusion that the paramyotonic stiffness is not essentially caused by involuntary electrical activity.

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### MATERIALS AND METHODS

The study was approved by the Ethics Commission of the Technical University of Munich and was car-

ried out in accordance with the Helsinki convention. All patients consented to the clinical tests, patients 2–5 also gave informed consent for an external intercostal muscle biopsy to be taken. The experiments reported here are a part of a larger study carried out with the biopsy material. Some of the results have been published in preliminary form.<sup>10,11</sup>

Five unrelated paramyotonia congenita patients were investigated, two of them from families that have not been described previously. All patients developed distinct muscle stiffness and weakness on exercising their muscles in the cold. These symptoms could be prevented by daily oral administrations of  $2-3 \times 400$  mg tocainide<sup>15</sup> (Astra, Wedel/Holstein, Germany) or  $3 \times 200$  mg mexiletine (Boehringer, Ingelheim, Germany).<sup>5</sup> None of the patients had ever experienced spontaneous attacks of weakness in the warm, such as those that occur in patients with hyperkalemic periodic paralysis.

**Patient 1.** This 21-year-old man had experienced muscle stiffness in the cold from his early youth.<sup>20</sup> During severe cold exposure, he also suffered from muscle weakness. Weakness also occurred after long-lasting strenuous work in a warm environment. His mother showed the same symptoms. The musculature of the patient was well developed and strong. At room temperature, no clinical signs of myotonia were present, but numerous myotonic runs were registered electromyographically. In several tests, the serum CK was 2–3 times normal. A biopsy from the calf muscle showed no histopathologic changes.

**Patient 2.** This 23-year-old man was a member of a family in which paramyotonia was diagnosed in 1980. As far back as he could remember, his fingers became stiff and cramped in the cold. Once he had forcefully closed the fist in the cold, he could not open the hand for a long time. He had been dismissed from military service because on several occasions he was unable to release the trigger of his gun. In severe cold, the exposed muscles became weak. During exhaustive muscular activity, stiffness occurred even in a warm environment. The brother, the mother, and other members of the patient's family throughout three generations had the same symptoms. The musculature of the patient was well developed and strong. Lid lag was detectable, percussion myotonia was absent. In the warm, muscle relaxation was initially normal, but on repeated hand closures, the hand opening be-

came successively slower (paradoxical myotonia). Myotonic discharges were detectable electromyographically. The serum creatine kinase (CK) and the serum aldolase were normal.

**Patient 3.** This 20-year-old patient had experienced muscle stiffness and weakness in the cold from his early youth. During muscular efforts in the warm, the working muscles became abnormally weak, although the serum potassium did not rise beyond physiologic levels. Such exercise-induced weakness, as well as the cold-induced weakness, disappeared only slowly within hours. Two brothers, a sister, and the father of the patient suffered from the same symptoms. The musculature of the patient was well developed and strong. Clinical signs of myotonia were not found in a warm environment, but myotonic runs could be detected electromyographically. In several tests, the serum CK was 3–4 times normal. A biopsy from the biceps brachii muscle showed no histopathologic changes.

**Patient 4.** This 42-year-old woman was a member of a family in which paramyotonia congenita was detected in 1982. The disease was present in herself, her father, and in her twin daughters. A description of this family and their symptoms has previously appeared.<sup>10</sup>

**Patient 5.** This 38-year-old man is patient "PWOM A" of an earlier report.<sup>5</sup>

**Clinical Measurements.** The isometric force of finger flexion and the EMG of the flexor digitorum longus muscle were recorded from all patients as described earlier.<sup>14</sup> The supinated forearm of the patients was fixed, with the fingers of the half-opened fist pressing against an isometric force transducer. The patients, who could observe the myogram on an oscilloscope screen, were asked to press the transducer bar maximally for a 2-second period and then to let go immediately. Two insulated platinum wires, their tips exposed for 1 mm, were inserted lengthwise into the flexor muscle 10 mm apart from one another for EMG recording. The forearm was cooled in a water bath. The muscle temperature was measured with a fine thermocouple inserted into the belly of the flexor muscle.

**In Vitro Measurements.** The biopsy of the external intercostal muscle was carried out as reported earlier.<sup>12</sup> The excised muscle specimen was placed in a thermos bottle with oxygenated, tetrodotoxin-

containing Bretag's<sup>1</sup> solution (see below) at 37°C, transported to the laboratory, and dissected into bundles about 3 mm wide and 1 mm thick. The length of intercostal muscle fibers is 10–15 mm. A bundle was placed in the experimental chamber as described before,<sup>12</sup> the rest of the muscle was stored at 37°C for later use. The bundle was suspended horizontally on its tendons between two stainless steel hooks, one of which was connected to a semiconductor strain gauge (Akers, Horton, Norway). The compliance of the strain gauge was such that a bundle, stretched to give maximal force, shortened by about 10% during tetanic stimulation. Stimulation occurred either via two silver point electrodes, placed on either side of the bundle at the far end with respect to the transducer hook, or via two silver wires running along either side of the bundle ("massive field stimulation"). Supramaximal monopolar pulses of 0.2 msec duration were administered as single shocks or in 30–50-Hz trains of variable duration. Extracellular recording of muscle activity occurred via two platinum wires whose insulation was removed for the last 3 mm of their length. They were placed on the surface of the muscle bundle perpendicular to the long axis, slightly off midlength, and 4 mm apart from each other. According to Rosenfalck,<sup>17</sup> this electrode arrangement allows one to record the activity of all fibers in a bundle having the dimensions of our preparations. We have convinced ourselves whenever spontaneous contractions could be observed through the dissecting microscope, that the action potentials of any twitching fiber were clearly registered irrespective of whether the fiber was lying at the surface of the bundle or deep in.

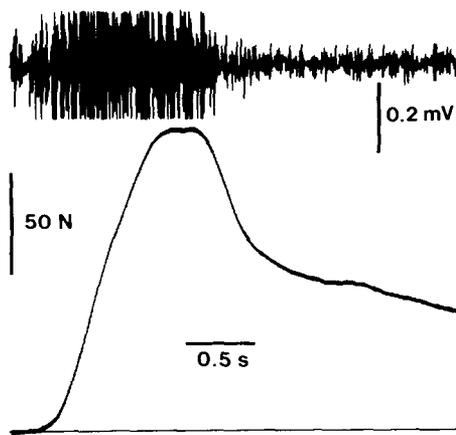
The experimental chamber was continuously perfused at a rate of 3 ml/min with oxygenated (95% O<sub>2</sub>, 5% CO<sub>2</sub>) Bretag's<sup>1</sup> interstitial fluid, having the following composition (in mM): NaCl, 107.7; KCl, 3.48; CaCl<sub>2</sub>, 1.53; MgSO<sub>4</sub>, 0.69; NaHCO<sub>3</sub>, 26.2; NaH<sub>2</sub>PO<sub>4</sub>, 1.67; sodium gluconate, 9.64; glucose, 5.5; sucrose, 7.6; pH 7.4. To avoid neurogenic interference, tubocurarine (10 mg/liter) was added to this solution. Tetrodotoxin (TTX), contained at 0.3 mg/liter in the solution used for transport, dissection, and storage of the muscle specimens, was washed out at the beginning of each experiment. In a few experiments, the potassium content of the solution was raised to 7 mM by the addition of KCl, without correction of the change in the osmotic pressure. The temperature of the bath was controlled and could be varied between 38°C and 25°C.

## RESULTS

**Clinical Measurements.** Some of the patients experienced an involuntary closure of the hand during severe cooling of the lower arm. However, substantial resistance to passive finger opening (paramyotonic stiffness) was never found before one or several active closures of the fist had been executed. The investigation of "spontaneous" (that is, cold-induced, but involuntary) events showed that low-frequency EMG activity and force development began 5 minutes after lowering the temperature and persisted throughout the cooling period of up to 30 minutes, at the end of which the force reached about 5% of a maximal voluntary contraction. On warming the lower arm, this force disappeared completely, and the amplitude of a subsequent maximal voluntary contraction was close to control.

When voluntary contractions were carried out in the cold, the relaxation occurred in two phases. During the first phase, the force decayed to between 80% and 5% of the maximal amplitude at the normal relaxation rate. During the second slow phase, the remaining force decayed in a roughly exponential manner, the half-time lasting up to minutes. In repeated contractions, the maximal force amplitude decreased, and the relative force amplitude at the beginning of the slow relaxation phase increased. When the lower arm was warmed after several voluntary contractions had been performed in the cold, the relaxation of maximal voluntary contractions was normal again, but the amplitude was always markedly reduced. In healthy controls, cooling of the forearm from 36°C to 29°C causes no more than a 5% decrease of the maximal finger force in a single 2-second contraction.<sup>9</sup> The relaxation time between 90% and 10% force amplitude is then increased from 0.10 to 0.14 seconds, but a second slow phase of relaxation does not occur.<sup>9</sup>

The electrical activity recorded during the "spontaneous" force development was sufficiently dense to account for the measured force. In contrast, the electrical activity recorded during the slowed relaxation of voluntary contractions in the cold was always badly correlated with the force. Figure 1 shows a result obtained with patient 1. Some spontaneous activity, just visible at the beginning of the EMG trace, developed during the cooling. During the voluntary contraction, the force rises rather slowly to a plateau and the EMG pattern is dense. After termination of the voluntary effort, the force falls with normal speed to about 60% of the maximal amplitude, and then the phase



**FIGURE 1.** Electromyogram (upper trace, spike amplitudes limited by tape recorder) and mechanogram (lower trace) during maximal voluntary isometric contraction of finger flexors. The lower arm of patient 1 had been cooled for 11 minutes in water at 10–12°C.

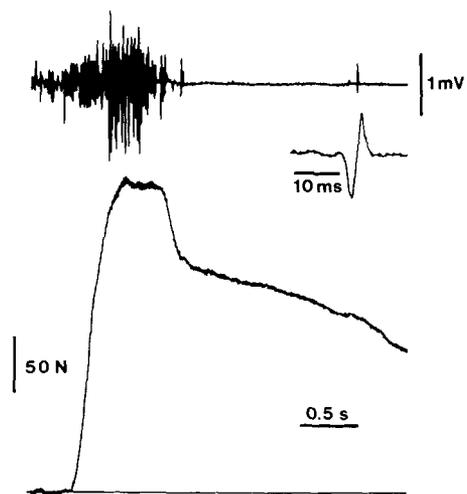
of slowed relaxation begins. It is accompanied by less activity than was present before the activation and, even more remarkable, there seems to be no correlation between the constant, low electrical activity and the rather high, but decreasing, force. This is in agreement with earlier observations.<sup>5</sup> The resistance to passive finger opening was high during the slow relaxation phase, and about as low as before the contraction, when the slow relaxation phase was terminated.

Patient 2 developed paramyotonic stiffness and slowed relaxation after repeated contractions even at room temperature. Figure 2 shows a record similar to that of Fig. 1, but made in the warm. Force development is faster because of the higher temperature. There was little normal relaxation in this record, so that 5 seconds after the termination of the voluntary effort, there is still 50% force present. Nevertheless, the EMG shows no activity at all. The recording system was sensitive, as can be judged from the single action potential occurring during the slow relaxation phase, which is also shown at higher speed. In the cold, the results from patient 2 were similar to those from patient 1 and all other patients.

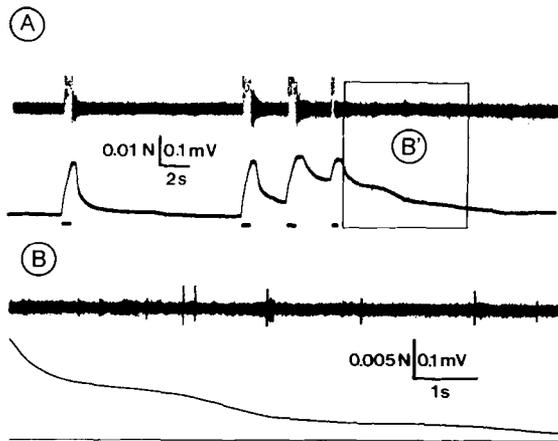
**In Vitro Measurements.** At 37°C, all preparations responded to single shocks and to tetanic stimulation with normal contractions. On cooling, the fibers from all patients, except patient 4, developed long-lasting spontaneous activity that could be detected both in the EMG and the force record. In fibers from patient 4, long-lasting activity was also triggered after the first contraction elicited by

stimulation. This kind of activity seemed to correspond to the spontaneous activity observed *in vivo*. On repeated stimulation in the cold, the preparations from all patients first exhibited slowed relaxation, later, their maximal force amplitude was also decreased. Figure 3 shows an example of such behavior recorded in a muscle from patient 3. During a series of four brief 30-Hz trains of stimuli, the slow relaxation phase increased with each successive response. Record 3B, which is the enlarged and time-expanded portion B' of record 3A, shows that some spontaneous electrical activity occurred during the long-lasting relaxation phase of the fourth response. Comparison with the same amount of activity between the first and second trains in Fig. 3A suggests that such activity during phase B' was not sufficient to produce the sustained force. Note that following the first, second, and third trains of stimuli, there was electrical after-activity, which subsided in less than 1 second. The fourth train produced the largest and longest slow relaxation phase, and yet after-activity was nearly absent. Thus, we observed electrical after-activity without much force production and sustained force without much after-activity. After-activity or slow relaxation phases were never observed in muscle bundles obtained from donors who had to undergo thoracic surgery for reasons other than muscle disease.

To test whether or not the slow relaxation



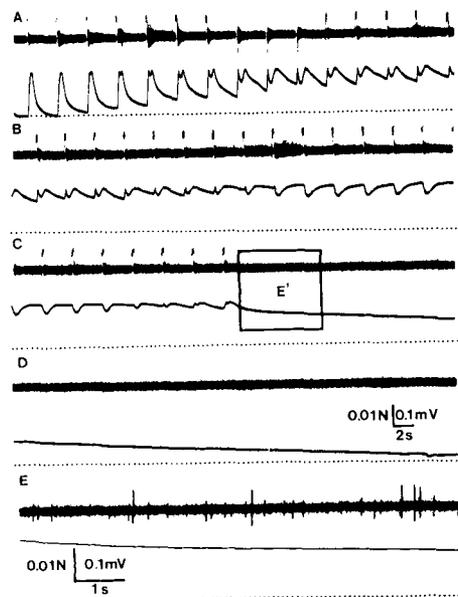
**FIGURE 2.** Electromyogram (upper trace, at a lower gain than in Fig. 1) and mechanogram (lower trace) during maximal voluntary isometric contraction of finger flexors. The lower arm of patient 2 was at body temperature, and the slowed relaxation had developed during a series of voluntary contractions. Note single action potential shown at increased speed.



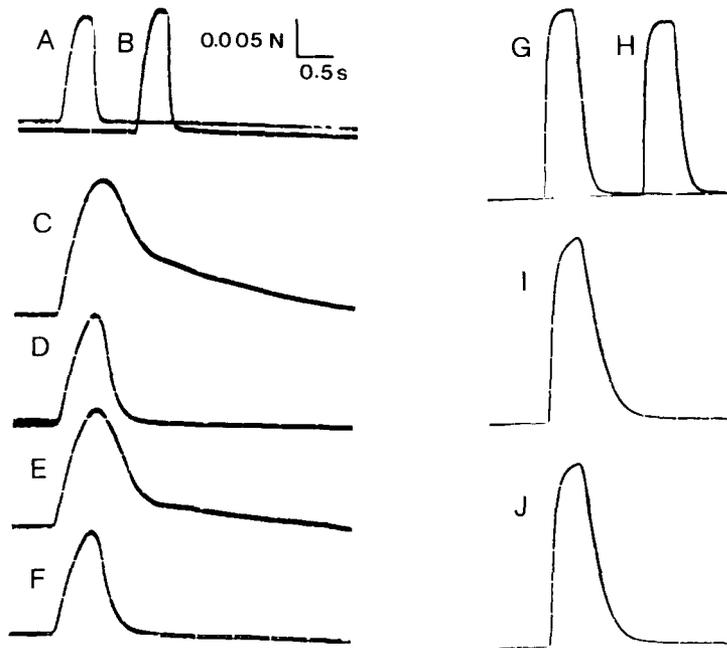
**FIGURE 3.** Electromyogram (upper traces) and mechanogram (lower traces) recorded from small intercostal muscle bundle from patient 3. Supramaximal stimulation with four 30-Hz trains is indicated below force trace. Traces **B** are the enlarged part **B'** from traces **A**.

phase could be influenced by variation of the membrane potential, we repetitively applied pulse trains in massive field stimulation (see METHODS). In this type of stimulation, each pulse depolarizes one side of the muscle fibers while it hyperpolarizes the opposite side, so that during the actual flow of current, the fibers are only partially activated. Only if after completion of the stimulus the action potentials elicited in the depolarized sides of the fibers spread to the formerly hyperpolarized sides, the fibers completely activated and able to develop their full force.<sup>18</sup> The complicated force changes obtained on massive field stimulation of a bundle from patient 3 are illustrated in Fig. 4. At the beginning of the experiment, the fibers responded with normal tetani, then they progressively developed a slow relaxation phase. As with the repeated application of pulse trains the conduction speed of electrical activation decreased, the full activation of the fibers was increasingly prevented during a train and occurred only in response to the last stimulus of each train. When the slow relaxation phase had become so large and slow that the bundle retained almost the full force between two pulse trains (as in line B of Fig. 4), the stimulation actually decreased the force. We interpret this decrease to be due to the hyperpolarizing effect of the stimuli. As the transient restoration of a high membrane potential and the accompanying reduction of the persisting force occurred in the almost complete absence of electrical activity (Fig. 4E), it is likely that the persisting force is identical to a depolarization contracture.

To study the nature of the slow relaxation phase further, we lowered the resting potential of the fibers in a bundle from patient 3 by exposing the muscle to a solution containing 7 mM potassium.<sup>7</sup> Intracellular potential measurements with conventional microelectrodes showed that the paramyotonic fibers assumed a mean resting potential of  $-71.1 \pm 2.7$  mV ( $n = 15$ ), which is close to the  $-70.5$  mV determined in fibers from normal donors.<sup>7</sup> After control responses at 37°C had been recorded in 3.5 mM (Fig. 5A) and 7 mM potassium (Fig. 5B), the bundle was cooled to 27°C and stimulated. The response showed a distinct slow relaxation phase (Fig. 5C). When the normal 3.5-mM potassium solution was readmitted, the slow relaxation phase was much smaller. Further tests carried out at 27°C alternately (Fig. 5D–F) at the two potassium concentrations clearly showed that the slow relaxation phase was easier to elicit and more pronounced when the fibers were



**FIGURE 4.** Electromyogram (upper traces) and mechanogram (lower traces) recorded from small intercostal muscle bundle from patient 3. Stimulation was with 50-Hz trains every 3 seconds. Records **A–D** are parts of one continuous record. In the course of the series, the slow relaxation phase develops to a degree such that the bundle barely relaxes between trains. Force development is increasingly impeded by stimulation, and full force only develops after termination of a train. For the explanation of this phenomenon, see text. The EMG trace occasionally shows increased activity that does not seem to correlate with mechanical events. During final slow relaxation, there is hardly any spontaneous activity, as illustrated in trace **E**, which is an enlarged section **E'** from trace **C**, with the large spikes slightly retouched for better visibility.



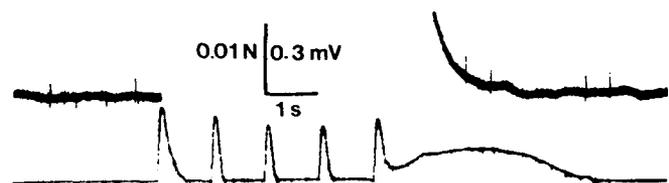
**FIGURE 5.** Isometric tetani recorded from small intercostal muscle bundles from patient 3 (A–F) and a healthy control person (G–J). The bundles were bathed in solutions of either 7 mM or 3.5 mM potassium concentration ( $K_0$ ). Massive field stimulation occurred with 50-Hz trains of 0.4-second duration. The concentrations were recorded in the sequence A–F and G–J respectively, 10–30 minutes after the solution changes. A and B are responses in 3.5 mM and 7 mM  $K_0$ , respectively, at 37°C, followed by 4 records made at 27°C.  $K_0$  was 7 mM in C and E, and it was 3.5 mM in D and F. Records G and H are responses in 3.5 mM and 7 mM  $K_0$ , respectively, at 37°C. Records I and J are responses in 3.5 mM and 7 mM  $K_0$ , respectively, at 27°C.

bathed in the 7-mM potassium solution, i.e., when they had low resting potentials. Bundles from healthy controls gave responses with fast relaxation when stimulated at 37°C in the 3.5- and 7-mM potassium solutions (Fig. 5, G and H, respectively). At 27°C, the relaxation was of course slower than at 37°C, but in neither the 3.5-mM potassium solution (Fig. 5I) nor in 7 mM potassium (Fig. 5J) had the relaxation a slow phase, as observed in the paramyotonic bundles.

Occasionally, we also noted spontaneous after-contractions that seemed to be of a different kind. Figure 6 shows a record from a bundle from patient 5. Stimulation occurred with single shocks at 1 Hz. The relaxation of the first response is slightly slower than that of the responses to the second, third, and fourth stimuli, but after the final fifth twitch, a force increase appeared that lasted for about 4 seconds and obviously was not directly related to the stimulus. The EMG was not recorded during the stimulation period because the amplifier was overloaded. When the amplifier became sensitive again, after the fifth response, the spontaneous activity during the after-contraction was as little as four single action potentials.

## DISCUSSION

The simultaneous mechanical and electromyographic measurements carried out in vivo and in vitro suggest that the spontaneous activity that may develop to a rather impressively dense pattern during cooling of a paramyotonic muscle is responsible for the generation of a resting force that can reach 5% of the maximal voluntary contraction amplitude. A much larger contribution to the paramyotonic stiffness, up to 80% of the maximal force amplitude and only slowly decaying, is caused by abnormal processes that follow muscle



**FIGURE 6.** Electromyogram (upper trace) and mechanogram (lower trace) recorded from small intercostal muscle bundle from patient 2. Five single stimuli were given in 1-second intervals. The EMG amplifier was overloaded during the period of stimulation. All spontaneous spikes were retouched.

activation in the cold. As these processes are poorly correlated with electrical activity, other causes must be considered for their origin. The most likely hypothesis for the pathomechanism is a failure of some of the fibers to repolarize after excitation in the cold. According to this concept, some fibers repolarize normally: these are responsible for the fast first relaxation phase. Other fibers stay depolarized and go into a state of contracture. The level of the membrane potential of paramyotonic fibers activated in the cold may pass the contracture threshold for a considerable time, and the durations of the slow relaxation phases reported here were well in the range of the durations of potassium contractures in human muscle.<sup>12</sup> Depolarization contractures are terminated either by membrane repolarization below the mechanical threshold or, if the membrane is not repolarized, by spontaneous muscle relaxation.<sup>6</sup> Spontaneously relaxed fibers cannot be activated before they are reprimed by membrane repolarization. The evidence available from earlier studies<sup>5,12</sup> and from the present experiments suggests that both mechanisms of contracture termination may occur: some fibers repolarize and are then ready for reactivation, others stay depolarized, relax, and remain paralyzed. Which of these alternative behavior pat-

terns a fiber will follow may depend on several parameters, e.g., the resting potential before stimulation, duration and frequency of stimulation, and duration and degree of cold exposure. The intracellular processes during excitation-contraction coupling have been intensively studied (for a review see Peachey and Adrian<sup>13</sup>). They are complex enough to provide a host of possibilities for the speculation about the defect in the paramyotonic muscle cell, for example, a slowed inactivation of the release of calcium from intracellular stores or a slowed reuptake of calcium by the sarcoplasmic reticulum. In frog muscle fibers, long-lasting depolarizations have been shown to also trigger a considerable calcium influx from the extracellular space.<sup>3</sup> This might also be the case in human muscle, and if so, this would provide another sarcolemmal site of possible disturbance. The wealth of available influences may explain the variability of the slow relaxation phase. It is also possible that fast and slow fibers are differently affected, at least it seems as if some fibers in a muscle may withstand permanent depolarization and paralysis better than others. A transient shortage of energy-rich phosphates and an abnormal change of the intramuscular pH have been excluded as reasons for the paramyotonic stiffness.<sup>9</sup>

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