

Fourteen patients with paramyotonia congenita were examined clinically. Patients of 3 families had no myotonia in a warm environment while in a cold environment they developed paradoxical myotonia (myotonia aggravated by repeated muscle contraction). Patients of a 4th family had myotonia associated with after-activity in a warm environment which was not paradoxical. This myotonia was aggravated by cooling. In a warm environment the resting muscles of all patients showed no spontaneous electromyographic activity except for occasional myotonic runs. On cooling, spontaneous fibrillations developed. This was most intense at 32°C–28°C (muscle temperature). On deeper cooling it ceased. In contrast, 5 patients with myotonia congenita did not show such activity during cooling. In all paramyotonic patients cooling (30°C–25°C) produced muscle paralysis, which outlasted rewarming by several hours. At 32°C–30°C muscle relaxation was slowed. Recording of electromyographic activity and isometric contractions of the long finger flexors during cooling revealed that the slowing of muscle relaxation in paramyotonia is not as closely linked to after-activity as is the slowing of muscle relaxation in myotonia congenita.

MUSCLE & NERVE 4:388–395 1981

CLINICAL STUDY OF PARAMYOTONIA CONGENITA WITH AND WITHOUT MYOTONIA IN A WARM ENVIRONMENT

ANTON HAASS, MD, KENNETH RICKER, MD,
REINHARDT RÜDEL, PhD, FRANK LEHMANN-HORN, MD,
REINHARD BÖHLEN, MD, REINHARD DENGLER, MD,
and HANS GEORG MERTENS, MD

Paramyotonia congenita, a rare muscle disease transmitted by an autosomally dominant gene, was originally described by Eulenburg.⁷ Becker^{1,2} examined 157 paramyotonic patients in West Germany and stated that the main features of the disease were myotonia and muscle weakness upon exposure to cold. The cold-induced myotonia is paradoxical insofar as it is aggravated by repeated muscle contraction. During deep cooling the myotonia disappears, giving way to flaccid paralysis, which may outlast rewarming by many hours.

The diagnosis of paramyotonia congenita is complicated by the fact that paradoxical myotonia has not been found in all patients with paramyotonia. There are families, of which the first were described in the last century,^{6,9} in which moderate to severe myotonia is present in a warm environment (ambient temperature > 20°C). The myotonia in these cases improves by repeated contraction (warm-up), and in a warm environment it cannot be distinguished from the myotonia in myotonia congenita. However, in a cold environment (ambient temperature < 15°C) the myotonia in paramyotonia congenita is intensified, whereas the myotonia in recessive generalized myotonia congenita is not.¹³ This contrasting feature might be used for differentiation between the two diseases. However, many authors believe that any kind of myotonia worsens with exposure to cold.^{11,14} Another diagnostic problem is posed by the observation that in some paramyotonic families episodes of generalized weakness occur similar to those in hyperkalemic periodic paralysis (adynamia episodica). For all these reasons the justification for paramyotonia as a nosological entity distinct from myotonia congenita or from periodic paralysis has been debated.⁴

From the Neurologische Universitätsklinik, Würzburg, West Germany (Drs. Haass, Ricker, Böhlen, and Mertens), Abteilung für Allgemeine Physiologie der Universität Ulm, West Germany (Dr. Rüdel), and the Neurologische Klinik und Poliklinik der Technischen Universität München, West Germany (Drs. Lehmann-Horn and Dengler).

Acknowledgments: The authors would like to dedicate this work to Professor Erich Kuhn, Heidelberg, on the occasion of his 60th birthday.

Address reprint requests to Dr. Rüdel at the Abteilung für Allgemeine Physiologie der Universität Ulm, Oberer Eselsberg, D-7900 Ulm, West Germany.

Received for publication October 7, 1980, revised manuscript accepted for publication January 5, 1981.

0148-639X/0405/0388 \$01.25/0
© 1981 John Wiley & Sons, Inc.

Table 1. Clinical data on 14 patients with paramyotonia congenita and 5 patients with myotonia congenita.^a

Disease, family, patient no.	Age (years)	Sex
Paramyotonia with paradoxical myotonia		
A		
1 "PWOM A"	38	M
2	11	F
B		
3 "PWOM B"	31	M
4	60	F
C		
5	25	F
6	17	M
7	19	F
Paramyotonia with myotonia in warm environment		
D		
8	59	F
9	40	F
10	30	M
11 "PWM D"	26	M
12	22	F
13	11	F
14	7	F
Recessive generalized myotonia congenita ^b		
15	35	M
16	26	M
17	62	F
18	54	M
Dominant myotonia congenita		
19	72	M

^aPatients 1-4 are identical to cases 1-4 in Haas et al.⁸

^bPatients not related.

To better understand the pathologic mechanisms of the three possibly related diseases, we found it necessary to specify the clinical symptoms of paramyotonia congenita more exactly. In the present study, we determined the temperature dependence of the paramyotonic features in 14 patients with paramyotonia congenita. These data were then used in the design of the accompanying in vitro study of the pathophysiology of the disease.¹⁰

CASE REPORTS

Fourteen paramyotonic patients from 4 families were investigated (Table 1). In all families the disease was dominantly inherited.

Paramyotonia Without Myotonia in a Warm Environment. The patients of families A, B, and C had no myotonia in a warm environment and could move without impediment. Some of them showed traces of percussion myotonia. After light cooling for 5 min with water of 24°C the first contractions were barely impeded. With continuing muscle effort,

paradoxical myotonia appeared. For instance, repeated closing and opening of the fist caused the finger movements to become increasingly slower, and when the eyelids were repeatedly closed, the gap between the lids became narrower. The myotonia caused by light cooling disappeared upon rewarming. During deep cooling for 30 min with water of 15°C the myotonia gave way to a flaccid paralysis, which did not disappear until several hours after rewarming. After deep cooling, the muscles of the forearm were distinctly swollen in some patients. Spontaneous attacks of generalized weakness have not been reported by any member of the 3 families.

Paramyotonia With Myotonia in a Warm Environment.

Family D is identical to kinship Q described by Becker.² All afflicted members except the 2 children (patients 13 and 14) constantly have myotonia in a warm environment. The myotonia is most apparent after muscle rest and improves during repeated contractions. During clinical examination the muscle symptoms in a warm environment

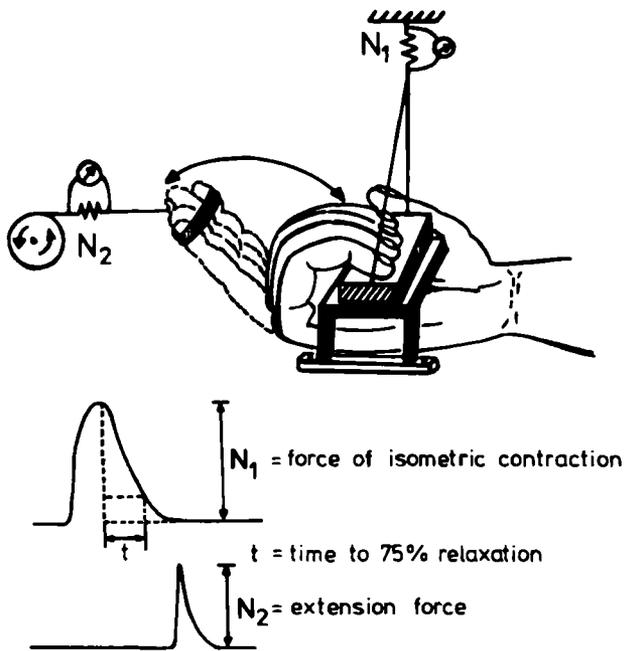


Figure 1. Schematic drawing of the set-up for determining the isometric force (N_1) of the long finger flexor and the extension force (N_2) for fist opening.

could not be distinguished from those of myotonia congenita. However, a cool draft would be enough to stiffen the fingers, making writing or playing the piano quite difficult. The facial musculature also would contract, and the eyelids could no longer be opened normally. This aggravated myotonia produced by light cooling could sometimes be improved by repeated contractions (warm-up). However, there was no warm-up during deep cooling (muscle temperature $< 30^\circ\text{C}$). During repeated closing of the fist, the fingers were so weak and so stiff in the first contraction that only very slight movement was possible. With further contractions the fingers remained in a flexed position and finally became paralyzed. The myotonia was most pronounced in 2 brothers (patients 10 and 11) and to a lesser degree in the sister, the mother, and the cousin (patients 8, 9, and 12). Patients 8 and 9 had noted a distinct exacerbation of their myotonia in a warm environment during pregnancy. In the children (patients 13 and 14), we could not detect myotonia in a warm environment, but on cooling, their finger movements were slowed, and repeated contractions aggravated the myotonia. On deep cooling, all patients from this family showed flaccid paralysis.

The 2 brothers (patients 10 and 11) had episodic attacks of generalized weakness several times per year, especially in the legs, which could

last from several hours to a whole day. This weakness occurred even in a warm environment after sitting or standing for a long time. It improved regularly with continuous movement. Two hours after the beginning of one of these attacks, a slightly increased level of serum potassium of 5.4 mmol/liter was recorded in patient 11. On one occasion this patient took potassium (120 mmol per os), which produced a slight aggravation of his myotonia and then a moderate generalized muscle weakness, especially in the legs. In contrast, no myotonia and no weakness could be provoked by a similar dose of potassium in patient 1 of family A.

The patients of family D, particularly both brothers, suffer greatly from their myotonia because it worsens immediately with the slightest cooling. They are therefore especially grateful for the successful therapy with tocainide (Astra, Wedel/Holstein, West Germany).¹² The stiffness, the weakness, and the episodic attacks of weakness have not reappeared during 1 year of medication with this drug. Mexiletine (Boehringer, Ingelheim, West Germany), 2–3 \times 200 mg per day, produced a similar improvement.

METHODS

In all patients the hand and the forearm were cooled in a waterbath (15°C , 30 minutes). The electromyographic (EMG) activity was recorded from the completely rested flexor digitorum longus in all patients except the children (patients 2, 13, and 14). For comparison, 4 patients with recessive generalized myotonia congenita and 1 patient with dominant myotonia congenita (see Table 1) were investigated in the same way. The EMG electrodes were 2 insulated platinum wires, exposed for 1 mm at the tip. These were inserted into the muscle belly 10 mm apart in a longitudinal direction. The temperature was measured by a needle probe, which was inserted about 15 mm into the muscle belly.

Three unrelated paramyotonic patients (1, 3, and 11 of Table 1) were selected for a special clinical examination. They will be given the names PWOM A, PWOM B, and PWM D because the former 2 had paramyotonia without myotonia in a warm environment (ambient temperature $> 20^\circ\text{C}$), and the latter had paramyotonia with myotonia in a warm environment. The patients were asked to press the fingers 15 times against a bar, which was connected to a force transducer (Fig. 1). This method records mainly the isometric force of the long flexor muscle of each finger, except the thumb. Then the maximal force and the time to 75%

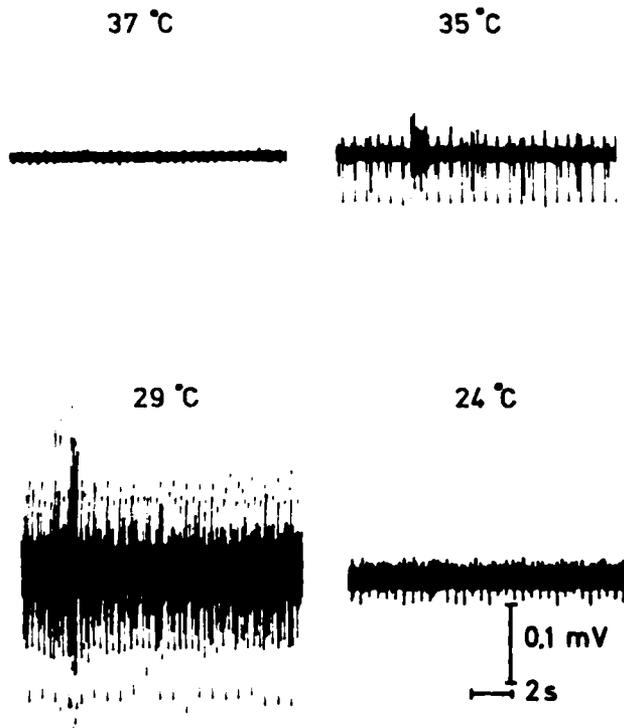


Figure 2. Examples of spontaneous electromyographic activity from the resting flexor digitorum muscle of patient PWOM A (paramyotonia without myotonia in a warm environment) at various temperatures.

relaxation were measured for each contraction. In patients PWOM A and PWM D, the paramyotonic stiffness of the cooled muscle was registered. For this purpose, another bar connected to an electric motor by a cord (Fig. 1) was used. The electric motor extended the fingers from the flexed position to an almost stretched position with a constant velocity of 80–140 mm/sec. The extension force was measured by a force transducer in the cord.

RESULTS

Spontaneous EMG Activity of the Resting Muscle. In all patients with paramyotonia and in all patients with myotonia congenita, the conventional EMG examination of the resting forearm muscles at 37°C showed myotonic runs on muscle percussion or when the needle electrode was moved. Without this mechanical stimulation no activity could be detected. On cooling, the muscles of all paramyotonic patients developed an intense spontaneous activity, which was mainly of the fibrillary type. Myotonic runs were rare, but runs lasting for several minutes without change in amplitude or frequency were frequently recorded (Fig. 2). The activity was most intense between

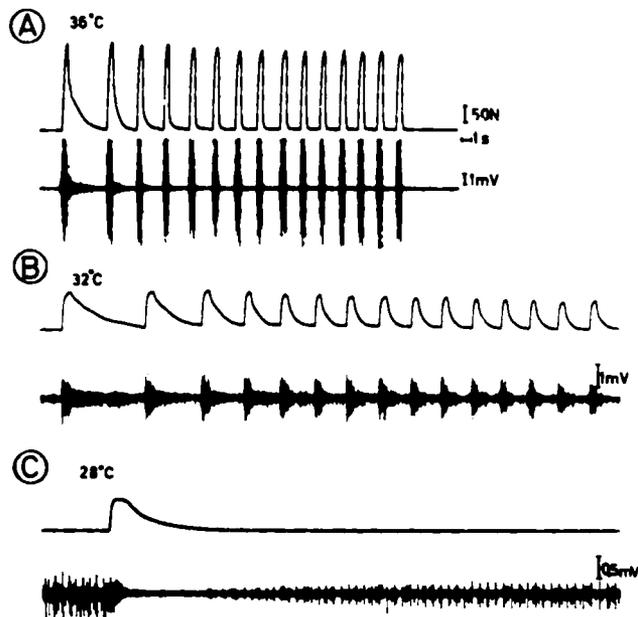


Figure 3. Isometric force (upper traces) and electromyographic activity (lower traces) at 36°C (A), 32°C (B), and 28°C (C) recorded from patient PWM D (paramyotonia with myotonia in a warm environment).

32°C and 28°C, and on further cooling it decreased. At 28°C, a single muscle contraction stopped the spontaneous activity for several seconds. Thereafter, the action potentials slowly reappeared (Fig. 3C). When the muscle was rewarmed, the spontaneous activity ceased. During deep cooling there was no activity at all.

This type of spontaneous activity could be detected in all paramyotonic patients from all 4 families. In contrast, the 5 patients with myotonia congenita, of whom 2 (patients 16 and 18) were severely afflicted, never showed such spontaneous activity during cooling.

When spontaneous activity was most intense in paramyotonic patients (at ~30°C), no remarkable stiffness could be detected during passive movement of the rested fingers.

Cold-Induced Weakness and Paralysis. In healthy male subjects the fingers developed a maximal isometric force of 200–250 N at 37°C. In 1 patient with myotonia congenita (patient 15) and in patient PWM D, the force at 37°C was normal (Fig. 4). Patients PWOM A and B had a significantly lower muscle force at 37°C in spite of their apparently strongly developed musculature. No decrement of isometric force in a series of 15 contractions at 37°C was found in any of these paramyotonic patients (Fig. 5A).

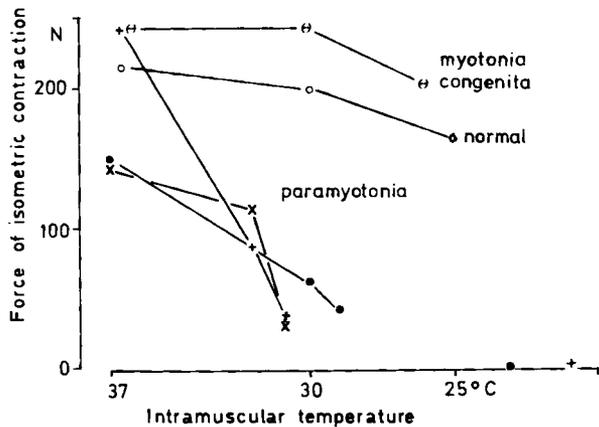


Figure 4. Isometric force as a function of temperature. Results from finger flexor of patient PWOM A (x) (paramyotonia without myotonia in a warm environment), PWOM B (●), and PWM D (+) (paramyotonia with myotonia in a warm environment) are compared with results from a healthy subject (○) and from patient 15, who had myotonia congenita (⊕). Each data point represents the mean of 10 consecutive contractions, taken for each patient and for each temperature on a separate day.

After cooling to 30°C–25°C, the isometric force of the 3 patients with paramyotonia was diminished by 70%–90% (Fig. 4), whereas the force of the healthy subject and of the patient with myotonia congenita was only slightly diminished (~10%). During repeated contractions at 32°C, the paramyotonic weakness increased (Fig. 5C). In patients PWOM A and PWM D, cooling of the resting forearm to 21°C produced paralysis (Fig. 4). The development of paralysis could be accelerated by muscle effort. After rewarming to 37°C, the force of the healthy subject and of the patient with myotonia congenita was as strong as before cooling. In the paramyotonic patients, force did not reappear for 3–4 hours.

Myotonia and Stiffness. At 37°C, patients PWOM A and B had no myotonia. The time to 75% muscle relaxation was normal (0.10–0.13 sec). However, in patient PWM D, the first contraction after muscle rest already had a slowed relaxation (0.45 sec). With repeated contractions, patient PWM D showed a typical warm-up (Figs. 3A and 5B).

After cooling to 32°C, the relaxation of the first contraction of patient PWOM A was moderately slowed and that of patient PWOM B was slightly slowed (Fig. 5D). In the following contractions, relaxation became increasingly slower, and after 15 contractions the time to 75% relaxation had in-

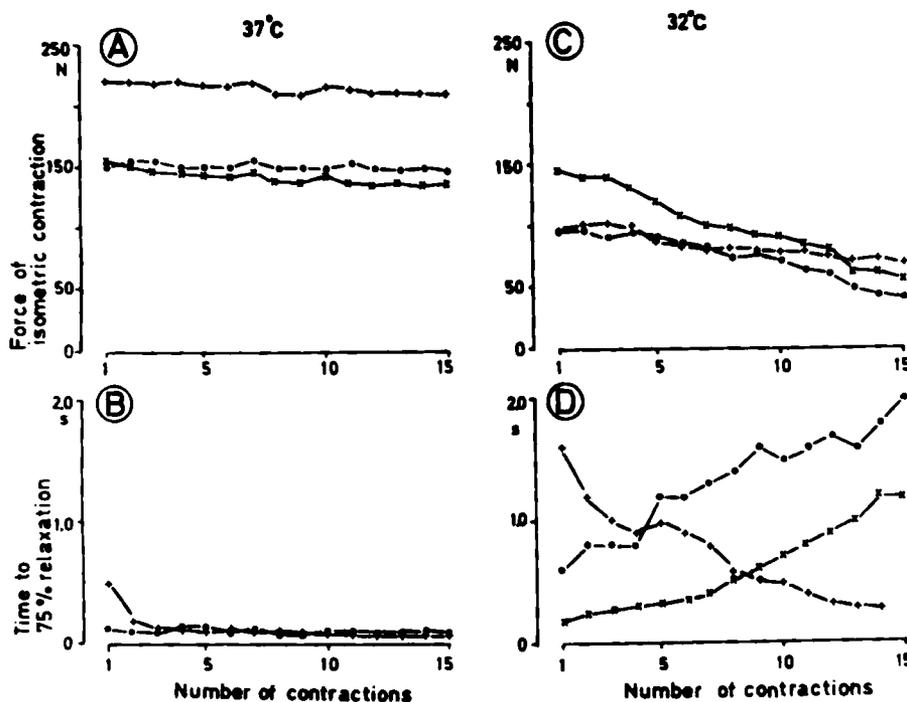


Figure 5. Maximum amplitude of isometric force (A and C) and time to 75% relaxation (B and D) in 2 series of 15 contractions at 37°C (A and B) and 32°C (C and D) in 3 patients with paramyotonia. x = patient PWOM A, ● = patient PWOM B, and + = patient PWM D.

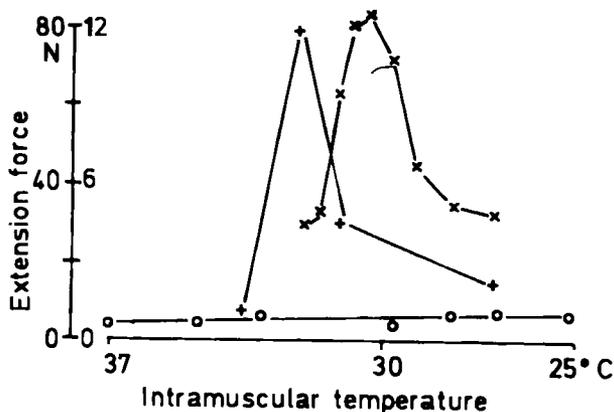


Figure 6. Force necessary to extend the fingers following an isometric contraction as a function of muscle temperature in patient PWOM A (paramyotonia without myotonia in a warm environment) (x) and patient PWM D (paramyotonia with myotonia in a warm environment) (+). The extension speed of the electric motor was different for patient PWOM A (80 mm/sec, right-side force calibration) and PWM D (140 mm/sec, left-side force calibration). Open circles illustrate the force necessary to overcome passive tissue resistance (left-side force calibration), measured in a patient with flaccid paralysis of the arm owing to damage of the plexus radialis and the cervical roots.

creased by a factor of 4 to 5. Both patients thus showed a typical paradoxical myotonia on cooling. Contrary to force amplitude, the relaxation became normal immediately after rewarming. In contrast, patient PWM D showed a slower relaxation in the first contraction after cooling than did patients PWOM A and B, but with repeated contractions his relaxation became increasingly faster (Figs. 3B and 5D).

In series of repeated contractions at reduced temperatures, the ability to open the fist following isometric relaxation decreased progressively in all 3 patients. This could have been caused partly by the cold-induced paralysis of the extensor muscles. Measurement of the isometric force of the extensor muscles at 32°C, however, showed that the paralysis of the extensor muscles had not progressed further than that of the flexor muscles. Rather, the resistance to stretching of the flexed fingers turned out to be high. This peculiar paramyotonic stiffness was quantified as the peak force which was necessary to extend the fingers after a short contraction. Figure 6 shows the extension force measured immediately after complete isometric relaxation as a function of muscle temperature. The extension force was greatest at about 30°C. On further cooling it became smaller because of the beginning paralysis. When measured 5 seconds after complete relaxation, the extension force was

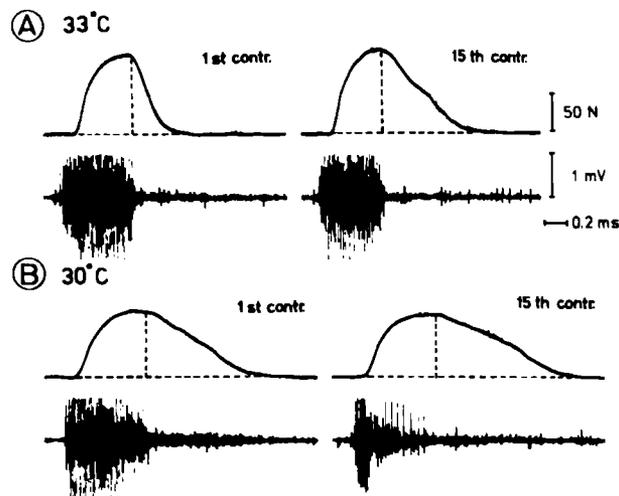


Figure 7. Isometric force (upper traces) and electromyographic activity (lower traces) of the flexor digitorum muscle in patient PWOM A (paramyotonia without myotonia in a warm environment). Recordings of the 1st (left) and 15th (right) contraction after muscle rest at 33°C (A) and 30°C (B).

much smaller, but a slowly vanishing stiffness remained for 2–3 minutes. The fingers became very stiff when the rested muscles contracted only once or twice after quick and deep cooling. The stiffness was not as marked if the cooling was slow (e.g., during 60 minutes) and if the patient was asked to contract the muscle repeatedly during the cooling.

The extension force necessary to overcome the resistance of inactive muscles was measured in a young man who suffered flaccid paralysis of the arm owing to a 1-week-old damage of the plexus brachialis and of the cervical roots (Fig. 6). The extension force of the denervated finger flexors was always small and almost unaffected by temperature changes.

EMG Activity During Muscle Contraction and Relaxation. When the forearm muscles of patient PWOM A were slowly cooled to 33°C, the muscle relaxation was markedly slowed. This was not accompanied by after-activity in the EMG (Fig. 7A)—only continuous spontaneous spike activity was present. At 30°C, fatigue of motor units with potential decrement during voluntary innervation was observed. During the first relaxation, low-voltage after-activity was present. This after-activity, however, was much less following the 15th contraction than that following the 1st contraction, although the slowing of relaxation had increased (Fig. 7B). Thus, the failure of relaxation in paradoxical myotonia seems not to be connected with myotonic after-activity.

With patient PWM D, at 36°C slowed relaxation of the first contraction was accompanied by myotonic after-activity (Fig. 3A). Both the slowing of relaxation and the after-activity decreased with repeated contractions (warm-up). After cooling to 32°C, the force was decreased. Also, the amplitudes of the motor unit potentials were smaller, and there was a decrement of amplitude during the voluntary effort. The relaxation was markedly slowed already in the first contraction, and the accompanying after-activity was increased as compared with that at 36°C. With repeated contractions at 32°C, a warm-up could be detected in the EMG as well as in the force trace (Fig. 3B). On further cooling to 28°C, a pronounced continuous spike potential activity was recorded (Fig. 3C). On voluntary effort the amplitudes of the motor unit potentials were very slow. The spontaneous firing ceased during relaxation to return slowly after several seconds. Thus the failure of relaxation at this temperature (28°C) cannot be explained by myotonic after-activity.

After rewarming from 28°C, the spontaneous activity disappeared, but myotonia with after-activity and warm-up did not reappear until several hours later. All these findings were regularly and repeatedly registered during several experimental sessions.

DISCUSSION

Three features were consistently found in all paramyotonic patients both with and without myotonia in a warm environment. (1) When a resting paramyotonic muscle is cooled, intense spontaneous activity is registered in the EMG. This activity disappears on prolonged deep cooling. (2) During deep cooling a paramyotonic muscle becomes increasingly weak until it is finally paralyzed. (3) On cooling, muscle relaxation is slowed. These cold-induced features have never been observed in any of our patients with recessive or dominant myotonia congenita. A nosological differentiation between these 2 diseases on the basis of the effects of cold temperatures therefore seems firmly established. Our results also confirm earlier findings¹³ that myotonia is not aggravated by low temperatures.

The investigation showed that myotonia is not paradoxical in all cases of paramyotonia congenita. We therefore agree with Burke et al.⁴ that the nature of myotonia should not be used as a feature to distinguish paramyotonia congenita from the dominant and recessive types of myotonia con-

genita. At 37°C, we observed myotonia only in paramyotonic patients from 1 family. This type of myotonia was nonparadoxical and resembled the myotonia in myotonia congenita insofar as the first contraction after rest was the most impeded, and with further contractions warm-up occurred. During muscle relaxation, myotonic after-activity could be recorded in the EMG. This myotonia was aggravated in a cold environment so that relaxation was much slower than in a warm environment. This is in contrast to findings in myotonia congenita.¹³

The pattern of spontaneous activity induced by cooling in paramyotonic muscle was characterized by low-frequency fibrillary discharges lasting several minutes. This kind of activity is clearly different from myotonic runs. In unclear cases, the diagnosis can therefore best be established by a continuous EMG registration from the resting forearm muscles during cooling in water (15°C, 30 minutes). The occurrence of intense spontaneous activity identifies the case as paramyotonia.

EMG activity similar to that occurring in paramyotonia has been observed in adynamia episodica at the beginning of a hyperkalemic attack of weakness,³ and this was shown to be caused by progressive depolarization of the muscle cell membrane.⁵ Therefore, it has been suggested that in paramyotonia the cooling provokes a decrease of the resting potential.^{4,8} This has been corroborated by the finding that the amplitudes of the motor unit potentials in the cold are very small. Beginning depolarization may lead to hyperexcitability causing spontaneous activity. Further depolarization leads to inexcitability causing muscle weakness and, when all fibers are depolarized, paralysis. Intracellular recordings from intercostal muscle fibers of 3 patients (1, 3, and 11) verified this hypothesis.¹⁰ These findings point to a distinct defect of the muscle cell membrane in paramyotonia whose consequences are similar to those of the defect in adynamia episodica. The two disorders differ in the way the depolarization is induced: by low temperature in paramyotonia and by high levels of serum potassium in adynamia. Another marked difference between the 2 diseases is that relaxation disorders are not observed in adynamia episodica, although weakness without paramyotonic stiffness can occur in some paramyotonic patients when they are challenged by potassium.

The slowing of relaxation is not expressed to the same degree in all muscles of a paramyotonic patient. In the biceps brachii the slowing of relaxation is distinctly less than in the finger flexors,⁸ and

in external intercostal muscles in vitro, it could not be detected at all.¹⁰ The slowing of relaxation and the high extension force necessary for finger opening after seemingly complete relaxation from isometric contraction are probably 2 aspects of the same phenomenon. In many instances no essential after-activity could be recorded during slowed relaxation or during increased resistance to passive extension, as already noted by Burke et al.⁴ Therefore, paradoxical myotonia is not as closely linked

to electrical membrane activity as myotonia is related to after-activity. In the absence of further experimental evidence, we can only speculate about the origin of the paradoxical myotonia. A prolonged activation of the contractile apparatus could be due to cold-induced alteration of the sarcoplasmic membranes similar to the defect of the surface membrane of the muscle cells, leading either to increased Ca⁺⁺ release or to slowed Ca re-uptake.

REFERENCES

1. Becker PE: *Paramyotonia Congenita (Eulenburg)*. *Fortschritte der allgemeinen und klinischen Humangenetik*, III. Thieme, Stuttgart, West Germany, 1970
2. Becker PE: Topics in human genetics. In *Myotonia Congenita and Syndromes Associated with Myotonia: Clinical-Genetic Studies of the Nondystrophic Myotonias*. Edited by Becker PE. Thieme, Stuttgart, West Germany, 1977
3. Buchthal F, Engbaeck L, Gamstorp I: Paresis and hyperexcitability in adynamia episodica hereditaria. *Neurology (Minneapolis)* 8:347-351, 1958
4. Burke D, Skuse NF, Lethlean AK: An analysis of myotonia in paramyotonia congenita. *J Neurol Neurosurg Psychiatry* 37:900-906, 1974
5. Creutzfeldt OD, Abbott BC, Fowler WM, Pearson CM: Muscle membrane potentials in episodic adynamia. *Electroencephalogr Clin Neurophysiol* 15:508-519, 1963
6. Delprat CC: Thomsen'sche Krankheit in einer paramyotonen Familie. *Dtsch Med Wochenschr* 18:158-161, 1892
7. Eulenburg A: Über eine familiäre, durch 6 Generationen verfolgbare Form kongenitaler Paramyotonia. *Zentralblatt der Neurologie* 5:265-272, 1886
8. Haass A, Ricker K, Hertel G, Heene R: Influence of temperature on isometric contraction and passive muscular tension in paramyotonia congenita (Eulenburg). *J Neurol* 221:151-162, 1979
9. Hlawaczek D: Ein Fall von Myotonia congenita kombiniert mit Paramyotonia. *Jahrbuch für Psychiatrie und Neurologie* 14:92-113, 1896
10. Lehmann-Horn F, Rüdell R, Dengler R, Lorković H, Haass A, Ricker K: Membrane defects in paramyotonia congenita with and without myotonia in a warm environment. *Muscle Nerve* 4:396-406, 1981
11. Lipicky RJ: Myotonic syndromes other than myotonic dystrophy. In *Diseases of Muscle*, Part 1, *Handbook of Clinical Neurology*, Vol. 40. Edited by Vinken PJ, Bruyn GW, Ringel SP. Elsevier/North Holland, New York, NY, 1979, pp 533-572
12. Ricker K, Haass A, Rüdell R, Böhlen R, Mertens HG: Successful treatment of paramyotonia congenita (Eulenburg): muscle stiffness and weakness prevented by tocainide. *J Neurol Neurosurg Psychiatry* 42:818-826, 1980
13. Ricker K, Hertel G, Langscheid K, Stodieck G: Myotonia not aggravated by cooling: force and relaxation of the adductor pollicis in normal subjects and in myotonia as compared to paramyotonia. *J Neurol* 216:9-20, 1977
14. Walton JN, Gardner-Medwin D: Paramyotonia. In *Disorders of Voluntary Muscle*, 3rd Ed. Edited by Walton JN. Churchill Livingstone, London, England, 1974, p 598