

Membrane Changes in Cells From Myotonia Patients

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I. INTRODUCTION

The myotonias are a group of genetically distinct hereditary diseases characterized by specific muscle malfunctions. They are interesting to the physiologist because much has been learned about muscle function from the study of the pathomechanisms underlying myotonia. This review classifies all diseases associated with myotonia, quantifies the myotonic signs as far as they have been worked out, and reviews the membrane changes detected in the various diseases. Finally, we discuss to what extent the clinical observations can be accounted for by the described membrane changes. A few short reviews on myotonia appeared recently (15, 34, 51). In addition, several comprehensive textbooks on muscle disorders contain chapters on myotonia, but they are written mainly for the clinician (223, 282, 325).

A. Glossary

The word *myotonia* was coined by Strümpell (307) 5 years after the appearance of Thomsen's (313) famous report on "tonic cramps in voluntary muscles in consequence of inherited psychic disposition," the first comprehensive description of the disease of myotonia congenita. The Greek components of the word *myotonia* are muscle ($\mu\nu\sigma$) and tension ($\tau\nu\nu\sigma$): a transient uncontrollable muscle tension during voluntary muscle contraction is indeed the prime feature of the clinical symptom called myotonia. The tension is caused by a temporary inability of the skeletal muscle fibers to relax normally, causing a prolonged contraction, sometimes also described as a slowed relaxation. The inability to have relaxation under control is experienced by the patient as muscle stiffness. Myotonic stiffness can be combined with muscle weakness or adynamia, a failure of the muscles to generate normal strength.

Myotonic stiffness and weakness do not occur spontaneously. They are a consequence of voluntary movement and depend on the patient's past activity. The highest probability for myotonia to be elicited is when a rested patient is about to perform a particularly strenuous movement. The relaxation of the first contraction may be relatively unimpeded, but the myotonia increases thereafter. A maximum is reached during the first three to four contractions. The myotonia decreases with continued muscle activity (313); this phenomenon is termed *warm-up*. In some diseases the myotonia increases with continued activity; this phenomenon is termed *paradoxical myotonia* (115).

A central nervous component has been postulated to contribute to the muscle stiffness, eliciting a *myotonic afterspasm* (93, 201). The afterspasm has been explained as part of a physiological reflex augmented by the myotonic reaction (191). It has been considered to constitute a major part of clinical myotonia (202), but this important feature certainly needs clarification.

Erb (113, 114) was the first to describe *percussion myotonia*: myotonic muscles react to a blow with the percussion hammer by becoming indented for many seconds. Erb was also the first to investigate the electrical parameters of myotonic muscle by means of faradic and galvanic currents. He found a lowered electrical threshold and an increased tendency to react to direct current with a prolonged contraction and termed the combination of these mechanical and electrical findings *myotonic reaction*.

On electromyographic (EMG) examination, myotonic muscles exhibit *myotonic runs* (201), repetitive activity commonly used to diagnose the disease. In very mild cases, myotonic stiffness might not be present, yet the EMG might reveal myotonic runs. This is termed *latent myotonia*.

Myotonia by definition is myogenic as opposed to neurogenic. Proof of this feature can be achieved with curare (38, 190). The myotonias are thus delineated from *neuromyotonia*, i.e., spontaneous motor unit activity origi-

nating from an unexplained hyperexcitability of the terminal motor nerve branches (130, 136, 163, 229, 241-243, 249).

In several neuromuscular diseases, particularly those associated with denervation, repetitive activity can be recorded in the EMG that is probably myogenic, because it does not disappear in the presence of curare (270). These characteristic discharges are often called *pseudomyotonic runs*. According to the glossary used in clinical electromyography (175), the expression pseudomyotonic run should now be replaced by the term *complex repetitive discharge* (CRD); however, there are also pseudomyotonic runs consisting of simple fibrillation potentials.

Much research is carried out on *model myotonias*, i.e., excised animal muscles and whole animals that were experimentally made myotonic via certain chemicals. A strain of goats also shows the symptoms of myotonia congenita closely resembling the human Thomsen-type myotonia. These goats have been extensively investigated (for reviews see refs. 48, 50). The results of these studies can be extrapolated to human conditions only with reservation.

II. MYOTONIC SYNDROMES

The classification of syndromes associated with myotonia is usually based on clinical symptomatology (203) and heredity (21). We choose a different order here, describing myotonia congenita first, because the pathomechanism is best understood in this disease. Myotonic dystrophy, clinically the most important hereditary muscle disease and more common even than Duchenne muscular dystrophy, is dealt with last, because myotonic dystrophy differs from the other syndromes in many respects, and unfortunately in this disease the defects responsible for the myotonia and for the dystrophy are not known.

Myotonia congenita exists in two genetically separate entities: the dominantly inherited Thomsen type, which was described more than 100 years ago (313), and the recessively inherited Becker type, which was recognized as late as 1957 (17, 18). Myotonia congenita is the disease in which the myotonic signs are expressed in their most distinct form, particularly in the Thomsen type. Myotonic stiffness is very pronounced, and transitory weakness has also been described in many cases (7, 39, 188, 189, 265, 271, 272, 306, 323). In the Becker type the transitory weakness often seems to bother the patients more than the stiffness (21, 265, 271). The myotonic stiffness is peculiar in the Becker type, because in a few patients some muscle groups show warm-up, whereas others present paradoxical myotonia (19). Morphological abnormalities of the muscle fibers are comprised of atrophy (particularly in the dominant type) and central nuclei (292). Several reviews on the clinical (20-22, 137, 177, 178) and pathophysiological (13, 15, 49, 51, 93, 181, 207) aspects of myotonia congenita have appeared. The occurrence in West Germany has been estimated at 1:23,000 for the Thomsen type and at 1:50,000 for the Becker type (21, 22). Heterozygous carriers of the recessive gene do

not present clinical abnormalities, but can sometimes be detected electromyographically by the sign of latent myotonia. Their frequency has been estimated at 1:108 (22).

Paramyotonia congenita was first described by Eulenburg (115) in 1886. Inheritance is always autosomal dominant in this disease. Stiffness is of minor importance as long as the muscles remain at normal body temperature. Whenever a paramyotonia patient is exposed to cold, muscle relaxation is very slowed and the stiffness is exacerbated by continued use of the muscles. This paradoxical myotonia is the reason Eulenburg termed the disease *paramyotonia*. During extended exposure to cold, the muscles become weak, and if the muscles are forcefully exercised, this weakness can develop into complete paralysis. In contrast to the transitory myotonic weakness, paramyotonic weakness can last for hours and continues even when the muscles have been rewarmed. Occasional morphological findings in the muscle fibers are atrophy and alterations of the tubular-reticular junction (292). In some families with paramyotonia, attacks of adynamia associated with hyperkalemia have also been reported (19, 98, 123, 129, 160, 192, 262). Some authors have claimed that paramyotonia and hyperkalemic periodic paralysis represent facets of the same nosological entity (98, 192), but this is unlikely (180, 264). An extensive monograph on the genetic and clinical aspects of the disease has been written by Becker (19), who estimated the frequency of the disease to be 1:178,000.

Adynamia episodica hereditaria, the hyperkalemic type of periodic paralysis first described in 1955 (151), is often named Gamstorp's disease (128). The disease with autosomal dominant inheritance occurs in three different forms: 1) in combination with paramyotonia as described above; 2) in combination with myotonia, usually with latent myotonia only (57, 74, 154, 176, 198, 200, 220, 230, 278); and 3) persistently without any signs of myotonia (19, 24, 31, 152, 225). Each of the afflicted members of a family presents one of the three forms. The major symptom of this disease is severe muscle weakness after strenuous work and lasts from several minutes to hours. In contrast to paramyotonic weakness, periodic paralysis sets in without preceding stiffness. The weakness can be induced by a potassium-rich meal as well as by low muscle temperature. Vacuolar myopathy is a histopathological sign of the disease (220). The clinical aspects of the periodic paralyses have been reviewed (62). We are aware of only two cases of hypokalemic periodic paralysis—familial primary or thyrotoxic—in which myotonia has been mentioned (200, 260).

Chondrodystrophic myotonia is a very rare disease detected by Schwartz and Jampel (293) in 1962 and first described extensively by Aberfeld et al. (1). Myotonia is only one of many symptoms of this recessively inherited disease, the more severe ones being dwarfism, multiple skeletal deformities, and unusual ocular and facial abnormalities. Generalized myopathy of the skeletal musculature is another outstanding feature that causes reduced muscle strength. Percussion myotonia is very prominent. During active mo-

tion, the stiffness fluctuates. It increases in the cold. Curare tests suggest that not all of the repetitive activity is myogenic (70, 122, 294, 310).

Myotonic dystrophy is also named Steinert's disease, although many cases have been described (e.g., 16, 177) before Steinert's (303) original report in 1909. This dominantly inherited muscle disease occurs with a frequency of between 1:18,000 (140) and 1:7,500 (314). Myotonic dystrophy has a late onset and a steady progression of all symptoms, which distinguishes it from the diseases listed above, all of which have an early onset, little or no progression, and no dystrophic changes (with the exception of severe cases of the Becker-type myotonia congenita). Muscular dystrophy is the most severe symptom, others being gonadal atrophy, cataract, sensorineural deafness, psychic and intellectual alterations, endocrine disturbances, and afflictions of heart and smooth muscle (147, 179). The muscle fibers may show many histopathological alterations such as atrophy, central nuclei, fiber splitting, and tubular aggregates (281, 292). Myotonic stiffness is usually fairly pronounced. It seems to increase in a cold environment (281), but careful experiments also show an increased relaxation speed in the cold (259). Myotonic weakness was not found in one search (191), but was demonstrated in others (226, 272). Reviews on the genetic, clinical, and pathogenetic aspects of the disease have appeared (147, 148, 177, 179, 202, 281).

In addition to the well-defined nosological entities listed above, a few rare familial myopathies with myotonia have been described (133, 170, 316). Sporadic myotonic runs (but no percussion myotonia or stiffness) have been found in certain nonhereditary diseases (e.g., polymyositis; 131, 172, 324, 332), and in denervation processes (44, 45, 270, 301). Prolonged contractions may complicate hypothyroidism (223) and disappear after treatment of the endocrine disorder. The slowed relaxation phase is, however, electrically silent. In a few cases, hypothyroidism (121, 162) or polyneuritis (174) was combined with myotonia. Becker (22) suggested that these patients were heterozygous carriers of the gene of recessive myotonia congenita and that the exogenous factors converted a latent myotonia into manifest signs.

Myotonia can also be temporarily acquired by ingestion of certain drugs or chemicals (see sect. VI).

III. QUANTITATION OF MYOTONIC SIGNS

Quantitation of the severity of myotonia is an important problem, because the myotonic signs are expressed differently in the various diseases, indicating the complexity of the pathomechanisms. The duration of myotonic afterdischarges induced by nerve stimulation or by percussion is extremely variable even if the stimuli are standardized (106). Results are reproduced better when the duration of the afterdischarges after voluntary maximal effort is determined (106, 199). In general the EMG is not very useful for a quantitative determination of a patient's performance (203). The most reasonable way to

assess a myotonia patient's overall functional capacity is to have the patient completely rested and then measure the time the patient needs to climb six stairs (27, 203).

A. Myotonic Stiffness

Myotonic stiffness is claimed to be easier to detect in contractions with shortening than in isometric contractions (108, 149, 191). Stiffness can be quantitatively assessed by recording the mechanogram of voluntary movements, most conveniently from the fingers (27, 145). Series of rhythmic hand openings and closings are used to study the progression of stiffness. Hand opening is generally slowed much more than hand closing. The stiffness is much more pronounced when each hand opening is preceded by an isometric closure of the fist (27). In cases of paramyotonia, complete inability to open the hand usually shows up at a time when the isometric force of the finger flexors is still substantial. At this instant, the hand can be forcefully opened, and the required force is a measure of the stiffness (273, 317). Another method is to measure the isometric force of finger flexion and evaluate the relaxation phase. Isometric contraction at 90° finger flexion gives the most sensitive results (273). In typical myotonic or paramyotonic stiffness, a maximal contraction of preset duration is followed by a two-phase relaxation, with a normal onset and a very slow ending. Aftercontractions have been described in some patients (93, 191, 273); i.e., the muscle begins to relax with the termination of activation, then contracts again spontaneously before it finally slowly relaxes (Fig. 1). Stimulation of the ulnar nerve allows an exact assessment of the influence of the stimulation frequency on myotonic stiffness (323). Mechanograms similar to those recorded *in vivo* are obtained when an excised myotonic muscle is directly stimulated *in vitro* (194, 273).

B. Myotonic Weakness

Myotonic and paramyotonic weakness are usually quantitated in repeated isometric contractions (Fig. 2). The importance of the transitory myotonic weakness can best be demonstrated after the myotonic stiffness has been removed by medication (265). The weakness was quantitatively assessed in patients with Becker-type myotonia congenita by repetitive stimulation of the ulnar nerve; force and EMG were recorded from the abductor digiti V (271). At a stimulation frequency as low as 5 Hz, the force amplitude decreased to zero within 5 s and only slowly began to recover after ~20 s of continued stimulation. At the same time, the extracellularly recorded action potentials became so small that they might not have exceeded the mechanical threshold. Absence of action potentials was not noted, so there is no indication of a failure of neuromuscular transmission, as is the case in myasthenia (58). At a stimulation frequency of 15 Hz, paralysis occurred within 3 s and lasted

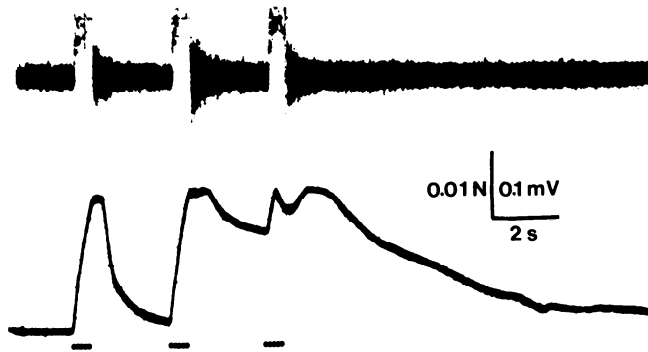


FIG. 1. Electromyogram and mechanogram recorded from excised intercostal muscle fiber bundle from paramyotonia patient. Direct stimulation with 3 trains at 50 Hz, indicated below mechanogram. Mechanogram shows paradoxical increase of prolongation of contraction after rest. An aftercontraction develops after response to 3rd stimulus train. Electromyogram shows afterdischarges. (From F. Lehmann-Horn and R. Rüdél, unpublished observations.)

>80 s. However, paralysis only occurred when the muscle had been rested for ~15 min; after a voluntary contraction of 5 min and subsequent nerve stimulation, the driven action potential barely decreased in amplitude. Drugs known to alleviate muscle stiffness (e.g., tocainide) increase the maximal force amplitude. They are also beneficial to patients because, although the amount of transient weakness is almost unchanged, the duration of weakness is substantially shortened (265).

C. Percussion Myotonia

Percussion myotonia is effectively elicited in the thenar muscle or in the tongue (179). A standardized blow can be delivered with a special mechanical device (106). The duration of the contraction is proportional to the

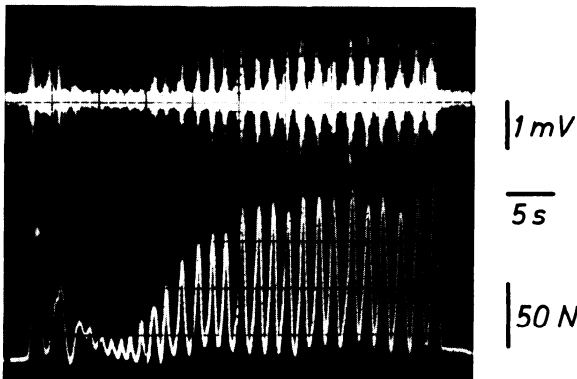


FIG. 2. Electromyogram and mechanogram from (recessive-type) myotonia congenita patient recorded during repetitive isometric contractions of biceps illustrating transient myotonic weakness after rest. Myotonic runs are obvious in EMG after 1st contraction; 2nd contraction is prolonged. [From Ricker et al. (265).]

intensity of the initial blow (93). The response is differentiated from myoedema, which presents as a painless localized mound of muscle, occurring as an indentation spreading over the length of the muscle fibers. Myoedema is electrically silent (289), whereas percussion myotonia is electrically active and in the myotonic goat has been blocked by arterial infusion of tetrodotoxin (TTX) (48). The long delay in relaxation is accompanied by "a confusion of very small action currents, which gradually dwindle in number as the contraction subsides" (93). The small-amplitude, high-frequency activity is similar to that of a fibrillating denervated muscle. Such activity is caused by independent activation of many single muscle fibers (94). The percussion stimulus presumably acts directly on the muscle fiber and not on the nerve, where any impulse would spread to many fibers and cause a regular series of large action potentials (93). Repeated stimuli produce unchanged responses (38). Percussion myotonia has been suggested to be caused by repetitive activity induced either by residual depolarization, deriving from a short burst of action potentials during the blow to the muscle, or by some direct depolarization of the mechanically deformed membrane (35, 50, 223).

D. Myotonic Runs and Related EMG Signs

The characteristic electrical signs of myotonia are the myotonic runs observed during and after voluntary activity, after mechanical stimulation (e.g., by movement of the EMG needle or from tapping on the muscle), or spontaneously. These runs consist of a short-lasting series of action potentials appearing as triphasic spikes or as positive sharp waves. The amplitude and frequency patterns of such runs differ in the various disorders associated with myotonia. The most often mentioned pattern is that of myotonic "dive-bomber activity," a discharge characterized by impulses that first increase in frequency and decrease in amplitude and then decrease in frequency and increase in amplitude. Evaluation of ~1,500 single runs from myotonia patients showed that <5% had dive-bomber characteristics (269).

In myotonia congenita the most common pattern (64% of 793 evaluated runs; 269) consisted of short-lasting bursts characterized by a rising frequency and a falling spike amplitude (Fig. 3A). The following results are quoted from a recent comparative EMG study of 20 cases—10 dominant, 3 recessive, and 7 unidentified "sporadics" (323). In 350 spontaneous myotonic runs the mean single-potential duration was 11 ms and the maximum frequency was 81 ± 3 Hz, somewhat less than in other studies (56, 219). The patterns of the spontaneous runs did not allow a distinction between the dominant and the recessive forms of the disease. Afterdischarges were always present on termination of short voluntary activation. During prolonged voluntary activation, the EMG pattern showed rarefaction and a decrease of the amplitude (to 28% within the first second); at the same time, the duration of the single potentials increased. During rhythmic voluntary activity, warm-up caused

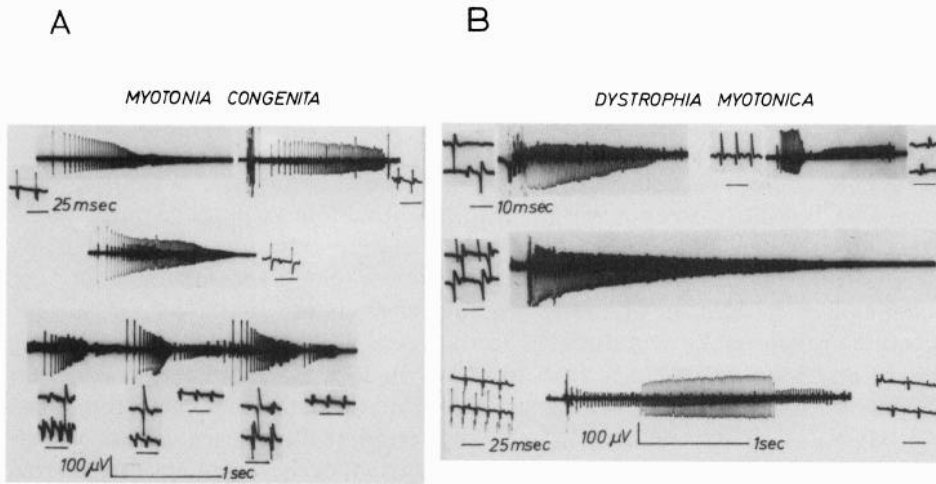


FIG. 3. Typical myotonic runs recorded from myotonia patients. *A*: in myotonia congenita, most common pattern is of increasing frequency and decreasing amplitude. *B*: in myotonic dystrophy, runs last longer and change little in frequency. [From Ricker and Boxler (263).]

a progressive shortening of the afterdischarges, best demonstrated in patients with recessive myotonia. Single motor unit potentials during mild voluntary activation were significantly different from control in duration (9.2 vs. 7.8 ms) and amplitude (1.7 vs. 2.4 mV). During repetitive nerve stimulation, the amplitude of the summed action potentials started to decrease after the first stimulus, at which time the myotonic runs began to appear. Myotonic runs never appeared after the first stimulus. Usually they started 1–80 ms after the final stimulus, the time of appearance of the runs varying greatly among the patients, even among family members. Differences between the dominant and recessive types of myotonia could not be ascertained.

In myotonic dystrophy, myotonic runs are less common than in myotonia congenita (58, 216, 268). The most common pattern (37% of 677 evaluated runs; 268) was different from the typical run in myotonia congenita: long-lasting runs with falling or unchanging frequency and amplitude were found (Fig. 3*B*). Whereas in myotonia congenita 81% of the runs lasted <1 s and the longest duration was ~10 s, 46% of the runs in myotonic dystrophy lasted >2 s and the longest duration was ~30 s (268). The maximal frequency was lower (40–60 Hz) and the frequency changes during a run were smaller than in myotonia congenita. The duration of the action potentials was 1–8 ms with a normal distribution, and the peak occurred at 4–5 ms. Positive sharp waves and CRDs were relatively common (99, 268). Electrical myotonia is unevenly distributed over the muscles of the body. Among 15 muscles examined in 25 patients the distal muscles of the upper extremity and the orbicularis oris showed the highest incidence of involvement (>90%), and the deltoid showed the lowest (38%) (305).

In paramyotonia congenita, myotonic runs similar to those seen in myotonia congenita may be recorded when the muscle temperature is $>35^{\circ}\text{C}$; however, the runs are much less common than in myotonia congenita (145). During muscle cooling, spontaneous activity increasingly develops, which resembles fibrillation (Fig. 4). In some patients, only occasional runs can be registered in the absence of voluntary muscle activity, but after activity the runs are always present for many minutes. The paramyotonic runs are of low frequency (~ 1 Hz) and can go on for tens of seconds without frequency change. Such activity is never seen in human myotonia congenita. When the muscles are paralyzed as a result of long-lasting exposure to cold, no spontaneous or voluntary activity can be registered (145).

In episodic adynamia, myotonic runs—if present at all—are registered in the interictal interval and are similar to those found in myotonia congenita. At the beginning of an attack of muscle weakness, the spontaneous activity changes to long-lasting runs of low frequency, which resemble the runs provoked by cooling in paramyotonia (152, 198). During the paralysis at the height of an attack, the muscles are silent.

In chondrodystrophic myotonia, spontaneous activity from all muscles can be recorded that is described as CRDs, with an abrupt beginning, a high and unchanging frequency, and an abrupt ending. The amplitude is usually constant, but sometimes a progressive decrease in amplitude is noted by a

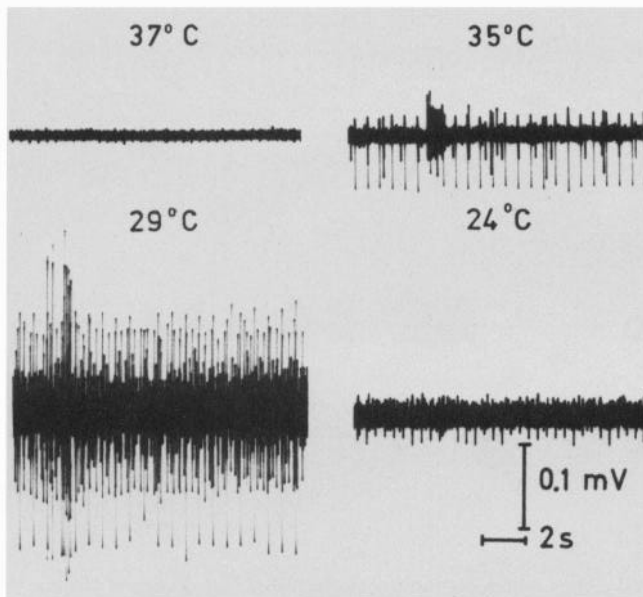


FIG. 4. Spontaneous activity recorded at different temperatures from resting flexor digitorum muscle of paramyotonia patient. Spontaneous activity increases with decreasing temperature and is low at 24°C , when paramyotonic weakness has developed. [From Haass et al. (145).]

single-fiber EMG (83). A CRD is characterized by the duration of the burst (seconds to minutes), the usually uniform pattern, the frequency of repetition within the burst (5–100 Hz), the number of component potentials in the repeating unit (2–40), and the maximal interpotential interval, which is defined as the time between the appearance of the first and last components of the repeating unit (1–150 ms) (167).

In some myopathies (112) [e.g., those caused by hypothyroidism (245, 328) or in Pompe's maltase deficiency (215)] and in various denervation syndromes [e.g., polyneuropathies, root lesions, and motor neuron diseases (44, 45, 77, 87, 112, 270, 291, 304, 320)] simple and complex repetitive discharges have been registered. In these diseases the runs can be recorded from a few sites of certain muscles. These sites show runs consistently and at different times, so it seems that the runs are based on morphological alterations in small bundles of muscle fibers. In an extensive study, 19 of 540 patients with denervation syndromes showed repetitive discharges that did not disappear on curare administration (270). Of the 472 runs evaluated, 20% were CRDs

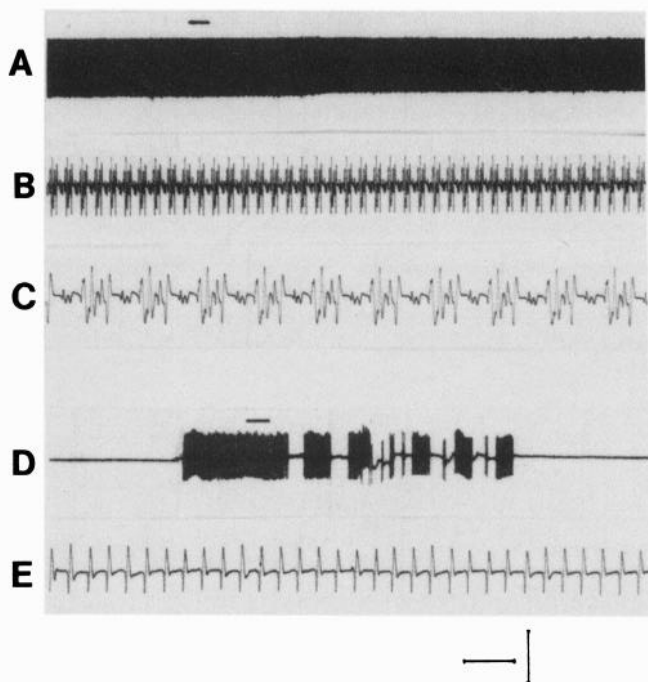


FIG. 5. Spontaneous pseudomyotonic runs recorded from biceps of patient with denervation syndrome. *A–C* show complex repetitive discharge; *D* and *E* show single repetitive spike potential. Bars in *A* and *D* mark positions from which records at faster time base are taken. Time calibrations: *A*, 8 s; *B*, 200 ms; *C* and *E*, 50 ms; *D*, 1 s. Amplitude calibrations: *A–C*, 200 μ V; *D* and *E*, 100 μ V. [From Ricker and Meinck (270).]

(Fig. 5A-C), the rest were series of single spikes (Fig. 5D, E) or positive sharp waves (10%).

IV. VARIABILITY OF MYOTONIC SIGNS

Some chemicals and drugs, as well as physiological and environmental conditions, have long been known to influence the degree of myotonia. These have been recently reviewed by Bretag (34). Substances that antagonize myotonia might be administered for symptomatic treatment; substances that aggravate myotonia are sometimes used for an easier clinical diagnosis, especially in cases of latent myotonia. Substances that induce myotonia are used in animals to produce *in vivo* or *in vitro* model myotonias, which are useful for the exploration of the pathomechanisms underlying the myotonic signs.

A. Chemical Agents Influencing Myotonia

The veratrinic agents generate a state of hyperexcitability in nerve and muscle, which can give rise to long-lasting tetanus-like contractions caused by repetitive activity (319). In early clinical descriptions, therefore, the similarities between myotonic and veratrinized muscles were sometimes noted (191). Veratrinic activity has been shown to be caused by alterations of the sodium-conducting channels (319). When it seemed that all myotonias were based on a defective chloride conductance of the muscle fiber membrane, it was argued that veratrinic agents should not be included among myotonia-inducing agents (48, 55, 185). Since then, myotonias without reduced chloride conductance and with altered sodium-channel properties have been described, so that the above delineation seems less justified (34).

Many monocarboxylic aromatic acids have the property of inducing myotonia by reducing the membrane chloride conductance. Anthracene-9-carboxylic acid (9-AC) is the most potent among them (55, 248). Another class of myotonia-inducing agents is hypocholesterolemic drugs. The blocker of cholesterol synthesis, 20,25-diazacholesterol (20,25-D), was shown to induce myotonia in humans (329, 330) and has since been used to study an animal model of myotonia (see sect. VI B). Triparanol (100), clofibrate (183), and nafenopin (23) induce myotonia in rats but apparently not in humans. There are extensive reviews on chemically induced myotonia (185) and on drug-induced myopathies (217). All drugs that induce myotonia may aggravate an existing myotonia.

Myotonia is intensified by all drugs that depolarize the muscle fiber membrane, either directly or via the end plate. Small doses of intra-arterially applied potassium chloride ameliorate myotonia, whereas large doses increase excitability and can cause tetanic contractions (104). The same doses cause no effect in healthy subjects. Administration of potassium tablets 1 h before

the clinical examination is diagnostically helpful in that it usually increases all myotonic signs (139, 228, 263, 288). Other examples of membrane-depolarizing agents are nitro compounds, e.g., dinitronaphthol (146). Examples of agents that act on the end plate are decamethonium (246), the choline esters acetylcholine (38, 190) and succinylcholine (40, 118, 217, 232), and, indirectly, the cholinesterase inhibitors neostigmine (171) and physostigmine (38). Diuretics may exacerbate clinical myotonia and can unmask a latent myotonia (36). A special case is acetazolamide, which exacerbated model myotonia in the rat (36) but had beneficial effects in humans (139, 184), perhaps due to its ability to lower systemic pH (277). Aggravation of myotonia was found with the β_2 -agonist fenoterol (264) as well as with β -blocking adrenergic agents (29, 143).

Reduction of extracellular calcium increases myotonia, and myotonia is antagonized by an increase of the extracellular calcium concentration (201, 312). This is also the case in model myotonia induced by monocarboxylic aromatic acids (124, 126, 284, 285), but low extracellular calcium does not enhance spontaneous activity in 20,25-D-induced model myotonia (126).

The amino acid taurine has been claimed to be an effective antimyotonic agent (102-105), but little convincing EMG or clinical evidence has been provided. Also, dantrolene, a blocker of the calcium release from the sarcoplasmic reticulum, antagonizes myotonic stiffness in patients (109).

All drugs that reduce the increased excitability antagonize myotonia. These are the blockers of the dynamic sodium-current channels, i.e., local anesthetics, antifibrillar and antiarrhythmic drugs, and related agents. The pure sodium-channel blocker TTX is highly effective, but the range between the antimyotonic and the toxic dose is very narrow (48).

B. Warm-Up Phenomenon

In human myotonias the effect of a full warm-up lasts ~ 5 min (27), in goat myotonia this time is 20-30 min (48). The prolongation of contraction and the myotonic runs that occur on electrical stimulation of a motor nerve decrease during repeated stimulation so that in the end the muscle behaves normally (38). The maximally effective stimulus in provoking this normalization is 50 Hz for 5 s (48, 318). It has been claimed that the central afterspasm is easily fatigued (93). However, not all myotonic signs are subject to fatigue: the percussion response remains unchanged with repetition (38). Also the sustained contraction in response to direct-current stimulation of a curarized muscle in situ and with microelectrodes in vitro showed a lack of fatigability (48). From these findings, Bryant (48) concluded that the neuromuscular junction may be involved in the warm-up mechanism. However, progressive decrease of the duration of contractions and afterdischarges was demonstrated in a directly stimulated excised rat diaphragm made myotonic by (2,4-dichlorophenoxy)acetate (298) or by replacing chloride in the extracellular

medium with an impermeant anion (26, 284). The increase of membrane conductance after a burst of action potentials might contribute to the membrane potential stabilization (286). The low-chloride model of myotonia was used for an *in vitro* study of the effect of extracellular potassium on the persistence of the warmed-up state (26). Under normal conditions and with 10-Hz stimulation, it took ~ 2 s to reach maximal myotonia and 20–30 s to achieve complete warm-up. When stimulation was terminated, test stimuli during the first minute yielded normal responses. Warm-up progressively disappeared during the following 6–8 min. Doubling the extracellular potassium concentration decreased the persistence of warm-up by 27%; halving it increased the persistence by 20%. Reducing the extracellular pH from 7.4 to 7.0 by gassing the bathing fluid with CO_2 was very effective in reducing both 2,4-D- and low-chloride-induced myotonia, and at a pH of 6.8 myotonia was absent. Based on these findings it was suggested that a decrease of the intracellular pH is the physiological basis of warm-up (26).

C. Temperature

The clinical manifestations of the myotonic signs are dependent on the variation of environmental parameters, the one most often discussed being temperature. Paramyotonic stiffness and weakness occur only in the cold, and the slightly slowed relaxation, which can be found in some patients at normal body temperature, becomes normal when the muscles are warmed to 39°C (144). The situation is less clear in the case of the myotonias. Walton and Gardner-Medwin (325) state that myotonia in all its forms is always made worse by cold such that this criterion is insufficient to distinguish paramyotonia from myotonia congenita. Becker (20) also claims that exposure to cold increases the symptoms of myotonia in about half the cases. Ricker et al. (267) examined 13 myotonia patients, 8 with the recessive type of myotonia congenita and 5 with myotonic dystrophy. The lower arm of a patient was put in a water bath that allowed the muscle temperature in the adductor pollicis to be varied between 20 and 40°C. The ulnar nerve was supramaximally stimulated, and the muscle action potential and isometric force were recorded. As in healthy controls, twitch force decreased and the muscle action potential increased in myotonia patients as the temperature was lowered. The myotonic prolongation of contraction was reduced in both congenital and dystrophic myotonia, so that the signs of myotonia were alleviated by the cold. This finding has since been confirmed (287). A decreased tendency to repetitive firing at low temperature was also found in 9-AC-induced myotonia (33) and is predicted by the Adrian-Chandler-Hodgkin (3) model of the membrane (33). Also in myotonic diaphragm fibers excised from 20,25-D-treated rats, lowering the bath temperature from 37 to 20°C greatly decreased the frequency of repetitive activity induced by long-lasting current pulses, and subthreshold oscillations were frequently seen (125, 126). With

increasing temperature, the subthreshold oscillations became fully formed action potentials, and the firing frequency steadily increased. On the other hand, in myotonic goats, local heating of a muscle halved the duration of the percussion response in a few minutes, and the application of an ice pack for the same time doubled it (48). This apparent discrepancy could be explained by the fact that in the human studies, no patient with the Thomsen-type myotonia, the disease that most closely resembles goat myotonia, was included (267, 287).

D. Environmental Factors

Many patients report short- and long-term variability of their symptoms. A systematic study of the influence of environmental factors has been carried out only with myotonic animals. Bryant et al. (54) observed myotonic signs over a period of 7 mo in a colony of eight myotonic goats. Myotonic attacks were induced daily by scaring each animal and grading the response—grade 0 was a normal reaction, the highest grade was a goat that would fall and be unable to right itself for several seconds. This scare response showed a linear correlation with the duration of the percussion myotonia. During the observation period, the intensity of myotonia varied to such a degree that on a particular day it was not possible to specify the rank of a certain goat in the group with respect to the general severity of its myotonia. No correlation with variations of the plasma electrolytes could be detected. There was no correlation of myotonia with small changes of indoor temperature, humidity, or atmospheric pressure. No seasonal changes or periodic variations could be detected. For several days, beginning with the day preceding parturition in five pregnant goats, myotonia became much less severe. Another unexplained finding with myotonic goats is the complete abolition of myotonic stiffness observed in the scare response after water deprivation for 3–7 days and the return of the myotonia shortly after the allowance of water intake (48, 61, 150). The goat findings are mentioned here to illustrate how poorly the variability of myotonic signs is understood.

V. MEMBRANE CHANGES IN MYOTONIC CELLS

Because of certain similarities in the clinical and electrophysiological findings, there were times when one general pathomechanism was held responsible for all myotonias, and this mechanism might be modified or combined with other defects to give the observed variability. A landmark in the investigation of normal and diseased human skeletal muscle was the first use of the external intercostal muscle as *in vitro* preparation that can be obtained without too much inconvenience to the donor and that provides intact muscle fibers for the experimenter (97). Extensive research with this

preparation has made it clear that there are various pathomechanisms of myotonia (10, 15). Each laboratory contributing to this research uses control muscles from healthy volunteers for comparison. Control values may differ between laboratories because of experimental techniques, differences in the composition of the synthetic extracellular fluids, and other unknown reasons (see Table 1). Action-potential parameters of human intercostal muscle fibers are given by Ludin (211, 212). Data on the muscle fiber ion and water contents and on cable parameters determined with two intracellular microelectrodes are provided by Lipicky et al. (208). Resting membrane parameters (186) and current-voltage relationships (passive membrane currents; 187, 196) have been determined with the three-microelectrode voltage-clamp technique. The active membrane currents have been investigated via the cut-fiber Vaseline-gap technique (53, 88, 89) and the loose-patch technique (6).

TABLE 1. *Determinations of membrane parameters of human intercostal muscle fibers*

Condition	Number of Patients	RP, mV	C_m , $\mu\text{F}/\text{cm}^2$	G_m , $\mu\text{S}/\text{cm}^2$	G_K , $\mu\text{S}/\text{cm}^2$	G_{Cl} , $\mu\text{S}/\text{cm}^2$	G_{Cl} , %	Ref.*
Normal controls	5	-70.8 (59)	6.2	506 (154)	106 (154)	500 (154)	82	202, 203
	15	-83.3 (221)	4.7	175 (121)	42 (121)	133 (121)	76	186
Myotonia								
congenita	4	-75.0 (36)	5.9	92†	64	28	30	207, 208
	2			557	101	456	82	207, 208
	5			71†	45 (119)	26 (119)	37†	202, 203
Myotonic								
dystrophy	4	-82.0 (43)	5.3	538†	95	443	82†	202, 203
	2		6.6	181†	85	96	53†	202, 203
Paramyotonia								
congenita								
37°C	7	-81.9 (257)	4.2 (36)	152 (64)	43 (19)	113 (16)	71	196, 197
27°C	7	-40.6 (278)	4.2 (36)	367‡ (28)	45‡ (16)	380‡ (11)	89	196, 197
Hyperkalemic								
periodic paralysis with myotonia								
	1	-83.0 (72)		150 (8)	57 (7)	93 (7)	62	198

Number of investigated fibers is in parentheses. RP, resting potential; C_m , fiber capacity; G_m , specific membrane conductance; G_K , potassium-component conductance; G_{Cl} , chloride-component conductance. * Absolute values of membrane conductances vary between the laboratories of Lipicky and Lehmann-Horn for reasons discussed in ref. 186. To appreciate abnormalities, the values obtained in the respective laboratories should be compared. † Values calculated by us from Lipicky's G_K and G_{Cl} data. ‡ Although the fibers had low resting potential, the conductance values were determined at -80 mV.

A. *Myotonia Congenita*

1. *History of low chloride conductance theory of myotonia*

In myotonia congenita the major membrane defect is a markedly diminished chloride conductance. The low chloride conductance mechanism of myotonia was first suggested and most extensively investigated by Bryant (49); his account of the birth of the hypothesis is as follows (49). In the late 1950s, myotonic fibers were thought to have properties similar to those of nerve fibers kept in a low-calcium medium or muscle fibers treated with veratrinic agents. Thus a low resting potential was expected even in rested myotonic fibers. The first experiments with intracellular microelectrodes on myotonic goat muscles revealed, however, a relatively normal resting potential. The action potential had a normal rising phase, but the falling phase had a slowed and prolonged afterdepolarization. The fibers lacked accommodation to a sustained depolarizing current, so that repetitive firing occurred along with a slow depolarization of the membrane. At about -40 mV the fibers became inexcitable. The most intriguing early result was a very high membrane resistance of these fibers, and in an attempt to determine the cause of this high resistance, the effects of replacing chloride in the extracellular medium by less permeant anions were investigated. Normal goat fibers in the chloride-free medium behaved remarkably like myotonic fibers in a chloride-containing medium. Not only was the membrane resistance equivalent to that of the myotonic fibers, suggesting a lack of chloride conductance, but the fibers had the typical myotonic excitability, e.g., low threshold, lack of accommodation, repetitive firing, and myotonic afterdischarge. This led to the proposal that the basis for myotonia was the congenital absence or reduction of the chloride conductance (44). Direct evidence for this hypothesis was later put forward by the determination of the chloride-component membrane conductance and of chloride fluxes in myotonic goat muscles, which were both found to be smaller than in normal goat muscle (47, 55, 204, 206).

2. *Passive properties of myotonic muscle fibers*

The first and only comprehensive pathophysiological *in vitro* study of human myotonic muscle was carried out by Lipicky and co-workers (202, 205, 207, 208). In four cases the resting membrane resistance was two to three times higher than normal, and this was accounted for by a low chloride conductance of only 30% of the total membrane conductance (207, 208), much less than the $\sim 80\%$ found in normal human muscle. An important indirect confirmation of this result came from another tissue. Based on the claim that a high passive chloride permeability in the thin ascending limb of Henle's loop plays an important role in achieving maximum urine concentration

(173), Campion and Peter (72) studied the renal concentration ability in patients with myotonia congenita after 12 h of water deprivation. Maximum urine osmolarity was much reduced (442 vs. 837 mosmol/kg), indicating that the defect in membrane chloride conductance is generalized in myotonia congenita.

The resting potential was normal (-86.8 vs. -87.2 mV) in situ (274) and in vitro (208, 224). An early (155) and a more recent (141) determination yielded much lower values. In the early study the patient probably had myotonic dystrophy (224); in the later study the results might have reflected the difficulties discussed by McComas and Mrozek (224). Resting potential and other parameters not yet determined in human myotonic muscle have been found quite normal in myotonia congenita of the goat (48, 90). For example, the ratio of the membrane permeabilities to sodium and potassium ($\alpha = 0.010 \pm 0.002$), which determines the resting potential of the membrane, as well as the intracellular potassium concentration ($[K]_i = 139 \pm 7$ mM) of myotonic goat fibers were not significantly different from normal. Intra- and extracellular chloride appeared to be in a Donnan equilibrium both in normal and myotonic goat muscle fibers with no indication of an active chloride transport.

The study of muscle fiber parameters from myotonia congenita patients (207) further revealed that the internal resistivity was reduced (75 vs. 123 $\Omega \cdot \text{cm}$), the membrane capacitance was slightly elevated (5.9 vs. 5.2 $\mu\text{F}/\text{cm}^2$), the mean water content was slightly reduced (788 vs. 808 ml/kg wet wt), and the intracellular potassium content was slightly increased (215 vs. 191 mmol/liter fiber water). The potassium efflux was normal (23.2×10^{-12} mol $\cdot \text{cm}^{-2} \cdot \text{s}^{-1}$); so were the potassium content (74 mmol/kg wet wt), the sodium content (98 mmol/kg wet wt), the chloride content (79 mmol/kg wet wt), and the mannitol extracellular volume (457 cm^3/kg wet wt). The overall mean fat content was normal (3.2% wet wt).

The study was later extended, and a reduced membrane conductance was reported for nine cases (202, 203). However, in the early study there were two patients with myotonia congenita in whom membrane resistance and the potassium and chloride component conductances were essentially normal (207, 208; see Table 1). Unfortunately, Lipicky and Bryant (207) did not present information regarding the genetic classification of their cases. Judging from the clinical evidence (21, 22), there is good reason to believe that the pathomechanisms of the dominant Thomsen and the recessive Becker types differ in more than just nuances. Thomsen-type myotonia congenita has the same mode of inheritance as Bryant's (48, 50) strain of myotonic goats, and the symptoms of the two diseases are very similar. The low chloride conductance mechanism, which is explained in detail below and which has been established in the myotonic goat, is therefore likely to be operant in the Thomsen-type myotonia. A different pathomechanism might be responsible for the Becker-type myotonia, and it is possible that the two cases with normal membrane resistance were of the recessive Becker type.

3. *Action potential*

Determination of the action-potential parameters is marred by serious difficulties. In one study (224), all the recorded activity was repetitive and exhibited prepotentials, indicating that the activity commenced at the microelectrode tip. In another study the fibers were depolarized, giving very low rates of rise and fall of the action potential (141). The overshoot seemed normal (141). The critical depolarization was reduced in human (8.8 vs. 11.8 mV; 224) and goat (32 vs. 37 mV; 48) fibers. Unfortunately there is no information on the afterpotential of a stimulus-provoked single action potential. This is of interest, because in the myotonic goat the most important changes were an increased and long-lasting depolarizing afterpotential, a reduced rheobasic current (11.5 vs. 34.4 nA), and an altered fraction of rheobase required to produce a second action potential (5–10 vs. 100%). Bryant (48) offers detailed information on the action potential and rheobasic excitation parameters of normal and myotonic goat muscle fibers.

A first mathematical explanation of the shape of the myotonic action potential was given by Bretag (32), who utilized the Hodgkin-Huxley parameters of the frog skeletal muscle fiber (3) and simulated the reduction of the chloride conductance in his computer program. The effect of this reduction was an increased afterdepolarization of the computed action potentials. Moreover, this afterdepolarization, under appropriate conditions, gave rise to a series of action potentials. With this mathematical model it was also possible to mimic the well-known antimyotonic action of a local anesthetic (12, 32): by decreasing the sodium-conductance term, the tendency for repetitive firing disappeared. The simple Hodgkin-Huxley model did not, however, produce typical myotonic afterdischarges, because it did not contain a term for a slow buildup of depolarization needed for the continuing activity that follows the cessation of the stimulus. Repetitive firing could be generated only for the time of a simulated constant-current pulse or it went on indefinitely.

4. *Tubular potassium accumulation*

The long-lasting depolarization that develops during repetitive stimulation of myotonic goat muscle fibers was elucidated when Adrian and Bryant (2) found that it was abolished by detubulation. Detubulated fibers did not generate afterdischarges, even though they were dissected from myotonic animals. The explanation for this finding was that intracellular potassium leaving the fibers during driven activity would accumulate in the transverse-tubular system (5). In detubulated fibers there is no such accumulation and hence no effect on the measured membrane potential. In myotonic fibers, in which chloride conductance is lacking, the accumulation causes ~ 1 mV of depolarization per action potential. This depolarization decays within seconds.

In a normal fiber with high chloride conductance, tubular potassium accumulation causes only ~ 0.1 mV depolarization per action potential, not enough to be of physiological importance. In other words, the afterdepolarization never reaches a level where the fast sodium current might be activated again, because the chloride conductance tends to clamp the surface potential to the chloride-equilibrium potential assumed to be near -80 mV (90). In myotonic fibers with a reduced chloride conductance this clamping is ineffective, and so repetitive activity occurs (2).

Adrian and Marshall (4) devised a mathematical membrane model that included an active tubular system with potassium-accumulation kinetics. On lowering the chloride-conductance term, this model produced repetitive afterdischarges of limited duration. However, adjustment of the sodium-activation kinetics also leads to sustained repetitive firing. Therefore, Adrian and Marshall pointed out that potassium accumulation is not necessarily the only reason for the instability of the myotonic membrane; they even questioned whether it contributes *the* critical instability. At least one more abnormality, perhaps of the sodium channels, must be present in myotonia congenita to account for the observed lack of accommodation.

5. Chloride channels

The systematic search for the cell defect in myotonia congenita has led to the investigation of the various ionic channels. This work has been done mainly with myotonic goats, but the results might also pertain to Thomsen-type human myotonia. Three possible explanations for the defect of the chloride channel in myotonia have been discussed (51): the channels may be decreased in number, blocked by an occluding substance, or altered in their selectivity for chloride. In mammals the chloride-channel density has been shown to be the same for surface and tubular membranes (101, 247); therefore, 60–90% of the chloride conductance of the fiber membrane is located in the tubules (247). Some early clues for deciding among the above-mentioned alternatives came from experiments with monocarboxylic aromatic acids, which induce myotonia in normal muscle by reducing the chloride conductance. Bryant and Morales-Aguilera (55) stated the requirements for myotonia-inducing activity of the carboxylic acids as follows: the molecule must be flat, because saturation of double bonds in the rings, producing a twisted structure, decreases the potency. The acid must be monocarboxylic; two or more carboxyl groups decrease the potency, and the compound is ineffective if the carboxyl is substituted by other groups. The position of the carboxyl group with respect to other groups on the molecule is critical (see also ref. 248). From these findings, Bryant and Morales-Aguilera suggested that the light but large hydrophobic end of the molecule anchors itself to the outer rim of the chloride channel, while the active carboxyl group reacts electrostatically with charged groups in the channel, causing a steric conductance

block. Palade and Barchi (248) questioned this hypothesis on the basis of their finding that the carboxylic acids alter the anion selectivity, which speaks against a simple steric block. Bryant (49) considered the possibility that hereditary myotonia in the goat might be mediated by a carboxylic acid or another similarly-acting compound after Krull et al. (176) reported myotonia induced by an unknown humoral substance. However, such a substance would have to be accumulated in the muscle fibers or irreversibly bound to the membrane, because serum from myotonic animals did not induce myotonia in normal muscles nor did myotonia "wash away" over many hours when myotonic fibers were kept in synthetic extracellular fluid. The likelihood of a carboxylic acid-like compound being responsible for goat myotonia was further reduced by the finding that the carboxylic acids lower the mechanical threshold of normal goat fibers from -58 to nearly -90 mV, whereas fibers from myotonic goats have an elevated mechanical threshold of -44 mV (49).

Furthermore, when Bryant (51) compared the permeability sequences for several anions in normal and myotonic goat muscle fiber membranes, he found that they did not differ. By contrast, 9-AC reversed the sequence of anion permeabilities in myotonic fibers the same way it did in normal fibers. From these results, Bryant (51) concluded that in myotonic fibers, chloride channels are normal but fewer. The reason for the decreased number of channels is not known. An abnormally low rate of channel synthesis and an interference with incorporation of the channels into the membrane because of membrane lipid alteration have been considered as possible reasons (51).

6. Sodium and potassium channels

These channels are characterized by the active currents determined in voltage-clamp experiments. Bryant and DeCoursey (53, 88) used the Hille-Campbell Vaseline-gap technique to study sodium currents in normal and myotonic goat muscle fibers. The current-voltage relationships as well as the activation parameters were found normal in myotonic fibers. The voltage for half-maximal activation (m_{∞}^3) was about -45 mV, with forward and backward rate constants $\alpha_m = 0.06$ ms⁻¹ and $\beta_m = 0.2$ ms⁻¹, respectively (3). The inactivation was slower in myotonic than in normal fibers. This was caused by a reduction of the backward rate-constant parameter for inactivation (β_h), indicating that the inactivation gates close more slowly in the myotonic fibers (3). Determination of the steady-state inactivation (h_{∞}) showed that the half-maximal potential was similar in normal and myotonic fibers and that the slope of the h_{∞} curve was less steep in myotonic than in normal fibers ($k_h = 15$ vs. 12 mV).

The potassium currents of normal and myotonic goat muscle fibers were studied by Valle and Bryant (321) with voltage-clamp techniques. The threshold potential for the delayed outward current was the same in both types of fibers (about -53 mV), but the average peak currents at 0 mV were twice

as large in myotonic fibers (1.8 vs. 0.9 mA/cm²). This result suggests that in the myotonic fibers, the density of potassium channels that rectify in the outward direction is twice as large as in normal fibers.

To study the effect of the myotonic abnormalities on the action potential, these kinetic parameters were substituted into a mathematical membrane model (51). The observed alterations in the sodium kinetics tended to increase the degree of myotonia. The less-steep slope of the h_{∞} curve increased the overlap of this curve with the m_{∞}^3 curve, resulting in a larger steady-state depolarizing sodium current in the threshold region of myotonic fibers. This and the decreased rate of inactivation of the sodium current increased the myotonia. The increase in outward-going rectifier channels also increased myotonia by increasing the maximal frequency of impulses in a myotonic train of action potentials, apparently because an increased potassium conductance promoted tubular potassium accumulation, one of the necessary conditions for the production of the myotonic afterdischarge. Computer simulation of the action potential showed that the cation conductance abnormalities observed in myotonic goat muscle fibers, although all directed toward membrane instability, are insufficient to induce myotonia in the presence of a normal chloride conductance. Thus the low chloride conductance remains the principle factor underlying goat myotonia.

7. Membrane composition

Kuhn and Seiler (178, 182) compared the fatty acid patterns of the sarcolemmal lipids from eight myotonia patients (four of each type) with those from eight normal controls. The dominant type differed from the recessive type and the controls by an increase of palmitic acid (C 16:0), stearic acid (C 18:0), and eicosatrienoic acid (C 20:3), as well as by a decrease of oleic acid (C 18:1), linoleic acid (C 18:2), and arachidonic acid (C 20:4). The results point to a defect in the structure of the membrane in the dominant form and to an enzyme defect in the recessive form. The differentiation between the two types of myotonia was very distinct.

8. Treatment

In myotonia caused by a reduced chloride conductance of the muscle fiber membrane, the most direct medication would be a drug that normalizes the chloride conductance. No such drug is available. Diazepam increases the chloride conductance in vitro (321a) but has not been used for treatment. α -Aminobutyric acid, known to increase the chloride conductance in central neurons and in skeletal muscle fibers of crustaceans (11, 30), has no effect on the chloride conductance of mammalian muscle (299). Antibiotics, which act as chloride ionophores in artificial membranes, are highly nephrotoxic and therefore cannot be considered for therapy of myotonia. Moreover, am-

photericin B, which strongly promotes the chloride conductance in artificial membranes, has no corresponding effect in the excised rat diaphragm (195).

Based on their finding that serum potassium was increased in myotonia patients (4.8 vs. 4.2 mM) and on their experience that oral administration of potassium aggravated an existing myotonia, Mertens and Grüttner (228) orally administered 60 g/day polystyrol sulfonic acid, a cation exchanger. They found that within 7 days, serum potassium had decreased to 3.7 mM and all signs of myotonia were minimized. Although this therapy was confirmed to be effective in one study (315), a more extensive trial found it to be of no practical value (199). Some serious side effects to be expected from extended treatment with an ion exchanger also contributed to its failure to become a generally accepted therapy.

Blockers of the fast sodium current having a wide therapeutic bandwidth are the drugs best suited for treatment of all myotonias (34). Quinine, suggested by Wolf (331), was the first drug used in patients with some success. Procainamide (120, 132, 240, 299), diphenylhydantoin (107, 240), sparteine (300, 322), *N*-propylajmaline (27, 299, 322), and quinidine (299) were also shown to have antimyotonic effects. With the arrival of highly use-dependent antiarrhythmic drugs, the attention was shifted to tocainide (92, 283) and mexiletine (81, 261). These drugs have a relatively long biological half-life (~15 h). An optimal therapeutic plasma concentration can therefore easily be maintained with 3×400 mg/day.

B. Paramyotonia Congenita

The characteristic feature of this disease is that the muscles contract and relax fairly normally at normal body temperature, and the cardinal symptoms—slowed relaxation and muscle weakness—are pronounced when the muscles are used in the cold. In most patients the symptoms are very prominent at a muscle temperature of 27°C. Normal human muscle develops 90% full strength at this temperature. Because no suitable animal model of this disease is known, it was necessary to study the parameters of muscle fibers from humans, which was done at 37°C and at low temperature.

1. Membrane parameters

Lehmann-Horn et al. (196) investigated paramyotonic intercostal muscle *in vitro* and found that at 37°C, the fibers had normal resting potential, normal membrane resistance and capacity, and in particular a normal chloride-component conductance (see Table 1). The current-voltage relationship of the membrane (passive currents) was normal (Fig. 6), and the fibers responded to stimulation with normal action potentials. When the muscle temperature was lowered, the membrane potential of many fibers began to decrease spontaneously. As the potential reached about -60 mV, long-lasting

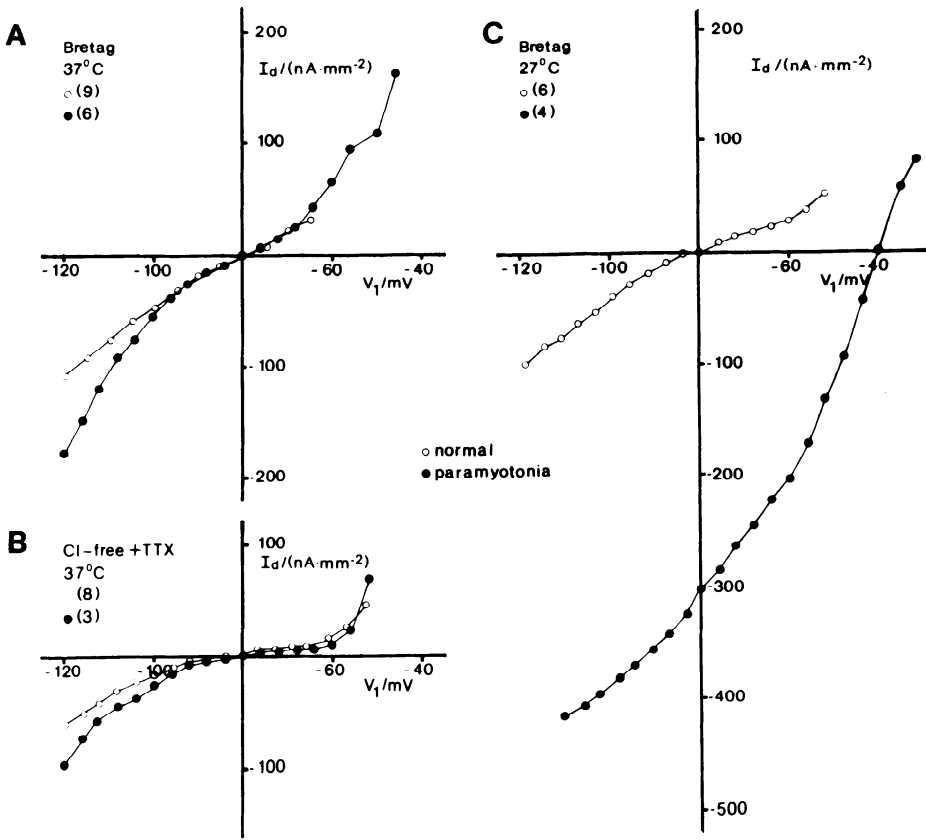


FIG. 6. Current-voltage relationships recorded from muscle fiber membrane of paramyotonia congenita patients (●) and controls (○). *Panels A and B* were recorded at 37°C. Total membrane conductance (slope of characteristics in normal extracellular medium, i.e., Bretag solution; *panel A*) and potassium-component conductance (slope of characteristics in chloride-free solution; *panel B*) of diseased muscles show no significant alterations. At 27°C (*panel C*), resting potential is reduced and total membrane conductance is increased in fibers from paramyotonia patients. Figures in *brackets* designate number of patients. [From Lehmann-Horn et al. (197).]

runs of spontaneous electrical activity at 1-5 Hz set in. The base line of the potential further decreased during these runs until the activity stopped (around -50 mV) and the depolarization ended (around -40 mV). After extracellular stimulation, the depolarization process was enhanced, and all fibers were affected. In such depolarized fibers the slope of the current-voltage relationship at 27°C was very steep, indicating an increase of the membrane conductance (Fig. 6). The conductance was also increased when the fibers were repolarized by inward current to the normal resting potential (-80 mV). Analysis of the component conductances showed that the chloride, and probably also the sodium, conductances were increased while the po-

tassium conductance remained unchanged. Membrane resting potential and conductance did not return to their normal values when the fibers were warmed up to 37°C, nor did the membrane repolarize when 0.3 mg/liter TTX was applied. Cold-induced membrane depolarization and spontaneous activity, however, could be prevented in fibers with high resting potential if TTX was applied prior to cooling. The administration of the use-dependent antiarrhythmic drug tocainide (266) or mexiletine (261) to patients prevented all paramyotonic symptoms during exposure to cold. From all these findings it was concluded that the depolarization was caused by an abnormal temperature dependence of the sodium conductance as the primary defect. The increase of the chloride conductance at 27°C in the presence of TTX (196) was not confirmed in a later study (197). In the absence of TTX, when the fibers were depolarized, the increase of the chloride conductance was in accordance with the prediction by the Goldman equation.

2. Paramyotonia associated with myotonia

One case showed considerable myotonia in a warm environment (196), i.e., prolonged contractions with normal warm-up and myotonic runs. On cooling, paramyotonic runs developed, and the slowing of relaxation increased during exercise, as is typical for paramyotonia. The fibers from this patient had a reduced membrane conductance (92 vs. 168 $\mu\text{S}/\text{cm}^2$) at 37°C, owing to a reduced chloride component. In the cold the chloride conductance was greatly increased, as in the other cases of paramyotonia.

3. Paramyotonic stiffness and weakness

Paramyotonic weakness is readily explained by the observed depolarization. There are, however, doubts that the paramyotonic stiffness can be fully accounted for by the involuntary repetitive activity (60, 145, 269, 326). These are based on a disproportionality between the amount of repetitive 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 (145). In vitro tests on excised paramyotonic muscle allow a better quantitative comparison of the total after-activity after a series of electrical stimuli and the delay of relaxation or aftercontraction (see Fig. 1). It is now clear from such studies that substantial aftercontractions may occur in the virtual absence of after-activity (194, 273). However, electromechanical coupling and the contractile apparatus of excised muscles from two paramyotonia patients appeared to be normal. In these muscles, contractures were induced at various temperatures by raising the potassium level in the absence of extracellular sodium or by the application of 2-50 mM caffeine (196). Mechanical threshold, time to peak, contracture amplitude, relaxation time, and recovery time after a contracture did not reveal any

abnormalities. No contracture responses were produced by 0.1 mM ACh. In vivo ^{31}P -NMR (nuclear magnetic resonance) spectroscopy revealed that there was no shortage of high-energy, phosphorus-containing metabolites during stiffness and that the pH was normal (193). The possibility remains that paramyotonic stiffness is caused by a depolarization-induced contracture (213), although a defect in the function of the sarcoplasmic reticulum has not been entirely ruled out (197).

4. Membrane composition

Kuhn et al. (119, 178) investigated the fatty acids and the lipids of the sarcolemma of two related paramyotonia patients via gas chromatography. In the fatty acid pattern the most impressive alterations were an increase of the (C 16:0) dimethylacetals and a decrease of oleic acid (C 18:1) (178). In the phospholipid composition there was a drastic decrease in the relative content of sphingomyelin (119). These results were recently confirmed in a study of the lipid composition of erythrocyte ghosts from another paramyotonia patient (G. Szymanska, A. Marx, I. Melzner, G. Sarzala, and R. Rüdél, unpublished observations). This study showed that the ratio of saturated to unsaturated fatty acids was generally increased. Again the relative sphingomyelin content was significantly decreased while the total content of phospholipids with respect to the membrane proteins was unchanged. Membrane cholesterol was normal (181). Further confirmation of these results is needed.

C. Hyperkalemic Periodic Paralysis

The characteristic feature of this disease is its episodes, lasting minutes to hours, during which the serum potassium concentration ($[\text{K}]_e$) rises from the normal value to 5 mM or higher. Concomitantly the skeletal muscles become adynamic or even paralyzed. Normal muscles retain nearly full strength at these potassium concentrations (199, 220). Muscle stiffness is not a characteristic feature of this disease, but spontaneous EMG activity, similar to that seen in myotonia and in paramyotonia congenita, was observed in some patients (152, 198). An animal model of this disease has recently been reported (168).

1. Muscle properties

From in vitro studies on curarized excised intercostal muscle (198), it became clear that the paralysis is caused by an abnormality of the muscle fibers themselves and that a neurogenic factor, or a humoral factor other than an increase in $[\text{K}]_e$, is not required. Cooling of the muscle to 27°C also

induced paralysis. In situ recordings of the membrane potential revealed nearly normal (37) or low (82, 225) values between attacks and suggested that further membrane depolarization is the immediate cause of paralysis during the attacks. In vitro recordings showed that at normal $[K]_e$, the muscle fibers have a normal membrane potential and normal membrane conductances (198). In contrast with normal fibers, the afflicted fibers were paralyzed in a medium containing 6–10 mM potassium.

In a muscle specimen excised from a hyperkalemia patient with myotonia, many fibers were spontaneously active even in normal solution (198). In a 7-mM potassium solution, spontaneous activity was increased, and the cells slowly depolarized to -54 mV, where excitatory sodium current is normally inactivated. The current-voltage relationship revealed that the depolarization was connected with an increased sodium conductance. Addition of 0.3 mg/liter TTX to the high-potassium solution made the depolarized fibers repolarize to near -70 mV, the value that normal muscle fibers attain in 7 mM potassium. These results have been confirmed with a preparation from another patient (F. Lehmann-Horn, K. Ricker, and R. Rüdél, unpublished observations). Insofar as the primary defect is an increased sodium conductance, the pathomechanism in hyperkalemic paralysis with myotonia seems similar to that in paramyotonia congenita. The abnormal rise in serum potassium and the associated depolarization lead to an enhancement of the hyperactivity. Further depolarization then ensues until the potential level at which inactivation occurs is reached, resulting in paralysis (78). There are, however, major differences in the experimental findings in hyperkalemia with myotonia and in paramyotonia. The depolarization may be reversed by TTX only in hyperkalemia, and there is no indication of an abnormally increased chloride conductance in depolarized fibers from the hyperkalemia patient. There is no muscle stiffness at the beginning of a hyperkalemic attack, and the recovery of force after normalization of the serum potassium level is fast.

The fibers from a hyperkalemia patient without myotonia did not depolarize more than normal fibers on exposure to a 7-mM potassium solution (198), and, in contrast with paralysis with myotonia, the fibers were hypoexcitable (198, 225). Thus the pathomechanism of weakness seems to be different in the variants with and without myotonia. Research on this disease is hampered by the rarity of the different variants.

2. Treatment

Hyperkalemic attacks are prevented by the administration of hydrochlorothiazide (192, 262, 290) or acetazolamide (159, 220, 276–278). The beneficial effect of these drugs is probably based on their capacity to lower the serum potassium concentration. Salbutamol, a β -stimulating agent, alleviates attacks probably via a stimulation of the Na^+K^+ pump (78, 84). In hyperkalemia

patients with paramyotonia, potassium-induced and cold-induced weakness react differently to pharmacological treatment (262, 275); only the former is prevented by hydrochlorothiazide. By contrast, all cold-induced symptoms but not the potassium-induced adynamia are prevented by tocainide or mexiletine (262).

D. Chondrodystrophic Myotonia

Among the symptoms comprising the Schwartz-Jampel syndrome, only the persistent electrical discharges that occur in all skeletal muscles are relevant to this review. With few exceptions (73, 209), the discharges are abolished by curare (70, 116, 122, 310). Some cases have been reported in which periods of electrical silence in muscles could not be found even when the patient tried hard to relax (73, 122, 293). Minimal voluntary movements, insertion of the EMG needle, or percussion of the muscle always initiated persistent activity of a regularly repeating pattern, i.e., CRDs (see Fig. 5). An interesting explanation for this type of activity has been put forward (167, 302). Muscle fibers in these patients might be connected by ephaptic junctions that create pathways for circling currents. Ephaptic electrical transmission between neighboring muscle fibers normally occurs during the embryonic development of human skeletal muscle but disappears soon after motor innervation has been established, i.e., long before birth. In the Schwartz-Jampel syndrome the pathway for electrical transmission may persist in adults (167). Electron-microscopic evidence for such ephapses has not been produced so far. The measurement of motor unit potential jitter may help to determine the origin of synchronization of neighboring muscle fibers, because neural and ephaptic transmission have different jitters. However, such measurements cannot be made in these patients, because postactivation activity prevents serial recording of motor unit potentials.

E. Myotonic Dystrophy

The relevant features of the many symptoms of this syndrome are myotonic stiffness and, to a lesser extent, the transient muscle weakness.

1. Muscle cell parameters

Although myotonic dystrophy (MyD) is the most common of all hereditary muscle diseases, there are relatively few electrophysiological studies of the muscle fiber membrane parameters. In vitro studies showed that the resting potential is lowered by 10–15 mV (141, 142, 155, 157, 224) and that the intracellular sodium concentration is increased (see refs. 158, 327). These findings are consistent with an increased sodium conductance at rest (156) and with

an altered stoichiometry of the $\text{Na}^+\text{-K}^+$ pump (161). In contrast to these findings, Lipicky (202) reported a high resting potential and a reduced intracellular sodium concentration (46 vs. 60 mmol/liter fiber H_2O). The fast sodium current (89) and the number of TTX-binding sites (95) were normal. Action potentials were blocked by 10^{-6} M TTX, indicating that the sodium channels are unlike those occurring in denervated muscle (141, 142). Repetitive activity was not very prominent in vitro (141, 202), certainly much less than in myotonia congenita. When the electrical threshold was determined with long-lasting depolarizing pulses, the action potentials were found to have an increased latency (202). The overshoot of the action potentials was reduced even at a conditioning potential of -80 mV (142). Lipicky and Bryant (202, 207) found a less-than-normal water content (738 vs. 803 ml/kg wet wt) but also a reduced potassium content. The intracellular potassium concentration was slightly lower than in normal muscle (181 vs. 190 mmol/liter fiber H_2O), and the potassium efflux was increased by 9%. The membrane capacitance was $6.4 \pm 1.9 \mu\text{F}/\text{cm}^2$, not significantly higher than the $5.2 \pm 0.6 \mu\text{F}/\text{cm}^2$ determined for normal fibers in the same study. The chloride conductance was investigated in six patients (202). In two cases it was abnormally low (53% of the total membrane conductance; see Table 1); in the other four cases it was 82%, as in controls. The renal concentrating ability was not significantly decreased (741 vs. 837 mosmol/kg; 245). Thus the pathophysiological mechanism of the myotonia in MyD seems in many respects different from that of myotonia congenita, but a clear hypothesis accounting for the available data still cannot be advanced.

Lipicky (202) reported qualitative abnormalities in the mechanical behavior of dissected muscle fibers. When stretched fibers were suddenly released, they went into contractures, sometimes slow and sustained, sometimes rhythmic. Impalement by a microelectrode produced a strong contracture, occasionally leading to cell rupture. The contractures occurred in fibers with normal membrane conductance, and they were not accompanied by potential change. Lipicky concluded that the abnormality may reside in the membrane systems associated with excitation-contraction coupling.

2. *Cultured muscle*

Aneurally cultured muscle from MyD patients have been investigated by two groups. Merickel et al. (227) reported a lowered resting potential (-42 vs. -52 mV in control cultures) as most significant alteration. Moreover the amplitude, overshoot, and afterhyperpolarization of the action potential were decreased, and there was a decreased amount of rectification in an outward direction measured in steady-state conditions; i.e., the membrane resistance was increased (neither normal nor MyD cells have a substantial chloride-component conductance). Based on these findings, an abnormality in the potassium conductance was proposed as a working hypothesis for the defect

in MyD (8). Tahmoush et al. (309) did not confirm these results. They pointed out that when cultured cells are matched according to length, width, and phase-contrast appearance, the mean resting potential, cable properties, and action-potential characteristics of control and MyD cells are similar. Nevertheless the limited membrane maturation attained by cultured cells may have masked a membrane defect. Whether the genetic defect of MyD is present in cultured cells therefore awaits culturing techniques that allow membrane maturation to approach that of adult muscle fibers.

3. Membrane ATPases

Many laboratories have looked for alterations of the membrane-bound ATPases. The results are conflicting and, in our opinion, the issue is still in abeyance. We merely outline the contrasts. Calcium uptake by isolated sarcoplasmic vesicles was found to be increased (177, 297) and decreased (258). Calcium uptake by intact erythrocytes was increased (254). Ouabain binding to the sarcolemma was increased two to three times (96), but the number of sarcolemmal ouabain-binding sites was reduced three to six times (95). Appel et al. (8) found little effect of ouabain on normal and MyD myotubes and concluded that the $\text{Na}^+\text{-K}^+$ pump is probably not directly involved in the repetitive-firing abnormality. Hull and Roses (161) found the ouabain-sensitive sodium efflux rate to be significantly reduced in fresh erythrocytes from patients. The stoichiometric ratio (ouabain-sensitive sodium efflux to ouabain-sensitive potassium influx) was close to unity in MyD erythrocytes, indicating a 2 Na^+ for 2 K^+ exchange, whereas it was 1.5 in the controls, favoring a 3 Na^+ for 2 K^+ active exchange. Other investigators have not found this difference (153). The $\text{Na}^+\text{-K}^+\text{-ATPase}$ and the $\text{Ca}^{2+}\text{-Mg}^{2+}\text{-ATPase}$ were also studied in erythrocyte ghosts. They were reported to be increased (169, 231), decreased (214), or without abnormalities (218).

4. Red blood cell membrane

In addition to the ATPase determinations just mentioned, other properties of the red blood cell membrane were studied with biophysical and biochemical methods. The assumption is that the membrane defect in this disease is generalized, so it can be studied in cells that function normally (for reviews see refs. 254, 255). Roses and Appel (279) reported a reduced protein kinase activity and a reduced phosphorylation of the membrane, a finding they later confirmed in the sarcolemma (280). They also found a reduced calcium-promoted potassium efflux in MyD erythrocytes (9). Butterfield et al. (63-67) were the first to apply electron-spin resonance (ESR) probes to aged erythrocytes and ghosts. Their results with various probes seemed to indicate slight alterations in the polarity and fluidity of the MyD membranes. Among various stearic acid methyl esters used as probes, the

one labeled at the 5 carbon (5-NMS) showed the greatest differences between MyD membranes and controls. However, these findings were questioned by others who used a similar method (127). An extensive description of the various probe techniques, their limitations, and the significance of the results, with special reference to the said discrepancy, has been given by Barchi (14). He concludes that it is not clear at this juncture, whether an abnormal membrane fluidity plays a significant role in MyD. Direct examination of the sarcolemma should give a more clear answer, because the abnormalities present in the sarcolemma may not be equally expressed in the erythrocyte membrane.

Chalikian and Barchi (75, 76), using fluorescent polarization techniques, found no difference in the absolute value of microviscosity at a given temperature or in the temperature dependence of this parameter when MyD and control membranes were compared. These investigators claimed that any significant generalized abnormality in the membrane fluidity of MyD erythrocytes would have been detected by at least one of the probes at some temperature within the wide range studied. They concluded that such an abnormality was unlikely to be present in MyD erythrocyte membranes (14).

Butterfield et al. (63, 65) labeled erythrocyte ghosts with sulfhydryl-reactive probes and noted that there were two classes of probe-binding sites: one was relatively free to move, and the other was essentially fixed within the ESR time scale. They calculated the ratio of the spectral contribution of weakly and strongly immobilized sites and found that it was significantly larger in MyD ghosts than in controls, indicating an alteration in either the lipid environment or in the conformation of the membrane proteins in MyD ghosts (63, 65). Because of the difficulties involved with such experiments, confirmation of these provocative results is needed (14).

5. Insulin sensitivity

Another membrane alteration of the muscle fibers in MyD is a decreased sensitivity to insulin, first detected in the forearm muscles in 1978 (236). Glucose uptake in the forearms is decreased at physiological and supraphysiological insulin levels. The defect is limited to skeletal muscle, since reduced glucose uptake was not noted in superficial fat and skin (235). Whole-body insulin resistance also occurs in MyD (25, 135, 235, 236, 311), and, unlike other conditions characterized by insulin resistance (e.g., obesity), basal insulin levels are normal (25, 28, 59, 235, 236, 257). In fact, the euglycemic insulin infusion method has revealed a moderately severe whole-body insulin resistance (234, 250). Glucose tolerance is normal, but marked hyperinsulinemia follows a glucose load. This is not a consequence of a decreased muscle mass, because wasted denervated patients do not show hyperinsulinemia in response to a glucose load and have a normal glucose uptake (235).

The decreased insulin-stimulated glucose uptake by MyD muscles is not

likely to be caused by type I muscle fiber atrophy (237) or by myotonia, wasting, or maldistribution of blood flow (236). It is probably not due to fewer functioning insulin receptors either, because large amounts of infused insulin do not increase glucose uptake to normal (235). The number of insulin receptors in MyD monocytes has been claimed to be reduced (117). However, because monocyte insulin affinity is increased in the basal state and fails to increase further (239), Moxley et al. (238) maintain that insulin binding by MyD monocytes may be altered in a way other than reduction in receptor number. They conclude that structural abnormalities of the muscle cell membrane in MyD may influence binding affinity, and this, rather than receptor number, may be responsible for the insulin resistance.

6. *Therapy*

Myotonia is usually a minor complaint of patients with MyD, and therefore symptomatic treatment is seldom required. Local anesthetics, antiarrhythmic drugs, and diphenylhydantoin are all effective antagonists of the myotonia in MyD. Diphenylhydantoin might be preferred because it does not affect conduction through the atrioventricular node, which is an important consideration in these patients (138). Successful treatment of many symptoms of MyD has been achieved with tricyclics. The aminergic effect of the tricyclics is thought to improve the impaired function of hormonal receptors (41-43).

VI. MODEL MYOTONIAS

The two most widely studied model myotonias are 9-AC- and 20,25-D-induced myotonia. We briefly discuss the similarities and differences between these and the hereditary human myotonias. For an extensive review of model myotonias see reference 185.

A. *Myotonia Induced by Anthracene-9-Carboxylic Acid*

The myotonia-inducing effects of the monocarboxylic acids were known as early as 1917 (256). Moffett and Tang (233) first showed the myotonic effect of 9-AC, Bryant and Morales-Aguilera (55) carried out the first extensive study of 9-AC on goat muscle *in vitro* and *in vivo*. They showed that 5×10^{-5} M 9-AC increased the membrane resistance by blocking the chloride channels.

1. *Electrical properties*

Barchi et al. (124, 248) confirmed that in excised rat diaphragm, 9-AC at 2×10^{-5} M reduced the chloride conductance by $\sim 60\%$ and at 5×10^{-5}

by >90%. The resting potential and the action-potential amplitude were not significantly altered. At an increased drug concentration, a moderate decrease in the maximum rate of rise of the action potential was noted (242 vs. 289 V/s at 5×10^{-5} M and 25°C; 124). The maximum rate of fall was not affected (about -70 V/s). The delay between a depolarizing pulse and the resulting action potential was increased in the presence of 9-AC (78 vs. 13.5 ms). This latency declined progressively as the pulse amplitude was increased, and additional action potentials appeared during the flow of current, an effect seldom seen in controls. With large pulses, long trains of action potentials appeared after cessation of the current injection. Although common at 37°C, these afterdischarges did not occur at 25°C, and the tendency toward repetitive activity declined.

2. Mechanical properties

Recording of isometric force revealed marked prolongation of contraction of 9-AC-treated rats *in vivo* (92; for 2,4-D-treated rats see ref. 110) and excised human intercostal muscle (H. Kwieciński, F. Lehmann-Horn, and R. Rüdél, unpublished observations). The 9-AC-induced myotonia was successfully antagonized by diphenylhydantoin (124) and tocainide (92). This effect is probably caused by direct or indirect action of these drugs on the activation of the fast sodium current (124).

3. Discussion

Anthracene-9-carboxylic acid-induced myotonia closely resembles the dominantly inherited myotonia congenita, because it reproduces the myotonic signs of muscle stiffness, percussion myotonia, lack of accommodation, myotonic afterdischarges, and warm-up. The membrane chloride-component conductance is reduced by 9-AC, and the myotonic signs can likewise be induced by the replacement of extracellular chloride by an impermeant anion. These facts underscore the importance of a high chloride conductance for the prevention of myotonia. As mentioned in section vA5, the alterations of the mechanical threshold in 9-AC myotonia and in goat myotonia go in opposite directions.

B. Myotonia Induced by 20,25-Diazacholesterol

The myotonia-inducing effect of 20,25-D was detected in 27 hypercholesterolemic patients who had been treated with this drug for several months (330). They developed myotonic stiffness, percussion myotonia, and myotonic runs in the EMG. After termination of the treatment, all myotonic signs disappeared within several months. 20,25-Diazacholesterol was then given

to goats (330) and rats (329), and the development of myotonia was confirmed. Similar effects were found with 25-azacholesterol (108, 134). Myotonia developed in the fast extensor digitorum longus (EDL) but not in the slow soleus (SOL), although the latter muscle also showed some of the membrane abnormalities (85).

1. Electrical properties

The first determination of the cable parameters of diaphragm fibers from 20,25-D-treated rats showed that chloride conductance was reduced to a third of control (284). Another group investigating rats treated for more than 6 wk maintained that chloride conductance was less reduced, not enough to explain the 20,25-D myotonia (125). This discrepancy was solved when a third group revealed that chloride conductance drops to 42% of control within 15 days of treatment, but raises again after day 35 (whereas potassium conductance stays unaltered all the time) (85). The drop in chloride conductance was found in both EDL and SOL (85). The resting potential of 20,25-D-treated muscles was normal (85, 125, 284). The upstroke and downstroke velocities of the action potential were significantly increased in EDL and SOL, but only EDL displayed afterdischarges (85). No major abnormalities of the action potential and no afterdischarges were detected in the diaphragm, but long-lasting current pulses produced repetitive activity explained by a defective accommodation process. Low external calcium did not increase the repetitive activity (125).

2. Mechanical properties

Percussion myotonia could not be elicited in rats treated for >6 wk, and the contractions of the excised diaphragm were only minimally prolonged (126). However, investigation of the time course of 20,25-D effects revealed that a 10-fold prolongation of the twitch occurs between days 10 and 40 of drug application (85). Only the fast EDL, not the slow SOL, was affected. The prolongation disappeared with continued stimulation (warm-up). It was suggested that this myotonia was a consequence of repetitive activity (85).

3. Desmosterol

20,25-Diazacholesterol inhibits the conversion of desmosterol to cholesterol by blocking the Δ^{24} -reductase activity. An accumulation of desmosterol in the serum of 20,25-D-treated rats was noted (329), causing an increase in sarcolemmal desmosterol content of fast and slow skeletal muscle (85) and of cardiac muscle (296). There is a close relationship between the onset of myotonia and the rise in sarcolemmal desmosterol content, the replacement

of every 10th cholesterol molecule by desmosterol being a sufficient cause of myotonia (252). Of course, it could be the reduction of the membrane cholesterol content that causes myotonia. No significant alteration in the fatty acid pattern of the sarcolemma was found, but there were significant increases in the activities of the $\text{Na}^+\text{-K}^+\text{-ATPase}$ (2.5-fold) and the $\text{Ca}^{2+}\text{-ATPase}$ (1.4-fold), whereas that of the $\text{Mg}^{2+}\text{-ATPase}$ was unchanged (253). By contrast, two other groups reported a decrease of the $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity (244, 295).

4. Discussion

The 20,25-D-induced myotonia is a model that seemingly gave inconsistent results, but this can in part be attributed to the time course of the 20,25-D effects. The chloride conductance is not as reduced as in some congenital myotonias and as in 9-AC myotonia. The importance of a low chloride conductance as a myotonia-inducing factor in 20,25-D treatment was questioned by the fact that the EDL was myotonic and the soleus was not when chloride conductance had fallen by the same amount (85). The accommodation process and the fast sodium current are altered in the 20,25-D myotonia, but whether these changes are similar to those found in human myotonias still cannot be decided. 20,25-Diazacholesterol myotonia has interesting features in common with MyD: cataracts and testicular atrophies develop with long-term 20,25-D treatment (251). The renal concentration ability was found to be significantly reduced (906 vs. 2,825 mosmol/kg) in 20,25-D-treated rats (252). In that respect, 20,25-D myotonia resembles myotonia congenita more closely than MyD (72). The importance of desmosterol for the development of 20,25-D myotonia led to the hypothesis that an altered sterol composition might also be the basis of the hereditary myotonias. However, a rigorous search for desmosterol in the plasma and sarcolemma of patients with myotonia congenita or MyD, as well as of goats with hereditary myotonia, did not show any such accumulation of desmosterol (252). In this respect, the 20,25-D model is markedly different from the hereditary myotonias.

VII. INFLUENCE OF MOTOR INNERVATION ON MYOTONIA

The large chloride conductance (relative to potassium conductance) is a special property of skeletal muscle that is probably acquired with motor innervation, because myotubes have a very small chloride conductance (8). The malfunction of the chloride channels in hereditary myotonia could therefore be caused by a malfunction of the motor nerves (48). The influence of motor innervation on myotonic signs has been studied by measuring the changes occurring after denervation of healthy muscles and by attempts at inducing myotonia in denervated muscle. We know of no reports describing the denervation-induced changes of muscle in hereditary myotonia.

When a muscle is permanently deprived of its motor innervation, its fibers depolarize. The major factors causing this depolarization are believed to be an initial increase of the membrane permeability to sodium and a reduction of the membrane capacity to actively pump cations. Many, frequently conflicting experimental results have to be considered in attempting a detailed elucidation of the depolarization mechanism (for review see ref. 221). Disagreement between results can in part be explained by the fact that different muscles in the same animal react differently to denervation and that muscles from different experimental animals behave differently (H. Lorković, personal communication). The changes relevant to myotonia are a decrease of the membrane chloride conductance to very low values and a rise of the potassium permeability by a factor of 2-3 (52, 71, 91, 210), which begin ~5 days after denervation and reach their full scale after 4 wk. Myotonia was expected as a consequence of the reduced chloride conductance, but when denervated muscle from normal goats was investigated *in vitro*, the typical myotonic runs were not observed on penetration with a microelectrode (52). This was explained as a consequence of membrane depolarization: some fibers with high resting potential showed "myotonic behavior," and local hyperpolarization of depolarized fibers toward control resting potential allowed repetitive activity to be produced during a long depolarizing pulse. Another factor that may explain the absence of repetitive firing in denervated fibers is a current-voltage relationship that is more linear than in nondenervated fibers (210). Afterdischarges characteristic of myotonia were absent. The action potentials of these denervated fibers were not blocked by 10^{-6} M TTX. Discharges with an abrupt beginning, some crescendo and decrescendo, and an abrupt ending have also been observed in patients with a chronic denervation process, as in amyotrophic lateral sclerosis (44, 45).

A question of some interest is whether drugs that induce myotonia in nondenervated muscle can induce myotonia in denervated fibers. Monocarboxylic aromatic acids did not generate myotonia in denervated muscle *in vivo* (166, 222) and *in vitro* (165, 166) after 10 days. Bathing a denervated muscle in a chloride-free medium was also ineffective in producing myotonia in denervated rat muscles (164) and in excised intercostal muscles from two patients with amyotrophic lateral sclerosis (G. Küther and F. Lehmann-Horn, unpublished observations). Two groups of authors could not detect myotonia in denervated muscles of 20,25-D-treated rats whose nondenervated muscles showed intense myotonia (68, 69, 86). However, another group investigating the EMG of denervated fast and slow muscles in 20,25-D-treated rats found insertion activity as well as repetitive activity and CRDs on slight movement of the electrode or after percussion (111). They also found myotonic aftercontractions that could be antagonized by dantrolene (109). Aftercontractions were also recorded from denervated rat muscle *in vivo* 1 h after the administration of 225 mg/kg (2,4-dichlorophenoxy)acetate (110). The equivocal results may be explained by the different stimulus conditions and in the different definitions of myotonia used by these authors. Eberstein and

Goodgold (110) have pointed out that repetitive stimulation is necessary for eliciting myotonia, whereas d'Alonzo et al. (86) maintain that myotonic slowed relaxation should be present in the response to a posttetanic single stimulus. They claim that Eberstein and Goodgold's slowed relaxation is a "contracture response after direct tetanic stimulation." This argument could be clarified by a simultaneously recorded EMG. Unfortunately, neither group has produced this evidence.

The results from the denervation experiments showed that influences from the motor neuron, e.g., action potentials, mechanical shortening, or "trophic factors," are needed to keep up the normally large chloride permeability of the skeletal muscle fiber. Using colchicine and the vinca alkaloids vinblastine and vincristine, drugs that block axoplasmic transport but not impulse conduction, Camerino and Bryant (52, 71, 79, 80) presented evidence that the resting component conductances of the skeletal muscle fiber membrane are under the control of factors transported by the neural microtubular system. Although the muscle fibers were capable of being activated by the poisoned motor nerves, the absence of these factors led to conductance changes similar to those produced by denervation (79). Because colchicine blocked only the factor increasing chloride conductance, leaving potassium conductance unchanged, two different factors seem to regulate the membrane conductance, one increasing the normally low chloride component and another suppressing the normally high potassium component conductance of unregulated muscle. The vinca alkaloids blocked both components. These results support speculations that some hereditary myotonias may have an indirect neurogenic basis (48).

VIII. CONCLUSION

Research on excised muscle from myotonia-patients and on model myotonias has clearly shown that several membrane defects may lead to myotonic signs and that not all such defects lead to an identical expression of all myotonic signs. This explains the clinical variations observed in the genetically separate diseases associated with myotonia.

Best understood is the low chloride conductance mechanism operant in myotonia congenita of humans and goats (sect. vA) and in model myotonias induced by monocarboxylic aromatic acids and by chloride-free media (sect. vIA). There are some doubts about its importance in the recessive Becker type of human myotonia congenita. Note that in goat myotonia, the paradigm case for the low chloride conductance mechanism, two additional changes have been described: a reduction of the backward rate-constant parameter describing the fast sodium current and a lowered mechanical threshold (sect. vA). These parameters have not yet been determined in the human myotonias.

The low chloride conductance mechanism seems to play a smaller role, if any, in the most common myotonic syndrome, myotonic dystrophy (sect.

vE), in paramyotonia congenita (sect. *vB*), and in model myotonias induced by blockers of cholesterol synthesis (sect. *viB*). For myotonic dystrophy, altered properties of the membrane-bound ATPases are discussed, and a change of the potassium-conducting systems is suggested, but these findings need further confirmation. An interesting alteration in this disease is the reduced insulin-binding capacity of the muscle fiber membrane. So far it is not clear whether it relates to the myotonia. In paramyotonia, hyperkalemic paralysis, and in 20,25-D myotonia the behavior of the sodium channels is abnormal.

The question remains, To what extent are the mechanical signs accounted for by the electrical processes? In muscles that show massive afterdischarges, as in myotonia congenita and in myotonic dystrophy, this uncontrolled activity may act as an extended tetanus causing prolonged contraction, i.e., myotonic stiffness. Afterdischarges are produced when a certain amount of potassium accumulates in the transverse-tubular system. This explains why myotonic stiffness is usually small in the first volitional contraction and why it increases to a maximum after the third or fourth contraction. The warm-up that occurs thereafter has been explained by the decrease in intracellular pH caused by the increased metabolism (sect. *iv*).

A myotonic afterdischarge may lead to either of two processes: 1) the membrane slowly attains a normally high and stable resting potential, or 2) the membrane depolarizes to a level at which the fast sodium current is inactivated either entirely or to a degree such that action potentials do not pass the mechanical threshold. The latter process might be the mechanism of myotonic transient weakness (sect. *iiiB*).

In paramyotonia congenita, afterdischarges are much less prominent than in myotonia congenita, and the cold-induced stiffness does not seem to be primarily caused by the long-lasting low-frequency runs. It may well be that the paramyotonic stiffness consists of a depolarization-induced contracture. Paramyotonic weakness or paralysis has been shown to be caused by a long-lasting membrane depolarization causing inexcitability (sect. *vB*). The persistence of the weakness after rewarming of a paramyotonic muscle is caused by a slowed recovery of the membrane potential. The mechanism of this slow recovery is not yet understood.

Progress in the understanding of the complex subject of myotonia has been made possible by the improvement of clinical methods. Quantitative measurements of the various myotonic signs were very helpful in ascertaining that the many facets of myotonia characterize certain clinical forms. The major contribution to the progress in understanding the various pathomechanisms of myotonia has come from electrophysiology. The vanguard of the research has successfully tackled goat myotonia. Much remains to be done to determine the electrophysiological parameters for all the human myotonias with a comparable accuracy. Such measurements are especially needed for the most common muscle disease, myotonic dystrophy.

A better understanding of the cell defects of myotonia requires that improvements be made in the biophysical and biochemical techniques used to study membrane properties at the molecular level. Much work has already been devoted to the investigation of the red blood cell membrane and sarcolemma from myotonia patients, but so far the results have been disappointing.

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