Effects of Acetazolamide on Myotonia

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Myotonia can occur in the periodic paralyses, particularly the hyperkalemic form. The beneficial response to acetazolamide in hypokalemic and hyperkalemic periodic paralysis has led us to study the effect of acetazolamide in 9 patients with disorders having myotonia as the major problem, 7 with myotonia congenita and 2 with paramyotonia congenita. Patients were studied before acetazolamide administration with glucose and potassium loading tests. All patients had an increase in myotonia with potassium, but no weakness occurred with either test. Acetazolamide treatment decreased myotonia in all patients and in 3 proved the most satisfactory therapy. Side-effects during acetazolamide therapy included paresthesias in 5 patients and renal calculus in 1. Flaccid weakness occurred in a patient with paramyotonia congenita. Acetazolamide treatment was associated in all patients with partially compensated metabolic acidosis and lowering of serum potassium within the normal range. Kaliuresis was also noted during introduction of therapy. Acetazolamide appears to be an acceptable treatment for occasional patients with myotonia who are unresponsive to or intolerant of other therapies.

Griggs RC, Moxley RT III, Riggs JE, et al: Effects of acetazolamide on myotonia. Ann Neurol 3:531–537, 1978

Myotonia sometimes occurs in the different forms of periodic paralysis, especially the hyperkalemic type [14, 15, 19]. The beneficial effect of acetazolamide on the episodic and interattack weakness in hypokalemic periodic paralysis [6, 20] led us to study the clinical and metabolic effects of acetazolamide in patients with disorders having myotonia as the major problem, myotonia congenita and paramyotonia congenita. Since there is occasionally an overlap between myotonia congenita and paramyotonia congenita and the periodic paralyses [3, 23], patients were studied prior to therapy for susceptibility to glucose and potassium loading. Because changes in serum potassium level have been noted to correlate with changes in myotonia [11] and arterial potassium concentrations have been noted to be increased in patients with myotonia congenita [7], we evaluated the degree of myotonia, as well as muscle strength, after potassium loading. To document the systemic effects of the dose of acetazolamide given our patients, we measured serum potassium levels and urinary excretion and assessed their blood acid-base balance.

Patients Studied

Six patients with autosomal dominant myotonia congenita included 2 sisters and an uncle from one kindred, a father and son from another, and 1 patient from an additional kindred. One patient without a family history possibly had autosomal recessive inherited myotonia congenita. Two patients from separate kindreds of autosomal dominant inherited paramyotonia congenita were evaluated. All patients had electromyographically documented classic myotonia. Responses to potassium chloride and acetazolamide are noted in Tables 1 and 2. The clinical features of the patients are described in the following case summaries.

Patient 1 (Myotonia Congenita)

A 32-year-old woman had a history of lifelong muscle stiffness worsened by cold and relieved by food. Although relieved by "warming up," the stiffness increased after rest following exercise. The patient was often so stiff in the morning she had difficulty moving at all until she had something sweet to eat. Her severe stiffness was painful and her muscles "hard" rather than weak. The patient's sister, mother, and son were afflicted with a similar illness.

Physical examination was normal except for marked generalized action and percussion myotonia elicited in numerous muscles. The myotonia improved with activity except on repeated eye closures. Procainamide therapy, 500 to 2,000 mg per day, caused improvement for fifteen years, but she developed arthralgias and antinuclear antibodies. Quinine was associated with intolerable tinnitus and diarrhea. Phenytoin treatment at a serum level of 1.2 mg per deciliter decreased the myotonia with no untoward effects.

Weakness was not provoked by immersion of the arm up to the elbow in water for one minute at 0°C or for six minutes at 10°C, but a subjective increase in muscle stiffness occurred. KCl loading was associated with severe sub-

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Accepted for publication Jan 24, 1978.

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Table 1. Oral KCl Loading in Patients with Myotonia

Disease	Patient No., Age (yr), and Sex	Dose (gm)	Effect on Myotonia	Maximum Serum K^+ (mEq/L)
Myotonia congenita	1. 32, F	4	Increased; painful cramps	6.45
	2. 30, F	4	Increased; painful cramps	5.84
	4. 14, M	3	Severe, generalized rigidity	5.50
	7. 20, F	12	Severe rigidity	5.50
Paramyotonia congenita	8. 25, M	9	Increased; painful cramps	5.15
	9. 19, F	9	Slight increase	6.81

Table 2. Treatment of Myotonia with Acetazolamide

Disease	Patient No., Age (yr), and Sex	Daily Dose (mg)	Myotonia	Current Treatment	Duration	Side-Effects
Myotonia congenita	1. 32, F	500	Diminished	Phenytoin	18 mo	Paresthesias, dysguesia, ?renal calculus[a]
	2. 30, F	500	Abolished	Acetazolamide	20 mo	Transient paresthesias, dysguesia
	3. 58, M	750	Diminished	Procainamide	36 mo	None
	4. 14, M	500	Diminished	Quinine	40 mo	Paresthesias
	5. 42, M	500	Diminished	Quinine	40 mo	Paresthesias
	6. 27, F	750	Diminished	Procainamide	12 yr	None
	7. 20, F	500	Diminished	Acetazolamide	12 yr	None
Paramyotonia congenita	8. 25, M	750	Abolished	None		Weakness[a]
	9. 19, F	500	Diminished	Acetazolamide	8 mo	None

[a]See text.

jective stiffness and a feeling of swelling and tightness with palpable rigidity in numerous muscles. The patient also complained of difficulty swallowing. Lid and grip myotonia increased markedly, but no change in strength occurred. Glucose loading was associated with a subjective decrease in myotonia but no weakness.

Patient 2 (Myotonia Congenita)

The 30-year-old sister of Patient 1 had a similar history. Pregnancy was associated with increased muscle stiffness. The patient had never had weakness. Examination was negative except for severe myotonia. By history, therapy with quinine was effective but led to severe thrombocytopenia and bleeding. Procainamide, 250 mg twice a day, decreased her myotonia, but antinuclear antibodies developed. Phenytoin, 300 mg daily, was associated with a subjective and objective decrease in myotonia, but a maculopapular skin rash developed and precluded further treatment.

Responses to potassium loading, cold immersion of the forearm, and glucose loading were similar to those of Patient 1. Following the KCl load, no change in strength occurred but a severe increase in myotonia was observed.

Patient 3 (Myotonia Congenita)

The 58-year-old maternal uncle of Patients 1 and 2 had a lifelong history of muscle stiffness that improved with exercise. Unlike Patients 1 and 2, he did not report any change in symptoms with diet. Aside from diabetes mellitus controlled with chlorpropamide, his health was unremarkable.

On examination there was generalized muscle hypertrophy; marked action and percussion myotonia were elicited in numerous muscles. Muscle strength was normal. Myotonia improved with exercise. Signs of slight peripheral neuropathy were present.

Although he could not tolerate quinine (which gave him diarrhea), his myotonia improved on procainamide, 500 mg per day.

Patient 4 (Myotonia Congenita)

A 14-year-old boy had had painless generalized muscle stiffness since early childhood. Symptoms were increased by cold, but he was always of normal strength. The patient's father and grandfather have a similar illness. On examination, his muscle bulk was generally large and his strength

normal. Aside from severe generalized action and percussion myotonia, he was normal.

Provocative testing with oral or intravenous glucose (65 gm with 10 units of insulin at 30 and 60 minutes) did not affect his strength. KCl loading (see Table 1) resulted in severe generalized myotonia with inability to speak or swallow. Cold immersion of the forearm (cf Patient 1) increased myotonia but was not associated with weakness. Treatment with quinine, 200 mg three times a day, decreased myotonia markedly.

Patient 5 (Myotonia Congenita)

The 42-year-old father of Patient 4 had a virtually identical history of lifelong muscle stiffness increased by cold and unassociated with weakness. Provocative testing with glucose and potassium was not performed; the patient's myotonia responded to quinine, 300 mg three times a day.

Patient 6 (Myotonia Congenita)

A 27-year-old woman had had difficulty walking since early childhood, with frequent stumbling. She noted stiffness of the limbs, face, and tongue exacerbated by cold weather and improved with exercise. The patient's mother had a similar illness.

Physical examination was normal except for severe action and percussion myotonia. Myotonia improved with warm-up except in the orbicularis oculi muscles. Following warm-up, strength was entirely normal, but she often required four or five attempts before achieving normal strength at any specific test.

Treatment with procainamide, 250 to 750 mg daily, proved effective in controlling her myotonia. Trials of quinine, 130 mg three times a day, and phenytoin, 200 mg daily, proved ineffective, but blood levels were not monitored and dosages were low.

Patient 7 (Atypical Myotonia Congenita)

A 20-year-old woman had had generalized myotonia from birth. In childhood, quinine treatment (1 gm daily) was beneficial but had to be discontinued when hearing loss occurred. Subsequently, procainamide up to 3,500 mg a day (100 mg per kilogram) and chlorothiazide (2,000 mg a day) were effective. At age 11, weakness of the hands was noted. Family history and detailed evaluation of parents and siblings were negative for myotonia or weakness.

Severe action and percussion myotonia was present in numerous muscles. Following a single forceful lid closure, the patient required ten minutes or longer to regain a normal facial appearance, and facial stiffness worsened with succeeding lid closures. When not treated, the patient had difficulty swallowing and dyspnea from chest stiffness. The patient had distal weakness and wasting and generalized hyporeflexia. There were no other features suggestive of myotonic dystrophy. Slit-lamp examination was negative; electrocardiogram and serum IgG were normal. When the patient was first tested after several years of procainamide treatment, antinuclear antibody was present but three lupus erythematosus preparations were negative.

Electromyography showed marked myotonia as well as a decrease in the size and duration of motor unit potentials; overly rapid recruitment was present. Serum creatine phosphokinase was four to five times normal. A left quadriceps muscle biopsy showed an increase in internal nuclei, occasional necrotic fibers, and many fibers with multiple irregular vacuoles in the cytoplasm.

The response to potassium loading tests was unusual. Oral administration of 15 mEq of potassium (as Potassium Triplex, containing 10% potassium acetate, potassium bicarbonate, potassium citrate), and on a subsequent day 30 mEq of potassium (as Potassium Triplex) resulted in an increase in forearm myotonia and equivocal weakness of forearm muscles. Subsequently the oral administration of 150 mEq of potassium (as Potassium Triplex) produced a rise in serum potassium to 5.5 mEq per liter and resulted in generalized stiffness and complaints of respiratory distress and inability to swallow. No change in strength occurred. Following potassium loading, the patient's serum creatine phosphokinase and serum glutamic oxaloacetic transaminase rose markedly and she developed pigmenturia. Because of the inability to swallow, intravenous hydration was given; serum potassium decreased to 3.3 mEq per liter and myotonia became minimal. Susequently, because of a suspected diagnosis of hyperkalemic periodic paralysis, acetazolamide was started and a dramatic decrease in myotonia was observed.

In summary, this patient's illness raised a question of hyperkalemic periodic paralysis, but she had never had an attack of weakness and her deterioration with potassium appeared to be an increase in myotonia rather than a change in strength. Her clinical features resembled those in cases of autosomal recessive myotonia congenita reported by Becker [1, 2] although the reports on these patients have not mentioned biopsy or electromyographic findings to compare with our patient. Her condition may be distinct from previously reported myotonic disorders.

Patient 8 (Paramyotonia Congenita)

A 25-year-old man with autosomal dominant inherited paramyotonia [5] has been reported previously [21]. Cold-provoked weakness as well as episodes of spontaneous weakness occurred.

Patient 9 (Paramyotonia Congenita)

A 19-year-old woman of German descent (separate kindred from Patient 8) had a lifelong history of muscle stiffness that was markedly increased by cold and episodic weakness lasting up to an hour after exposure to cold air or water. She has not had persistent weakness or episodic fluctuation in strength unassociated with cold. The patient's brother, father, and paternal grandfather had a similar illness.

On examination, the patient was of normal bulk and strength but had marked generalized action and percussion myotonia. Myotonia of the orbicularis oculi and grip muscles increased with repeated contractions. The remainder of her examination was normal.

Oral loading with 9 gm of KCl was associated with an increase in orbicularis oculi and grip myotonia as well as

severe generalized muscle stiffness and pain. No change in strength occurred. Oral or intravenous glucose loading did not result in any change in strength.

Immersion in cold water (cf Patient 1) was associated with marked weakness of grip lasting two hours, with only trace movement remaining in all intrinsic hand muscles. No myotonia was present on an electromyogram at this time.

Methods and Materials

Metabolic Studies

All studies were conducted in the Clinical Research Center of the University of Rochester. Prior to admission, each participant received a detailed explanation of the procedures to be used and the attendant risks. Each signed a consent form for the protocol to be described. Metabolic studies were performed in the morning with the patient at bedrest and following a ten-hour overnight fast. Patients were maintained on a constant daily diet consisting of protein, 1.5 gm per kilogram; fat, 1.4 gm per kilogram; carbohydrate, 4 gm per kilogram; calcium, 20 mg per kilogram; sodium, 45 mg per kilogram; potassium, 55 mg per kilogram; phosphorus, 25 mg per kilogram; and total calories, 35 cal per kilogram of body weight. Patients were placed on this diet for at least three days prior to all metabolic studies. All venous blood samples were drawn with the patient totally at rest, without a tourniquet, slowly through a 19-gauge scalp vein needle (Butterfly 19 infusion set, Abbott Laboratories, North Chicago, IL) placed in a forearm vein. The venous line was maintained between samples with physiological saline. The first milliliter of blood extracted with each sample was discarded.

Glucose Loading

Each patient received oral glucose loading of 1.5 gm per kilogram to a maximum of 100 mg except Patients 3 and 6. In the patients with paramyotonia congenita, loading with intravenous glucose and insulin was also performed. Patient 8 was given 200 gm of glucose and Patient 9, 136 gm of glucose (3 gm per kilogram) in 500 ml of water intravenously over sixty minutes. At thirty and sixty minutes, 10 units of regular insulin were administered intravenously. Electrolytes, electrocardiogram, myotonia, and strength were followed as previously described [21]. No change in strength was observed in any of the patients with myotonia congenita. One of the patients with paramyotonia (Patient 8) demonstrated moderate weakness in all muscle groups tested [21]. This patient's myotonia also decreased. The other patient with paramyotonia congenita developed slight weakness of iliopsoas and anterior tibial muscles. Orbicularis oculi myotonia diminished moderately.

Potassium Loading

The effects of potassium loading on myotonia and strength were assessed in all except Patients 3, 5, and 6. Three or 4 gm of KCl was administered orally, and if no definite change in strength or myotonia was observed, subsequent tests with up to 9 to 12 gm were given. Potassium was administered as KCl in a 25% oral solution except for Patient 7, who was given Potassium Triplex. Myotonia was monitored as described for the acetazolamide trial.

All patients developed worsening of myotonia at either low- or high-dose potassium administration (see Table 1). In none was any weakness observed. In fact, in the patients with paramyotonia congenita, strength subjectively increased in both the examiners' and the patients opinion. As has been noted in the individual summaries, the increase in myotonia was dramatic in 5 of the 6 patients and a moderate increase occurred in Patient 9. All these patients continue to single out the potassium loading as the most painful and severe episode of myotonia they have had in their life and continue to mention the dramatic worsening that occurred. The administration of potassium to Patient 6 produced transient severe rigidity, elevation of serum creatine phosphokinase, myoglobinuria, and subsequent oliguria.

Venous potassium monitored during KCl loading rose to high normal or slightly above normal range with an average increase of 2 mEq per liter (see Table 1).

Acetazolamide Administration

Medication was administered in open trial to all patients and then repeated in a single-blind fashion with placebo-identical capsules in 5 of the 7 patients with myotonia congenita (see Table 2). Acetazolamide in a dosage of approximately 10 mg per kilogram was given with monitoring of myotonia using timed documentation of lid lag, orbicularis oculi, and hand-grip myotonia; percussion myotonia was timed at the wrist extensors and thenar eminence. In 3 cases, subsequent blind photographic documentation of myotonia during placebo and medication was obtained. Myotonia was evaluated after an overnight fast with careful attention given to avoiding having "warm-up" of muscles to be tested prior to timing or photographic documentation.

Serum and urinary electrolytes and arterial blood gases were studied during the first two days of acetazolamide administration while patients received a constant diet.

Results

Clinical Results of Acetazolamide Trial

Table 2 indicates the clinical response to acetazolamide. In all patients there was a subjective and objective (timed) decrease in action myotonia, occurring within eight hours in orbicularis oculi and one or more other sites.

Treatment with acetazolamide was continued in patients if other antimyotonic agents (quinine, procainamide, or phenytoin) proved less effective or produced severe side-effects (see Patient summaries). In 3 of the 9 patients, acetazolamide has been continued and remains the optimal therapy for their myotonia. Side-effects occurred in 6 of the 9 patients tested. These included paresthesias in 5 of the 7 patients with myotonia congenita and generalized weakness in 1 patient with paramyotonia congenita, as previously reported [21]. A renal calculus present in Patient 1 has an uncertain causal relationship to the acetazolamide therapy because no baseline abdominal roentgenogram is available to

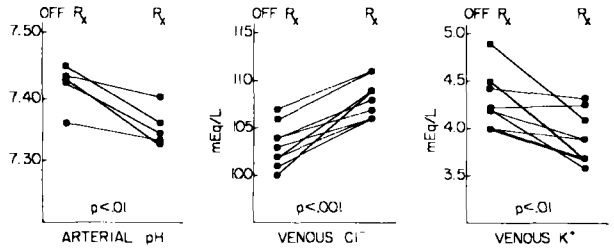

Fig 1. Studies of arterial blood pH, venous serum chloride, and potassium in the untreated state (OFF R_x) *and during acetazolamide administration* (R_x).

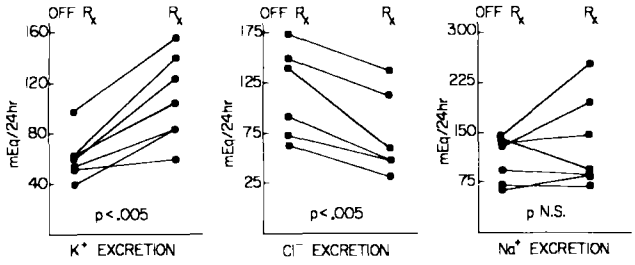

Fig 2. Studies of urinary excretion of potassium, chloride, and sodium during the introduction of acetazolamide. Values represent the mean 24-hour excretion for the three days prior to administration (OFF R_x) *and the two days after initiation of acetazolamide* (R_x).

compare with that obtained after the brief trial of acetazolamide.

Metabolic Effects of Acetazolamide

A comparison of arterial blood gases on and off acetazolamide shows a significant lowering of arterial pH in all 5 patients studied (Fig 1). Total carbon dioxide and P_{CO_2} also decreased. Venous electrolyte determinations demonstrated an increase in chloride in all 9 patients and lowering of potassium in 8 of the 9 patients (Figs 1, 2). No significant change in serum sodium occurred.

Urinary electrolytes during the first two days of acetazolamide administration demonstrated a significant kaliuresis in all 7 patients studied and a fall in chloride excretion in the 6 patients studied (Fig 3). No consistent or significant change in sodium excretion occurred.

The time course of the effect of acetazolamide on myotonia and venous potassium was studied in the patient with the most severe myotonia (Patient 7). A 17-gauge polyethylene catheter was introduced into an antecubital vein, threaded toward the wrist, and palpated to be deep within forearm muscle. Venous serum was obtained every one to two hours for thirty-six hours (see Metabolic Studies).

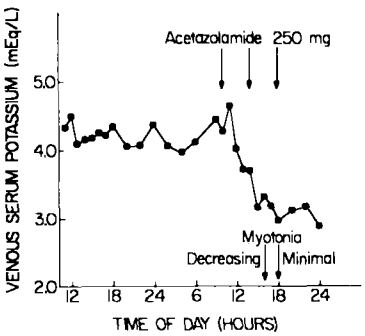

Fig 3. Effect of acetazolamide (dosage as shown in upper arrows) *on venous potassium in Patient 7. As myotonia improved* (lower arrows), *potassium declined.*

After a control period of twenty-four hours, 250 mg of acetazolamide was administered orally every eight hours. The patient remained on constant diet throughout the determinations and ate at identical times on each day of the study.

During the first twenty-four hours (control period), venous potassium remained between 3.96 and 4.49 mEq per liter (Fig 3). Two hours after the initiation of acetazolamide, serum potassium began to decline and within eight hours reached a nadir of 2.95 mEq per liter, remaining between 2.86 and 3.19 mEq per liter during the subsequent sampling. Myotonia improved concomitant with the lowering of venous potassium.

Discussion

The treatment of myotonia with quinine, procainamide, or phenytoin is frequently successful [3, 17]. The occurrence of side-effects with these agents occasionally contraindicates their use, necessitating alternative therapeutic agents. Acetazolamide provides that alternative for some patients. All 9 of our patients had a subjective and objective decrease in myotonia with acetazolamide treatment. The decrease in myotonia occurred within six to twelve hours, and in the 4 patients treated on a long-term basis, persisted for the duration of therapy (eight months to twelve years). In 3 patients acetazolamide is the most satisfactory agent for the treatment of myotonia, and therapeutic effectiveness has been maintained for up to twelve years. Two of these patients had side-effects which contraindicated the use of other myotonic agents, and 1 had not obtained an adequate therapeutic response to any agent but acetazolamide. Since crossover studies comparing acetazolamide with other antimyotonic agents have not been carried out, no true comparison of the efficacy of the several agents can be made. Although we do not propose that acetazolamide is necessarily the drug of choice for treatment of myotonia, it

should certainly be considered for the patient allergic to, intolerant of, or otherwise unresponsive to the usual antimyotonic agents.

Reported side-effects of acetazolamide include paresthesias [4, 16], anorexia [16], weight loss [16], renal failure [8], renal calculi [4, 18], osteoporosis [12], and hematological and hepatic dysfunction [16]. Paresthesias were observed in 5 of our 9 patients but resolved in the 1 patient continued on therapy when dosage was lowered. The higher frequency of paresthesias in these patients contrasts with a lower incidence observed in patients with hypokalemic periodic paralysis treated with acetazolamide [6].

One of the patients (No. 2) was found to have a renal calculus. The patient's dosage of acetazolamide was small (500 mg per day) and the treatment brief (six weeks), and since no baseline roentgenogram was available, the exact relationship of the renal calculus to therapy is uncertain. Nonetheless, the reported occurrence of renal calculi [4, 18] with acetazolamide suggests that an abdominal film should be obtained prior to treatment and followed sequentially if therapy is to continue on a long-term basis.

One of the patients with paramyotonia congenita (Patient 8) had a diminution in myotonia but developed quadriparesis within twelve hours of starting acetazolamide treatment [21]. This adverse effect was unanticipated and suggests that acetazolamide should be given with caution in this condition. The myotonia in a second patient with paramyotonia congenita improved during acetazolamide treatment and no weakness occurred. The 2 patients also differed in that only Patient 8 has had episodic attacks of weakness unassociated with cold. It is not otherwise clear from the clinical or metabolic data obtained on the 2 patients why their responses differed. Weakness during long-term acetazolamide treatment has been reported previously [10].

The mechanism of effectiveness of acetazolamide in myotonia is not known. The metabolic changes observed in our patients were those known to occur with carbonic anhydrase inhibitors [13, 16, 20]. A slight metabolic acidosis was observed in all patients studied. Although it has been suggested that metabolic acidosis is important in the therapeutic response to acetazolamide in hypokalemic periodic paralysis [9, 20], it is not known why acidosis would lessen myotonia. Studies with another agent producing acidosis, for example, ammonium chloride, such as have been done with hypokalemic periodic paralysis [6, 9, 24] might help clarify this possibility.

The observed lowering of serum potassium may relate to the decrease in myotonia following acetazolamide treatment. It is noteworthy that myotonia worsened, often to an extreme degree, with potassium administration in all our patients. A slight reduction in myotonia with decrease in serum potassium levels has been reported by others [11]. In recent studies of myotonia congenita [7] we have found that arterial potassium was elevated in the basal state (4.90 ± 0.17 versus 4.05 ± 0.05). Patients with myotonic dystrophy and paramyotonia congenita did not appear to have a similar elevation [7]. Since acetazolamide administration produces marked kaliuresis and a lowering of serum potassium, it is possible that changes in potassium balance or flux across muscle may be important in the beneficial response to acetazolamide. The observation that thiazide diuretics, which are also kaliuretic, improve myotonia [22] supports this possibility. Studies of patients with myotonia contrasting the response to thiazides and acetazolamide with that to potassium-sparing diuretics such as triamterene or spironolactone have not yet been performed but might be of interest with regard to this possibility.

Supported in part by grants from the Muscular Dystrophy Association, Inc, and US Public Health Service Grant RR 00044 from the Division of Research Resources of the National Institutes of Health.

We thank Mrs Gwendolyn Starks and the other nursing and technical staff of the Clinical Research Center.

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