The phenomenon of myotonia comprises a lingering relaxation of muscle after contraction, and a slow tonic response to stimuli of an electrical or mechanical nature. The condition may be ameliorated or even extinguished by repeated effort. Although well known and the commonest form of hereditary muscular disorder seen in young adults, it is, nevertheless, a rare condition.

Three distinct forms of the disturbance are recognized: (a) Myotonia congenita, where the disability exists in a simple form; (b) myotonia atrophica, in which the defect is associated with muscle wasting of typical distribution; and (c) paramyotonia congenita, a disorder in which myotonia and weakness are especially prominent on cooling and may be associated with muscle atrophy. It is doubtful whether the three conditions are in fact entities and there is much overlapping between them. The literature of these conditions has frequently been reviewed, most recently by de Jong (1956) and can probably best be summarized by saying that so far no unanimity has been arrived at either in describing the physiological or pathological factors underlying the condition or in arriving at a uniformly satisfactory method of treatment for the disability.

Liversedge and Newman (1956) reported on the satisfactory effect of cortisone in myotonia and concluded that it was probably due to a modification of the susceptibility of the muscle cell membrane to potassium ions. They were in doubt as to whether the actual elimination of potassium from the body was a factor. It was felt that this point could be further settled by a procedure specifically directed towards removing potassium, the more so since long-continued administration of cortisone is frequently accompanied by undesirable side-effects which may be serious (Allanby, 1957). It was decided to investigate the effect of a potassium-binding ion-exchange resin for this purpose. This method of treatment had previously been used by Grüttnер and Mertens (1953) in a case of myotonia congenita with satisfactory results but has not been reported before in Great Britain and there is no record of the results of treatment of a case of myotonia atrophica. Incidental investigation was made into the biochemical changes caused by exhibition of quinine and procaine amide as control substances.

Methods

Relaxation time was recorded by Chief Technician W. Glayzer using the method of Liversedge and Newman (1956) with surface electrodes and an eight-channel Ediswan electroencephalograph.

Muscle power was recorded under the direction of Squadron Leader Lough using a dynamometer.

Electromyography was carried out by Wing Commander P. R. Travers and Squadron Leader C. B. Wyndham Parry, M.B.E., of the Royal Air Force department of Physical Medicine, using concentric needle electrodes.

Total and differential blood counts, Wassermann and Kahn reactions, chest radiographs, E.C.G., E.E.G., and slit lamp examination of the eyes were carried out on admission.

Serum sodium, potassium, chloride, and bicarbonate levels were estimated twice weekly and calcium, phosphate, magnesium, cholesterol, urea, creatine, and creatinine once or twice weekly. Serum proteins, liver function tests, blood sugar and total lipid and phosphate fractions were also estimated on admission and a glucose tolerance test carried out. Urinary sodium and potassium were measured daily throughout the course of treatment and urinary creatine and creatinine, 17-oxosteroids, and total ammonia and titratable acidity estimated once weekly. The results of these tests are only included when thought significant.

Case Reports

Case 1.—An 18-year-old airman was referred to hospital after weakness in the muscles of the right forearm and hand had been discovered at a routine medical examination.

He stated that for several years he had experienced difficulty in keeping his mouth closed, especially when tired, and in addition his tongue appeared to "tighten up" after he had been speaking for some time. Further questioning revealed that a younger brother aged 12 had begun to experience similar symptoms. No other
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member of the family was affected as far as could be ascertained, and there was no familial history of cataract.

On examination he was a well-nourished boy with incipient frontal baldness, facial atrophy, and weakness of the peri-orbital muscles. The sternomastoids and shoulder muscles were grossly atrophic, giving him a swan-necked appearance. The muscles of both forearms and hands, particularly the right, were wasted and he had extreme difficulty in writing more than a few sentences. Myotonia was present in the muscles of both hands and he required several seconds to release his grip after a hand shake. Percussion myotonia of the tongue and shoulder muscles was elicited.

A chest radiograph, E.C.G., E.E.G., blood count, Wassermann and Kahn and slit-lamp examinations were all normal.

An electromyogram on February 18, 1957, on the extensors of the right forearm showed the classical picture of dystrophia myotonica. Exceptionally high frequency discharges on volition of small duration but normal amplitude were obtained. On tapping the muscle a prolonged outburst of high frequency discharges with a pronounced after-discharge was obtained. Similar but less obvious signs were seen in the right biceps.

The serum potassium level was 6 mEq./l., serum sodium 152 mEq./l., plasma chloride 107 mEq./l., plasma bicarbonate 31.2 mEq./l., blood urea 25 mg. per 100 ml.

The serum calcium level was 5.9 mEq./l., phosphate 4.1 mg. per 100 ml., magnesium 2.8 mg. per 100 ml., serum cholesterol 149 mg. per 100 ml., serum creatinine 1.16 mg. per 100 ml., and creatine 0.30 mg. per 100 ml.

The urinary sodium was 320 mEq. in 24 hours and potassium 115 mEq. in 24 hours. The output of 17-oxysteroids was 6 mg. in 24 hours and creatinine 1.5 g. in 24 hours. No creatine was present.

The fasting blood sugar was 75 mg. per 100 ml. and a glucose tolerance test gave a very flat curve. This was not due to glucose being delayed in the stomach as a barium swallow showed a normal rate of emptying.

Serum protein and liver function tests were normal and estimations of phosphate and lipid fractions gave results which were within normal limits.

The relevant findings on the case are charted in Fig. 1.

The patient was observed for four weeks and on April 4, 1957, potassium exchange therapy was started. The initial dosage of a bresolin A was 45 g. per day taken in three divided doses of 15 g. with meals. This was continued until April 18, 1957, when, as the serum potassium had dropped to 3.8 mEq./l. the resin was stopped for one day and then re-started in a dosage of 15 g./day. This dosage was continued until April 29,
1957, when the treatment was stopped as our attention had been drawn to the paper of Liversedge and Newman and we wished to use their method of measurement of myotonic time.

The strength of the hand grip was originally 12 lb., but under treatment it increased until it reached a maximum of 44 lb. on April 22, 1957. Thereafter it fell progressively with cessation of treatment to its previous level of 12 lb.

On May 18, 1957, treatment was started with quinine dihydrochloride as a control, given as one 5-grain tablet four times a day. At this dosage level the patient complained of tinnitus so the dosage was adjusted until the amount of quinine given was just below that which would cause tinnitus. This was found to be 15 grains per day and the patient was maintained on this until June 2, 1957. No subjective or objective relief was gained.

On June 10, 1957, a second course of potassium-binding resin was begun in a dosage of 30 g. three times a day. The duration of myotonia began to drop from values in the region of 6 to 7 sec. and the power of the right hand began to increase within a few days of the start of the treatment. On June 27, 1957, a second electromyogram was carried out with the following report:—

"On volition there were predominantly normal action potentials with only a very few typical high frequency discharges. Percussion of muscle produced only a transient increase in the rate of fibrillation and no true myotonia. The myographic picture appears to have changed to a marked extent as compared to that obtained on May 27, 1957."

Treatment was continued and by July 2, 1957, the patient was able to write sufficiently freely to sit a university entrance examination. The duration of myotonia had decreased to about two seconds and the power of his grip had risen again to a value in the region of 40 lb. On July 26, 1957, treatment was stopped.

During the periods of resin therapy there was a marked decrease in excretion of urinary potassium. In this time the patient did not become acidic, the bicarbonate level never falling below 25 mEq./l. and there was no change in serum or urinary levels of creatine and creatinine.

Case 2.—A 21-year-old airman was admitted to hospital complaining of stiffness of his hands and legs dating from early childhood. This stiffness was most noticeable when he attempted to move suddenly after a period of rest. Three months before admission he had a fall while playing cricket and on the following day he found he was unable to release his hand grip. As far as we could ascertain no other members of the family were affected.

On examination he was a well-built, muscular boy. He had myotonia in both hands and percussion myotonia could be demonstrated in the muscles of the forearms and shoulders. There was no measurable loss of power. The patient was not very cooperative and investigation and treatment were reduced to a minimum.

A chest radiograph, E.C.G., E.E.G., Wassermann and Kahn reactions, blood counts, and slit-lamp examination were all normal.

An electromyogram gave a classical picture of myotonia congenita.

The serum potassium level was 5.4 mEq./l., sodium 141 mEq./l., chloride 104 mEq./l., and plasma bicarbonate 23 mEq./l., serum cholesterol 210 mg. per 100 ml., and urea 33 mg. per 100 ml., serum calcium 5.7 mEq./l., inorganic phosphate 4.5 mg. per 100 ml., and magnesium 2.3 mg. per 100 ml.

The blood sugar was 90 mg. per 100 ml. and a glucose tolerance test gave a normal curve. Liver function tests and estimations of phosphate and the lipid fraction gave results which were within normal limits.

The urinary sodium was 191 mEq./24 hours and potassium 66 mEq./24 hours. The output of 17-oxosteroids was 2.1 mg./24 hours, creatinine 1.9 g./24 hours, and creatine 0.2 g./24 hours.

Treatment was started on June 24, 1957, with potassium-binding resin ("resonium A") in a dosage of 30 g. three times a day. The myotonia improved markedly within a short time, as shown in Fig. 2.

Subjectively the patient noted the stiffness in his legs had practically gone and he was able to release his grip much more easily than before. Percussion myotonia could no longer be elicited after three weeks of treatment, which was stopped on July 22, 1957. A second electromyograph was refused. The serum potassium and calcium levels dropped slightly but not to the same degree as in Case 1. No other biochemical changes were noted.
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Case 3.—An airman of 19 was admitted complaining of inability to release the grip of both his hands and of increasing stiffness in his jaw since the age of 16. His father was found to be suffering from the same disease, and in his case the symptoms appeared when he was aged 35.

On examination he was found to be a well-built youth. He had marked myotonia both in the jaw muscles and in the hands. Percussion myotonia could be demonstrated in the jaw, tongue, and both arms. There was no loss of power.

A chest radiograph, E.C.G., E.E.G., slit-lamp examination, Wassermann and Kahn reactions, and blood counts were all normal.

An electromyogram was carried out on July 4, 1957, with the following reports:

“A needle electrode was inserted into the flexor carpi ulnaris. Positive insertion potentials. At rest irregular fibrillation potentials with some sporadic isolated muscle potentials of up to 300 mv. was elicited and on volition profuse activity with high frequency potentials of up to 1,800 mv. Considerable after-activity continued for about seven to eight seconds after voluntary relaxation had begun. A myotonic response was obtained on percussion of a muscle belly. The changes were characteristic of myotonia.”

The serum potassium level was 4.9 mEq./l., sodium 136 mEq./l., chloride 111 mEq./l., plasma bicarbonate 28.8 mEq./l., blood urea 34 mg. per 100 ml., serum calcium 5.7 mEq./l., phosphate 4.5 mg. per 100 ml., magnesium 2.9 mg. per 100 ml., serum cholesterol 135 mg. per 100 ml., serum creatinine 1.1 mg. per 100 ml., and creatine 0.23 mg. per 100 ml. Liver function tests, serum proteins, and estimations of phosphate and lipid fractions were all within normal limits.

The urinary sodium was 238 mEq./24 hours, potassium 107 mEq./24 hours, 17-oxy steroids 8.3 mg./24 hours, creatinine 2.7 g./24 hours, and creatine 0.16 g./24 hours.

Treatment was begun on July 9, 1957, with procaine amide hydrochloride as a control in a dosage of 0.5 g. four times a day. On July 16, 1957, the dosage was increased to 3 g. daily but at no time were any beneficial results obtained and the therapy was stopped on July 19, 1957. Treatment with ion exchange resin was begun on July 21, 1957, in a dosage of 30 g. three times a day with steady response. This dosage was increased to 45 g. three times a day one week later with further improvement. Because of side-effects it was impossible to maintain the increased dosage of resin and it was decided to attempt to potentiate the effect of the lower dose of the resins by increasing potassium excretion. Diamox...
(acetazolamide) was given for one week for this purpose but proved ineffective. However, progress continued on the lower dosage. The patient found he could release his grip much more easily than before and the percussion myotonia could no longer be elicited. A second electromyogram was carried out on September 11, 1957, showing a very marked change in the myographic picture. (1) There was practically no insertion potential. (2) There was no electrical activity at rest. (3) There were very few high-voltage potentials on volition and the interference pattern was now almost normal. (4) Electrical activity died away within two or three seconds of voluntary relaxation. These changes showed a considerable return towards normality in the myographic picture.

The patient has been discharged on the resin and his improvement has been maintained. His father, who suffers from the same disease and has been treated with procaine amide, regards the improvement as so satisfactory that he wants to start taking potassium-binding resins himself.

**Discussion of Biochemical Results**

All three patients obtained objective and symptomatic relief from myotonia when treated with the potassium-binding resins.

The only biochemical changes of note obtained during therapy were in the serum potassium and calcium levels.

In Cases 1 and 2 (Figs. 1 and 2) the fall paralleled closely the clinical improvement of the patients as judged by a decrease in the degree of myotonia. On cessation of treatment on two occasions in Case 1, the serum potassium and calcium rose to their pre-treatment level as the myotonia returned.

In Case 3 there was no significant change in serum potassium or calcium level and yet the myotonia improved rapidly (Fig. 3). The explanation of this may be simply due to the fact that this patient was allowed home frequently and that the rise of serum potassium closely paralleled these visits, possibly due to the fact that the patient did not take the resins while at home. On the other hand, it may be that the action of these resins is not simply to lower extracellular potassium but also to the intracellular potassium. This would be followed by a movement of sodium into the cell and the relief of the myotonia might be due to alterations in the extracellular/intracellular ratio of sodium. Against this is the fact that neither in this case nor in the other two cases were there any changes in the serum sodium. To elucidate this point further, assays of intracellular potassium and sodium should be carried out during treatment with these resins.

The fall in serum calcium in Cases 1 and 2 was comparatively slight and it is improbable that by themselves these changes could cause any significant changes in the muscle excitability. There was also no significant alteration in the serum potassium/calcium ratio which could account for the clinical improvement in these cases.

None of the patients became acidotic, the plasma bicarbonate staying within normal limits in all three cases.

The urinary excretion of potassium was decreased in all the patients during resin therapy as illustrated in Case 1 (Fig. 4). Serum and urinary creatine amon.
creatinine levels showed no alterations during treatment.

No biochemical changes of significance were noted during treatment with quinine in Case 1 or procaine amide in Case 3.

Discussion

The relationship between muscle function and potassium has recently been reviewed by Grob, Liljestrand, and Johns (1957), and they point out that the resting potential difference in muscle cell membrane is principally related to the difference of potassium concentration between the inside and outside of the cells. This resting potential difference largely determines the excitability of the muscle since the lower the resting potential the more easily it is depolarized and vice versa.

In myotonic muscle the intracellular potassium may be reduced by as much as one half (Cumings, 1939). In the presence of a normal extracellular (serum) potassium level it is apparent that the resting potential of such muscle will be materially lowered and the muscle show increased excitability. Since the ratio in man between intra- and extracellular potassium is roughly 30 to 1 and the dependence of resting potential on the potassium differential is a logarithmic one (Ling and Gerard, 1949), a small lowering of extracellular potassium can compensate for a marked change in the intracellular content. It has, moreover, been shown by Flear, Cooke, and Quinton (1957) that there is no interdependence between the exchangeable body potassium and the serum potassium, so that quite wide variations in intra- and extra-cellular movement can take place without any linked effect.

In our experiment which resulted in a decrease of extracellular potassium it seems reasonable, therefore, to assume little change in the decreased intracellular potassium and to explain the decrease of myotonic irritability as being directly due to a reduction of muscle excitability. That this is a fundamental factor is supported by the fact (Norris and Chatfield, 1955) that action potentials which entirely parallel those found in myotonia may be seen in the pure dystrophies and in denervated muscle, in which the intracellular potassium may be similarly reduced. At our request Wing Commander Travers carried out the following experiment.

The arm and hand of a normal control were immersed in cold water at 40° F. until cramp was produced by voluntary effort.

"Normal interference pattern with inlays of short duration potentials were seen. These resembled those in untreated myotonia. On allowing the limb to warm up the myograph tracing returned to normal and no cramp was experienced."

The effect of cold is decremental of intracellular potassium and is the trigger factor in the variety of the condition known as paramyotonia. It is our contention that the basic factor in myotonia is an alteration in muscle excitability due to shift in the potassium ratio, and that similar electrical findings can be demonstrated in muscle whenever minimal excitability occurs either for physiological or pathological reasons.

There are, however, certain distinctive features in myotonia which cannot be accounted for on this simple basis. First, in our experiment the power of muscle action in the case of dystrophia myotonica showed an increase with treatment and resulting decreased muscle excitability. The work of Grob, Johns, and Harvey (1957) demonstrated that in normal muscle increased muscle excitability resulted in increased power. Secondly, the same authors found that exercise resulted in a decrease of intracellular potassium. It would be expected, therefore, that repeated contractions of myotonic muscle would cause a similar lowering of intracellular potassium with heightened excitability and exaggeration of the myotonic response. The contrary is the case and the myotonic state works off with repeated movement. Thirdly, the specific action of myotonic muscle which is seen clinically as a symptom and electrically as "dive bomber" potentials has no parallel in the other conditions of lowered intracellular potassium. It is apparent that these distinctive features occur only under conditions of stimulation of the muscle either by nervous impulse or mechanical stress.

The action of both these stimuli is mediated by the release of acetylcholine and we suggest that the specific factor in myotonia is a defect in acetylcholine action. The action of acetylcholine in producing muscle contractions depends on two factors. First the excitability of the muscle, and secondly the available concentration of acetylcholine. In the presence of the state of easy depolarization produced by a low intracellular/extracellular potassium ratio, the initial clinical myotonic response to release of acetylcholine by stimulus is easy to understand. The particular phenomenon of working off could be explained if a mechanism existed whereby acetylcholine in excess was initially made available by stimulus and the source rapidly exhausted. This could presumably occur if myotonic muscle had an intrinsic defect of acetylcholine binding power comparable to that demonstrated in epileptic cerebral cortex (Tower, 1952).

It remains to comment on our finding of increased muscle power in the case of myotonia atrophica concurrent with decreased muscle excitability. Grob et al. (1955) showed that in the presence of
free acetylcholine muscle fails relatively in its ability to contract within half a minute, possibly by the setting up of a non-polarizable block and that this may last for up to half an hour. If we are correct in our assumption of an excess of free acetylcholine in myotonic tissue the loss of power can be accounted for by such a mechanism.

Summary

Two cases of myotonia congenita and one case of myotonia atrophica were treated with potassium-binding resin and showed objective and subjective relief.

Myotonia was greatly diminished in all cases and the abnormal electromyograms restored to normal form. In the case of myotonia atrophica the muscle power was greatly increased.

An explanation of the results is offered on the basis of the effect of potassium on the resting cell potential.

A hypothesis is advanced as to the pathology of the condition.

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