CORTICOSTEROID MYOPATHY*

BY

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Since its description Cushing (1932) a high incidence of muscle weakness has been reported in spontaneous hypercorticism. Plotz, Knowlton, and Ragan (1952) noted an incidence of over 50 per cent. in 222 patients and Müller and Kugelberg (1959) confirmed the presence of a myopathy electromyographically. Experimental muscle lesions have been produced in rabbits fed large doses of cortisone (10 mg./kg. body weight: Ellis, 1956), and myopathy complicating therapy has been frequently reported in human beings and attributed to cortisone, prednisolone, triamcinolone, and dexamethasone (Harman, 1959; Golding, Murray, Pearce, and Thompson, 1961) although compounds containing a fluorine atom in the 9α-position appear to produce the highest incidence. In fact Walton (1964) felt that triamcinolone should not be used on this account.

The relationship of dosage of steroid to incidence of myopathy is undetermined. Perkoff, Silber, Tyler, Cartwright, and Wintrobe (1959) reported six patients with myopathy after ACTH and prednisolone therapy, and concluded that affected patients had, on the whole taken a large dosage over a long period, but from their data no definite rules emerged and it was clear that there was no simple linear relationship between the quantity taken and the development of myopathy.

The present study has been undertaken to investigate electromyographically what factors are involved in the production of steroid myopathy.

Methods

Technical Data of the Equipment

The electromyograph was a twin-channel standard rack-mounted Medelec, with a ruler-type time-base giving 10 and 1 msec. divisions. The input impedance of the amplifier was 2 megaohms with 50 picofarads, in parallel with an inphase rejection ratio of 1:1000 at a kilocycle per second (kcps). The frequency response from 3 DB points (1/√2) was from 1·6 cps at the lowest to 5 kcps at the highest with the time constant at 100 msec. The needles were standard Medelec electrodes with a leading off core of 0·34 sq.mm.

Technique

This was a modification of the statistical analysis of muscle action potentials as recorded by Buchthal and Clemmesen (1941), Buchthal, Guld, and Rosenfalck (1954), Yates (1963). A concentric needle electrode was inserted into the deltoid, this muscle was easy to examine and likely to show evidence of a limb girdle myopathy. Minimal active abduction of the arm allowed separate action potentials to be seen and photographed. When a suitable potential had been recorded the needle was moved to another area of the muscle and the procedure repeated until about twenty separate potentials were available for analysis. As each potential appeared the camera was started, the film paper (Kodak RP 30) running at right angles to the oscilloscope at 1 in. per second. The repetition rate was three per sec. and the time-base of 30 msec. for one sweep.

With these settings one msec. was equivalent to just under one mm. of horizontal deflection. When the film was developed the tracings appeared vertically one above the other about 1 cm. apart and with an amplification set at 100 μV or 250 μV per cm. individual potentials did not interfere with each other. With practice twenty or more separate potentials could be recorded two or more times on 12 to 15 feet of film paper. The variation between duplicate records in this study was up to 8 per cent., a little larger than but of the same order as that reported previously (Buchthal and others, 1954; Yates, 1963).

The measurement taken from the recorded potentials was from the take-off from the base-line to the return. If the base-line was not flat, then the record was discarded. When twenty or more potentials had been measured, the mean was calculated and this was defined as the mean potential duration (MPD).

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Patients

64 patients with rheumatoid arthritis and one with ankylosing spondylitis were investigated. All had complained of pain around the shoulder region at some stage of their illness; 51 were being treated with prednisolone and fourteen with a combination of aspirin and chloroquine; of these patients seventeen had some active disease of the shoulder joint or shoulder girdle whilst 34 had no such disease that was clinically apparent.

These patients were compared with 33 normal controls from differing age groups.

The patients who were taking prednisolone were split into three groups according to the degree of hypercorticism, using a modification of the scheme suggested by Popert (1962). The mildly affected patients showed a slight degree of facial mooning only, while the moderately affected patients had obvious mooning together with bruising, subconjunctival oedema, striae, or increase in facial hair; the severely affected had most of the features of Cushing’s syndrome, including severe osteoporosis with or without vertebral collapse.

Normal Controls

The age distribution of the 33 normal controls ranged from 15 to 70 yrs (median 41). No difference was detected between the sexes, but the MPD rose from 10.2 msec. at 20 years to 11.2 msec. at 70 years (mean for whole group 10.8). The regression line is very similar to that of Yates (1963) based on the examination of 28 normal subjects (Fig. 1 and Table I).

No obvious difference was found between the potentials recorded from the deep or superficial parts of the muscle (superficial potentials being those recorded 1-2 cm. under the skin). This agrees with the findings of Moritz (1963), but not with those of Buchthal and others (1954) who found some difference and attributed it to a reduction of the leading off area of the cannula of the needle in the superficial parts of the muscle. As far as possible the

![Graph](image)

Fig. 1.—Mean potential duration of deltoid muscle by age in 33 normal persons with a straight regression line fitted according to the equation MPD (msec.) = 9.701 + 0.026 years of age.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Persons</th>
<th>Hypercorticism</th>
<th>Mean Age (yrs)</th>
<th>Mean MPD ± 99 per cent. fiducial limits (msec.)</th>
<th>P of Difference of Mean MPD from Normal Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Persons</td>
<td>33</td>
<td>—</td>
<td>41.0</td>
<td>10.8 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>Not on steroids</td>
<td>14</td>
<td>—</td>
<td>53.0</td>
<td>10.6 ± 0.5</td>
<td>&lt;0.60 (not significant)</td>
</tr>
<tr>
<td>Patients with Rheumatoid Arthritis or Related Disease</td>
<td>51</td>
<td>None or Mild 34 Moderate 12 Severe 5</td>
<td>50.3 51.2 51.6</td>
<td>10.1 ± 0.3 8.9 ± 0.4 7.7 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
very superficial parts of the muscle were avoided in this study (less than 1 cm. deep) so that possible variation from this source was not encountered.

**Definite Myopathies**

For purposes of comparison eight patients suffering from definite myopathies with muscle weakness were examined (median age 32·7 years, range 16 to 50); three patients had severe thyrotoxicosis, one had Cushing's syndrome, two had Duchenne muscular dystrophy, and two had polymyositis. All MPDs were well below the normal 99 per cent. fiducial limits, mean 7·7 msec. (Fig. 2 and Table II).

**Table II**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age (yrs)</th>
<th>MPD (msec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyrotoxicosis</td>
<td>50</td>
<td>8·0</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>8·6</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>8·4</td>
</tr>
<tr>
<td>Muscular dystrophy</td>
<td>16</td>
<td>7·3</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>6·3</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>25</td>
<td>7·7</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>7·3</td>
</tr>
<tr>
<td>Cushing's disease</td>
<td>30</td>
<td>8·0</td>
</tr>
<tr>
<td>Mean</td>
<td>32·7</td>
<td>7·7</td>
</tr>
</tbody>
</table>

**Mean Potential Duration and Muscular Weakness Correlated with Active Local Disease**

All the patients with weakness of the deltoids were divided into two groups, regardless of steroid therapy, depending upon clinical evidence of active arthritis in the shoulder region. Active arthritis was defined as pain with or without limitation of the shoulder joint or shoulder girdle. The individual MPDs were compared with normal (Fig. 3). Only six patients had values in the normal range and five of these had some evidence of active local disease, while the rest of the patients had results throughout the myopathic range and with no difference between the groups. Thus it would appear that active joint disease can give rise to weakness which is not myopathic in type, but the combination of muscle weakness together with a low MPD must indicate a myopathic change.

**Fig. 3.—Mean potential duration of deltoid muscle in 28 patients with shoulder girdle weakness.**

**Patients with Rheumatoid Arthritis and Ankylosing Spondylitis**

(a) Not taking Corticosteroids (fourteen patients with rheumatoid arthritis).—All fourteen patients complained of pain in the shoulder region at some time during their illness; nine had symptoms or signs of a shoulder lesion at the time of examination and three of these had shoulder girdle weakness, all their MPDs fell within the normal range. The mean MPD for the whole group was 10·6 msec. SE ± 0·5 (median age 53 years, range 27 to 67). Although the age distribution is not identical with that of the normal controls, the mean MPD does not differ significantly (Fig. 4, overleaf, and Table I).

(b) Mildly Hypercorticol (34 patients with rheumatoid arthritis).—Although most of the MPDs of this group fall within the normal 99 per cent. fiducial limits, all the readings lie below the normal regression line (Fig. 5, overleaf and Table I). The mean is 10·1 msec. SE ± 0·3, and this difference compared with normal is highly significant (P <0·001). 25 of the 34 patients were 50 years old or more (median age 50 years, range 27 to 67). Owing to the small sample of younger patients it is not possible
to construct a valid regression line for the group, but these data suggest that older patients tended to have their MPDs depressed more than the others by corticosteroids. Eight patients had weak deltoid muscles, but since only two of these had clinically normal shoulders this weakness was considered unlikely to be true muscle weakness.

The duration of administration of corticosteroid varied from a few months to more than 5 years (mean 26.2 mths) (Fig. 6, opposite). Conventional laboratory investigations included haemoglobin, white cell count, erythrocyte sedimentation rate, and serum titre of rheumatoid factor, none of which bore any relationship to muscle weakness or to MPD.

(c) Moderately Hypercorticoid (twelve patients with rheumatoid arthritis).—All of these patients had clinical shoulder weakness but in seven the shoulders (joints and girdles) were clinically normal. Ten had MPDs well below the normal 99 per cent. fiducial limits and only two patients fell within the normal range. The mean MPD was 8.9 msec. \( \text{SE} \pm 0.4 \) (Fig. 7, opposite, and Table I). The median age for the group was 51.2 years (range 37 to 63). This mean MPD gives a highly significant difference from normal \( (P < 0.001) \). This group is smaller than the previous one and in contrast the values showed no tendency to fall in the older patients.
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The duration of corticosteroid administration treatment varied from a few months to over 5 years (mean 26·2 mths) (Fig. 6). The conventional laboratory investigations, haemoglobin, white cell count, erythrocyte sedimentation rate, and titre of rheumatoid factor in the serum showed no correlation with muscle weakness or with MPD.

(d) Severely Hypercorticoid (four patients with rheumatoid arthritis and one with ankylosing spondylitis).—These patients were much weaker than the others and often had difficulty in sitting upright; only two of them had completely normal shoulders (median age 51 years, range 38 to 65). The MPDs were much below the lower limits of normal, with values similar to those of the myopathic patients (mean 7·7 msec. SE ± 1·4). As with the other corticosteroid treated patients this difference, compared with normal, is highly significant (P < 0·001) (Fig. 7 and Table 1).

Like the mildly hypercorticoid patients, this group shows an apparent fall in MPD with age, the oldest patients having the lowest values. But this sample is too small to draw valid statistical conclusions. The dosage of prednisolone varied and was of the same order as in the other groups (mean 18 mg. daily) (Fig. 8, overleaf), but, turning to consider the duration of administration (Fig. 6) these patients had been receiving corticosteroids for longer than the others and, although the numbers are small, the mean of 43 months may have some bearing on the muscle weakness. As with other groups the laboratory investigations showed no correlation with MPD or muscular weakness.

Discussion

Muscle weakness due to corticosteroid myopathy is often difficult to assess by clinical methods because of local joint deformity and pain. The most convenient, and probably the most reliable, technique is electromyographic. Measurement of MPD has its drawbacks, for it can be tedious both for the patients and for the examiner, but it is reasonably accurate and certainly better than assessment of the motor unit pattern.
Why corticosteroids produce myopathy is not clear, but such changes may result from their general katabolic action on a wide variety of tissues in general and on muscle in particular. Biopsy reports on patients with a low MPD have been disappointing; Yates (1963) found no specific histological changes using conventional techniques. Golding and others (1961) found fragmentation of myofibrils, disruption of the sarcoplasmic reticulum, and enlarged mitochondria in specimens examined under the electron microscope, but did not consider these changes specific. Shortening of the motor unit action potential duration in myopathy has been attributed to a reduced motor unit area and a falling out of individual muscle fibres (Buchthal, Rosenfalck, and Erminio, 1960) and this seems to be the most likely explanation.

One very important point to establish is that local disease in a neighbouring joint does not affect the MPD. In this study all the patients with rheumatoid arthritis not taking corticosteroids fell within the normal range. Amick (1960) also found no difference from normal in MPD of the hand muscles in patients with active local arthritis; and in a similar study on the deltoid muscle Yates (1963) found no lowering of the MPD in the presence of active arthritis of the shoulder. However, in the latter series, the MPD was depressed in those patients who were having corticosteroid therapy or suffering from coincidental thyrotoxicosis with muscle weakness. Moritz (1963), on the other hand, concluded that there was a correlation between active local joint disease and lowering of the MPD, but when his data were examined it appeared that for the deltoid muscle he had only eleven controls and it was not clear which of his affected patients were taking corticosteroids. Even if one accepts Moritz's findings that the MPD is depressed by active local disease, these would be marginal compared with those recorded in many of the hypercorticoid patients of this study.

In the patients taking corticosteroids the apparent lowering of MPD with age (Figs 5 and 7) is not convincing, since each group is too small to allow statistical analysis. However, if these 51 patients are compared with normal, the older patients (with the exception of two in their sixties who were grossly hypercorticoid) behaved substantially the same as the younger ones. The conclusions must be that the apparent differences are due to selection rather than to a different reaction, and that older patients are not more likely to develop myopathy than younger ones.

Although clinical grading of hypercorticism is not easy, it did seem to correlate well with corticosteroid myopathy. A quantitative measurement would be desirable but no adequate indices are available. 24-hour 17-ketogenic steroid excretion is little better than clinical assessment. The measurement of urinary cortisol excretion after a loading dose of hydrocortisone (Popert, Grayzel, Longson, and Gowenlock, 1964), although an excellent test, is complicated and not yet a practical proposition in the ordinary circumstances of hospital practice.

Some of the patients in this series were taking very large quantities of corticosteroid (up to 110 mg.
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prednisolone daily) without developing signs of hypercorticism. Since it is the circulating excess that produces the side-effects, clearly these patients must be utilizing corticosteroid in a way which differs from normal (Grayzel and Longson, 1964). There are several possible explanations for this:

1. Patients with rheumatic disease may bind more steroid to protein than normal but there is some evidence against this. Sandberg and Slaunwhite (1959) found the binding capacity of transcortin (the α globulin concerned with cortisol binding) in four patients with rheumatoid arthritis to be somewhat raised but within normal limits, and Chen, Mills, and Bartter (1961) found that prednisolone was bound to a lesser extent to protein than was cortisol.

2. Renal defect could account for a high circulating steroid level, but in renal failure the plasma concentration of non-metabolized cortisol is normal (Beisel, Di Raimondo, and Forsham, 1964).

3. Corticosteroid could be undergoing metabolism at various additional sites in rheumatic disease. Dougherty, Berliner, and Berliner (1961) have shown that reticulo-endothelial cells, fibroblasts, and lymphocytes all metabolize corticosteroid to varying degrees and such cells are found in abundance in inflammatory tissue.

Thus, a patient with very active and widespread inflammatory disease may tolerate a dosage much higher and for much longer than another less severely affected (Popert and others, 1964). It is the steroid that is left over that produces the hypercorticism of which myopathy is one feature. This is similar to the situation in spontaneously occurring Cushing’s syndrome.

The point that emerges from this study is that there is no fixed dose or duration of administration above which prednisolone is likely to produce myopathy. Although the severely hypercortioid patients had been on the average taking prednisolone for longer than the others, only five were available for examination, so this finding may well be misleading and it would be wrong to incriminate any definite time period. For example, one patient in the mildly hypercortioid group, a woman of 52 years with rheumatoid arthritis had been taking prednisolone continuously for 5 years without developing myopathy and her MPD was 10.4 msec.

—well within the normal range.

How long a patient can tolerate a hypercortioid state before developing muscle weakness is another question which the present data cannot answer. However, it can be concluded that, if clinical hypercorticism is present, then the MPD will be reduced (a yardstick of incipient myopathy) and if the hypercorticism worsens then the MPD will fall even lower and the muscle weakness will progress pari passu.

Summary

1. Corticosteroid myopathy has been measured electromyographically, using the mean potential duration of the deltoid muscle as the parameter of measurement.

2. The normal range was defined by examination of 33 healthy persons of various ages.

3. Eight patients with myopathy were examined to confirm that MPD was lowered in this condition.

4. Twelve patients suffering from rheumatoid arthritis, with or without evidence of disease in the shoulder joint or shoulder girdle, had the MPD measured on the deltoid muscle. Since all fell within the normal range it seems that local joint disease does not lower MPD.

5. Fifty patients with rheumatoid arthritis and one with ankylosing spondylitis, all taking corticosteroids (prednisolone), were examined; their hypercorticism was classified clinically into three degrees as mild, moderate, or severe. The MPD was lowest in the group of patients with the severest degree of hypercorticism. Dosage levels and the duration of administration of corticosteroids did not appear to be directly related to lowering of MPD.

I wish to thank Prof. J. H. Kellogg for allowing me to examine many of his patients and Dr. F. R. Ferguson for permission to use his patients as controls. I also wish to thank Miss F. Bier for her help with the statistical analysis and Dr. R. Ollerenshaw for the illustrations.

REFERENCES


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Discussion
Dr. A. St. J. Dixon (London): This was a most beautifully illustrated paper. Were you able to read the tracings "blind"?
Dr. COOMES: Yes.
Dr. W. A. BOURNE (Brighton): How much does this apparatus cost?
Dr. COOMES: £2,000.
Dr. D. A. H. YATES (London): In these endocrine myopathies there may be loss of intramuscular protein. Do you know if anabolic steroids prevent steroid myopathy?
Dr. COOMES: I have been able to study six patients who were taking part in an Arthritis and Rheumatism Council trial of anabolic steroids. Three were taking anabolic steroids and three were not. All had a low mean potential duration and anabolic steroids had no effect on the myopathy.

Myopathie corticostéroïde

RÉSUMÉ
(1) La myopathie corticostéroïde fut mesurée électromyographiquement en se servant de la durée moyenne du potentiel (mean potential duration = MPD) du muscle deltoïde comme paramètre.
(2) L’écart normal fut défini par l’examen de 33 sujets normaux de différents âges.
(3) Huit malades atteints de myopathie furent examinés pour confirmer la basse valeur de la MPD dans cette affection.
(4) Douze malades souffrant d’arthrite rhumatismale, avec ou sans atteinte de l’épaule, furent soumis à la même épreuve portant, comme chez les autres, sur le muscle deltoïde. L’écart normal des résultats semble montrer que la maladie articulaire locale ne fait pas baisser la MPD.
(5) On examina cinquante malades atteints d’arthrite rhumatismale et un malade souffrant de spondylarthrite ankylosante, tous traités par un corticostéroïde (prednisolone). Leur hypercorticisme fut classifié cliniquement en trois grades: benin, modéré et sévère. La MPD fut la plus basse dans le groupe des malades atteints de l’hypercorticisme le plus sévère. La dose et la durée de la thérapie corticostéroïde ne semblaient pas se rapporter directement à la baisse de la MPD.

Miopatia corticosteroide

SUMARIO
(1) La miopatía corticosteroide fue medida electro-miográficamente sirviéndose de la duración media del potencial (mean potential duration = MPD) del músculo deltoide como parámetro.
(2) Los límites normales fueron determinados por el examen de 33 sujetos normales de varias edades.
(3) Ocho enfermos con miopatía fueron examinados para confirmar el valor bajo de la MPD en esta condición.
(4) Doce enfermos con artritis reumatoide, con o sin el compromiso del hombro, fueron sometidos a la misma prueba, también en el músculo deltoide. Los límites normales de los resultados parecen mostrar que la enfermedad articular local no hace bajar la MPD.
(5) Se examinaron cincuenta enfermos con artritis reumatoide y uno con espondilartitis anquilosante, todos tratados con corticosteroides (prednisolona). Su hiper-corticismo fue clasificado clínicamente en tres grados: benigno, moderado y grave. La más baja MPD fue encontrada en el grupo de enfermos con el hiper-corticismo más grave. La dosis y la duración de la terapia no parecían relacionarse directamente con la baja de la MPD.
Corticosteroid myopathy.

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