CORTICOTROPHIN AND CORTISONE THERAPY IN DERMATOMYOSITIS

BY

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The first report of the treatment of acute dermatomyositis by corticotrophin was published in 1949 by Elkinton and his colleagues; it described the case of a moribund 5-year-old boy suffering from the disease which remitted after a four-weeks course of corticotrophin, following on two shorter unsuccessful trials. Thorn *et al.* (1950), in their paper on corticotrophin and cortisone, mentioned three cases, in two of which improvement occurred. This was not sustained according to Wedgewood *et al.* (1953), who described 10 cases and concluded that a cure by these hormones may be expected in the acute case only.

The following three instances demonstrate success and failure from the use of corticotrophin in this condition.

Case 1

A woman aged 30 was admitted to hospital on January 12, 1955, with a four days' history of sore throat, profuse sweating, mild rigors, general malaise, and cramp-like pains. The latter began in the calves and later spread throughout the legs, also involving the shoulders, neck, arms, wrist, and fingers; this was accompanied by an erythematous rash on the upper limbs and face. The patient stated that a painful bilateral swelling had occurred in the wrists and in the first and second metacarpo-phalangeal and inter-phalangeal joints, but this was not evident on admission. Three weeks previously the patient had developed an upper respiratory infection, which persisted until the present illness.

The past history included scarlet fever at the age of 5 and very frequent sore throats as a child. The patient's last period was on December 1.

Examination showed a very ill woman, who remained motionless because of the painful musculature; temperature 99.8° F. (37.7° C.); pulse 106. An erythematous macular rash was present on the extensor aspects of the fingers, hands, forearms, and shins. Bilateral muscular tenderness was elicited in the upper trapezius, sternomastoids, upper arms, and quadriceps; there was also some tenderness at the dorsum of the right wrist and in the right calf and abdominal musculature. There were no contractures except for some limited flexion of the right wrist. Vaginal examination was negative.

Investigations.—Chest x-ray examination negative. Electrocardiogram, abnormally low T waves in all leads. Urine: albumin +; 24-hour urinary excretion of creatine, 120 mg. Haemoglobin, 13.1 g./100 ml.; white-cell count, 27,550 per c.mm. (polymorphs 91%, lymphocytes 9%). Plasma proteins, 7.4 g./100 ml. (albumin 3.8 g., globulin 3.6 g.). Biopsy of right biceps muscle showed normal tissue.

A preliminary trial with salicylates, penicillin, and chlor-tracycline proved fruitless. The disease progressed rapidly with a steadily rising temperature; wasting and weakness became evident in the muscles of the shoulder-girdles, arms, flexor aspect of the forearms, small hand muscles, thighs, and especially in both calves; the latter showed extreme contractures which, together with some anterior tibial weakness, resulted in bilateral foot-drop. The knee-jerks became absent and the ankle-jerks weakened.

On January 23, with a temperature of 105° F. (40.6° C.) and a pulse of 120, corticotrophin gel, 60 mg. twelve-hourly,

was given. A response occurred within twelve hours, when the temperature became normal and the pulse fell to 90. On the following day muscle tenderness disappeared, the knee-jerks returned, there was more movement at the ankles, and the rash was resolving. Some vaginal bleeding occurred, and blood clots were passed; vaginal examination (Mr. H. R. Arthur) was negative, and it was thought to be a delayed menstrual period. This was followed by a recurrence twelve days later and a foetal abortion on February 10, accompanied by marked shock due to blood loss. The patient was transfused with 4 pints (2.3 litres) of blood, and rapid recovery ensued. The abortion took place two days after an attempt to reduce the corticotrophin, which was accompanied by a rise in temperature and a recurrence of muscular weakness. These symptoms cleared on reinstituting the original dose of 60 mg. twelve-hourly.

After thirty days' treatment with corticotrophin the patient was feeling very well; a Cushing-like physique had developed, with a brown pigmentation on the face, upper limbs, and trunk; transient hypokalaemia was treated by added potassium chloride. Muscle contractures were absent, but some wasting was still evident. The leucocytosis was still present, but soon began to resolve. The corticotrophin dosage was reduced gradually by 5 mg. daily and was finally stopped on April 15; total dosage was just under 5 g. A further electrocardiogram proved normal. At the follow-up nine months later the patient was healthy with a normal musculature and a gradually resolving Cushing-like facies.

Case 2

A 49-year-old woman was admitted to hospital on February 25, 1955. A two-months history of increasing evening lassitude included five weeks in which she suffered from severe myalgia. Initially there was dull pain in the right calf on walking, followed by involvement of the left. The pain increased in severity and was present on resting, until she was unable to rest her calves on the bed because of great tenderness which caused insomnia. An occasional rigor occurred and a productive cough developed. Two weeks before admission similar pain appeared in the arms, affecting the triceps muscles especially.

Examination showed a cheerful but exhausted thin pale woman with an extremely high malar flush and early clubbing of the fingers; temperature 101° F. (38.3° C.); pulse 98. She was coughing up about 6 fl. oz. (170 ml.) of purulent sputum daily. The lungs demonstrated extensive coarse crepitations at both bases, especially on the right side. Great bilateral tenderness was present in the biceps, forearm, and calf muscles, the latter obviously being very wasted.

Investigations.—Chest x-ray examination and electrocardiogram normal. Sputum: mixed flora, no acid-fast bacilli present. Urine examination normal. Haemoglobin, 9.1 g./100 ml.; white-cell count, 19,350 per c.mm. (polymorphs 88%, lymphocytes 6%, monocytes 6%). Plasma proteins 5.3 g./100 ml. (albumin 2.75 g., globulin 2.55 g.).

Transient pain in the left arm with weakness of the hand appeared on March 8, followed two days later by a sudden sharp pain in the same area, extending from shoulder-tip to wrist and lasting four hours; this was succeeded by bilateral paraesthesiae in the dorsal and palmar surfaces of the hands and fingers, especially the left. A bilateral palmar erythema simulated that of hepatic failure, but other clinical evidence of this entity was absent and liver-function tests, including alkaline phosphatase, thymol turbidity, zinc sulphate, flocculation, and van den Bergh, proved normal. On March 16 the upper limbs showed wasting of the upper arm musculatures and thenar eminences; muscle contractures of both elbow-joints, with painful extension limited to 160 degrees; and painful limited flexion of the left wrist at 120 degrees. General muscular weakness and lower-limb wasting greatly increased and the skin was very dry and scaly. An easily evident lesion of the lower motor neurone developed in both hands; this was pronounced in the left hand, which showed a progressive main-en-griffe. X-ray

examination of the cervical vertebrae showed marked spondylosis, which was thought to have caused the nerve lesion. Biopsy of both biceps muscles showed a non-specific change—namely, some atrophy of the muscle fibres and patchy sarcolemmar nuclear proliferation; skin biopsy proved normal. Three-day urinary creatine-creatinine estimation was within normal limits, but, as the daily figures diverged widely, it is thought that the collection of specimens was incomplete and therefore meaningless.

Simultaneously with the above course of events the administration of penicillin, streptomycin, or chlortetracycline did not seem to affect the general illness or the sputum, which was produced in quantities of 4 fl. oz. (114 ml.) daily. Atelectasis of the left lower lobe occurred; this was resolved by bronchoscopy. There was never any evidence of lung abscess or empyema, and thus the purulent sputum originated in the bronchial tree. The temperature ranged from 99 to 100° F. (37.2 to 37.8° C.), and the pulse rate remained around 90 a minute; anaemia and leucocytosis persisted. A second trial with streptomycin, 1 g. twelve-hourly, was begun on March 25 and continued while the patient was on corticotrophin; the disease did not alter during the initial week on this antibiotic.

On March 31 corticotrophin gel, 60 units twice daily, was given intramuscularly. In forty-eight hours the patient was afebrile and greatly improved symptomatically. Lower-limb tenderness disappeared; the upper limbs became less painful, until pain was limited to the left hand; and the elbow-joint contractures resolved in one week. The patient was maintained on corticotrophin for thirty-four days, receiving 2.2 g. in all, the dose being gradually decreased after an initial seven days. A further atelectasis of the left lower lobe occurred; it was re-expanded by bronchoscopy, which revealed no intrabronchial disease (Mr. W. C. Barnsley).

On stopping the corticotrophin recovery was complete, except for some paralysis and wasting of the small muscles of the left hand, which resolved on physiotherapy over a period of some months. The sputum decreased rapidly and eventually cleared. Nine months later the patient had gained weight and remained symptom-free.

Case 3

A woman aged 47 was admitted to hospital on February 18, 1955, with a history of aching limbs, accompanied by an erythematous rash for four months, and painful swelling of both arms, with limited movement for six weeks; she was bed-ridden for this latter period. The menopause had occurred at the age of 44 and a recent curettage for vaginal haemorrhage proved negative.

On examination the patient was grossly weak and unable to sit up in bed unsupported; temperature 100° F. (37.8° C.); pulse 116. There was a generalized scaling facial erythema, but this was only mildly evident in the peri-orbital areas; it principally involved the sides of the neck and V area of the chest, was present slightly under the chin, and was accompanied by some retro-auricular scaling and pityriasis capitis. The dorsa of the hands and fingers were erythematous, with multiple small telangiectasia in the nail-folds and dyskeratosis of the cuticles. A marked symmetrical oedema was present in both arms from the mid-brachial area distally, and mild oedema was found in the sacral and lower-limb areas. Tenderness of the upper-arm and thigh muscles was evident and most of the limb muscles were very weak—namely, sternomastoids, upper trapezius, abductors and adductors of shoulders, flexors and extensors of elbows, small muscles of hands, hip-joint flexors, quadriceps, and hamstrings; the calf and anterior tibial muscles were weak to a less extent, and bilateral elbow-joint contractures limited extension to 135 degrees; thus the patient was unable to lift hand to mouth, flex neck on chest, or elevate legs off the bed.

Investigations.—Chest x-ray examination negative. Electrocardiogram normal. Urine: albumin +; three-day urine creatine-creatinine excretion in mg.: 830, 582, 698, 499, 738, and 421, respectively. Haemoglobin, 12.3 g./100

ml.; white-cell count, 9,100 per c.mm. (polymorphs 72%, lymphocytes 23%, monocytes 5%). Plasma proteins, 6.2 g./100 ml. (albumin 3.4 g., globulin 2.8 g.). Plasma electrolytes and blood urea were normal. Biopsy of right biceps muscle: "Marked muscle oedema, with a little diffuse and some focal infiltration with lymphocytes, atrophy of some muscle fibres, with quite marked sarcolemmar nuclear proliferation."

Treatment with corticotrophin gel, 60 mg. twelve-hourly, was begun on February 26. An instantaneous improvement occurred; the temperature and pulse fell to 98.4° F. (36.9° C.) and 84 respectively, and the rash started to disappear. The patient became very cheerful and her general condition gradually improved, although the muscles remained as previously, with the exception of the arms, which she was able to elevate to an increasing degree.

On March 5 transient dysphagia and concomitant soft-palate paralysis occurred, which resulted in regurgitation of fluid nasally. Tracheal aspiration caused a collapsed right lower lobe, which was easily expanded by immediate bronchoscopy, the patient being too weak for effective physiotherapy. Penicillin administration was begun, and was continued daily. Dysphagia was still present on the following day; a Ryle tube was passed, and the patient was fed with a well-balanced fluid diet. The dose of the hormone was increased by giving corticotrophin, 80 mg. intravenously over a period of twelve hours, without any clinical improvement taking place.

The patient was deteriorating rapidly, being very weak and unable to cough up sputum. Plasma electrolytes and white-cell count were as previously. Corticotrophin was discontinued and cortisone, 75 mg. twelve-hourly, was given; some transient subjective improvement was apparent, but forty-eight hours later, on March 12, she died. The terminal day showed: white-cell count 16,000 per c.mm. (polymorphs 92%); a mild hypokalaemia (3.1 mEq per litre) was present, which was thought to be insignificant. Total dosages were corticotrophin, 1.44 g.; cortisone, 300 mg.

Necropsy (Dr. R. D. Eastham).—Skin: no macroscopic abnormality; sections taken from forehead, cheek, neck, arm, chest, and thigh showed a very severe and extensive change consistent with dermatomyositis—namely, atrophy of the epidermis, with hydropic degeneration of the basal-cell layer, oedema of the corium, with a very marked lymphocytic infiltration. Muscle: obviously pale and wasted in all regions; sections taken from the pharynx, chest, arm, abdomen, and thigh showed a very severe dermatomyositis—namely, extensive fragmentation of the fibres, loss of transverse striation, hyalinization, vacuolar degeneration, proliferation of the nuclei, and marked lymphocytic infiltration. The diaphragmatic muscles showed mild lymphocytic infiltration, which might be construed as early involvement. Heart: normal. Kidneys: moderate arteriosclerosis, some mild degree of fibrinoid necrosis of the glomeruli. Lungs: early bronchopneumonia present.

Discussion

In the absence of treatment, approximately 50% of patients die inside a period of some weeks to a few years. A few may recover entirely; others improve to some extent and remain stationary, or become chronically crippled (O'Leary and Waisman, 1940; Sheard, 1951).

Cortisone and corticotrophin give varying results in this condition; there is no doubt that the most favourable results are obtained in an acute case, which is characterized by rapid onset of pyrexia, leucocytosis, general toxæmia, erythematous rash, and painful myopathy.

Single cases which satisfied these criteria and which responded to the drugs are reported by Elkinton *et al.* (1949), Oppel *et al.* (1950), Suzman and Rudolph (1951), Williams and Bowler (1951), Clein (1953), Wilson (1954), and Domzalski and Morgan (1953). In each instance the temperature was at least 101° F. (38.3° C.) and there was a typically distributed rash with tender musculature. A leucocytosis

occurred in three instances; three cases showed a negative muscle biopsy (Clein; Wilson; and Domzalski and Morgan); Williams's case had a six-months history and showed marked change in the biopsy; Suzman and Rudolph's patient demonstrated a mild non-specific muscular change; muscle biopsy was not mentioned in the case reported by Elkinton *et al.*, but would be presumably positive in view of the extensive disease. The duration of the illness was under three months in all these cases, except that reported by Williams. In every case response to corticotrophin or cortisone was almost instantaneous, the temperature falling to normal inside twelve hours to four days; the rash and muscle tenderness soon disappeared and power returned with a normal range of movement. Domzalski and Morgan's case deviated from this generalization in that an initial short administration of the drugs failed and an unusual exfoliative dermatitis took some months to clear.

Acute dermatomyositis failing to respond to corticotrophin and cortisone has been reported by Kierland *et al.* (1952), Wedgewood *et al.* (1953), Smith (1955), and in Cabot Case Report 38151 (1952). The latter was given cortisone, 75 mg. daily for a fortnight, without improvement, and an exacerbation occurred on cessation of treatment. Smith stated that some slight improvement occurred, but the patient died on the sixth day of treatment from hepato-renal failure. Case 17 of Wedgewood *et al.* responded transiently to the drugs; it was felt that the initial response was non-specific—that is, the muscular weakness was not really affected; the patient died after 18 months from gastro-intestinal haemorrhage. A dramatic response, such as happened in the successfully treated cases described above, never occurred in these instances.

The cases mentioned here as chronic dermatomyositis differ from those previously described in: (1) the less toxic condition of the patient and the absence of any marked pyrexia or leucocytosis, and (2) the duration of disease, which averaged more than twenty months. Authors reporting such cases are: Ragan (1950), Thorn *et al.* (1950), Shy and McEachern (1951), Anderson (1952), Gross (1952), Kierland *et al.* (1952), Ross (1952), Wedgewood *et al.* (1953), and Wilson (1954). Shy and McEachern's patient had 2½ years' history of dermatomyositis, characterized by an atrophic skin oedema, weakness and wasting of all four limbs, and dysphagia; slow improvement occurred on cortisone. Thorn *et al.* mention three cases, two of which had a two-months history before therapy and responded initially, but further follow-up showed only suggestive improvement, and one of these patients died from the disease (Wedgewood *et al.*, 1953). The third case reported by Thorn *et al.* did not respond to corticotrophin but slightly improved on cortisone.

Nine children suffering from the more chronic form of the disease were treated with the drugs by Wedgewood and his colleagues. Most of these cases were also treated with testosterone, which makes therapeutic assessment of the effect of corticotrophin and cortisone almost impossible. Seven patients showed some improvement. One instance was a child who suffered from the disease from the age of 2 years and 3 months to 8 years. In that case many acute exacerbations occurred, some of which cleared spontaneously; others were treated by cortisone, with response in some of the treated episodes. When the disease finally remitted there was marked muscular atrophy with some limitation of movement. Another patient was only slightly influenced by corticotrophin, but responded steadily to a prolonged course of testosterone. Only three patients were cured, two died, and four were either crippled or retained the illness in an active state.

Kierland *et al.* report three non-acute cases. One patient improved, with partly restored muscle function, and another improved gradually but probably spontaneously rather than because of the drug. The cases described by Wilson and by Gross showed some clearing of the rash, but otherwise no improvement. There was a very transient improvement, which lasted for a few days, in Ragan's two cases, while Anderson's patient showed a poor response. Thus these

cases showed a rather poor or, more usually, non-existing response to corticotrophin and cortisone—in marked contrast to the rapid cure achieved in the successfully treated acute cases.

These hormones have been used in the treatment of dermatomyositis in association with malignant disease, and the results vary. Schwachman (1950) reported the case of a child with acute leukaemia who developed dermatomyositis which cleared rapidly with corticotrophin. Simpson (1953) described a patient who had had a mastectomy in 1943, followed by excision of a local malignant recurrence in 1949; three years later acute dermatomyositis occurred, which responded immediately to corticotrophin. Mitchell and McCarthy (1955) described an instance of acute dermatomyositis in which cortisone caused a temperature fall and some fading of the rash, but otherwise no alteration of the course; at necropsy carcinoma of the aortic glands was revealed. Oppel *et al.* refer to a patient with carcinoma and dermatomyositis who showed no improvement on the hormones.

A negative muscle biopsy, as in Cases 1 and 2 described above, is a frequent finding in the acute stage of dermatomyositis (Clein; Simpson; Wilson). The absence of a skin rash in Case 2 does not invalidate diagnosis (O'Leary and Waisman, 1940; Sheard, 1951; Cotel, 1952). Case 3 differed from the successfully treated patients in the lower pyrexia, absence of leucocytosis, positive muscle biopsy, gross muscular weakness, and marked oedema; this patient also appeared to be less acutely ill on general examination, in contrast with the extremely acute toxic course of Case 1 before treatment.

Summary

Three cases of dermatomyositis treated by corticotrophin and cortisone are reported. The literature on this form of therapy is reviewed.

It may be deduced from this review that cortisone or corticotrophin can be a life-saving drug in the acute fulminating attack of dermatomyositis, and in such a case the effect when it occurs is very dramatic. The drug usually fails to improve the more chronic form of the disease, but in view of the occasional success claimed in this category it should never be withheld. Likewise, in dermatomyositis associated with neoplasm a curative effect of the former process by the hormones has been described.

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