CORTISONE AND ITS ANALOGUES IN THE TREATMENT OF THE RHEUMATIC DISEASES

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Cortisone and ACTH have been the focus of high hopes and grave fears and the centre of heated argument ever since their dramatic effect on rheumatoid arthritis was first announced by Philip Hench of the Mayo Clinic in 1949.

Because of the suffering caused by rheumatoid arthritis and the long history of frustration and failure to find a cure, they were hailed at first with little critical assessment.

Though the reports from the Mayo Clinic spoke always of 'investigation' never of 'treatment,' in the first wave of enthusiasm this discrimination was ignored.

Medical judgment was hampered by the scarcity of cortisone. When supplies increased it became evident that the drug was a suppressive agent, not a cure, and that its use was complicated by side effects.

The first trial of cortisone resulted from years of study of rheumatoid arthritis by Philip Hench. He had been impressed by the fact that the symptoms and signs of the disease were alleviated in pregnancy and an attack of jaundice. Hench had come to the conclusion that there might be an anti-rheumatic substance 'X' stimulated by these two conditions. E. C. Kendall, also of the Mayo Clinic, had isolated, among other adrenal cortical steroids, compound E, later called cortisone, and a small amount was available for trial. Together Hench and Kendall decided to investigate the effect of cortisone in rheumatoid arthritis.

Originally cortisone was manufactured from ox bile and the expense of commercial preparations was high. Continuous efforts have been made by pharmaceutical firms all over the world to use cheaper starting materials and less expensive processes. They have succeeded and the cost of cortisone has been lowered.

In 1949 Hench, Kendall, Slocumb and Polley published their first account of the effects of cortisone and ACTH in rheumatoid arthritis and in rheumatic fever.

During the next few years, as physicians began

to weigh up the clinical value of cortisone and ACTH in the treatment of rheumatoid arthritis, a wide divergence of opinion became apparent.

Reports of large series of cases treated satisfactorily with cortisone over long periods were published from Denmark (Fischer and Brochner-Mortensen, 1953), France (Coste *et al.*, 1953), the United States (Ward *et al.*, 1953; Boland, 1955; and Bunim *et al.*, 1955), and Great Britain (Copeman *et al.*, 1952).

In 1954, 1955 and 1957 the Medical Research Council and Nuffield Joint Committee published the results of trials in which they compared the effects of cortisone and aspirin in early cases of rheumatoid arthritis. They found that there was no difference between the two groups. In 1957 the Empire Rheumatism Council published the results of a three-year trial of cortisone and aspirin, given continuously in later cases of rheumatoid arthritis. They also found no statistical difference between the effects of the two drugs. These trials have been criticized on the grounds that with the techniques used it was perfectly possible for some patients to respond to cortisone and for others to respond to aspirin, and yet for there to be no statistical difference between the two groups as a whole.

Physicians who have used cortisone and ACTH for some years in the treatment of rheumatoid arthritis and have reached the conclusion that they have a practical place in therapy have recognized that up to date there are two outstanding limitations:

1. Only certain patients are suitable for these drugs.
2. Both the physician and the patient must accept the necessity for long-term treatment and constant supervision in order to avoid or minimize side effects.

It has become clear that, in selected cases, treatment with cortisone or its analogues can restore independence to patients who were crippled.

Selection of Cases of Rheumatoid Arthritis for Steroid Therapy

There is a tendency for some cases of rheumatoid arthritis to be mild and in others there are long periods of remission. Because of the risk of complication with steroid therapy, the likelihood of prolonged or indefinite treatment, and the necessity for constant supervision, in this country it is considered unwise to undertake such treatment until other methods have been tried.

Many cases improve with a regime of salicylates and in some cases a period of rest alone will be followed by a remission.

On the other hand, if steroid therapy is to be used it should be started before there is much permanent bone damage or deformity, as it will have no effect on cartilage erosion or on a joint capsule contracted by fibrosis.

There are certain absolute contra-indications to the use of long-term steroid therapy and these are: diabetes, severe psychological upsets or psychosis, peptic ulceration and severe joint damage.

Pattern of Response to Steroid Therapy in Rheumatoid Arthritis

During the early trials of cortisone and ACTH large doses were given and the response was dramatic. Patients stated that they 'felt as though their limbs were unlocked,' and those who were bedridden or confined to a chair were able to move easily in a few days. The pain and inflammation was suppressed rapidly and they could feed and dress themselves within 48 hours, after being dependent on others for months or years. However, it was soon clear that side effects also occurred rapidly, and that prolonged treatment with these large doses was impractical. In addition, rapid transition from crippling to mobility resulted in weak muscles being over used and strained, and bones which had become osteoporotic from the disease being subjected to sudden stress which, in some cases, produced fractures.

It has, therefore, become the practice to start with smaller doses so that the improvement is gradual and side effects are avoided.

Now most physicians using steroids in rheumatoid arthritis give an initial dose of 50 mg. of cortisone or 15 mg. of prednisone or prednisolone.

The dose of cortisone may be raised to 75 mg. a day if there is no response, and to 100 mg. a day for short periods, but in most cases this last dosage will produce side effects if administered for long periods.

Black *et al.* (1957) have shown that the incidence of peptic ulceration increases markedly when the dose of prednisone or prednisolone is raised above 15 mg./diem.

With moderate dosage of steroids the pattern

of improvement is slow, but satisfactory. It is usually a week or more before improvement can be measured though the lassitude accompanying rheumatoid arthritis may disappear more quickly. Joint tenderness lessens though it is not usually abolished. Joint swelling is diminished, but also may not entirely disappear. Movement increases, but is dependent on the amount of permanent joint damage present. With a satisfactory response the power of the grip usually doubles and, in general, the ability to perform simple movements such as dressing and light work is restored. Many patients on long-term steroid treatment have returned to the occupation which they had been forced to abandon. With the increased movement, muscles gain strength, but organized rehabilitation is necessary in the early stages of treatment so that correct exercises can be taught.

The Figure shows the amount of change that can be expected on a long-term regime. Function improves more than objective signs and patients should regain their independence and be able to return to work though the disease is still active and only suppressed by the hormones.

In the early days of investigation with these drugs fear was expressed that the dose requirements would increase, but over some years of observation this has not proved to be the case.

It has become accepted practice that adequate suppression of symptoms and signs should be obtained with the lowest possible dosage, and frequent attempts are made to reduce the amount

administered on a long-term programme of treatment.

Routine Supervision

The routine management of cases on long-term steroid therapy is probably best carried out at a clinic where all these cases are seen at the same session. With the use of small doses, where it may be difficult to be sure whether the anti-inflammatory effect is satisfactory, methods of measurement such as strength of grip, amount of joint tenderness and the carrying out of certain movements which can be timed, are useful.

Regular weighing to check any tendency to obesity and the testing for glycosuria, blood pressure and an examination for oedema, should be carried out.

Patients should be questioned about dyspepsia. Analgesics are allowed, and it is helpful to know the number being used daily.

Estimation of the sedimentation rate is useful as it will tend to return to normal if the underlying disease is going into remission, and will rise if the arthritis is more active and if a higher dose of steroid is necessary.

It is probably wise to have a chest X-ray every six months to exclude any tendency to re-activation of an old tuberculous focus.

Ankylosing Spondylitis

There is a small place for the use of steroids during exacerbation of acute back pain. However, for the routine treatment, deep X-ray therapy, at any rate for one course, is thought to have more effect on the disease process, and for spinal pain butazolidin has proved more effective than cortisone.

Rheumatic Fever

The place of cortisone treatment has not yet been decided. There is no doubt that fever and joint symptoms are controlled more rapidly with the hormones than with salicylates, but patients tend to relapse when the drugs are withdrawn. In an attempt to solve the problem a co-ordinated study was set up at 12 British, Canadian and American centres. The results showed that there was no long-term advantage from cortisone or ACTH over salicylates. The results have been criticized on the grounds that the hormone dosage used was too low. A number of experienced American observers have expressed the opinion that the hormones in a relatively high dosage given for three months or more are more likely to reduce the incidence of cardiac damage than salicylates. Illingworth *et al.* (1957), in a comparative trial in 200 cases, showed that cortisone was superior to salicylates, and that cortisone combined with sali-

cylates, especially in high dosage, is superior to cortisone alone.

Side Effects with Long-term Steroid Therapy

During the treatment of rheumatoid arthritis with cortisone or its analogues for longer than a few weeks it is almost inevitable that some side effects of a minor or major nature will occur. They may be abolished by lowering the steroid dosage, but in some cases it is not found possible to avoid them entirely at a level of administration that causes adequate suppression of symptoms.

The majority of side effects occur more commonly in women than in men, and are seen more frequently during the menopause.

Severe Side Effects

Peptic Ulceration

This is the complication most feared by physicians who have treated patients with cortisone and its analogues for a number of years. The exact mechanism by which ulceration is produced is not yet known. Numerous studies by Gray and his associates (1951) have established the clinical importance of the effects of adrenal steroids on gastric function. Cortisone has been shown, both in normal persons and in patients with Addison's disease, to cause an increase in basal and nocturnal hydrochloric acid secretion associated with a pronounced rise in the pepsin content of gastric juice. It appears that the action of cortisone on the cells of gastric mucosa may be a direct one and not mediated through nervous pathways. From studies by Savage *et al.* (1957) and by West (1957) it is clear that peptic ulceration is much more common during long-term treatment with cortisone and its analogues than with corticotropin.

The practical difficulty with patients on cortisone who develop peptic ulceration is that the digestive symptoms may be masked so that the first indication of such a complication may be haemorrhage or perforation.

Masked Infections

The original observations of Hench on the dramatic effect of cortisone and corticotropin upon rheumatoid arthritis called attention to the capacity of adrenocortical hormones to suppress the process of inflammation.

Cortisone and ACTH have been shown in numerous studies to be capable of suppressing the inflammatory response to a wide variety of inciting agents including chemical irritants, foreign protein and micro-organisms. These hormones also inhibit the general systemic signs of inflammation such as fever and toxæmia.

As far as is known any antibiotic or sulphonamide preparation can be used in the normal way,

and as effectively, without alteration in steroid dosage.

Adrenal Cortical Failure Caused by Excessive Stress

The capacity of the body to respond to stress is profoundly modified in the presence of a deficiency or excess of adrenocortical hormones. During long-term treatment with cortisone a state of involution occurs in the adrenal cortex, and so its ability to respond to extra stress is diminished.

This means that in the event of inflammation or operation an increased dose of cortisone should be given. Surgeons have been impressed by the fact that in rabbits wound healing is inhibited by very large doses of steroids and may be reluctant to increase the dosage for fear that wounds may not heal normally.

However, Popert and Davis (1958) have reported that wound healing occurs normally after operation in patients on long-term steroid administration, and that fatalities have occurred from adrenal failure when cortisone was withdrawn before minor surgical procedures.

It should be routine practice to give extra cortisone to cover surgery or other emergencies, and it is recommended that 100 mg. cortisone be given intramuscularly 24 hours before and on the day of operation. This should be increased before major operations such as adrenalectomy and may be withdrawn more slowly. The object is to provide a depot of adrenal steroid in case of need by the body, particularly if oral administration should not be possible over the operation period.

Intravenous hydrocortisone should also be available to be used if there is a dangerous fall in blood pressure after operation.

Moderate Side Effects

Obesity

This may be a troublesome problem in long-term treatment, particularly in women at the menopause. Cortisone and its analogues cause an increase in appetite and patients may have difficulty in restraining themselves from over-eating. Most patients with rheumatoid arthritis are underweight, and it has been found by experience that once the weight has returned to normal, and there is a tendency to gain more, it is wise to impose dietary restrictions, particularly with regard to carbohydrates.

Osteoporosis

Steroid hormones increase the output of calcium and phosphorus. It has been shown that intensive adrenocortical stimulation results in a derangement of the normal long bone growth in rats.

Albright (1942) has shown that anti-anabolic effects of oxysteroids can result in osteoporosis.

This can be serious in a disease such as rheumatoid arthritis which in itself produces osteoporosis.

It is important that long-term steroid therapy should not be undertaken in cases where osteoporosis is severe. In such cases fractures of the vertebrae and long bones have occurred.

Facial Rounding (Moonface)

This is common in women on long-term steroid therapy. It does not appear to be due to water retention but to an increase of subcuticular fat. Many patients do not object to the change and prefer it to the rather haggard appearance produced by rheumatoid arthritis. Others object to it strongly. It does not increase with prolonged administration, and in some cases, after years of continuous cortisone, has been seen to diminish and disappear.

Psychological Disturbances

Definite improvement in the mental outlook of patients almost always occurs while cortisone and its analogues are being administered, and sometimes an exaggerated sense of well-being may develop. It is natural in a chronic disease such as rheumatoid arthritis, with the fear of permanent crippling always present, that dramatic relief of pain and disability should result in a return of self confidence.

It is important that a careful evaluation of the patient's personality and family history should be carried out where hormone treatment is contemplated. If there is a probability of psychosis it should not be prescribed.

Local Hydrocortisone

Hydrocortisone acetate appears to have the most marked anti-inflammatory action of all the oxysteroids when used locally. Hollander *et al.* (1951) have shown that there is a substantial reduction of leucocytes and especially of polymorphonuclear leucocytes in an inflammatory joint effusion within a few hours of the intra articular injection of hydrocortisone.

It has also been shown that there is a change in the mucin fraction of the synovial fluid with a rise in the viscosity. It appears that the effectiveness of an intra articular agent is related to its solubility in the fluid, and that as hydrocortisone acetate is the least soluble steroid it is the most effective.

Studies on the recovery of the steroid from joint fluid after injection indicate that the substance is taken up by the synovial cells.

This local anti-inflammatory effect has been widely used in the treatment of a number of conditions associated with the rheumatic disorders.

Local inflammatory conditions of the soft tissues such as epicondylitis (tennis elbow), sub-acromial

bursitis (peri arthritis of the shoulder), inflammation of the tendo-achilles and stenosing tenosynovitis (de Quervain's disease) have responded to accurately-placed injections of hydrocortisone acetate, saving weeks or months of physiotherapy.

Intra articular injections have become routine treatment in rheumatoid arthritis and in some cases of osteoarthritis where there is an inflammatory effusion. The usual precaution against sepsis must be taken when a joint is injected.

There are two drawbacks to this aspect of treatment. The first is the difficulty and pain of injecting certain small joints such as those of the fingers and feet. Another difficulty arises from the fact that the effect of local hydrocortisone acetate only lasts a short time, probably a few days, so that the procedure may have to be repeated at frequent intervals if there is a recurrence of inflammation. Clearly it is not feasible to inject even large joints, such as the knee, more than once a month and this can only be repeated on a limited number of occasions.

Constant Progress

Pharmaceutical—The Cortisones

Chemical research has constantly aimed at providing other steroid substances which would have an anti-inflammatory and anti-rheumatic effect without the disadvantage of side effects. The following substances have been manufactured and tried in rheumatoid arthritis.

1. The first was *hydrocortisone acetate* which is now considered to be the main anti-inflammatory glucocorticoid produced by the adrenal gland. Its local effect is more pronounced than cortisone and so it has become the steroid of choice for intra-articular and soft tissue injections.

Hydrocortisone by mouth, in a dosage of 70 mg. a day or less, has been found valuable in long-term treatment up to four years in cases which exhibit a marked tendency to obesity and facial rounding on cortisone.

2. *9- α -fluoro-hydrocortisone* has also been tried. Its anti-inflammatory action, at least ten times stronger than cortisone, is accompanied by marked sodium-retaining effects. In preliminary studies almost all patients developed signs of fluid retention at an early stage and this disadvantage precludes its use in rheumatoid arthritis.

A number of other steroid compounds have been given pilot trials, but none were satisfactory until the advent of:

3. *Dehydrocortisone* or *prednisone* and

4. *Dehydrohydrocortisone* or *prednisolone*.

Studies have been carried out in a number of countries and many reports of small series have been published. A Medical Research Council/Nuffield trial has reported that prednisone is

superior to cortisone in its suppressive effect, but that the incidence of 'moonface' was higher in the prednisone-treated group. Most observers agree that these substances are four or five times more potent than cortisone acetate in rheumatoid arthritis, and that the sodium-retaining effects are less. However, they do cause endocrine side effects such as obesity and rounding of the face, and have a particular propensity to produce dyspepsia and peptic ulceration. It seems, therefore, that they are superior to cortisone in the long-term treatment of rheumatoid arthritis when sodium retaining effects have become troublesome, but inferior when there is a tendency to dyspepsia. In a two-year study Fearnley *et al.* (1957) have reported favourably on the long-term use of prednisone in rheumatoid arthritis.

There is no doubt that a large number of other steroids will be produced for trial in the hope of finding one that has anti-inflammatory action without the drawback of side effects.

Physiological and Biochemical

At that same time as the pharmaceutical industry has been working on modifications of the steroid structure to produce more effective and less harmful substances, biochemists and physiologists throughout the world have been attempting to discover the mode of action of cortisone and ACTH. They have made considerable progress.

It was considered at first that in the many conditions where cortisone is effective there might be some abnormality of the adrenal cortex, but all efforts to show this have failed to demonstrate adrenal failure in rheumatoid arthritis.

The present methods of measuring adrenal activity are not satisfactory and, in the main, consist of measuring the large variety of adrenal metabolites, such as the 17 hydroxycorticosteroids in bulk. Improvements in the estimation of the different products of the adrenal cortex may show some abnormality in rheumatoid arthritis, but with the methods at present available to biochemists, although patients with this condition frequently have a low level of adrenal cortical activity, the figures are within the normal range.

The estimation of 17 ketosteroid output, which includes androgen and oestrogen end-products, was the only method available until Appleby *et al.* (1955) published a practical method of estimating the amount of 17 hydroxycorticosteroids in urine.

From time to time it has been suggested that the action of salicylates in rheumatic disorders is due to their effect on the pituitary or adrenal glands. Estimations of adrenal activity by the methods available have shown there is no evidence for this assumption.

Measurement of the amount of hydrocortisone

in the blood has proved difficult because of the large amount of plasma required for estimations, but the method of Porter and Silber has become established.

Important progress in the scientific knowledge of cortisone metabolism has been made. It has been found that there is a diurnal variation in the level of blood hydrocortisone throughout the day in normal subjects. The mean value is high at 8 a.m., though in some people this is delayed till 10 a.m., and falls during the next four hours. After a short rise it falls again and is low between 4 p.m. and 6 p.m. Studies done throughout the night have shown a low level at 3 a.m., followed by a rise to the morning peak.

Investigations on rheumatoid patients have shown that the blood hydrocortisone is high, but that there are greater fluctuations throughout the day than in normal subjects.

Work on the physiological dispositions and metabolic fate of hydrocortisone in man have been carried out following intravenous infusion. In normal subjects the half life in plasma averaged 1.9 hours. Following the infusion of tracer quantities of hydrocortisone -4-C ¹⁴ metabolites appears in the plasma in substantial quantity in two hours. Normal subjects excrete over 90 per cent. as urinary metabolites in 72 hours. Liver disease delays the excretion of hydrocortisone.

The Future

As the recent advances in the estimation of blood hydrocortisone levels continue it should soon be possible to adjust the dosage of the cortisones by scientific calculation instead of by balancing clinical improvement against side effects.

However, in spite of the somewhat crude regime which has, of necessity, ruled the dosage of cor-

tisone and its analogues since their introduction in 1948, a large number of patients who had failed to respond to other treatment and who were crippled with rheumatoid arthritis have been relieved of pain and enabled to return to work.

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