Drug Treatment of Disease

CORTICOSTEROIDS IN TREATMENT OF RHEUMATIC DISORDERS

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When in 1949 Hench demonstrated the effect of large doses of cortisone in patients with rheumatoid arthritis, there were high hopes that a true "antirheumatic" drug had been born. It became rapidly apparent that this new substance was not curative and had no lasting effect on the disease process, relapse occurring soon after it was discontinued. Hench and his clinical colleagues, Slocumb and Polley, were careful to avoid the word "cure" and emphasized that the drug only suppressed the inflammatory and certain other features of the disorder.

Though the word "antirheumatic" has been widely used since then in connexion with these and other drugs, it means singularly little, and can mean little, until we know more of the aetiology of these disorders. Relief of pain and reduction in tissue swelling occurs in a number of diseases other than rheumatoid arthritis. The corticosteroids cannot truly be said to be specifically "antirheumatic."

Corticotrophin and cortisone and its analogues are used to-day in selected cases of rheumatoid arthritis, rheumatic fever, gout, Reiter's (Brodie's) disease, ankylosing spondylitis, psoriatic arthropathy, the arthropathy associated with ulcerative colitis, and the so-called "pararheumatic" disorders—systemic (disseminated) lupus erythematosus, polyarteritis nodosa, scleroderma, dermatomyositis, and cranial arteritis. In all these disorders they produce symptomatic relief in varying degree. The indications for their use and the contraindications to it in these different disorders are in some measure a matter of individual opinion, but certain facts have been learnt in the hard school of experience in the six or seven years that these substances have been used in Great Britain.

In general it may be said that it is far easier to start steroid therapy than to stop it. The early improvement noted on such therapy in any of these disorders may be maintained for months or years, but, unless natural remission sets in, all too often so-called "side" effects become more apparent as the drug's beneficial effects become less so, and with the passage of time one finds oneself treating a state of hypercortisonism induced by therapy in addition to a partly suppressed arthritic process. The moon-faced somewhat obese patient with striae and other signs of hypercortisonism, but still with active rheumatoid arthritis, is all too well known to most of us.

Available Corticosteroids

At present there are available for treatment of the rheumatic disorders:

- Corticotrophin (hospitals only)
- Cortisone
- Hydrocortisone (cortisol)
- Prednisone
- Prednisolone
- Triamcinolone
- Methyl prednisolone
- Dexamethasone

With the exception of corticotrophin, which is given by intramuscular injection, the usual route of administration is by mouth. The tablets in common use are: 25 mg. cortisone acetate, 20 mg. cortisol, 5 mg. prednisone and prednisolone, 4 mg. triamcinolone and methyl prednisolone, and 0.5 mg. dexamethasone. These doses are very roughly equivalent and exert approximately the same action on inflamed tissues except for dexamethasone, where the equivalent dose is probably 0.75–1.0 mg.

For continued day-to-day long-term suppressive therapy in rheumatoid arthritis it is considered safer by most clinicians not to exceed 3 tablets as a regular daily dose with the older preparations—that is, cortisone 75 mg., cortisol 60 mg., prednisolone and prednisone 15 mg. Though larger dosage may be permissible over short periods, continued therapy for weeks or months will in time produce undesirable so-called side-effects even at this conservative dose level. For this reason the daily dose should be kept as low as is reasonably possible.

Trial and Error

What are the essential differences in the orally administered corticosteroids and when should one be given and when another? A good deal of trial and error is required. What suits one patient admirably may not suit another so well. As we have noted above, the relative potency of the different substances is reflected, except with dexamethasone, in the strength of the tablet; 25 mg. of cortisone equals 20 mg. of cortisol, 5 mg. of prednisone or prednisolone, 4 mg. of triamcinolone or methyl prednisolone, and about 0.85 mg. of dexamethasone. There is no particular reason for giving a smaller dose of a stronger substance if the overall effect is virtually the same.

The practical advantages of prednisone, prednisolone, triamcinolone, methyl prednisolone, and dexamethasone are that they cause less retention of sodium, and therefore of water, than do cortisone or cortisol. Moon face, gastro-intestinal disturbances, mental upsets, osteoporosis, and other features of therapeutic Cushing's syndrome occur, however, with all these substances, and we have not been impressed to date by any significant difference in the incidence of these side-effects with the different steroids. Claims of diminished incidence of side-effects of one sort or another are made for each new steroid as it arrives, but clinical experience usually shows up such claims as wanting in whole or in part.

Corticotrophin deserves a short paragraph to itself. It is at present available only to hospitals and treatment centres and cannot be prescribed on form E.C.10. It may be given intravenously to stimulate adrenocortical secretion, but is usually administered by the intramuscular route, the long-acting form being the preparation most widely used. Some workers claim that gastric symptoms are less severe with

corticotrophin than with orally administered steroids, but nevertheless they do occur. Peptic ulceration may be aggravated and the patient suffer perforation or bleeding. When the ordinary preparation is given by intravenous injection, or by intramuscular injection of 10–15 units every hour for 4–6 injections, a therapeutic effect is obtained within a few hours. When the “retard” form is given intramuscularly, therapeutic effects are not usually apparent for some 24 hours or more. Drawbacks to the use of corticotrophin are that it must be given parenterally, and that it occasionally causes allergic local reactions. In such cases its therapeutic efficacy is much diminished, and patients with rheumatoid arthritis, for instance, experience a rapid return of symptoms. In its early days (1950–2) the strength of corticotrophin varied in different batches, so that considerable variations in the patient's condition occurred on a constant dosage. This is now much less of a problem. To-day, also, one does not see the deep-brown pigmentation owing to contamination of preparations of corticotrophin with M.S.H. (melanocyte-stimulating hormone) which large doses sometimes caused in the early period.

Mode of Action

Given orally or by intramuscular or intra-articular injection, the various steroids exert their action in the inflammatory rheumatic disorders by increasing vascular stability, lessening inflammatory exudation and so reducing swelling, stiffness, and discomfort, and increasing the range of movement of a joint. There is an increased sense of well-being in many cases and an increased appetite, energy, and drive, but with triamcinolone appetite tends to diminish and the patient to lose weight. The sedimentation rate tends to fall to, or towards, the normal range and the blood picture to improve.

The exact mode, or modes, of action of these substances is still imperfectly understood, and when treating a rheumatic disorder it is as well to keep in mind the fact that all the body systems may be affected to some degree by steroid therapy. One is altering the tissues not only of the inflamed joints but of the patient in his entirety.

Hazards of Corticosteroid Therapy

These are well known and there is no need to dilate on them. Three, however, are of particular importance in the rheumatic disorders.

1. *Gastric Irritation.*—This manifests as dyspepsia with or without peptic ulceration, and has seemed to be more common in the rheumatoid group of patients than in any other. These patients, unlike, for instance, those with ulcerative colitis or asthma, usually take a regular additional daily dose of aspirin, which may also produce gastric symptoms. Gastric ulceration is more common than duodenal, suggesting the possibility of a local concentrated action by the tablet on the gastric mucosa. Many patients' dyspeptic symptoms lessen appreciably when tablets are crushed and taken with food or drink, followed by an antacid.

2. *Withdrawal Syndrome.*—On a regular daily dose of a corticosteroid, the patient's own adrenal glands become functionally depressed. In the face of any serious form of stress, the dose must therefore be increased and never reduced or discontinued. Patients should be told of this fact, for there is a tendency for both patient and doctor to reduce or stop treatment at the onset of, for example,

acute gastro-enteritis. To combat this we issue cards to all patients on steroid therapy stating the dose and preparation, and emphasizing the fact that increased stress, whether it be acute infection or an emergency operation, calls for increased dosage. To cover a major abdominal operation, for instance, some 300 mg. or more of cortisol or cortisone is usually given. Sudden stopping or major reduction of dosage in rheumatoid arthritis in the face of stress may be followed not only by signs of adrenal exhaustion and exacerbation of the arthritis, but occasionally by peripheral neuritis, probably a sign of a flare-up of a previously suppressed arteritis. The risk of impaired healing after surgery can be ignored in practice, for normal healing of tissues occurs on full dosage; the withdrawal syndrome is a far bigger and more real hazard.

3. *Osteoporosis and Fractures.*—In rheumatoid arthritis there is often some osteoporosis, partly the result of the disease and partly due to relative immobility. As corticosteroids also cause osteoporosis, the incidence of severe osteoporosis and fractures is higher at the higher dose levels and in the more crippled and disabled patients who cannot get about. For this reason prolonged steroid therapy should never be given to bed-ridden or chair-fast subjects. Particular attention should be given to so-called pleurisy pains, which may be due to fractured ribs, and to backaches, which may be due to crush fractures of vertebral bodies.

Intra-articular Injections

Hydrocortisone acetate, hydrocortisone or prednisolone tertiary butyl acetate, and prednisolone trimethyl acetate are now available for local intra-articular instillation. The effective dose ratio of the two is near unity; the 4 : 1 prednisolone : hydrocortisone ratio of efficacy when taken by mouth does not apply when these preparations are injected into the joints. Given intra-articularly, the effect milligram for milligram of these substances is very similar.

The duration of action is variable, even when the same substance is given into the same joint of the same patient in the same dose. Relief may be for a few hours only, for days, weeks, or very occasionally months. In the last case the local injection would appear to have broken a vicious cycle, the inflamed joint going into natural remission. These preparations may also be helpful in treating swollen osteo-arthritic joints, knees in particular. This is the only use of steroid treatment in degenerative joint disease, though recent controlled work (Miller *et al.*, 1958) has not shown it to be better than injections of inert substances, such as saline.

Rheumatic Fever

The steroids, it seems, have not replaced salicylates in the treatment of rheumatic fever. A joint co-operative study at twelve centres in the United States, Canada, and the United Kingdom four years ago (1955) found little difference in the cardiac condition one year after the completion of six weeks' treatment with cortisone, corticotrophin, or aspirin. There was no evidence that any of these three agents resulted in uniform termination of the disease, and on all forms of treatment some patients developed fresh manifestations of the disorder. Treatment with set doses of corticotrophin or cortisone resulted in more rapid control of certain acute manifestations, but there was an increased tendency for these to reappear on stopping therapy in the patients treated with steroids. Treatment with the hormones led to more rapid disappearance of rheumatic nodules and of soft apical systolic murmurs, but, as stated above, the cardiac

status after one year was virtually the same in all three treatment groups.

Illingworth *et al.* (1957), on the other hand, in a careful, controlled study, found that the cardiac status after one year was better in those treated with both cortisone and salicylate than with either substance alone. Cortisone alone, they concluded, was better than salicylates alone, but combined treatment gave the best results of all. Both these excellent papers should be read in their entirety. Prophylactic therapy aimed at eradicating the responsible haemolytic streptococcus appears to be producing early results.

Rheumatoid Arthritis

As has already been said, cortisone and its analogues do not cure, but merely suppress, the active features of the disease process. They also affect many other systems of the body to a greater or lesser degree and have a wide and variable effect on the patient himself as well as on his arthritis. It is important, therefore, to keep steroid therapy in reserve unless progress without it is progressively downhill and unsatisfactory in spite of a proper programme of adequate rest, analgesics, and splinting. Controlled trials by the joint committees of the Medical Research Council and Nuffield Foundation (1957a and b) in the early case, and of the Empire Rheumatism Council (1957) in the average later case, both trials covering periods of three years, have shown no real difference between those patients treated by aspirin and those by cortisone. Nevertheless, steroid therapy is still used fairly widely in the treatment of rheumatoid arthritis when other measures have not been adequate to prevent deterioration or arrest of the disease.

What are the contraindications and what are the indications for their use?

Almost absolute contraindications are peptic ulceration and psychosis; relative contraindications are diabetes mellitus and active tuberculosis. Steroid therapy may be used in these last two conditions provided adequate therapeutic control of them can be maintained. Steroid therapy is not indicated in the largely or entirely burnt out case, when residual changes only are present. It is essentially an anti-inflammatory agent for use when actual inflammatory changes are causing symptoms and signs. It is contraindicated in the bed-ridden or chair-fast case unless mobilization can be effected.

Indications are relative to each individual case. They include active inflammatory progressive disease affecting several or many joints when other measures have proved inadequate, and pseudo rheumatic fever, with high fever and systemic upset, with the patient deteriorating on orthodox therapeutic measures.

Steroid therapy should never be begun because the subject cannot rest enough or will not take sufficient time off work. Such cases are very difficult to treat; for economic or personal reasons they feel they must work on. Steroid therapy merely allows these patients to injure their affected joints more by doing too much at work, and it is these subjects who so often show the worst therapeutic results and the major complications of such therapy. Cortisone and its analogues must never be given when the patient will not co-operate by resting properly; they are supplementary to such general measures and do not replace them.

Dosage for Rheumatoid Arthritis

The regular daily dose should be the smallest which enables the patient to get through his restricted day with the minimum of disability and pain. The dose should occasionally be tentatively reduced to find out if the disease has subsided or become less active and to see if a smaller dose can be effectively given. Such dose reduction should be slow and gradual, half a tablet at a time, and the next reduction should not be made until a further three weeks or more has elapsed.

Daily doses above 75 mg. of cortisone, 60 mg. of cortisol, 15 mg. of prednisolone or prednisone, 12 mg. of triamcinolone, or 2.5 mg. of dexamethasone should not be given over long periods. If higher dosage than this is required for more than a few weeks it is wiser to discontinue steroid therapy gradually, for unwanted effects will soon appear, and the physician may find himself treating active rheumatoid arthritis in a case of Cushing's disease, often with superadded dyspepsia.

Gout

Corticosteroids may be used to treat the acute episode when colchicine or phenylbutazone prove unsatisfactory. They are not suitable as suppressive or uricosuric agents in this disease.

The usual practice is to give a short course of some six or seven days, the dose being reduced daily; colchicine, $\frac{1}{2}$ mg. once or twice a day, is continued for a further ten days subsequently to prevent "rebound" attacks on withdrawing steroid therapy. The initial dose varies according to individual requirements, but 60 units of corticotrophin, 30–40 mg. of prednisone or prednisolone, or equivalent doses of the other substances will probably be necessary on the first day, the dose being then reduced daily by one tablet (5 mg.) or 10 units. Higher dosage may be necessary in some cases, and in very acute or resistant cases intravenous or repeated intramuscular injections of corticotrophin.

Polyarteritis Nodosa and Systemic Lupus Erythematosus

In these more serious conditions the same dosage rules apply as with rheumatoid arthritis, but higher dosage is permissible and occasionally absolutely necessary. At high dosage a close watch must be kept for signs of intercurrent infection and suitable antibiotic therapy rapidly instituted at the first sign of it. There is no evidence that the natural history of these disorders is fundamentally altered by steroid therapy, and renal disease in the later stages is unaffected. Dosage, as with rheumatoid arthritis, should be as low as is compatible with a reasonable existence. The dangers of sudden withdrawal or too rapid reduction of dose are greater than with rheumatoid arthritis, new visceral and polyneuritic manifestations rapidly appearing with high fever and an increase in circulating L.E. cells. With all its drawbacks, steroid therapy is the best at present available in the symptomatic control of these conditions.

Cranial (Temporal) Arteritis

In this painful febrile disorder, steroid therapy relieves the typical bitemporal headache rapidly and effectively in most cases, and diminishes or eliminates the fever and general malaise. Blindness, however, may

still occur despite a dose which effectively relieves all other symptoms, but it may be that, in some at least of such cases, therapy has been started too late or in too low a dosage. Low-grade fever and diffuse aches and pains may persist in some of these, usually elderly, patients, with raised sedimentation rate, for some weeks or months subsequently. It may be due to a diffuse residual subacute arteritis, which often responds very satisfactorily to small doses of steroids.

Dermatomyositis and Scleroderma

In many cases steroid therapy may cause some symptomatic improvement in these disorders, but all too often the improvement wears off after some months of treatment. Steroid therapy will not prevent progression of the disease or deterioration in the patient's condition, and is not as effective in these disorders as in the others mentioned.

Conclusions

Steroid therapy suppresses symptoms but is not curative. So-called "side" effects—that is, features of Cushing's syndrome—may be expected if one gives adrenocortical hormones in pharmacological rather than physiological doses to patients with intact adrenal glands. Dyspepsia, with or without peptic ulceration, is an even greater drawback to this form of therapy. There is relatively little to choose between the various steroids available for therapy; some patients benefit more with one, other patients with another. We have now quite a range of effective substances to turn to, all giving much the same side-effects, though the newer ones are preferable if the patient becomes loaded with salt and water. It is important to remember that the patient as a whole, as well as his joints and ligaments, is affected by this form of hormone therapy: the withdrawal syndrome is a not infrequent unpleasant reminder of this fact.

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Letter from Sir Alan Herbert to the "Daily Telegraph" (January 30): "Sir,—I hope that your great paper will refuse to print the half-baked and meaningless word 'breathalyzer' again. What idiot invented it? May I inform him that there is no verb 'alyse' and no noun 'alyser' or 'alysis'? 'Breath-analyser' would be harmless but long. Why not 'breath-tester'? A sports correspondent in another paper writes about a 'heart-ometer,' which recorded the action of a runner's heart. If 'cardiometer' is too much for his readers, why not 'heart-meter' or 'heart-recorder'? And why that fancy 'o'? What is a 'hearto'? Any Briton is entitled to despise Latin and Greek, especially if he has not had the opportunity to study them. But he should modestly refrain from inventing and spreading crazy words with bits of Latin and Greek in them which he does not understand."

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Bretylium Tosylate

"Darenthin" (Burroughs Wellcome).

Chemistry.—This is N-O-bromobenzyl-N-ethyl-N: N-dimethyl-ammonium *p*-toluenesulphonate, and has the following structural formula:

Pharmacology.—Bretylium tosylate selectively blocks transmission in the postganglionic adrenergic sympathetic autonomic nerves and prevents the release of adrenaline and noradrenaline at the nerve endings. It is therefore a peripheral vasodilator and is advocated for the control of hypertension. It does not reduce, but potentiates, the effects of injected adrenaline or noradrenaline, and it does not prevent the release of these amines from the suprarenal medulla, whose nerve supply is cholinergic. Thus it would not be expected to control the hypertension of pheochromocytoma, which may indeed actually increase if bretylium is given.

Therapy.—Though it does not attack the primary causes of hypertensive disease, bretylium has a site of action hitherto unavailable for clinical use. The chief importance of a hypotensive drug with a new site of action confined to the sympathetic system is that it may offer effective control of the blood-pressure with fewer side-effects than the drugs hitherto in general use, all of which have obvious and often serious disadvantages.

Bretylium can control hypertension in man, but sometimes very large doses are needed, possibly owing to erratic absorption from the intestine. In cases that are not controlled by 2–3 g. a day it is probably best to combine the bretylium with another hypotensive drug such as pempidine, chlorothiazide, or reserpine, which can then probably be used in small enough dose to avoid serious side-effects. The drug is supplied in scored, coated 200-mg. tablets. The initial dose may be 100 mg. orally three times a day, increased by 100–200 mg. per dose daily. Bretylium can also be given intravenously or intramuscularly, but no data on its clinical utility by these routes are yet available.

Some tolerance may occur. Patients with slightly defective renal function have been treated without mishap, but caution is obviously essential if the drug is given to those with severe renal failure. The supine blood-pressure is often but little reduced, and, as with other hypotensive drugs, the fall is mainly seen in the erect posture.

Side-effects.—In therapeutic doses bretylium does not block autonomic ganglia, and so patients are spared the often intolerable parasympathetic side-effects of ganglion-blocking drugs—constipation, dry mouth, blurred vision, impotence, etc. As with all potent hypotensive drugs, postural hypotension may be severe, and among other side-effects noted there have been diarrhoea, parotid pain, failure of ejaculation, and blocked nose.

It is clear that the introduction of bretylium marks an advance in the drug control of hypertension, but it, like other drugs, can fail, and it may in some cases give best results when used in combination. Its site of action is new and the drug has the advantage of more selective action than ganglion-blocking agents, whose effective use is inevitably accompanied by very tiresome side-effects.

N.H.S. Basic Price.—100 tabs. 200 mg., 35s.