CORTISONE IN PRACTICE

BY

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[As we announced last week, on December 5 the Ministry of Health and Department of Health for Scotland are freeing cortisone and hydrocortisone for general prescription by the profession in the United Kingdom. Oral, parenteral, and topical preparations will be available. Corticotrophin (A.C.T.H.), however, will continue to be supplied only through hospitals (see Journal, November 12, p. 1217). We interrupt our weekly series on emergencies in general practice to print this article on cortisone, written by Professor D. M. Dunlop at our request.]

The release of cortisone for use in practice places a powerful weapon in the hands of the medical profession which must be employed with wisdom and propriety. The use of most modern potent drugs carries with it the risk of inducing harmful side-effects. This is particularly so in the case of cortisone, which, besides modifying disease processes, exercises a profound influence on the physical and even the mental attributes of patients. Further, its immediate dramatic and seemingly salutary symptomatic effects in various conditions may tempt the doctor to employ it in circumstances in which its use may be unjustifiable from a long-term point of view. Cortisone is a two-edged weapon, and it is necessary before using it to balance very carefully the beneficial effects which may be expected to accrue against the risks which its use involves. A vast literature has grown up on the subject in the last few years, and there are still wide divergencies of opinion in regard to the efficacy of cortisone in various diseases and its mode of action. Hence it is difficult to do justice to the subject in a short article, which must necessarily be dogmatic and contain generalizations which lack the qualifications necessary for strict accuracy.

In order to appreciate the practical use of cortisone in various diseases it is necessary to make short reference to its more striking effects on metabolism and on the function of different organs and tissues. In the space available it is impossible to discuss these in detail and only the more important applications to clinical conditions are considered.

Physiological Role : Effects on Carbohydrate, Protein, and Electrolyte Metabolism

Cortisone is one of the steroids identified as a product of the adrenal cortex. The action of another steroid—hydrocortisone—is qualitatively similar, although quantitatively hydrocortisone is more potent. The importance of cortisone physiologically lies in the part it plays in the essential maintenance of normal carbohydrate and electrolyte metabolism.

It affects carbohydrate metabolism in various ways. Gluconeogenesis from protein is stimulated so that liver glycogen stores are increased. There is a decreased sensitivity to insulin, so that, when cortisone is given to diabetics, hyperglycaemia and glycosuria are exacerbated. Its prolonged administration to seemingly non-diabetic individuals may very occasionally induce a diabetic state which usually subsides on cessation of treatment. It may be that those who develop glycosuria in response to cortisone are in reality predisposed to diabetes.

By stimulating the conversion of protein to carbohydrate large doses of cortisone induce a negative nitrogen balance,

but the increased appetite which it also stimulates usually compensates for this protein catabolic effect. The synthesis of proteins from amino-acids is also impaired, and this may contribute to the slow healing of wounds which has been demonstrated frequently in the experimental animal but which is rarely encountered in the cortisone-treated patient.

Large doses of cortisone cause potassium loss with sodium retention and a consequent tendency to oedema. A low-salt and high-potassium intake is therefore desirable for patients who are likely to require cortisone in high dosage for more than a few days. Under such circumstances 2 g. (30 gr.) of potassium citrate should be given four times a day.

There can be no doubt whatever of the value of cortisone when used as replacement therapy to make good a deficiency, just as thyroid extract is used in myxoedema. Only small doses need then be employed, the hormone being used for its physiological rather than for its pharmacological effects.

Pharmacological Role : Effect on Inflammation and Infections

Apart from cortisone's remarkable action in enhancing the body's response to stress, its most important therapeutic effect is to inhibit the inflammatory reaction of tissues to infective, toxic, or allergic agents. The hormone reduces cellular exudate, diminishes abnormal capillary permeability, inhibits the formation of new vessels and of granulation tissue, and suppresses the fibroblastic reaction of repair. This suppressive action on inflammation occurs irrespective of the primary cause and is entirely non-specific. While the fever and toxæmia accompanying inflammation, which are suppressed by the hormone, may of themselves, if excessive, be detrimental and even lethal, it must be remembered that inflammation is a protective reaction, and that to interfere with this process may be harmful. Cortisone enhances infections of all kinds—pyogenic, tuberculous, and viral—as it allows the parasite to flourish without an immediate reaction on the part of the host. Indeed, the usual evidences of infection may be entirely masked so that they may be overlooked and no remedial measures taken. Further, chronic or dormant pre-existing infections may be aggravated or reawakened.

The administration of cortisone modifies the reaction of the host to certain offending agents, but it has no effect on the agent itself and does not "cure" a single disease. In certain diseases the noxious aetiological agent may persist indefinitely and a return of signs and symptoms follows the withdrawal of the hormone. This "rebound" may take a peculiarly virulent form. Cortisone has therefore to be given indefinitely in such disorders if suppression of their manifestations is to be maintained. Unfortunately the suppressive dose may have to be so large that it cannot be given for long periods without the patient developing undesirable side-effects. This may necessitate the abandonment of treatment, and result in a recrudescence of the disease sometimes in a particularly violent form. Hence in chronic conditions it is not always easy for the doctor to decide whether the use of the hormone is indicated or contraindicated. The decision is not so difficult if a patient is desperately ill and a fatal issue is otherwise likely, or if the inflammatory or allergic reaction is intermittent or self-limiting and the hormone can be given for a short time to tide the patient over a crisis till spontaneous recovery occurs. Further, in the eye, nose, or skin it is often possible to produce a high local concentration of cortisone without any danger of inducing systemic effects.

Effects on Organs and Tissues

Cortisone depresses the function of the adrenal cortex, causing failure of its hormonal secretion. Cessation of treatment is followed by a resumption of cortical activity, but if treatment has been prolonged this may take time to occur. In such circumstances the dose of cortisone should be reduced by stages before it is finally stopped, or it should be followed by a course of corticotrophin for some days to galvanize the dormant cortex into activity once more.

Intensive cortisone treatment may cause hirsutism of the face and body, loss of scalp hair, acne vulgaris, and purple striations, which are all manifestations of Cushing's syndrome. There are also an accelerated blood flow in the skin capillaries, increased skin temperature, and sweating.

The most important effect of cortisone on bone is a tendency to cause osteoporosis which may occasion collapse of the vertebrae in elderly patients undergoing prolonged treatment with the hormone.

As hypertension is a characteristic of Cushing's syndrome it was feared that cortisone might produce hypertension even in patients with a normal blood pressure. Though these apprehensions have not been realized as fully as was expected it is essential to employ cortisone with great circumspection in patients suffering from hypertension or heart failure in view of its sodium-retaining properties.

Most patients develop some degree of euphoria on starting treatment, and this may be of advantage in counteracting the depression of toxic states. On the other hand, cortisone exaggerates neurotic, psychotic, or epileptic tendencies and should be employed only for very compelling reasons in those with an unstable mental background.

The secretory functions of the stomach are stimulated by cortisone, which exacerbates the symptoms of peptic ulceration and may cause haematemesis. Perforation of peptic and colonic ulcers—particularly gastric ulcers—occasionally results from such treatment, and as the signs and symptoms of the resulting peritonitis may be masked the diagnosis is rendered particularly difficult.

Some signs and symptoms of hypercorticism are unavoidable if large doses of the hormone are given for a long time—particularly the moonface. By using a smaller dose, however, it is often possible to achieve considerable though not complete suppression of the manifestations of the disease while avoiding the more serious repercussions of hypercorticism. When cortisone is needed to save life the contraindications to its use become relatively unimportant. Further, the dangers may be much reduced if specific treatment of the underlying disease is given coincidentally—for instance, antituberculous chemotherapy in a patient with a tuberculous history, and increased insulin dosage in the case of a diabetic. Nevertheless, the presence or even the history of tuberculosis, peptic ulcer, mental instability, diabetes mellitus, hypertensive cardiac failure, or osteoporosis makes treatment with cortisone unusually hazardous unless it is employed in small doses for replacement purposes. An x-ray examination of the chest should be made to exclude pulmonary tuberculosis before starting treatment.

Preparations, Routes of Administration, Dosage

The standard oral preparation is tablet of cortisone acetate (*B.P. Addendum*, 1955) containing 25 mg. of the drug; each tablet costs about one shilling. Injection of cortisone acetate (*B.P. Addendum*, 1955) is a suspension of cortisone in saline (25 mg. per ml.), for which the only suitable route of administration is by intramuscular injection. In general, cortisone is best given by the mouth, the chief exceptions to this rule being found in the case of patients who are vomiting, comatose, or under general anaesthesia. The hormone acts more quickly and for a shorter time when it is swallowed than when it is injected, and the interval between successive doses should be six hours. When given by injection the effect lasts for twelve to twenty-four hours and the equivalent daily dose is about 20% less than the oral one.

The other important adrenal hormone preparation is hydrocortisone. It differs chemically from cortisone only in slight changes in the structure of the steroid molecule. The action of both hormones is similar, but the effect of hydrocortisone is more potent. It is obtainable in solution in 50% alcohol in 20-ml. ampoules containing 100 mg. of the hormone and costs 11s. 9d. an ampoule. It should be used for intravenous administration in acute conditions of adrenocortical insufficiency. The most effective way to use it is to dilute the contents of an ampoule in 500 ml. of isotonic glucose or saline solution, which is then given by intravenous drip infusion. Hydrocortisone has also been usefully employed locally by intra-articular injection, in the form of nasal drops or eye-drops (1% solution), or incorporated in an ointment containing 2.5% of the drug.

The dosage of cortisone is a matter for individual adjustment. The condition is usually brought into remission with initial amounts of 100 to 300 mg. daily, after which the dose is gradually reduced to the minimum maintenance level at which useful, if not complete, control of symptoms can be achieved without producing excessive side-effects. The upper limit of dosage which is unlikely to be accompanied by side-effects varies from patient to patient. It may be taken as fairly certain, however, that side-effects will ultimately be produced by prolonged treatment with daily doses exceeding 75 mg.

Therapeutic Use in Various Diseases

To Induce Hypercorticism

Rheumatoid Arthritis.—Though the remarkable clinical effects of cortisone were first demonstrated by its ability to suppress the functional disability induced by rheumatoid arthritis, and though there can be no doubt that by its use both the local and systemic evidences of the disease can be inhibited, yet it is probable that it has only a limited application in this disorder. Worth-while control of symptoms may not be obtained by a dose of 75 mg. a day, side-effects may still occur even with this dose during long-term treatment, and tolerance appears to increase with advancing age. Further, there is evidence to suggest that the ultimate state of such patients given prolonged cortisone treatment is no better than those receiving adequate doses of aspirin—a far cheaper and less dangerous therapeutic agent. Nevertheless, cortisone may be used with advantage to check rapidly worsening destructive disease in patients who have failed to respond to ordinary treatment or to facilitate certain stages in physical therapy or rehabilitation. The most suitable cases are those in which functional disability exceeds anatomical joint damage. *The more conservative methods such as adequate rest, aspirin, and physiotherapy should always be tried first, as these will produce remission in at least 50% of cases. The same remarks apply to treatment of ankylosing spondylitis by cortisone.*

Collagen Diseases.—Whatever may be the aetiology of the tissue damage in diseases such as disseminated lupus, polyarteritis, temporal arteritis, dermatomyositis, and scleroderma, there is clear evidence that cortisone modifies the tissue reactions in such disorders. Since no other treatment will alter the course of these grave diseases, the same arguments as have been advanced against the routine treatment of rheumatoid arthritis by cortisone should not be applied to them. Hormonal treatment may be life-saving during the acute episodes and may occasionally tide the patient over his illness until an admittedly rare spontaneous remission occurs. Perhaps systemic lupus gives the most gratifying response, particularly when treatment is given before renal involvement occurs.

Acute Rheumatism.—It is possible by cortisone treatment to suppress pyrexia, pain, and swelling in the joints throughout the course of an attack of rheumatic fever, which is a self-limiting disease lasting for a few weeks, and seldom longer than two months. Such treatment does not prevent recurrent attacks in the future, and some time must elapse before it is known whether it will reduce the incidence of valvular damage. It is questionable whether cortisone is

more effective than salicylates in suppressing the symptoms of acute rheumatism, and it is possible that both operate in a somewhat similar manner. Cortisone may be the more powerful drug of the two, but, in the absence of definite evidence that its employment reduces the incidence of valvular damage, its use, either alone or in combination with salicylates, should be reserved for the most severe progressive cases which cannot be adequately controlled by salicylates, and especially when pericarditis is present, as this is often dramatically relieved by cortisone. On occasions it must be confessed that cortisone is ineffective in the control of the rheumatic process.

Sarcoidosis.—This granulomatous condition may be benign and may not significantly affect the health of the patient, so that no treatment is necessary. On the other hand, it may cause serious illness and even death. Clinical improvement can be obtained in a number of such cases by the use of cortisone, which gives more consistent results than any other therapeutic measure. It acts by preventing the formation of granulomatous tissues in the early stages before irreversible pulmonary fibrosis and emphysema have resulted.

Allergic Diseases.—The response to cortisone of asthma, hay-fever, perennial rhinitis, atopic eczema, exfoliative dermatitis, serum sickness, urticaria, angioneurotic oedema, and drug sensitivities is usually rapid and favourable, and may be life-saving. Nevertheless withdrawal always leads to a return of symptoms unless the offending allergen is no longer operative or unless spontaneous remission from natural desensitization has occurred. Many allergic manifestations may be comparatively trivial or may respond rapidly to traditional treatment with sympathomimetic or antihistamine drugs. Cortisone is of particular value for patients dangerously ill with resistant status asthmaticus, in whom it may prove life-saving, and for patients with chronic disabling asthma who have failed to respond to orthodox treatment. Such patients may often be enabled to live satisfactory lives by the daily administration of small doses of cortisone. It may be that it is in this common condition that hormonal treatment will have its most widespread application.

Blood Diseases.—Cortisone has been increasingly used in the treatment of blood diseases during the last few years, but only in acquired haemolytic anaemia of the auto-antibody type, in idiopathic thrombocytopenic purpura, and in acute leukaemia have favourable responses been obtained with any regularity. The hormone should be the primary treatment in both the former diseases. Splenectomy should be reserved for those patients who show no sign of a remission as the result of hormone therapy or who relapse when the administration of the drug is discontinued. In the latter circumstances splenectomy plus cortisone treatment may be effective. There is no doubt that a remission may be induced frequently in acute leukaemia by the use of full doses of cortisone, but it is rare for such remissions to last for longer than three to six months in spite of maintenance treatment.

Ulcerative Colitis.—A considerable subjective improvement with gain in appetite and reduction of diarrhoea often follows the use of cortisone in this condition. Objective improvement has been less striking, but in those patients in whom diarrhoea is most diminished sigmoidoscopic examination usually shows a decrease in the inflammatory reaction. The effect is particularly dramatic in patients suffering from their first attack. Cortisone seems to be much less effective in disease of long standing in which permanent organic changes in the bowel have taken place, but even in these cases hormone therapy may be a valuable pre-operative measure, and critically ill, exhausted, or debilitated patients may thereby be improved enough to permit of elective surgery.

Nephrosis.—The aetiology of nephrosis is unknown, and the means by which cortisone sometimes improves the condition is still debatable. Nevertheless there is no doubt that after a short intensive course of the hormone a free diuresis and a diminished protein loss often ensue when it is sud-

denly withdrawn. The ideal dosage and length of treatment remain to be determined, but the administration of 100 to 300 mg. of cortisone daily for five to fifteen days is usually recommended. The course is repeated at intervals depending on a return of the oedema.

Dermatological Conditions.—The beneficial use of cortisone in suppressing manifestations of atopic eczema has been already noted. Its use, however, is justifiable only in severe, extensive, and disabling examples of the disease in which the alternative is a prolonged and tedious treatment entailing considerable inconvenience and incapacity. Hydrocortisone ointment is useful in infantile eczema, neurodermatitis, and pruritus ani and vulvae, but as it is very expensive it is unsuitable for widespread application, and in any case its use should be restricted to cases which have failed to respond to other local and general measures. Cortisone is the only drug which will control satisfactorily pemphigus vulgaris, vegetans, and foliaceus. It should be given to suppress the crises of these diseases, in which its use may be life-saving.

Ophthalmological Conditions.—One of the most promising fields for treatment with cortisone has been found in ophthalmology. It can often be used topically in the form of hydrocortisone eye-drops without any danger of producing systemic effects, and it has the ability to block the inflammatory phase not only of allergic ophthalmic reactions but also those due to bacterial and toxic agents. Administration seems, therefore, to be ideally indicated in acute iritis and iridocyclitis, in which, unless the inflammatory process is promptly checked, serious consequences such as cataract and glaucoma may occur. Many other ophthalmological conditions respond favourably to cortisone, but specialist advice should be obtained before its use.

Replacement Therapy

When cortisone is used as replacement therapy it should be remembered that endogenous adrenocortical output is lacking, and the patient is thereby rendered peculiarly sensitive to stresses and infections. It is therefore important to ensure that once treatment is started it is continued indefinitely, and that supplementary cortisone should be given during any intercurrent illness or infection.

Addison's Disease.—This is an incurable disease and treatment must take the form of permanent replacement therapy. Fortunately in deoxycortone acetate and cortisone we now have two synthetic steroids which enable this replacement to be undertaken satisfactorily—the former correcting the disturbed electrolyte metabolism of the disease and the latter combating the hypoglycaemia and failure to resist stress which also characterize it. For maintenance purposes only small daily doses of cortisone are necessary of from 12.5 to 25 mg., though in crises large doses of intravenous hydrocortisone should be given. Cortisone has been so successful in improving the prognosis for such patients that many believe that injections or implants of deoxycortone are now superfluous and that sole reliance can be placed on oral cortisone. Under these circumstances rather larger daily doses of from 25 to 50 mg. are necessary, but it is my impression that a small replacement dose of cortisone and an implant of about 300 mg. of deoxycortone is still the preferable form of treatment for most cases.

Bilateral Adrenalectomy.—Since the introduction of potent replacement therapy bilateral adrenalectomy has become a practical procedure for patients suffering from metastatic cancer of the breast or prostate or from malignant hypertension. Cortisone is given as follows: 200 mg. on the day before operation, 300 to 400 mg. on the day of operation, 200 mg. on the day after, gradually reducing the dose on succeeding days depending on the condition of the patient. The ultimate maintenance treatment is the same as for Addison's disease.

Hypopituitarism.—Remarkable improvement occurs in hypopituitarism as the result of permanent treatment with cortisone. Patients who may have been in a practically dormant, hibernating condition for years can thereby be

restored to a relatively normal life. The dose used approximates to that required in Addison's disease. In addition the replacement of other hormones, defective from the lack of trophic stimuli from the pituitary, is usually necessary.

SIR HENRY DALE, O.M., F.R.S., ON HUMANITY'S RISING DEBT TO MEDICAL RESEARCH

In his Stephen Paget Memorial Lecture on November 17, 1955, Sir Henry Dale said it was more than twenty-four years since he had lectured to the Research Defence Society in commemoration of its founder. He had very precious memories of Stephen Paget's most endearing personality, and especially of the selfless devotion with which in his later years he had given the whole of his effort and interest, sacrificing his health and, in the end, his life to the defence of medical research. Paget had no personal or professional advantage to gain in founding the Society. He was inspired by a strong passion for the truth, and by a hatred for what he recognized as an essentially cruel attack upon scientific researches more directly humane than most in their aims as well as in their results. Paget toured the country in 1914 to counteract the attempt to persuade the men of the new armies to refuse the protective inoculation against the enteric fevers. That particular cruelty was defeated, so that there was no repetition of the tragedy which had overtaken the armies in South Africa for lack of such protection.

Prevention of Diphtheria

Medical knowledge, Sir Henry continued, had owed essential features of its permanent structure to experiments involving the use of animals ever since William Harvey laid its first scientific foundation; and to-day it must become ever more difficult to accept any effective service from medicine without accepting at every turn the applications of knowledge directly arising, or less directly derived, from such experiments. When he had lectured to the Society in 1931 the results of the active protection against diphtheria and tetanus by inoculation with the inactivated toxins of the respective bacteria were not yet available for citation. Only a few years later, however, convincing evidence of the success of the inoculation against diphtheria could have been presented. The record of its application in Hamilton, one of the larger cities of Ontario, was one which was early made available. In 1925 the systematic inoculation of children was begun, and the effect was dramatic. So steeply did the curve fall that after 1930 there were no more deaths from diphtheria in Hamilton, and after 1933, when the inoculation had been in effective action for eight years, no more cases. This achievement was repeated in one after another of such centres of population on the North American continent, leaving no room for doubt that wherever the preventive inoculation of children could be fully applied and maintained diphtheria could be completely abolished. It was not till 1940 that our own Ministry of Health found it practicable to inaugurate a full-scale undertaking, with the preventive inoculation of all children as its aim; and this was not fully under way till 1942. Immediately, however, the enemies of medical research launched a counter-campaign to induce timid mothers to refuse the protection for their children. Their effort was less successful than might have been feared, or than they must be supposed to have hoped. In 1940 there were still in England more than 45,000 cases of diphtheria, and more than 2,400 of these were fatal. Then, with the inoculation becoming effective, the numbers fell steeply and steadily, until in the last full year, 1954, there were only 173 cases, and only 9 deaths from the disease. Of the nine deaths recorded in 1954 six were in children under 15, and all of these occurred in the minority who had not been inoculated; and among all the children of any age who had received the inoculation within the last five years there were no deaths in 1954.

Tetanus in the Second World War

The value of preventive inoculation against tetanus was a more recent discovery. Fortunately the arrangements had been made in advance for this active immunization of the armies of the second world war. Here again, however, there was an organized effort to persuade the soldiers to avail themselves of a legal right to refuse this protection. The British Expeditionary Force, which was brought back from Dunkirk in 1940, had fought a gruelling rearguard action over soil which experience had shown to be highly dangerous as a source of the tetanus infection; and they had been transported home under conditions which made inevitable a long delay in the cleaning and dressing of their wounds. Yet, in the more than 16,000 wounded in that army, there were only seven cases of tetanus; and these were all in men of the 10% who had been persuaded to refuse the protective inoculation; among the 90% who had been inoculated there was no tetanus. And so the records continued for the rest of the war. Those for the Mediterranean campaign gave an opportunity for comparing the experience of the South African troops, who had not been inoculated, with that of the Australian and British troops, who had. Among less than 4,000 South African wounded there were five cases of tetanus, while among more than 8,000 Australian wounded there were none, and among more than 27,000 British there was only one, in a man whose immunization was doubtful. In so far, then, as the campaigns of persuasion to refuse inoculation had been successful those who had conducted them could not escape the responsibility for agonizing deaths of children in diphtheria, and of soldiers in tetanus, which could clearly have been prevented.

It was now more than thirty years since those then working in the National Institute for Medical Research had been asked by the Medical Research Council to take part in research on the problem of the diseases due to the so-called ultramicroscopic viruses. They chose dog-distemper for investigation. In due course Sir Patrick Laidlaw and Mr. Dunkin elaborated a method of preventive inoculation which was not only effective in protecting dogs from distemper but, since it broke new ground, gave a lead in certain directions to the search for methods of immunization against other diseases due to virus infections, of men as well as of other animals. The method of conferring immunity against distemper was greatly improved and simplified, so that the material for the inoculum, or vaccine, now successfully used for immunizing dogs, was no longer obtained from infected dogs and ferrets but from cultures of the virus on incubated eggs containing chicken embryos. But from the time the preventive treatment first became available, even to the present day, there had been a persistent campaign to induce owners to refuse the protection for their dogs.

Specific Chemotherapy

Sir Henry Dale then reviewed some of the advances in medicine since 1931. "You cannot, in fact, move anywhere in modern medicine without the use of knowledge produced by experimental researches, in a large proportion of which it has been necessary to make some use of experiments on living animals." In his lecture of 1931 his only reference to a specific, chemotherapeutic remedy for an infection was to "salvarsan." Ehrlich's earlier attempt to discover a specific remedy for an infection had been halted for many years. As early as 1891 he had experimented on the possibility of treating malaria in man with methylene blue. Some thirty-five years later it occurred to the research workers of the Bayer Company, in Elberfeld, that the malaria-like infections of certain small birds could be used for a preliminary trial of substances for an antimalarial action. These malaria-like blood-parasites of birds had helped Ronald Ross, many years earlier, to recognize a mosquito as the natural transmitter of malarial infections. They were able, by tests on such artificially transmitted infections in small