REFRESHER COURSE FOR GENERAL PRACTITIONERS**CORTISONE AND A.C.T.H.—I**

BY

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The administration of A.C.T.H. or cortisone raises the concentration of adrenal cortical hormone in the circulating blood and presumably also in other body fluids. This may be of very great benefit at certain stages in a variety of disease states, but why this should be so is still by no means clear.

There is abundant evidence that animals and indeed humans without adrenal glands resist the stresses of trauma, infection, toxic substances, and adverse environmental conditions much less well than do those with healthy adrenal tissue. There is also plenty of evidence that the adrenal cortex is very readily stimulated by such stresses to liberate increased amounts of adrenal cortical hormone into the blood stream. Even psychological stress will produce this result: screwing up one's courage, for instance, involves such adrenal cortical stimulation. It would seem that the increased concentration of hormone in the blood helps the cells of the body to resist adverse trends in the internal environment, though how this is achieved is unknown. It may be that the adrenal hormones strengthen the cell membrane or lower its permeability. It has been suggested that the adrenal cortical hormones provide the cells "with an asbestos suit protecting them from the fires of infection." Although such a statement explains nothing, it nevertheless provides a useful working concept of what it is hoped to achieve by therapy with A.C.T.H. or cortisone. Such a concept takes no account of specific diseases; it merely considers disease in general as a damage to the tissues of the body. But this is the proper way to regard the use of cortisone. The results of therapy are quite empirical and little is to be gained from pushing theory further than this simple generalization.

A substance with so fundamental an action brings its own responsibilities: it must not be given indiscriminately. By protecting against disease, it may reduce or eliminate some of the traditional signs or symptoms of disease. Thus the temperature associated with infection may be reduced to normal, even though the infection itself persists or even extends; the malaise of a toxæmia may be eliminated, even though the disease causing it is unaffected; the sedimentation rate, an important clinical sign of disease, may be reduced to normal. With all these improvements in the state of the patient a false sense of security may be produced in those in whom the disease process is not actually under control. Perforation of gastric ulcers and extensive peritonitis have occurred in patients on cortisone, and have remained undiagnosed because the traditional indications of the catastrophe were masked. Because of such dangers, it is of great importance that a complete diagnosis should be made before cortisone or A.C.T.H. therapy is attempted. These drugs should never be given as a last resort to patients with undiagnosed disease who appear to be resistant to the more usual forms of treatment. They must not be regarded as the last refuge of the therapeutically destitute. Cortisone and A.C.T.H. are not known to cure any disease: they only alleviate some of the manifestations;

other aspects of the disease process may remain unaffected, and to these the patient may still succumb, in spite of full cortisone therapy.

As already stated, the essential process in A.C.T.H. or cortisone therapy is to raise the concentration of adrenal cortical hormone in the circulating blood. The hormone concerned is very probably a steroid called compound F (17-hydroxycorticosterone). Its chemical formula is known and it can be manufactured. It can be detected in small amounts in blood or body fluids and occurs in higher concentration in the blood of the adrenal vein. Although cortisone itself, which is a mildly oxidized relative of compound F, is probably absent from circulating blood, it has very much the same physiological actions as the natural hormone. It is likely that cortisone acts by being converted into compound F within the body. When compound F becomes available commercially it will probably prove even more effective than cortisone.

Principles of Therapy

Cortisone is usually supplied either as tablets of acetate to be taken by mouth, or in the form of a suspension of finely divided crystals of cortisone acetate in a saline medium, suitable for intramuscular but not for intravenous injection. It is stored at room temperature.

When cortisone acetate is taken by mouth it is quickly absorbed and the therapeutic effect is rapid, but the amount in the blood falls back in a few hours to its original level. It is therefore best given twice a day or oftener. Cortisone acetate injected intramuscularly behaves differently. It is relatively slowly absorbed and much will often persist at the injection site after 12 or 24 hours. If daily injections are given, more and more will collect at the injection sites, producing a depot of cortisone which is only slowly absorbed. Blood levels will thus rise more slowly than with oral cortisone, and the maximum effect may not be attained until injections have been given for several days. When injections cease, absorption will often continue from these depots for a week or more. Therapeutic effect will thus diminish gradually. The cortisone acetate suspension can be given orally if desired. It is readily taken mixed with a little milk, and is then rapidly absorbed.

When cortisone is administered by either method the patient's own adrenal glands tend to be inhibited and gradually pass into a state of disuse atrophy. This is not a serious matter if cortisone continues to be administered, but if therapy is suddenly stopped the patient may find himself without either administered or self-produced hormones and may pass temporarily into a state like Addison's disease. To avoid this risk the dose should be tailed off gradually so as to give the patient's own adrenals an opportunity to resume normal function. Tailing off is probably the more necessary when cortisone is given orally, because with injected cortisone the depot effect provides for this to some degree.

Adult dosage of cortisone varies according to circumstances from 25 mg. to 200 mg. per day.

A.C.T.H., or adrenocorticotrophic hormone, is a highly purified protein fraction of the anterior pituitary lobe of cattle or other animals which has the unique power of stimulating the adrenal cortex to greatly increased activity, to hypertrophy, and to much augmented production of its

own hormones. It is stable in the dried state and is readily soluble in normal saline or water. Like most protein-type therapeutic substances, it is destroyed by the digestive juices of the stomach and small intestine, and so is inactive when taken by mouth. It must therefore be administered by parenteral injection, either intramuscularly or intravenously.

When A.C.T.H. enters muscle some of it is probably destroyed locally and some enters the blood stream to pass ultimately to the adrenal gland. Circulating A.C.T.H. is unstable and is fairly rapidly destroyed, probably within 15 minutes. It follows that when A.C.T.H. is injected intramuscularly only a small part becomes available for adrenal cortical stimulation: perhaps two-thirds or more of the total is destroyed either locally or in the blood stream. Not only this, but an injected dose is available for only a relatively short time, and adrenal stimulation probably starts to subside an hour or two after the injection. There are several methods for overcoming this difficulty. Injections may be repeated at frequent intervals; for this purpose, four times in the 24 hours is usually recommended. A given daily dose of A.C.T.H. produces considerably greater stimulation when given in divided doses over the day than when given as a single daily injection. A second method of producing more continuous stimulation is by a process analogous to that with zinc protamine insulin. A.C.T.H. can be incorporated in a gelatin base, and the resultant gel, which becomes fluid on gentle warming, is protected from rapid destruction after injection and is liberated slowly from the injection site over a number of hours. With this gel a single daily injection can provide continuous gentle stimulation of the adrenal over the greater part of the 24 hours. The third method is to administer the A.C.T.H., dissolved in saline, as a slow intravenous drip over a period of six to eight hours a day. A prompt response is obtained and the efficacy of a given dose is increased by 5 to 15 times, an important point where supplies are restricted. Though this is a very economical method of administration it clearly has several disadvantages. It is unsuitable except for patients confined to bed and in hospital; it needs constant supervision, is an encumbrance to the patient, and may occasionally lead to venous thrombosis. Although all three methods are still in use, the daily injection of A.C.T.H. gel is generally the method of choice.

Obviously A.C.T.H. will have no clinical effect if the adrenal cortex is diseased, as in Addison's disease, or if for any other reason it is unable to respond. Although in the great majority of patients the adrenal cortex is responsive, yet it is desirable to have some indication that this is so. It is most readily done by carrying out eosinophil counts; if a sufficient output of adrenal hormones has been achieved the eosinophil count will fall practically to zero. A check such as this is of considerable value during A.C.T.H. therapy, since in addition to adrenal unresponsiveness it occasionally happens that the sample of A.C.T.H. is either inactive or of low activity. In suitably equipped hospitals, observation of a rise in output of 17-ketosteroids or of so-called 11-oxysteroids is an additional check on the activity of the A.C.T.H.

When, after a course of injections to which the patient has responded, the A.C.T.H. is stopped abruptly, the hypertrophied and over-acting adrenal cortex is suddenly deprived of its stimulus. It is liable then to become inactive for a few days, and in this period, as with cortisone, adverse withdrawal phenomena may occur. The dose of A.C.T.H. should therefore be tailed off gradually to a low level before finally stopping treatment.

Contraindications to Therapy

Perhaps the most important single contraindication is ambiguity of diagnosis. Great harm may be done by giving these drugs to unsuitable patients. An improvement in well-being and indeed a euphoria, with fall in temperature and sedimentation rate and possibly some gain in weight, may easily give an entirely erroneous impression that the drug is doing good, thus diverting attention from the need

for treatment by more traditional and orthodox methods. Undiagnosed fevers and abdominal disorders of uncertain nature are examples where the drug should in general be avoided.

The second major contraindication is ignorance on the part of the physician of the physiological effects of the drugs. There are certain overdose effects which should always be watched for, and these are considered below. They are all very real, and more harm than good may be done if any of them are allowed to develop too far unchecked.

In certain clinical states A.C.T.H. or cortisone should be given with special caution, and preferably only by those already experienced in its use and in the dangers of overdose. Important among such relative contraindications are congestive heart failure with oedema, diabetes mellitus, and hypertension if it is already producing symptoms. Special caution is also necessary in any person who shows or has shown evidence of a psychopathic personality, as this can easily be made worse or a latent abnormality may become manifest.

Since A.C.T.H. is effective only by virtue of its stimulation of the adrenal cortex, it should not be expected to succeed in patients with seriously diseased adrenal glands, as in Addison's disease. Conversely, in states of adrenal hyperactivity, such as Cushing's syndrome, further stimulation with A.C.T.H. will only aggravate the disorder.

Particular caution is necessary in giving the drug to any person with active or latent tuberculosis, as there is considered to be danger of lighting up the activity.

Metabolic and Overdosage Effects

The same general metabolic effects are produced by both cortisone and A.C.T.H., but overdose phenomena are rather commoner with A.C.T.H. because the response to a given dose of A.C.T.H. varies considerably from person to person. There is a mild but appreciable tendency to sodium and water retention during the first few days. Occasionally this may be sufficient to produce manifest oedema; in persons who are in any way sensitive to sodium retention, such as those with early congestive failure, signs of aggravation such as weight increase or rise in jugular venous pressure must be carefully watched for. If any adverse tendency is detected or even suspected, it will usually be wise to restrict the sodium intake, at least during the period of early therapy.

The drugs also cause a tendency to increased renal loss of potassium. In prolonged intensive therapy this may become sufficient to be of clinical importance. Muscular weakness and electrocardiographic changes may suggest an excessive potassium loss. Since potassium deficiency may be insidious in onset and difficult to detect, it is wise to ensure an adequate intake by supplementing the ordinary diet with 2 or 3 g. of potassium chloride. There may be also an increased calcium excretion in the urine. This is seldom of any clinical significance, but in patients with disturbed calcium metabolism, such as those with the steatorrhoea of non-tropical sprue, attacks of tetany have occasionally been provoked.

Carbohydrate metabolism is profoundly altered by these drugs. Sensitivity to insulin is decreased so that the blood sugar tends to rise, and in the established diabetic insulin requirements may be temporarily but very considerably increased. For this reason it is wise to be very cautious in administering the drugs to known diabetics. Their effect on blood sugar may be sufficiently great in non-diabetics to produce glycosuria. Such glycosuria is not, by itself, adequate reason for lowering or stopping dosage.

Adrenal cortical stimulation also usually involves the increased production of adrenal androgens. This may lead to mild evidence of masculinization in females, with a tendency to acne, amenorrhoea, or even hirsutism. These androgenic effects are usually negligible unless therapy with A.C.T.H. is intensive and prolonged. They are promptly reversed when treatment is stopped, and are not usually reasons for curtailing it.

Less clearly related to the known effects on metabolism are the psychological changes. The improvement produced by the drugs in a susceptible disease such as rheumatoid arthritis is so marked that a dramatic increase in well-being and optimism is to be expected. Yet the mental stimulation and optimism, amounting to frank euphoria, often occur to a degree far in excess of what can be accounted for by such physical improvement. They appear largely to be direct effects of the drugs themselves and may occur even when the disease process has in no way been affected. Thus one scientist patient with advanced myeloid leukaemia was stimulated to plan many new scientific activities although no alleviation of his leukaemia occurred and he was dead within a week. In people of different make-up there may be depression rather than euphoria. This depression, together with insomnia, may become progressively more severe until frank psychotic tendencies become apparent. Though these mental changes are usually reversible, they should call for a careful review of therapy, and in general the dosage should be reduced.

[Part II will appear in our next issue.]

Refresher Course Book.—The first collection of articles of this series (fully revised) are available as a book containing 55 chapters, price 25s. Copies may be obtained either direct from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or from booksellers.

3-D AT CARDIFF

A three-dimensional surgical film in colour was shown at the Annual Meeting in Cardiff, presented by Ethicon Suture Laboratories. Entitled *Mediastinal Tumours*, it was made in Washington and was projected by special equipment lent from America. Each member of the audience was equipped with light polaroid spectacles, and there seemed to be few, if any, complaints of headache or visual discomfort. The film showed the surgical technique for the removal of such tumours in considerable detail, two operations being demonstrated, one for a thymoma by a left approach, the other for a cyst above the right diaphragm. The three-dimensional effect greatly enhanced the film's usefulness, especially as its subject lay within a body cavity. The relations of the various structures were immediately seen, and the highlights reflected from the moist organs were no longer the source of confusion they often were in two-dimensional films.

The film included a good spoken commentary, mostly descriptive of the steps being performed but interspersed with some general observations on the subject, such as the acceptable advice that all patients with mediastinal tumours should be subjected to exploratory thoracotomy, and that aneurysm can most reliably be excluded by angiocardiography.

Advantages of Stereoscopic Effect

The film lasts about 40 minutes, and thus for most purposes is unnecessarily long. The experienced surgeon will learn little from it, for the operations are among the simplest performed within the thorax, and the ordinary doctor would probably have preferred more clinical or pathological facts and less technique. These are minor criticisms, applicable to a great many medical films. No doubt the film is directed especially at the trainee surgeon—a small group for whom it is ideal. Other audiences will probably be more interested in the film itself than in its subject. The stereoscopic effect is a definite advance, making the surgical technique notably easier to understand and visualize. This film, indeed, gives a clearer view than that obtained by most visitors to a crowded operating theatre, and others by the same process, perhaps showing more complex operations, or new ones, will be warmly welcomed—especially if condensed versions, omitting all but essential details, are available for showing to practising surgeons.

SUPPLEMENTARY LIST OF APPROVED NAMES

The General Medical Council has authorized the following "approved names" selected by the British Pharmacopoeia Commission. The list supplements the consolidated list of names published in January and the supplementary list printed in the *Journal* of April 18 (p. 882).

Approved Name	Other Names
Bromazine	2 - (4 - Bromodiphenylmethoxy) - ethyldimethylamine. "Ambo-dryl."
Carbimazole	2 - Carbethoxythio - 1 - methyliminazole. "Neo-mercazole."
Cetomacrogol 1,000	Polyethylene glycol 1,000 monocetyl ether.
Chloropromazine	3 - Chloro - 10-(3-dimethylamino-propyl)-phenothiazine. "Largactil" is the hydrochloride.
Dextromethorphan	(+) - 3-Methoxy-N-methylmorphinan.
Dextrophan	(+) - 3-Hydroxy-N-methylmorphinan.
Dihydrallazine	1 : 4 - Dihydrazinophthalazine. "Nepresol."
Dimenhydrinate	8-Chlorotheophylline salt of (2-diphenyl - methoxyethyl)dimethylamine. "Dramamine."
Hydrocortisone	17-Hydroxycorticosterone. "Hydrocortone."
Insulin zinc suspension	Insulin lente.
Insulin zinc suspension (amorphous)	Insulin semilente.
Insulin zinc suspension (crystalline)	Insulin ultralente.
Iproniazid	N - isoNicotinoyl - N' - isopropylhydrazine.
Isophane insulin	NPH insulin.
Levomethorphan	(-) - 3-Methoxy-N-methylmorphinan.
Levorphan	(-) - 3-Hydroxy-N-methylmorphinan. "Dromoran" is the tartrate.
Macrogol 4,000	Polyethylene glycol 4,000.
Macrogol 400	Polyethylene glycol 400.
Methoxamine	β - Hydroxy - 2 : 5-dimethoxy- α -methylphenethylamine. "Vasylax" is the hydrochloride. An antibiotic produced by a strain of <i>Streptomyces fradiae</i> .
Neomycin	(-) - 2-Amino-1-(3 : 4-dihydroxyphenyl)ethanol. (-)-Noradrenaline. "Levophed."
Noradrenaline	An antibiotic produced by <i>Streptomyces rimosus</i> . "Terramycin."
Oxytetracycline	2-Phenylindane-1 : 3-dione. "Dindevan."
Phenylindanedione	2'-Morpholinoethyl ether of morphine. "Ethnine."
Pholcodine	5-Ethylhexahydro-5-phenylpyrimidine-4 : 6-dione. "Mysoline."
Primidone	2'-Diisopropylaminoethyl xanthen-9-carboxylate. "Pro-banthine" is the methobromide.
Propantheline	($\pm$) - 3-Methoxy-N-methylmorphinan.
Racemethorphan	(+) - 3-Hydroxy-N-methylmorphinan.
Racemorphan	o-Hydroxybenzamide.
Salicylamide	Sodium salt of a trivalent antimony derivative of gluconic acid. "Triostam."
Sodium antimonylgluconate	N-Glucosyl derivative of sodium p-aminophenylstibonate.
Stibamine glucoside	Tetrahydrofurfuryl nicotinate.
Thurfyl nicotinate	"Trafuril."
Amendments	
Sodium Stibogluconate	Sodium salt of a quinquivalent antimony derivative of gluconic acid. "Pentostam."
Ethyl methimazole	This Approved Name is now replaced by Carbimazole (see above).