PRACTICAL PROBLEMS OF CORTISONE AND ADRENOCORTICOTROPHIC HORMONE ADMINISTRATION IN CHRONIC DISEASES

R. R. H. LOVELL, M.D., M.R.C.P.

Rheumatism Research Unit, St. Mary's Hospital Medical School, London

Wilfred Trotter (1935) observed of medicine that one of its elements is an experimental science, but a large part of it obeys the very different discipline of a practical art. As with any drug, the assessment of the place of cortisone and adrenocorticotrophic hormone (A.C.T.H.) in therapeutics belongs to the realm of experimental science. But the discipline of the practical art of medicine, unfettered by the chains of experimental science, progresses at a less pedestrian pace. It is in the natural course of things therefore that, three years after Hench and his Mayo Clinic colleagues (1949) introduced these substances as new and powerful methods of investigational therapy, an assessment of their place in medicine should still have to be based largely on the practical medical artist's most popular canvas, the clinical impression.

Problems of Assessing Results

Before reviewing some problems concerning practical aspects of their administration in chronic diseases, it is worth while considering briefly some of the problems of assessment of cortisone and A.C.T.H. as therapeutic agents. While rheumatoid arthritis, being the commonest and most pressing problem, affords the main context for this discussion, much that may be said applies also to acute rheumatism and the so-called collagen diseases, which include polyarteritis nodosa and disseminated lupus erythematosus. The answers to three questions are needed. Firstly, does hormone administration suppress the disease symptoms? Secondly, do more cases recover if treated than if untreated? Thirdly, in the fatal diseases, is the death rate altered by treatment?

In considering methods of answering these questions, and indeed when reviewing clinical impressions of therapeutic hormone effects, cer-

tain features of these diseases must be remembered. Their natural course is very variable and they are often characterized by unpredictable exacerbations and remissions. The proportion of cases which recover is unknown. Some of these diseases are ill-defined entities, which may prove to include a variety of different conditions with different natural histories. Add to this background the fact that many thousands of patients with the commonest of these diseases, rheumatoid arthritis, have been treated with gold salts for over twenty years, yet the clear demonstration whether or not the course of the disease is affected by gold is still lacking, then it is evident that the full therapeutic assessment of cortisone and A.C.T.H. in these diseases is likely to be a somewhat protracted experiment.

Clearly, in 1952, knowledge does not permit useful discussion of the possibility that cortisone and A.C.T.H. decrease mortality in this group of diseases. Nor can much useful comment be made on the influence of cortisone and A.C.T.H. in promoting recovery from these diseases, except to note that, in rheumatoid arthritis, experience with prolonged cortisone administration (Boland, 1951) has confirmed earlier clinical impressions that relapse generally follows withdrawal of therapy.

There is rather better evidence on which to decide whether cortisone and A.C.T.H. suppress symptoms of these diseases and Hench's Nobel Lecture (1952) contains a very full list of references. Hench remarks that, if attention is confined to those diseases about which opinion seems fairly unanimous after one or two years of experience, 'one finds that about 15 or 20 diseases can be modified markedly or suppressed almost completely, at least temporarily.' Limited personal experience accords with that of others in

including rheumatoid arthritis, polyarteritis nodosa and disseminated lupus erythematosus in this group.

Problems of Case Management

Because of their effects in diseases whose natural courses have been strikingly altered by no other known remedies, these substances will be used and abused in the day-to-day practice of medicine for a long time before their indications and value have been fully assessed. Certain general principles of case management, albeit based on clinical impressions, are therefore of some practical importance. Some of these principles in relation to chronic diseases may be stated thus:

(1) Because continued relief of symptoms after stopping treatment is rare and unpredictable, it should not be anticipated in planning the management of a case.

(2) These hormones can become drugs of addiction. Like other drugs of addiction their withdrawal may be associated with distressing symptoms.

(3) Cortisone and A.C.T.H. suppress the inflammatory components of diseases. They do not restore tissues which have been destroyed and they do not relieve symptoms arising from tissue destruction.

(4) Because it can be taken by mouth or by single daily intramuscular injection, cortisone has been used in most studies of prolonged hormone administration. When given continuously for as long as fourteen months, suppression of natural adrenal cortical function has been only temporary (Boland, 1951). It seems that prolonged continuous administration may be a safe procedure.

(5) For every individual, there is a dose of hormone below which appreciable symptomatic relief is not attained; this may conveniently be called the critical dose and it has to be determined by trial and error in each case. The critical dose varies in individuals from time to time, presumably with fluctuations in activity of the disease process.

(6) Maintenance of the critical dose is necessary for effective therapy. Whether or not it can be maintained depends on whether this dose is one which causes intolerable 'side effects.' These are really undesirable physiological hormone effects and are reversible when drug administration is stopped.

(7) The incidence of side effects is unpredictable in any individual. They are commoner with high than with low doses, and in women at or past the menopause than in younger women and men (Ward and others, 1951). It follows that until the experiment is made in each individual, a forecast cannot be given that the maintenance of a critical dose will be practicable.

(8) Among the commoner side effects are the following: (a) Increased mental activity, which may be associated with difficulty in sleeping, requiring hypnotics. (b) Voracious appetite, which may lead to large weight gains calling for dietary restriction. (c) Sodium and chloride retention, which may lead to obvious oedema and may be associated with increased jugular venous pressure, rise in blood pressure and cardiac enlargement. This may be modified by limitation of sodium chloride intake to less than 1 g. daily and by administration of diuretics. Rounding of the facial contours is very commonly seen; it sometimes worries female patients, as do mild hypertrichosis and acneiform eruptions. Rarer side effects include glycosuria. This may be renal in type, or may indicate a true reduction in carbohydrate tolerance, when severe diabetic symptoms may develop requiring insulin for their control. Psychoses have been reported, generally in patients whose personalities were previously odd. Alkalosis with low serum potassium and chloride has been reported, for which potassium chloride may be given by mouth. The sudden return of mobility to elderly osteoporotic subjects may lead to spontaneous fractures. References to reports of these and other side effects may be found in Hench's Nobel Lecture (1952).

(9) Because of these side effects, certain diseases form relative contraindications to treatment with cortisone and A.C.T.H. These include hypertensive and valvular heart disease, diabetes mellitus, mental disorders and severe osteoporosis.

(10) Cortisone and A.C.T.H. modify reactions to infection without affecting the causal organisms themselves. Under the influence of these substances, infections may develop or spread and because the usual symptoms may be suppressed the gravity of the infection may not be appreciated. The symptoms of articular, pulmonary and laryngeal tuberculosis may be relieved during treatment, though tubercle bacilli remain in the tissues (Hench and others, 1950; Le Maistre and others, 1951). Hart and Rees (1950) showed an enhancing effect of cortisone on tuberculosis in mice and the possibility that a similar effect may occur in man has to be kept in mind. The symptoms usually associated with infections by pyogenic organisms may also be greatly modified by cortisone and A.C.T.H. as has been clearly shown in cases of pneumonia (Kass and others, 1950). Thus, whenever apparently trivial intercurrent illnesses develop during hormone administration, recourse to blood cultures, leucocyte counts and radiological examination of the lungs should not be delayed.

(11) Wound healing may be delayed during cortisone and A.C.T.H. administration. Though

in practice this does not always lead to trouble, the precaution may reasonably be taken of leaving sutures in place for longer periods than usual when operations are performed on patients under the influence of these hormones.

Conclusions

It is clear from these considerations that cortisone and A.C.T.H. are not the ideal therapeutic answers to chronic disabling diseases. The greatness of their discovery lies rather in the future possibilities of therapy which they have revealed. Yet in some diseases and especially in rheumatoid arthritis, they provide for some cases the most effective therapy at present available. When their prolonged administration is tolerated they may, by restoring working capacity, even now prove an economical form of treatment. In other cases their administration raises more problems than it solves. In any individual it is to be remembered that the assessment of their usefulness and practicability as therapeutic agents can only be made

by experiment ; the possibility that the experiment may have to be terminated must be faced by both doctor and patient from the start. Thus at the present time the decision whether or not to use cortisone or A.C.T.H. as a means of therapy in an individual case is not an easy one. Much fundamental work needs to be done before a rational basis for their use in chronic diseases is achieved.

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DELAYED HAEMORRHAGE FOLLOWING TRAUMATIC RUPTURE OF THE NORMAL SPLEEN SIMULATING SPONTANEOUS RUPTURE

By R. W. BAILLIE, M.B., F.R.C.S.E.

In writing of spontaneous rupture of the normal spleen, Hamilton Bailey stated: 'Forgotten trauma should be accepted as the cause. If that theory is discarded, we are plunged into a morass of speculation in which it is unprofitable to linger.'

The following case is recorded because it illustrates so well the truth of the above statement. In it rupture of the normal spleen followed upon an injury so insignificant as to be immediately forgotten by the patient, not associated by him with the subsequent abdominal catastrophe and, indeed, which he could only recollect after some days' reflection.

The patient, an athletic-looking young man of 31 years, was admitted in the early hours of the morning of January 8, 1950, as a perforated peptic ulcer. He complained of waking up on the

morning of the previous day at 8 a.m., i.e. 20 hours previously, with severe central abdominal pain which spread all over the abdomen and radiated into the base of the neck posteriorly. The pain eased off somewhat by midday, but became worse again in the evening. He had vomited twice during the course of the day and in the evening he fainted once.

There was no previous history of indigestion, but he had suffered from right renal colic two years before and his appendix had been removed at about the same time.

On examination, the temperature was 98.2° F. and the pulse varied between 80 and 92 per minute. The patient showed no gross pallor, but was extremely distressed, the pain being so severe that he was unable to lie down flat on the bed, and