Edinburgh Medical Journal

January 1952

HORMONES OF THE ADRENAL CORTEX IN CLINICAL MEDICINE

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THE adrenal cortex is the last of the important endocrine glands to yield its secrets to the investigator, but before the chemist could begin to study the nature of its secretion, it was necessary first for the physiologist and the clinician to define the problem.

Those who have watched adrenalectomised dogs pass into the critical stage of adrenal insufficiency and those who have attended patients who had Addison's disease know the full significance of the statement, " The hormones of the adrenal cortex are essential for life." During the past twenty years I have been asked questions such as, " Do you think the hormones of the adrenal cortex will ever have a place in clinical medicine ? " " Do you think it is worth while to continue chemical work on the study of the adrenal cortex ? " To these questions, repeated on many occasions, I always replied in the affirmative, not because of any prophetic vision but simply because I have watched adrenalectomised animals pass into the critical stage of insufficiency which was terminated by death.

At this time, when the daily press and medical journals carry an ever-increasing number of articles concerning the effects of cortisone, it seems important to point out that cortisone was not suddenly discovered as an abundant product ready for use.

The total time required for the current investigation of the adrenal cortex is now twenty-one years, of which six-sevenths were spent in the chemical laboratory. The ratio of the time required for the chemical work compared to the time cortisone now has been used in clinical medicine is approximately the same as the ratio of that portion of an iceberg which is submerged below the surface of the water to the shimmering spectacle seen above the water. As time passes, these relationships of course will change, but I hope that in future years the dramatic clinical effects of cortisone will not obscure the long and arduous chemical work which made cortisone available.

Shortly after it had been shown that adrenalectomised animals

Cameron Prize Lecture read before the Faculty of the Medical School of the University of Edinburgh, 9th October 1951.

could be maintained by control of the intake of sodium, potassium and chloride, Steiger and Reichstein prepared desoxycorticosterone by partial synthesis. It was then found that this steroid produced a great effect on the metabolism of electrolytes.[10, 21]

But as time passed, it was observed that treatment with desoxycorticosterone did not restore to normal strength patients who had Addison's disease; indeed, some patients died while taking doses of this steroid which adequately controlled the metabolism of electrolytes.

The clue which suggested the next step was provided by the use of the extract of the adrenal cortex. With the extract it was possible to maintain patients who had Addison's disease in a condition much closer to normal, and it became obvious that some hormone or a group of hormones other than desoxycorticosterone was essential.

The situation was indeed complex, for no less than 28 different members of the steroid family had been separated from the gland,[21] and it seemed possible that only a combination of several of them would be equivalent to the secretion of the adrenal cortex.

Answers to the many problems posed could come only from the preparation of many of these steroids in amounts sufficient for use in clinical medicine. But at the time this became apparent, only two laboratories were engaged in this work. One was that of Professor Reichstein in Zurich, Switzerland, and the other was in the laboratories of biochemistry at the Mayo Foundation, Rochester, Minnesota.

From a commercial viewpoint, the production and sale of desoxycorticosterone was not attractive. The number of patients who had Addison's disease was small, and in 1940 pharmaceutical companies, with one exception, were not much interested in further exploration of hormones of the adrenal cortex. The exception was Merck & Co., Inc., and at this time I wish to express my admiration for the unprecedented contributions they have made. For the past ten years the research laboratory of Merck & Co., Inc., and my laboratory at the Mayo Foundation have co-operated, each within its own sphere, in progress toward a common goal—to make the hormones of the adrenal cortex available for clinical use.

In addition, it should be pointed out that for eighteen years the Mayo Foundation supported what some thought might well be an unrewarding investigation. This also is without precedent, and perhaps never will be equalled. Finally, I wish to pay a warm tribute to my many associates and assistants. They have been listed elsewhere [13]; without them the project could not have been completed.

I shall not attempt to describe in detail the work which culminated in the large-scale production of cortisone. You probably know that the starting material was desoxycholic acid, which was prepared from the bile of sheep and cattle. Five alterations are involved in the conversion of the bile acid into cortisone. Between the years 1940 and 1946 methods were devised in my laboratory by which four of

the alterations could be accomplished. The product thus obtained was not cortisone, or " compound E," as it was then known, but was the closely related steroid compound A.

The preparation of cortisone involves all the steps required for the preparation of compound A, and in addition it is necessary to introduce a hydroxyl group at C-17 of the steroid nucleus. To-day there are four methods which will accomplish this step. One of these recently has been devised in my laboratory,[11] but for the first production of cortisone this step was carried out by a method discovered in the research laboratory of Merck & Co., Inc., by Dr L. H. Sarett.[23] This contribution was most timely, for it permitted investigation of the effect of cortisone in clinical medicine in the summer of 1948.

The cost of cortisone to the patient has been brought quickly within the reach of many, and it is certain that the cost will be lowered still further. Pharmaceutical manufacturers other than Merck & Co., Inc. are now interested, and starting material from plants probably will be utilised. Methods for the total synthesis of the steroid nucleus recently reported by Professor Woodward of Harvard University and by Professor Sir Robert Robinson of Oxford may be the answer to an unlimited supply of the hormone.[22, 39]

Furthermore, large amounts of all the family of pregnene derivatives closely related to cortisone,[19] including compound F, designated " hydrocortisone," are available to the physiologist and the clinician.[36] It has been shown that Addison's disease can be treated successfully with a daily dose of a combination of a few milligrams of desoxycorticosterone and from 15 to 25 mg. of cortisone.

The control of cortical adrenal deficiency is now so satisfactory that surgeons do not hesitate to remove the adrenal glands from patients when this operation seems desirable. At the Mayo Clinic almost complete adrenalectomy has been performed on 40 patients who had Cushing's disease.[20, 29] Substitution therapy was used at first, in the form of an extract of the adrenal cortex, but more recently cortisone has been employed. In some instances, small amounts of desoxycorticosterone also have been used to control the metabolism of electrolytes. This procedure has been a life-saving measure.

More recently, Huggins has completely adrenalectomised a group of patients who had carcinoma of the prostate gland.[8] Growth of the tumour is influenced by androgens, and Huggins decided to remove the two principal sources of the steroids: the gonads and the adrenal glands. Quite apart from the control of the carcinoma, which remains to be determined, it is a source of great satisfaction to be able to maintain these adrenalectomised patients in a normal condition by substitution therapy.

We can now answer some questions concerning the many steroids separated from the adrenal cortex other than cortisone and hydrocortisone. It appears probable, that the adrenal cortex retains within the gland the large group of physiologically inactive steroids which

presumably represent intermediate stages in the elaboration of the two end products, cortisone and hydrocortisone.

The urine of patients and the blood of experimental animals, after administration of ACTH, was found to yield hydrocortisone and not cortisone. Recently, Conn and his co-workers administered 400 mg. of hydrocortisone daily to a normal person and produced many of the effects which are associated with stimulation of the adrenal cortex with ACTH.[1] These results leave little doubt concerning what steroid is released from the adrenal cortex when it is strongly stimulated, but they do not reveal the nature of the secretion of the adrenal cortex under mild stimulation. Zaffaroni, Burton and Keutmann observed the presence of both cortisone and hydrocortisone in normal human urine, and Schneider separated about 50 mg. of cortisone from 1000 litres of urine of normal young men.[24, 40] Subsequently he also succeeded in the isolation of hydrocortisone.

These results may be explained by the chemical structure of these two hormones. Hydrocortisone appears to be the primary product when C-11 is oxygenated, whereas cortisone is formed by further oxidation of hydrocortisone. When the adrenal cortex is under strong stimulus, hydrocortisone may be discharged before it can be converted into cortisone by the oxidising enzymes in the adrenal cortex, but under more normal conditions cortisone is elaborated from hydrocortisone and is secreted from the gland. This must be true in the adrenal cortex of cattle, since cortisone has been isolated from this source and in amounts which are greater than the quantity of hydrocortisone present.

The conclusion that, of the 11-oxygenated group in the secretion of the adrenal cortex, only cortisone and hydrocortisone are present in significant amounts is a great simplification. But one other characteristic of the secretion must be considered. Cortisone alone, even in large doses, cannot restore a patient who has Addison's disease to a normal condition. When this disease is present sodium and chloride are rapidly lost, and it is necessary to control this failure in the metabolism of electrolytes. This is achieved by the administration of an extract of the adrenal cortex or of small amounts of desoxycorticosterone. Such treatment shows that, in addition to cortisone or hydrocortisone, the secretion of the adrenal cortex contains at least one other hormone which is essential for the metabolism of electrolytes. There are reasons to believe that this hormone is not desoxycorticosterone. The early work on the adrenal cortex carried out by Wintersteiner and Pfiffner indicated that there is a constituent of the amorphous fraction which is essential for normal renal activity.[10] Almost twenty years have passed since this work was completed, but the chemical nature of the amorphous fraction still remains unknown.

I have mentioned the fact that employment of an extract of the adrenal cortex eventually led to use of the 11 oxygenated steroids in Addison's disease. However, in clinical trials other than this,

administration of an extract of the adrenal cortex was disappointing. In the treatment of burns, shock, anorexia nervosa, rheumatoid arthritis and other clinical conditions the uniformly negative results seemed to give clear warning that the full measure of the function of the adrenal cortex had been taken and that nothing more remained to be discovered. But, in 1943 my former colleague, Dr Dwight J. Ingle, included the following paragraph in a paper read at a hormone conference.

"Although the past nine years have brought more new advances in this field than has any other decade, the known facts still defy full explanation by any simple concepts and the problems yet untouched are multitudinous. I should like to venture the prediction that investigators who have not yet entered the field will some day, many decades hence, be listed among the pioneers in adrenal cortex physiology." [9]

At the time this was written, eight years ago, almost everyone regarded the paragraph as interesting but superfluous, and as the years passed the pessimism deepened. This attitude appeared to be justified and was strengthened by clinical trial in 1946 of compound A, 11-dehydrocorticosterone. It was found to be of little value in the treatment of Addison's disease.[30]

The development of the hormones of the adrenal cortex as therapeutic agents did not come through the orderly advances made by physiologists on experimental animals. The transition from what was known about the effect of cortisone in Addison's disease to the much wider use of this hormone in clinical medicine was the result of investigations on patients.[5, 6, 7, 35]

Regarding the problem in retrospect, it is easy to understand now why these clinical results did not become evident from use of the extract of the adrenal cortex which had been available for fifteen years. Throughout this interval there was no evidence that the adrenal cortex could modify in any significant way such conditions as rheumatoid arthritis, choroiditis, sprue or silicosis. Even if an extract had been tried, the daily requirement would have been far greater than anyone envisaged, and we know that the oral or parenteral administration of an extract of the adrenal cortex is not a satisfactory way to use these hormones.

In an extract of the adrenal cortex all the material is in aqueous solution. It is rapidly absorbed and rapidly metabolised or conjugated and rendered inactive. Experience has shown that cortisone or hydrocortisone should be given as a slightly soluble suspension which provides a reservoir from which the hormone can slowly diffuse and maintain a certain concentration in the blood and tissues for long periods.

The elaboration of cortisone by enzymes through the selective oxidation of pregnane is carried out within the adrenal cortex, and although other steroids when administered to the patient may be

converted into cortisone or hydrocortisone by the adrenal cortex, the availability of the latter two hormones to the body does not appear to be increased significantly.

Contrary to the oxidative effect of the enzymes in the adrenal cortex, enzymes in other tissues of the body tend to modify cortisone in the opposite direction, since reductive changes are induced.[14]

The rate at which these changes modify the structure of cortisone is one factor which determines the length of time during which this hormone can function, and this appears to be important in relation to the daily dose which is required. In some diseases, or at least in some cases, the symptoms are controlled only with relatively enormous doses of cortisone. For one patient who had lupus erythematosus, daily doses of 200 and 500 mg. proved to be inadequate, but the use of 2300 mg. in one day was followed by a remission.[4]

Progress recently has been made by several investigators in an attempt to explain the fate of large amounts of cortisone administered to the human being, and also to determine how much of this hormone is excreted in the urine of normal persons.

During the early stages of the investigation, extractions of urine yielded but small amounts of corticosteroids as measured by liberation of formaldehyde from a ketol or glycol side chain at C-17. Only 3 or 4 mg. were excreted per day when 100 mg. of cortisone was administered, but it has now been observed that corticosteroids are excreted in combination with glucuronic acid, and that after the glucosidic linkage has been broken, large amounts of steroids can be recovered. Venning has reported the separation of about 25 mg. of corticosteroids after the administration of 100 mg. of cortisone acetate.[34] Mason has found as much as 30 mg. in the urine of a normal man.[15] Corcoran has found similar amounts of corticosteroids per day in the urine of a normal person.[2] All this material was not cortisone, but it is probable that for the most part it was derived from cortisone or hydrocortisone. It is also probable that the quantity excreted in the urine was not equal to the total amount of cortisone and hydrocortisone which was delivered to the body in the secretion of the adrenal cortex.

The extension of the use of cortisone from rheumatoid arthritis to 20 or more other diseases rapidly followed the observation that the symptoms of rheumatic fever, hypersensitivity and certain lesions of the skin were relieved by this agent, and investigations soon were made on the effects of cortisone on the family of diseases designated the " collagen diseases." [12, 13]

A recent compilation by the medical department of Merck & Co., Inc., has listed some of the diseases which are modified by cortisone (Tables I and II).[17]

The influence of cortisone on the diseases associated with deficiency of the endocrine glands is readily explained as the effect of substitution therapy. In the adrenogenital syndrome, cortisone apparently relieves

an abnormal stimulation of the adrenal cortex by suppression of the adrenocorticotropic hormone.[37]

In the compilation of the chart, periarteritis nodosa was placed among the diseases on which cortisone has a transient effect, and burns were omitted. More recent results suggest that cortisone is helpful in burns, and that periarteritis nodosa should be placed among the diseases beneficially affected by cortisone.

TABLE I

Response to Cortisone in Various Diseases. Beneficial Effect often Dramatic

Endocrine diseases
- Addison's disease
- Panhypopituitarism
- Adrenogenital syndrome

Collagen diseases
- Rheumatoid arthritis
- Rheumatoid spondylitis
- Rheumatic fever
- Psoriatic arthritis
- Still's disease
- Lupus erythematosus disseminatus (early)
- Periarteritis nodosa

Various allergies
- Bronchial asthma
- Hay fever
- Angioneurotic œdema
- Drug sensitisation
- Serum sickness

Dermatosis
- Exfoliative dermatitis
- Pemphigus

Inflammatory eye diseases

TABLE II

Response to Cortisone in Various Diseases

Results thus far encouraging :—
- Burns
- Dermatomyositis
- Psoriasis
- Retrolental fibroplasia
- Agranulocytosis
- Certain forms of anæmia

Results thus far encouraging, but may be variable :—
- Acute gouty arthritis
- Ulcerative colitis
- Regional enteritis
- Nephrotic syndrome
- Pulmonary granulomatosis

Transient beneficial effects observed :—
- Scleroderma (early)
- Alcoholism

Transient beneficial effects observed, but ultimate prognosis unaltered :—
- Acute leukæmia (lymphocytic or agranulocytic)
- Lymphosarcoma
- Chronic lymphatic leukæmia
- Multiple myeloma
- Hodgkin's disease

A group of 16 patients who has periarteritis nodosa have been treated with cortisone or ACTH by Dr R. M. Shick and his associates at the Mayo Clinic, and results obtained for 13 of them recently have been reported.[27] In each case the diagnosis was confirmed by biopsy. The duration of symptoms varied from three weeks to ten months. Cortisone was administered at a dose of 300 mg. the first day and 150 to 200 mg. daily thereafter for six weeks, after which the dose was gradually tapered off.

Certain clinical phenomena that followed the administration of cortisone and ACTH are worthy of note. They include (1) prompt

subjective relief, (2) subsidence of fever, in most cases within twenty-four to seventy-two hours, (3) gradual decrease of the sedimentation rate, (4) partial relapses, in some cases, after withdrawal of the hormones, and (5) improvement of the patients in these cases after treatment was resumed.

Three of the patients died ; the disease of the remaining 13 patients apparently was in remission when they were last observed one to eighteen months after treatment, although evidence of residual vascular damage had persisted in most cases. At necropsy in 2 cases evidence of complete healing of all arterial lesions was found. In the process of healing, however, fibrous obliteration of the lumina of the involved vessels had occurred, resulting in widespread visceral infarction.

The complete disappearance of all histologic signs of active inflammation in 2 cases within three weeks, and three months after biopsy had disclosed the presence of acute arteritis, is a unique occurrence, and is difficult to interpret as coincidental.

To compile the list of diseases which are influenced by cortisone emphasises how great is the problem which confronts the clinician interested in research. To find the explanation of who cortisone influences such diverse conditions will not be easy.

One of the first attempts to explain the physiologic activity of cortisone was a study of the effect of this hormone on the metabolism of the electrolytes and protein. Used within the range of the daily dose which was found to be effective, the hormone caused only minor changes in the metabolism of electrolytes. When cortisone was used in larger amounts, however, it caused retention of sodium and loss of potassium and chloride. In addition, loss of nitrogen indicated a breakdown of protein.[31]

It is possible that the answer to the problem of how cortisone produces its effects lies hidden among the results already obtained ; but if this is so, the answer is well hidden.

Investigations concerning the diseases responsive to cortisone have been carried out in three different fields : (1) the endocrine glands, (2) bacterial infections, and (3) immunochemistry. The suggestion that many of the diseases influenced by cortisone are caused by a disturbance in the endocrine system comes from Selye, who proposed the hypothesis in the form of the adaptation syndrome.[25] You are familiar with the observations of Professors Pickering and Meiklejohn concerning this hypothesis, and I agree with their conclusions.[16, 18]

The essential part of the concept of the adaptation syndrome is that the secretion of the adrenal cortex is altered : that the hormones which control mineral metabolism, that is, the amorphous fraction, are secreted in abnormal amounts, and hence are a cause of the collagen diseases.

Some observations which make this hypothesis unacceptable are these : clinical investigation has shown that in the presence of rheumatoid arthritis and rheumatic fever, mineral metabolism is not

altered significantly, nor does cortisone in therapeutically active doses modify the metabolism of the electrolytes in an important way.

If the hypothesis of the adaptation syndrome is valid, the presence of abnormal amounts of steroids in the secretion of the adrenal cortex should afford an increase of corticosteroids in the urine. Quite the contrary is indicated in the fact that investigators have found that the daily output of steroids in many patients actually is less than the normal amount.

Although the administration of large amounts of cortisone will relieve the symptoms of rheumatoid arthritis, at the same time the activity of the adrenal cortex is suppressed, and several days or weeks may elapse before an increase of the 17-ketosteroids in the urine indicates that the activity of the adrenal cortex has been restored.[32, 33] However, the severe pain and even swelling of the joints may recur within a few hours after the administration of cortisone is stopped. It is difficult to ascribe the return of symptoms to a product elaborated in the adrenal cortex which is hypoactive.

Stimulation of the adrenal cortex with ACTH furnishes more evidence. One reason it seemed desirable to determine the influence of large doses of ACTH on rheumatoid arthritis was to find out whether or not stimulation of the adrenal cortex would increase the severity of the symptoms. If a product of the adrenal cortex was an ætiologic factor in this disease, as suggested by the adaptation syndrome, then stimulation of the gland should cause an exacerbation of the symptoms. The hormone, ACTH, was first used as a therapeutic agent in rheumatoid arthritis at the Mayo Clinic in February 1949. The result was not an exacerbation of the symptoms ; the symptoms were suppressed.[6]

Finally, there is the possibility that the production of an excess of the amorphous fraction and less than the normal amount of cortisone could result in the suppression of the effect of cortisone.

In addition to the evidence that the output of steroids may be less than normal in the presence of rheumatic arthritis, it is also true that the symptoms of rheumatoid arthritis are not increased by the administration of desoxycorticosterone. Neither is the antirheumatic effect of cortisone suppressed significantly by desoxycorticosterone. These observations are important in view of the fact that desoxycorticosterone exerts an influence in much the same direction as does the amorphous fraction, and if an antihormone action were involved, the response to cortisone should be lessened in the presence of desoxycorticosterone.

The foregoing results on patients stand in the way of acceptance of the adaptation syndrome as a probable hypothesis concerning the cause of the collagen diseases. The latest suggestion made by Selye that release of the hormones which affect mineral metabolism is influenced by the growth hormone instead of ACTH does not make the hypothesis more plausible in the light of the chemical and clinical results which are at hand.[26]

The second field of investigation is bacterial infection. I am not competent to review the extensive literature, but a causal relationship between infection and the collagen diseases has not been established to the satisfaction of all investigators.

The employment of chemotherapy and of powerful antibiotic agents has not been beneficial in the acute stage of the collagen diseases, but it has been shown, particularly in rheumatic fever, that antibiotic agents may reduce the incidence of recurrence.

One common condition in many of the collagen and in some infectious diseases is the presence of inflammation. Cortisone relieves the painful and swollen condition of a joint in tuberculous infection as effectively as it does the pain and swelling in a similar joint in a patient who has rheumatoid arthritis.[6]

The cortisone-induced breakdown of defensive measures which wall off infected areas, as in tuberculosis, may result in spread of the infection, but this same effect of cortisone in another disease may be useful in connection with an effective antibiotic agent.[3]

It has been found that in typhoid fever chloromycetin reduces the temperature to normal within forty-eight hours, but that if cortisone is given with the antibiotic agent, the temperature of the patient becomes normal within fifteen hours.[28, 38]

The third subject which has attracted the attention of investigators is the field of immunochemistry. But before this is considered it should be pointed out that cortisone exerts a protective action against a large number of chemical irritants and some antigenic substances. The severe reactions of the tissues associated with silicosis and the toxic effect of salts of beryllium are ameliorated. It is probable that one explanation of the favourable effect of cortisone in so many different syndromes is the protection of the tissues which it affords. But a still closer bond may exist.

Rheumatoid arthritis and rheumatic fever perhaps are not far separated in their nature and in their response to cortisone. Similar comparisons hold for some other members of the collagen diseases. It is possible that these relationships are based on some reaction perhaps of an immunologic nature which is common to all of them.

There are several ways in which cortisone could influence a state of hypersensitivity which is present in many diseases responsive to cortisone. It has been suggested that cortisone could modify the rate of formation of antigen, the formation of antibody, or the combination of antibody with antigen. It could modify the release of toxic material produced by the combination of antigen and antibody, or it could simply protect the cell from the effects of such toxic material.

Much work remains to be completed by investigators in many fields before the clinician will be able to make full use of the hormones of the adrenal cortex as therapeutic agents, but I should like to return briefly to the chemical work that made possible the use of cortisone and hydrocortisone. Three years ago a dark cloud of pessimism

shrouded the chemical investigation of the adrenal cortex. To make the first few grams of compound E had cost a king's ransom and Merck & Co., Inc., had decided that unless some wide use was found for it, they would not produce more of this hormone of the adrenal cortex. That dark cloud began to recede on 21st September 1948, for on that day the place of cortisone in clinical medicine assumed a new importance. It could then be seen that the stone which had been rejected by the builders was to become the head of the corner.

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