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THE ADRENAL CORTEX AND RHEUMATOID ARTHRITIS*

BY

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On September 21, 1948, at Rochester, Minnesota, 100 mg. of one of the hormones of the adrenal cortex designated "compound E" was injected intramuscularly into a patient who had rheumatoid arthritis. On September 28 Dr. Philip S. Hench had to depart from Rochester for London in order to deliver, on October 15, his Heberden Oration before members of this society. Those of you who heard Dr. Hench at that time may have been impressed with the vigour with which he presented the message which he brought to you, but I can assure you that his mind was troubled. On the one hand, there was reason to hope that perhaps something great had been accomplished. On the other hand, there was the disturbing thought that it might not be possible to repeat the result obtained in that single case on September 21.

So far as the patient back in Rochester was concerned everything was most satisfactory. She had been progressively disabled for five years, but after injection of the adrenal hormone for a few days all pain and stiffness had disappeared and she walked out of the hospital in a gay mood. Although this remarkable event had brought turbulence to the mind of Dr. Hench, it had nothing to do with the content of his Heberden Oration, since his manuscript had been prepared some time before the first injection of compound E was given. You will remember that Dr. Hench presented evidence which showed that rheumatoid arthritis is a reversible disease, and he suggested that some substance X, probably a constituent of the body, could bring about remission of the symptoms. If you will read the lecture (Hench, 1949) you will not find a discussion of the relationship of the adrenal cortex to rheumatoid arthritis. Indeed, what little mention of this he had made in an early draft was deleted, for neither Dr. Hench nor I wanted to make a premature announcement of what we hoped to show concerning the nature of substance X.

For many years Dr. Hench had searched for some clue that would reveal the nature of substance X (Hench, 1950). He had investigated the effect of jaundice induced by lactophenin, the influence of bile acids and their derivatives, bilirubin, lecithin, and an extract of the adrenal cortex. But the first injection of compound E, or cortisone, as it is now known, was not accidental, nor was it based on a hasty decision. During the previous ten years Dr. Hench and I frequently had discussed

the nature of rheumatoid arthritis and had decided to use cortisone as soon as it became available.

The unhappy combination of events which troubled Dr. Hench when he gave the Heberden Oration in 1948 can be understood easily. The result of the injection of cortisone was too gratifying and too important to be ignored; it appeared to be the answer to years of frustration, and yet it was necessary to refrain from any mention of the treatment of a single patient before the Heberden Society. To give the Heberden Oration in 1951 is a source of great satisfaction to me, for now you know that the first patient has been followed by many thousands of others, and that the early misgivings have been replaced with assurance based on the knowledge that cortisone brings relief from the symptoms of rheumatoid arthritis, despite the fact that we do not yet know just how this is accomplished.

I wish it were possible to make a statement concerning the identity of substance X. But substance X has never been isolated as a chemical compound. It was described only in terms of its physiological activity, which was related to the physiological activity induced by both pregnancy and jaundice. Cortisone may well be substance X so far as pregnancy is concerned, but the relationship between jaundice and rheumatoid arthritis still remains obscure. Perhaps in jaundice less of X is required, but speculation alone about this matter cannot bring the answer. As more work is carried out, the influence of jaundice on rheumatoid arthritis will become evident. As we come to know more and more about cortisone the importance of the identity of substance X grows less, but the significance of the message delivered in 1948 by Dr. Hench—namely, that rheumatoid arthritis is reversible—will continue to gain importance, for ultimately this fact will be concerned with the aetiology and treatment of the disease itself.

There is another difference between the subject matter of the Heberden Oration of 1948 and that of 1951. Dr. Hench presented his results in terms of clinical experience. The chemical aspects of the problem were not mentioned in any important way. But in 1951 a discussion of the relationship of a product from the adrenal cortex to rheumatoid arthritis can be stated in the precise chemical terms of structural organic chemistry, and the daily requirement of a pure crystalline compound can be expressed in milligrams. But perhaps the greatest difference is in the attitude of the specialist

*Heberden Oration read before the Heberden Society, London, England, on September 19, 1951.

and the public towards rheumatoid arthritis. The subject, rheumatology, has come into its own. The sustained interest is based on recent advances in our knowledge of the hormones of the adrenal cortex, and it is my privilege to-day to tell you something about these new results.

Chemical Phase of the Investigation

Almost twenty years were required for the chemical phase of the investigation. During the first ten years the chemical nature of the adrenal cortex was explored. This work was carried out by Professor Reichstein and his associates in Zurich, Switzerland, and in the biochemical laboratory of the Mayo Foundation at Rochester, Minnesota, by my associates and myself. At this time I wish to express my appreciation for the essential contributions made by my associates, without whose help the investigation could not have been completed. In addition, important contributions came from the laboratory of biochemistry of Columbia University. These were made between 1933 and 1936 by Drs. Wintersteiner and Pfiffner (Reichstein and Shoppee, 1943; Kendall, 1950a, 1950b; Kendall *et al.*, 1946-51).

By the year 1940 it was generally agreed that the 28 steroids that had been separated from the gland could be divided into four groups. First were certain sex hormones—androgens, oestrone, and progesterone—which were not characteristic of the adrenal cortex. Second was a group of steroids which were found only in the adrenal cortex, but which were physiologically inert. Third were six derivatives of Δ^4 pregnene, all of which possessed physiological activity. Fourth was a residue which remained after separation of the crystalline compounds. This fraction, which has been available for about fifteen years, exerts a strong effect on renal function, and indeed is essential for the control of the metabolism of electrolytes, but its chemical nature has not been established and it is still known as the "amorphous fraction."

After the six crystalline compounds had been isolated from the adrenal glands and their structure had been determined, it became apparent that before any investigation could be carried out in the field of clinical medicine some source for these hormones other than the adrenal cortex would have to be found. This was true not only because of the expense involved in the isolation of the hormones but also because the supply of adrenal glands was limited.

For this reason, attempts were made in Professor Reichstein's laboratory and in my own to devise methods by which these steroids could be prepared from some starting material other than the adrenal cortex. Professor Reichstein was the first to prepare 11-desoxycorticosterone, corticosterone, 11-dehydrocorticosterone, and 17-hydroxy-11-desoxycorticosterone (Reichstein and Shoppee, 1943). However, except for 11-desoxycorticosterone, the method which was used could not be employed for large-scale production of these compounds. A suitable procedure for large-scale production of 11-dehydrocorticosterone (compound A) was devised in my laboratory during the years 1940 to 1944, and by the end of 1946 Dr. L. H. Sarett, in the research laboratory of Merck & Co., Inc., expanded the scope of this method by the addition of one more step which resulted in hydroxylation at position 17. This afforded 17-hydroxy-11-dehydrocorticosterone, first called "compound E" and now designated "cortisone" (Sarett, 1948). In 1950 a close relative of cortisone was prepared in the research

laboratories of Merck & Co., Inc. This is 17-hydroxycorticosterone, first called "compound F" and now designated "hydrocortisone" (Wendler *et al.*, 1951).

But merely to describe the preparation of these steroids from starting material derived from bile, rather than from the less abundant adrenal cortex, is an incomplete statement of the contributions of the chemist. New means to carry out some of the essential changes in the starting material have been found. The hydroxyl group at C-17 can be introduced by no fewer than four different methods, and the yield for one of the steps—introduction of the double bond in ring A—has been improved in my laboratory to such an extent that the amount of starting material originally required for the daily maintenance of 35 patients will now furnish the same amount to 93 patients (Kendall *et al.*, 1946-51).

An Outstanding Contribution to Medicine

The production of cortisone by Merck & Co., Inc., is without precedent, and the distinguished record of their contribution to medicine will be appreciated by an ever-increasing number of grateful patients. The rapid decrease in the cost of cortisone is to-day an important factor in the use of this hormone in clinical medicine. However, still further reductions in the price of cortisone will occur, since the chemist has not yet finished investigating methods for the production of this hormone. The innermost portion of the molecule, ring C, has now come within the reach of the chemist, and new sources of starting material from the plant kingdom will soon be available. Most significant advances have come from the laboratory of Professor Woodward and his associates at Harvard University and from the laboratory of Professor Sir Robert Robinson at Oxford. They recently have reported the total synthesis of the steroid nucleus, and the way is now open for the application of this knowledge to the total synthesis of cortisone (Robinson, 1951; Woodward *et al.*, 1951).

Organic chemists have made important contributions to another phase of the work which already has been of help to the physiologist and the clinician. This work is the preparation of 50 or more steroids, closely related to cortisone, so that it has been possible to determine the physiological significance of the various functional groups in the molecule (Polley and Mason, 1950).

Finally, still other chemists have devised methods for the determination of adrenocortical steroids in the blood and urine. These results indicate the amount and distribution of the steroids in the secretion of the adrenal cortex, the fate of cortisone after it has been administered, and some insight into the daily amount of cortisone that can be produced by the normal human adrenal cortex.

Physiological Studies

In the meantime, physiologists have studied the mechanism which controls the activity of the adrenal cortex and the various influences which affect the stimulation of the gland through the release of the adrenocorticotrophic hormone of the anterior pituitary body, designated A.C.T.H. All these are recent advances, and many of them have been stimulated by the results which followed the injection of cortisone on September 21, 1948.

It is interesting to recall the circumstances which prevailed at the time of the first injection, for as we review them now it is evident that the method devised for the administration of the first dose of cortisone conformed

remarkably to the conditions which we now know are essential. In short, it was necessary to furnish the hormone in a form which would be absorbed slowly over a period of several hours. If the rate of absorption had been too fast or too slow the result could have been misleading. Moreover, if the daily dose had been too small the result would have been negative. Fortunately, the first use of cortisone demonstrated to Drs. Hench, Slocumb, Polley, and me its influence on rheumatoid arthritis, and further work has added more information which confirms the early observations (Hench *et al.*, 1950; Kendall, 1950a).

A modification in the method of administration, helpful alike to physician and patient, was made when it was found that cortisone acetate can be administered orally. The daily dose required is about the same as the amount given by parenteral administration.

Chemical Specificity of Action of Cortisone

One of the first questions which were asked concerning the effect of cortisone was in regard to the chemical specificity of its action. It seemed probable that the essential functional groups in cortisone might be incorporated in some other steroid which could be prepared more easily, or that perhaps a quite different chemical structure would be as good or better. It must be admitted that some of the examples of this sort of juggling are encouraging. Diethylstilboestrol demonstrates what can be done in the family of oestrogens. Another recent contribution is the preparation of a compound which has a structure resembling that of histamine. This compound strongly stimulates gastric secretion, but is entirely free from the many other effects of histamine (Rosiere and Grossman, 1951). Cocaine simplified to "novocain" and many other examples could be given, but in the case of cortisone the problem is not so simple. The influence of cortisone has been shown to be specific; so far as we know, it is not shared with any other steroid except hydrocortisone. We also know that both cortisone and hydrocortisone are elaborated in the adrenal cortex, and appear to be the steroids which have survived the processes of selection throughout the long ages of evolution. This, of itself, is a warning that the task of finding a substitute will not be a short or an easy one (Polley and Mason, 1950).

At any rate, no substitute is known to-day, and many steroids have been tested. Unfortunately, the technique of testing has been unsatisfactory in much of this work. The patient who has rheumatoid arthritis or some other responsive disease is the only possible test object, and for the evaluation of any new product the psychic responses of both the patient and the clinician are involved. This has resulted in some disagreements, such as arose in the study of a combination of desoxycorticosterone and vitamin C. Pregnenolone, the 21-acetoxy derivative of this steroid, and the sex hormones also have enjoyed their brief interval in the limelight, but it is now generally agreed that none of these can be regarded as a substitute for cortisone (Kendall, 1950b).

Physiological Effect or Pharmacological Response?

Another question concerned the nature of the effect of cortisone: whether it could be regarded as physiological or simply as a pharmacological response to a massive dose of a steroid. A partial answer can now be given to this question. The answer is based on two aspects of the problem. The first relates to the physio-

logical response of the adrenal cortex itself. In the recent investigations of Venning (1951), Mason (personal communication), and Corcoran *et al.* (1951) the amount of corticosteroids conjugated with glucuronic acid in the urine has been determined, as well as the amount of corticosteroids in the free form. These results indicate that from 30 to 60 mg. of corticosteroids may be excreted daily by a normal man, unaided by the administration of A.C.T.H. Since the total quantity of cortisone or hydrocortisone available is the sum of the amount produced in the adrenal cortex plus the amount administered, and since the production of cortisone in the adrenal gland is suppressed by administration of the hormone, the total amount available may come within the physiological range. Certainly, many patients who have rheumatoid arthritis are notably relieved by a daily maintenance dose of less than 60 mg. of cortisone.

The second consideration is the highly effective manner in which cortisone is delivered to the tissues by way of the secretion from the adrenal cortex, compared with the rate of absorption of the hormones when given parenterally or orally. It is impossible to determine how much of any injection is utilized effectively, but, whatever this amount may be, it is probably much less than the total. This would tend to bring the actual minimal requirements closer to physiological amounts.

The small quantity of cortisone required to bring about a remission of the symptoms of rheumatoid arthritis in some patients indicates that the normal human adrenal cortex can provide the necessary amount of its hormones. It seems probable that throughout the span of human life the adrenal cortex may provide protection during the potentially dangerous phases of a latent or subclinical attack of rheumatoid arthritis, and it would appear profitable to inquire into the activity of the anterior pituitary body and the adrenal cortex to determine whether failure on the part of either of these glands is associated with symptoms of rheumatoid arthritis.

I should like to engage in a bit of speculation to the effect that the reason the lower animals do not have rheumatoid arthritis or rheumatic fever may be that they are more adequately protected by a higher concentration of the hormones of the adrenal cortex within their tissues. Perhaps, in the evolution of mankind, a closer adjustment of the activity of the adrenal cortex results occasionally in a failure of this safeguard, and as a result rheumatic fever and rheumatoid arthritis run their course.

Nature of Rheumatoid Arthritis

From the vantage point provided by the many research projects which have been briefly reviewed, a few questions concerning the nature of rheumatoid arthritis can be answered. Rheumatoid arthritis is not an endocrine disease in the usual sense of the term. No combination of overactivity or underactivity of the ductless glands appears to be important in the aetiology of rheumatoid arthritis. Although the administration of cortisone and hydrocortisone can bring about a remission in the symptoms of rheumatoid arthritis, accompanied by a nutritional gain in weight and suppression of synovitis, these results cannot serve as a basis for the hypothesis that a deficiency of the hormones of the adrenal cortex is the cause of rheumatoid arthritis. The incidence of rheumatoid arthritis in the presence of Addison's disease is not significantly increased above that of a coincidental relationship.

There are other possibilities in a consideration of the adrenal cortex and rheumatoid arthritis. One is the effect of an alteration in the distribution of the constituents of the secretion from the gland. It has been shown that the adrenal cortex not only elaborates crystalline steroids, among which are cortisone and hydrocortisone, but that in addition important physiological activity is present in the amorphous fraction. Theoretically, it would be possible for the gland to produce excessive amounts of the amorphous fraction and insufficient amounts of cortisone and hydrocortisone. If this were true, the normal balance between the two types of hormones would be altered. The effect of cortisone might be suppressed, and the overabundance of the amorphous fraction would be unrestrained from exerting an influence which would be abnormal (Selye, 1950a, 1950b).

This hypothesis does not seem probable. The amorphous fraction is concerned with the metabolism of electrolytes, but in rheumatoid arthritis mineral metabolism is not altered significantly. Desoxycorticosterone also modifies the metabolism of electrolytes, and does so in much the same direction as does the amorphous fraction, but the administration of desoxycorticosterone to a patient who has rheumatoid arthritis does not cause an exacerbation of the symptoms, nor does it block the favourable effect of cortisone.

An observation which indicates that the symptoms of rheumatoid arthritis are not produced by abnormal amounts of the amorphous fraction has to do with the results of abrupt cessation of the administration of cortisone. It is well established that large doses of cortisone suppress the activity of the adrenal cortex. After a patient has been relieved of painful symptoms by the use of cortisone the symptoms may return within a few hours if administration of the hormone is stopped. It is not probable that the symptoms can result from a return of activity of the adrenal cortex. There may be a delay of several days before the amount of 17-ketosteroids in the urine indicates restoration of the activity of this gland (Sprague, 1950b).

Other Possible Causes

Another way in which the adrenal cortex might be the cause of rheumatoid arthritis is by the elaboration of a product not normally present. But studies thus far have not provided support for this hypothesis, since investigators frequently have found less than normal amounts of 17-ketosteroids and corticosteroids.

If some rheumatogenic agent were produced by the adrenal cortex, then stimulation of the gland should lead to an exacerbation of the symptoms. Such a demonstration would provide convincing evidence, and was one of the reasons why A.C.T.H. was administered to a patient who had rheumatoid arthritis. When this was tried for the first time at the Mayo Clinic in February, 1949, the symptoms of the disease did not become worse; on the contrary, stimulation of the gland with A.C.T.H. produced a remission of the disease (Hench *et al.*, 1950).

Since rheumatoid arthritis does not appear to be a metabolic disease caused by a disturbance in the endocrine glands, and since there are good reasons for believing that the disease is not produced by an intra-articular bacterial infection or a virus, the search for the nature of the causative agent has been directed to still other possibilities. The use of cortisone in a large number of clinical conditions has afforded results which

indicate a field of research that may be fruitful. I refer to a study of the state of hypersensitivity and the phenomena associated with allergens, antigens, and antibodies, and the results of their interaction. It has been shown that cortisone can modify the effect of a large number of chemical irritants and protein antigens. For example, cortisone ameliorates the severe reaction of the tissues to salts of beryllium, and it also will lessen the response to the tuberculin reaction. Whether rheumatoid arthritis is caused by a foreign agent, such as an antigen, has not been established, but it is possible that cortisone could cause a remission in the symptoms of rheumatoid arthritis by protecting the tissues from such an agent. It could modify the rate of production of the antigen or the rate of production of an antibody, or it could protect the tissue from the effect of the products formed by combination of the antigen with the antibody. Further work in this field may yield important information concerning the aetiology and treatment of rheumatoid arthritis.

A Clinical Study

While research concerning the aetiology and optimal treatment of rheumatoid arthritis is in progress, the availability of cortisone has permitted its use by rheumatologists in the United States and to a more limited extent in other countries.

Practically 100% of patients who have active rheumatoid arthritis respond in some degree to the administration of cortisone. Furthermore, the extent of the relief has been satisfactory in a high percentage of the patients. Problems have arisen in connexion with long-continued administration of the larger amounts of the hormone which are required to control the symptoms in some patients. Recently a group of 100 patients who had rheumatoid arthritis were treated with cortisone at the Mayo Clinic. The result of the investigation furnishes an example of what can be expected at the present time in the treatment of rheumatoid arthritis with cortisone (Ward *et al.*, 1951).

Most of the patients were not admitted to hospital. Seventy-three received cortisone orally from the beginning, 27 at first received cortisone intramuscularly and then orally. Only one patient was not relieved when cortisone was given by mouth. This patient did respond when cortisone was given parenterally.

There were five objectives to the study. These were to determine: (1) the dose of cortisone required to suppress the symptoms; (2) the rate at which the initial dose could be reduced; (3) the long-term maintenance dose; (4) the effect of withholding cortisone; and (5) the percentage of patients in whom side-reactions developed.

There was a wide range (from 38 to 200 mg.) in the daily dose of cortisone required to suppress symptoms. The symptoms of a third of the patients were suppressed by 75 mg. or less, and 20% were relieved by a daily dose of 50 mg. From two days to two weeks was usually required to obtain the degree of suppression desired before reduction of the dose was started.

Dosage

In passing from the suppressive to the maintenance dose, the best results were obtained when reduction of the daily amount of cortisone was made in small decrements and at intervals of several days. The daily dose of cortisone could be reduced more rapidly for those

patients who had responded quickly to the suppressive doses. The rapidity of reduction was determined in each case by the patient's clinical—that is, the symptomatic—response, not by the sedimentation rate or other laboratory findings.

The maintenance dose was determined by two factors: reasonable control of symptoms and the occurrence of "side-effects." Eighty-six per cent. of the patients were maintained on a daily dose of 75 mg. or less, and more than half the patients received 50 mg. or less each day.

The effect of withdrawal of the hormone from most of the patients cannot be reported, since 89 of them were still under treatment as this was written. Symptoms returned in 9 of 11 cases when the administration of cortisone was deliberately discontinued. At the time of writing one of the two remaining patients had been in remission for two months; the other had been free of symptoms for ten months.

Side-effects developed in about half of the patients, but the occurrence of these effects did not necessitate discontinuation of the administration of cortisone to any patient during the study. At times the daily dose was reduced in order to control side-effects. These side-effects were related to the dose of cortisone and to the sex and age of the patients.

Busy practising clinicians are disconcerted because some patients cannot take optimal antirheumatic doses of cortisone indefinitely, and because symptoms return when the use of the hormone is discontinued. Therefore they raise, somewhat prematurely, questions concerning the long-range value of cortisone as a therapeutic agent. But the fact that rheumatic symptoms are suppressed by cortisone and return when cortisone is withheld has provided a challenge to clinical investigators which they expect to meet and solve by more study. At the present time many questions have been answered satisfactorily. Some questions remain to be answered, but the advances in our understanding of rheumatoid arthritis which have come during the past three years lend assurance that further research will be well repaid (Sprague, 1950a; Sprague *et al.*, 1950).

In the acute phase of rheumatic fever cortisone will abolish the symptoms, and it seems to protect the heart from damage. Whether cardiac changes will occur after the acute phase has passed will not be known for some years, but the results to date are encouraging.

Conclusion

The two syndromes—rheumatoid arthritis and rheumatic fever—are not far separated in their nature and in their response to cortisone. Similar comparisons hold for some of the other collagen diseases. Perhaps the most hopeful aspect of the study is the wide portion of clinical medicine which is influenced by this hormone. The unexpected and far-reaching influence of cortisone on many diseases may be produced through its control of some causative agent which is common to all of them. The nature of this agent is unknown, but I agree with Professors Pickering (1950) and Meiklejohn (1950) that the hypothesis of the adaptation syndrome of Selye (1950a, 1950b) is not acceptable.

To-day it can be said that cortisone will relieve the pain and symptoms of rheumatoid arthritis, and it constitutes a life-saving measure for other syndromes, but to the clinician interested in research it will be a key which will unlock the doors of barriers and reveal secrets long hidden.

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THE INFLUENCE OF UNILATERAL NEPHRECTOMY ON THE PRODUCTION OF EXPERIMENTAL ARTHRITIS IN THE ALBINO RAT

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[WITH SPECIAL PLATE]

The production of an acute mono- or poly-arthritis by repeated injections of deoxycortone acetate (D.C.A.) has been demonstrated by Selye *et al.* (1944) in rats subjected to removal of the left kidney and given 1% saline to drink. Outside Selye's own laboratory this finding has been confirmed by Pirozynski and Akert (1949). Other investigators (Harrison, 1946; Kuzell, personal communication) using Selye's methods were, however, unable to produce arthritis in rats. Selye (1946a) at first suggested that this may have been due to feeding the rats a diet inadequate in protein content; more recently (Selye, 1950) he has stated that the cause of the "inconstancy in the production of arthritis by D.C.A. has not yet been elucidated, but presumably it depends upon the presence of conditioning factors such as some local irritant."

In view of this inconstancy and the discrepancy between the results of different investigators, it was decided to reinvestigate the problem. Since in the original experiments (Harrison, 1946) it was possible to control all of the experimental techniques used by Selye *et al.* (1944) except that of nephrectomy, it seemed that the manner of performing this operation might be a possible cause of the discrepancy. This supposition appeared more likely since it has been shown (Harrison, 1951) that interruption of an adrenal artery in the rat or rabbit results in an area of necrosis