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The Present Status of Cortisone and ACTH in General Medicine

By Philip S. Hench, M.D.

Dr. Philip S. Hench, of the Mayo Clinic and Professor of Medicine at the University of Minnesota (Mayo Foundation), addressed a meeting of the Experimental Medicine Section on "The present status of cortisone and ACTH in general medicine". The meeting, to which members of the Sections of Endocrinology, Medicine, and Physical Medicine were invited, crowded out the Barnes Hall and the proceedings were relayed to the West Hall. The chair was taken by the President of the Section, Professor R. A. McCance, who was accompanied by the President of the Society, Lord Webb-Johnson.

Dr. Hench projected a film showing the results of cortisone or ACTH in a number of cases of rheumatoid arthritis studied by himself and his colleagues Drs. E. C. Kendall, C. H. Slocumb and H. F. Polley. It revealed the striking improvement in the posture and movements of patients and the disappearance of joint pain on pressure following a few days' use of the hormones, also the return of symptoms when, without the patient's knowledge, the hormones were withheld and a neutral substitute given.

At the close of the lecture Professor McCance expressed the thanks of the assembly to Dr. Hench. He said that the lecture had demonstrated how much could happen in eighteen months of medical research, and he wondered what further achievement there would be to record if they made a date with Dr. Hench in eighteen months' time. They had to thank not only Dr. Hench himself, but the Past President of the Society, Sir Henry Dale, who had got Dr. Hench to come, and the Nuffield Foundation which had made his visit possible.

Dr. Hench began his lecture with the statement that about 28 crystalline compounds and an amorphous residue had been separated from the adrenal cortex. One of these, Kendall's compound E, renamed cortisone, had been found to possess marked physiological potency. The anterior lobe of the pituitary secreted several hormones, one of which, the adrenocorticotropic hormone (ACTH) had the power to stimulate the adrenal cortex to pour forth its own products. Cortisone, according to some, was only one (though perhaps the chief) of the products which the adrenocorticotropic hormone stimulated the adrenal cortex to secrete; others took the view that cortisone, or a cortisone-like substance such as compound F, was the only hormone made by the adrenal cortex.

Differences Between Cortisone and ACTH

Several differences between cortisone and ACTH had to be noted. The absorption and distribution of ACTH was rapid; hence it must be given three or four times a day at first; that of cortisone acetate was slow, and one daily injection usually sufficed. ACTH, being a protein, sometimes produced foreign protein reactions; cortisone, being a crystalline substance, induced no such reactions. An important difference was that cortisone and ACTH were not, clinically or physiologically, equal milligramme for milligramme. Apparently 100 mg. of ACTH might stimulate the production of 200 or more mg. of cortisone; so that doses of about 40 mg. of ACTH were comparable with those of about 100 mg. of cortisone.

Within recent months it had been found that both agents not only influenced a few relatively rare endocrine conditions, but might affect rather profoundly many diseases which appeared to be non-hormonal and to have no connexion with the

pituitary or adrenal gland. In this broader sphere both were found to have anti-rheumatic properties, first in rheumatoid arthritis and then in acute rheumatic fever. Their suppressive effect on the "collagen" diseases then became apparent. They were also found to possess marked anti-allergic activity and to have a limited influence on certain blood dyscrasias.

The value of these agents as research tools could not yet be assessed, nor their merits as therapeutic agents finally predicted, but it appeared to be sufficiently established that a surprising variety of inflammatory reactions of widely different nature and causation could be suppressed, at least temporarily, by their administration.

Rheumatoid Arthritis

Dr. Hench here recapitulated the investigations which had led up to the first administration of cortisone in a case of rheumatoid arthritis in September 1948 and then the use of ACTH in such cases in February 1949. Improvement in the symptoms and signs of rheumatoid arthritis generally developed within two or three days, sometimes within a few hours, after daily injections of cortisone or ACTH were started. A diminution first of subjective and later of objective phenomena occurred, with a sense of well-being and increased psychomotor activity. Sedimentation rates went down and hæmoglobin concentrations increased. Electroencephalograms revealed changes in the alpha waves in patients during the administration of these hormones. The potency of these hormones when given alone having been established, orthopædists had begun to study their effects in conjunction with non-surgical procedures for correcting resistant flexion contractures.

Some patients had now received the hormones more or less continuously for several months. Relief of symptoms usually continued for as long as the hormones were given, but afterwards relapses had occurred, usually within one or two months of cessation of hormonal usage, though certain patients retained much, sometimes almost all, of their relief for several months without the hormones.

Rheumatic Fever

The acute manifestations of rheumatic fever had been quickly abolished by adequate doses of these hormones—apparently more quickly and consistently than by salicylates or other previous remedies. Fever, acute polyarthritis, tachycardia, and "toxæmia" usually disappeared promptly within a few days. Symptoms of acute rheumatic carditis were lessened or abolished—at least in some cases—and there were reductions in cardiac size. Within the limits of short follow-up studies, no definite signs of new, or increased old, carditis had developed from the acute attacks which were suppressed by the hormones.

It was the opinion of Dr. Hench and his colleagues, among them the cardiologists Drs. Arlie Barnes and H. L. Smith, that the hormones apparently did not "cure" the rheumatic condition even in those cases in which the abolished symptoms did not return on the stoppage of the hormonal injections; nor, probably, did they shorten materially the natural course of the acute rheumatic state or protect the rheumatic susceptible from his next attack.

Acute rheumatic fever developed when the latent rheumatic state of the susceptible was activated by the presence of an unknown irritant, commonly related to certain hæmolytic streptococcal infections. To this acute irritant certain tissues of the patients reacted sharply to produce the characteristic clinical picture of the disease. The acute phase of rheumatic fever might be defined as the time during which the unknown irritant was present or during which the tissues reacted to this irritant.

Cortisone and ACTH seemed to buffer the tissues against the irritant. The exudative reactions quickly subsided, and there was ground for thinking that even the proliferative reactions might be suppressed. If this was so, maximal protection could only be provided by continuing to give the hormone for the full duration of the acute rheumatic state (six to twelve weeks). After the acute state had passed the patient should be shielded by chemoprophylaxis (oral penicillin or sulphonamides) against the dangers of subsequent streptococcal infections.

Other Conditions

Dr. Hench then passed in review a large number of conditions in which the hormones had been used with varying results. In a few cases of osteoarthritis the symptoms had been moderately or markedly relieved; in others not at all. Acute gouty arthritis had been rapidly subdued. Three patients with pulmonary tuberculosis (without arthritis) had shown marked subjective improvement when given ACTH, but the pulmonary lesions in one case progressed during its use and in another increased after discontinuance. In two patients with proved tuberculous arthritis (without pulmonary lesions) cortisone brought about a decrease of articular symptoms and sedimentation rates, but tuberculin and other tests remained positive.

In disseminated lupus erythematosus some of the clinical features were usually markedly suppressed by cortisone or ACTH, but the incidence of adverse hormonal effects appeared to be higher in this disease than in most others. In some cases psychic aberrations, convulsive seizures, retention of fluid, and transient hypertension developed. Articular lesions with psoriasis had been more responsive to the hormones than had the skin lesions, which often seemed to require higher doses.

Cases of chronic ulcerative colitis had been studied. In a case with arthritis, cortisone, given for thirty-five days, induced a complete articular remission, also a symptomatic remission of the colitis which had lasted for seven months.

The hormones appeared to be strongly anti-allergic. A rheumatoid patient, given cortisone, was coincidently relieved of his hay fever. Marked remissions in perennial asthma or bronchial asthma with status asthmaticus had also been reported. Post-hormonal remissions lasted from one week to five months. A severe case of infantile atopic eczema, a few cases of urticaria or other skin reactions from sensitivity to penicillin, gold salts, or other drugs, and cases of allergic rhinitis had also been relieved.

One of the most promising fields of usefulness for these hormones was in acute and subacute inflammatory diseases of the eye. Marked and prompt results had been reported in uveitis, scleritis, iridocyclitis, and the like. Until recently hormones had been given intramuscularly for these ocular conditions, but now studies in local application of cortisone in eye drops or in ophthalmic ointment were being made by Drs. Olson, Peterson *et al.* at the Ford Hospital and by Drs. Henderson and Hollenhurst at the Mayo Clinic.

At the Mayo Clinic a few patients with periarteritis nodosa had had prompt subjective relief with the use of cortisone or ACTH. The local and systemic symptoms in two cases of cranial arteritis were apparently controlled by cortisone. In certain cases of leukæmia temporary remissions of varying duration and degree had been induced by a first or sometimes by a second course, but subsequent courses had been increasingly ineffective. In cases of nephrosis a beneficial diuresis with loss of œdema might be induced. In certain neurologic and psychiatric conditions (acute

poliomyelitis, acute multiple sclerosis, amyotrophic lateral sclerosis, myasthenia gravis, catatonia, schizophrenia) results had been negative or inconclusive.

Mode of Action of the Hormones

The physiological effects of cortisone and ACTH, Dr. Hench continued, appeared to be non-specific, by which he meant that if large enough doses were given for a sufficient length of time an effect could be demonstrated in almost everyone, normal or otherwise. Nevertheless, the ability of the hormones to ameliorate markedly almost the whole symptom-complex of certain diseases appeared to be group-specific. In affording this relief they did not kill germs or remove "unknown irritants", and therefore they did not *per se* cure the diseases the symptoms of which they modified so profoundly. But in some unknown manner they appeared to provide the susceptible tissues with a shield-like buffer against a wide variety of irritants. How they accomplished their anti-rheumatic effect was, to use a Churchillian expression, "a riddle wrapped in a mystery inside an enigma". They did not extinguish the fire, nor, carpenter-like, repair the damage, but they provided an asbetos suit in which the patient, like Shadrach, Meshach, and Abed-nego, walked unscathed in the furnace. If the protection was not discarded until the end of the natural duration of the "fire" the patient remained well.

"Side Effects"

The hormones were in general well tolerated, especially if given for only a few weeks; but sometimes a variety of undesirable effects might occur, some of them of little importance, others presenting certain hazards. Fairly frequent effects were mild irritability, initial retention (generally mild) of sodium chloride and water, mild hypertrichosis, acneform eruption, and "round face". Rare or rather rare side effects were transient reduction of carbohydrate tolerance, hypopotassæmic hypochloræmic alkalosis, major alterations of psyche, and spontaneous fractures in elderly osteoporotic persons. Owing to its potential effects cortisone or ACTH should be used with caution in hypertensive cardiovascular disease, diabetes mellitus, tuberculosis, old rheumatic carditis with decompensation, latent or frank psychoses, and senile osteoporosis. As a result of intensive studies side effects were now assuming a less prominent position; they were features to be respected, but not to be feared.

To obviate these side effects, and also to overcome the disadvantage of limited supply and high cost, an intensive search had been made for other steroids, more or less related chemically to cortisone. Except for compound F (not yet synthesized) the search so far had been fruitless. About 50 of these "mysteroids" (as Hollander of Philadelphia calls them) had been tested for clinical activity in rheumatic and other patients, and none had given significant results. As several of them differed from cortisone only in a single configuration, it appeared that the chemical structure of cortisone was remarkably specific.

Plan of Administration

Each of the responsive diseases might need a different plan of administration, and dosages might vary from case to case and from time to time in the same case. Children seemed to require about the same doses as adults with the same disease. Fairly large suppressive doses were required at first for a few days or weeks, and then, when the condition was well under control, smaller doses could be given for a short time in certain conditions and for prolonged periods in others. In the acute crisis of disseminated lupus erythematosus or severe rheumatic fever and carditis the initial period doses might be, for example, 300 mg. for the first day, and 200 mg.

daily until improvement was definite. The basic policy must be to provide the greatest symptomatic relief possible consistent with the avoidance of significant side effects.

Current Developments

Although the method for producing cortisone had not been shortened, as a result of further investigation some of the steps in the partial synthesis had been made less costly and productive of greater yields. The price had now dropped to 50 dollars per gram, and Merck's supplies were now sufficient to make cortisone available in limited amounts to all approved American hospitals, with growing supplies available for foreign medical centres. In the development of ACTH the pituitaries of whales were being collected and utilized by Scandinavian scientists.

Attempts had also been made to find some material which, when given with cortisone, would enhance the effect of doses too small to produce side effects.

On the development of compound F, which, according to certain data, was the ultimate product of the adrenal cortex rather than compound E (cortisone), Dr. Hench said that this substance until recently could be obtained only by extraction from adrenal glands. No method for its synthesis had so far been developed, but the development of a method for the biological conversion of compound F from substance S (Reichstein) had just been announced.

A patient with severe rheumatoid arthritis was given in May 1949 an oral preparation of a highly concentrated adrenal cortical extract. The patient received about 20 capsules daily (100 mg.) of a mixture of compounds E and F. The response was excellent and essentially the same as with intramuscular injections on the same patient. The sedimentation rate rapidly became normal and the patient almost completely free from symptoms.

In June last, at the meeting of the American Rheumatism Association, excellent preliminary results were forthcoming with Merck's cortisone given orally to four patients by Dr. Richard Freyberg of New York, and these results had been confirmed at the Mayo Clinic. Cortisone tablets had now been given to about 25 rheumatoid patients at the Mayo Clinic with very satisfactory results. It was very encouraging to find that cortisone was effective when given by mouth in doses approximating to those which were effective when given intramuscularly. Dr. Hench added, however, that the administration of such preparations must be carefully controlled by the physician, or serious abuse of the hormone might result. The tablets for experimental use were made from small amounts of sterile cortisone taken from the main supply, and none would be generally available in this form for some time to come.

In conclusion Dr. Hench said:

"As cortisone and ACTH have been found to influence profoundly many different cells and tissues of the body so they are having a marked effect on widely diversified fields of biological and clinical research. New vistas for investigation have been revealed. New concepts are being developed in the spheres of clinical physiology, clinical pathology, and clinical medicine. Much remains to be learned about ACTH and cortisone, about their mode of action, and the optimal method for their administration, especially in chronic diseases such as rheumatoid arthritis. The remark is still true, that this is not the beginning of the end of the problem of rheumatic diseases, but perhaps it is the end of a beginning. But so much progress has been made in recent months that the limited application of these hormones as therapeutic measures for at least certain acute conditions appears properly to be impending."