EFFECTS OF CORTISONE AND ACTH IN RHEUMATOID ARTHRITIS

R. H. FREYBERG

From Cornell University Medical College and the Hospital for Special Surgery, New York, N. Y.

FROM information made available by Dr. James Carlisle of Merck & Co., and by Dr. John R. Mote of Armour Laboratories, it is estimated that in America up to January 1, 1950, Cortisone has been studied in approximately 160 patients with chronic rheumatic disease, and ACTH in about 175 cases. The majority of these patients had rheumatoid arthritis. Since only nine reports of *clinical* experiences with these hormones in rheumatoid arthritis have been published, much of this discussion is based upon the experience of the author and his co-workers,* and upon visits, conferences and reports not yet published.

There is practically uniform experience that rheumatoid arthritis in its various manifestations is quickly and greatly improved when Cortisone or ACTH is administered. With Cortisone a definite pattern of improvement is the rule: First, there is great reduction of stiffness (non-articular) which allows easier and greater range of joint motion, even of the inflamed joints; second, there is reduction often to complete loss of pain at the joints and in non-articular connective tissue; third, progressive decrease in the joint inflammation occurs; articular tenderness is usually the last sign to abate. The time required for these changes to be completed varies from a few days in early stages of the disease to several weeks in older and more severe arthritis. In early cases complete remission usually occurs with disappearance of all abnormal physical signs; in cases of longer standing, some swelling, and effusion may persist although all symptoms frequently subside. Destructive changes of cartilage and bone, ankylosis, ligament calcification remain unchanged. Subcutaneous nodules, bursitis, tenosynovitis and other non-articular features of the disease improve or vanish concurrent with improvement in the arthritis. While these rheumatic abnormalities are improving there

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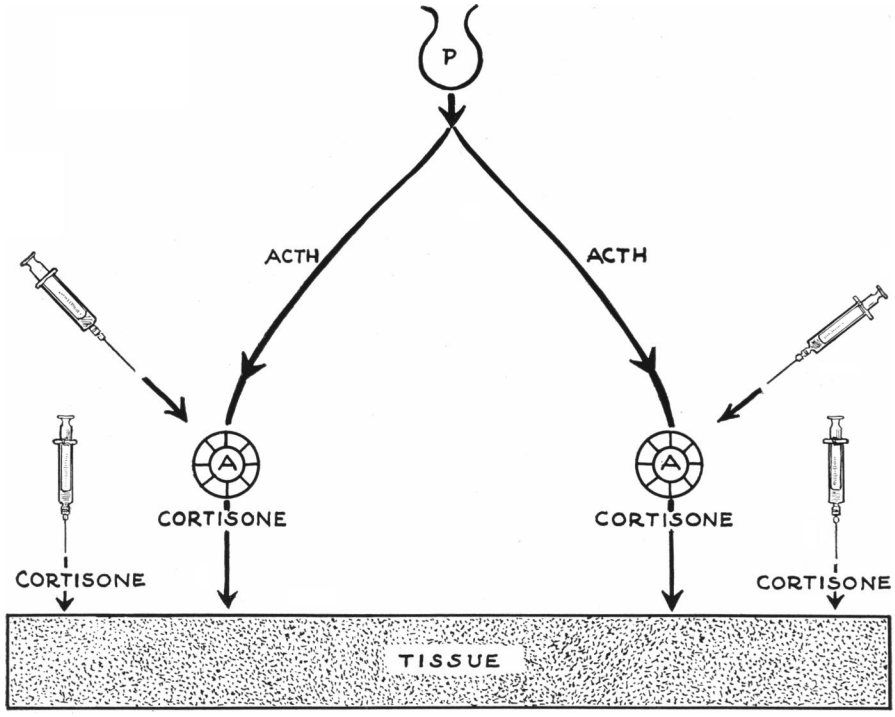

Figure 1—Diagramatic sketch showing the stimulation of the adrenals by adrenocorticotropic hormone from anterior pituitary. Note that effectiveness of ACTH depends upon elaboration of Cortisone which has its effect on the tissues. Similar results are obtained if ACTH is injected to stimulate the adrenal cortices or if Cortisone is injected directly into the tissues.

is comparable improvement in appetite, food consumption, weight, strength and general sense of well-being. Laboratory abnormalities change toward or to normal. A small amount of arthritis may appear for a few days during Cortisone administration but it is indeed minor. On cessation of Cortisone relapse usually occurs; the speed and degree of relapse vary unpredictably under different circumstances.

Juvenile rheumatoid arthritis (Still's disease) and rheumatoid spondylitis respond in all ways similar to classical rheumatoid arthritis. Up to this time we have observed these benefits in six cases of rheumatoid spondylitis. In patients with psoriasis and arthritis (three in the author's group) both conditions improve.

The three predominant attributes which characterize Cortisone are: 1) dependability, 2) speed of action, and 3) the high order of benefit effected.

Potent ACTH (Armour's product has been used in almost all reported studies to date) effects the same dramatic changes seen with Cortisone. Variations, in benefit (usually small) that have been observed between the two hormones can be explained entirely upon differences of amounts of cortico-sterone added to the organism. It must be emphasized that when Cortisone is injected only one cortico-sterone is being added to the human organism and its dose can be regulated at will, whereas the effectiveness of ACTH depends upon the patient's adrenal response to stimulation (Figure 1) so that in addition to a variable dose of ACTH there may also be a variable capacity or degree of cortical response. Although infrequent there have been instances of adrenal response inadequate to effect good results.[1,2] Also there have been instances in which, while continuing doses of ACTH which effected good initial cortical stimulation and clinical benefit, there was progressively less adrenal response as shown by less eosinopenia and relapse in the arthritis. Because ACTH functions through adrenal stimulation and because *all* cortical functions are stimulated, its use may be more complicated than is that of Cortisone.

The manner of action of these hormones is not known. The large amounts required suggest that the connective tissue needs to be flooded with Cortisone—a sort of mass action effect. The speed of response strongly suggests that the benefit is obtained at the tissue level through beneficially altered enzyme-system function; other possibilities include change in antigen-antibody relationship, or tissue permeability. The basic cause of the inflammation and other pathologic changes remains unaltered, directly, by Cortisone, as shown by the relapse following cessation of the hormone; moreover precisely the same joints again become inflamed and nodules, effusions, etc., reappear similar to the prehormone conditions. Complications include undesired metabolic or hormone effects which may have "toxic" importance. Some of these will be amplified by others on the panel. In patients with rheumatoid arthritis, edema from sodium retention, potassium depletion, partial hypercortico-adrenalism (facies of Cushing's syndrome, acneiform eruption, hypertrichosis without hypertension and usually without glycosuria), irregular menstruation, hypomenorrhea, temporary amenorrhea with symptoms of menopause, occasional increases in basal metabolism, diabetic carbohydrate metabolism, insomnia, unexplained tachycardia, excitability and mental depression have been observed.[2,3,4]

Occasional complications have been severe,[4] but in our experience with 17 patients who received Cortisone and 16, who received ACTH, no serious complications have been encountered and some of these patients received hormone over long periods, as long as 160, 150, 145 and 120 days. We have had no problem of diabetes, of major nervous or mental changes, and only mild endocrine complications (mild rounding of the face, fuzzy hair growth and irregular menses). Edema responded promptly or could be prevented by restricted sodium intake and the use of ammonium chloride or mercurial diuretic. As reported by others,[3] in our experience all complications or undesired effects have been completely reversible. There is decidedly greater chance for complications in females due to their more complex gonadal functions, and we have seen greater tendencies for endocrine complications in females in the pre-menopausal age. In three male patients who received Cortisone for 160, 145 and 120 days no side reactions occurred and excellent benefit was maintained.

Another set of problems surrounds the dose and schedule of administration. To accomplish remission with Cortisone acetate in adults with rheumatoid arthritis we have found, as did Hench and co-workers[3] and most others, that approximately 100 mgm. daily is required for a period. Divided doses seem to have no advantage over single daily injections. After remission has been accomplished we have found repeatedly that 100 mgm. three times weekly (Monday, Wednesday and Friday) maintain most or all of the benefit for long periods. Some patients with rheumatoid arthritis and spondylitis have been kept in good remission by this plan for 60 to 100 days, as long as this plan has been observed to date. Boland[5] has reported maintenance of good results with 50 mgm. of Cortisone acetate daily. In one of our patients with rheumatoid spondylitis 100 mgm. three times weekly, on Monday, Wednesday and Friday, maintained benefit; when 50 mgm. were given daily, the arthritis worsened; when 100 mgm. were given on three successive days at the first of each week, during the non-treatment days significant worsening occurred, and when 100 mgm. were again given on alternating days maintenance of good remission again obtained. Hench[6] has reported that in some patients intermittent treatment, periods of daily injection separated by periods of several weeks rest from treatment, has given good results in several patients with less relapse after each period of injections. Many more studies are needed to determine best

methods of administration of this hormone over long periods.

There is some question whether complete clinical remission with return to normal erythrocyte sedimentation rate is preferred in stubborn cases if large doses of hormone are required for long periods. It may be better to maintain a good but not complete remission, using less hormone. We have done this in a few patients with satisfaction to the patient and physician. There should be less chance for complications in this plan. It is closer to what Hench has referred to as "coöperating with, rather than taking over completely" the function of the adrenals.[6]

Administration of ACTH is quite different from that of Cortisone. Here the object is to get effective stimulation of the adrenal cortices and experience has shown this is accomplished better by injections of hormone in smaller doses 4 times daily rather than from the entire daily dose given in one injection. The dose of ACTH should be regulated according to the eosinophil response (or other dependable laboratory tests of cortical stimulation) and by clinical results. ACTH dosage has varied more than Cortisone. After 25 mgm. of ACTH (*Armour standard*) 4 times on first day, doses of 10 or 15 mgm. 4 times daily have usually given good remissions, which can thereafter often be maintained for varying periods with smaller amounts. Warning is given that different batches of ACTH have different potency, that mgm. dosage of different lots cannot be compared, that all doses must refer to a biologic standard.

In children, our small experience suggests that dosage of these hormones is not a factor of body size, but depends more upon severity of disease. It has also suggested that to get good antirheumatic effects as much may be needed as in an adult, and that the metabolic and endocrine complications may be greater in the child because of the larger ratio between hormone dose and body size.

Combinations of two or more hormones and of a hormone and enzymes are being investigated. Our results with combined use of adenosine triphosphate and Cortisone or ACTH have been no better than obtained with the hormones alone.

Many substances chemically similar to Cortisone are being studied as possible substitutes. We have made clinical tests with Compound S, progesterone, 17-hydroxy progesterone, Δ^5 pregnenolone, acetoxy pregnenolone, testosterone and 6 other steroids. None have been found beneficial as we used them. These studies are continuing. There is sug-

gestion that if Cortisone be administered for long periods adrenal-cortical atrophy may result, or that adrenal hypertrophy and atrophy of the anterior pituitary may follow prolonged ACTH administration. Whether such changes occur, and if so, their significance and prevention or compensation are further problems requiring investigation. The possible development of undesirable immune reactions, particularly from the protein structure of ACTH, and of allergy from both hormone preparations pose other problems.

All of these unanswered questions should be fully appreciated and many need solution before these hormones can be considered for practical therapy. But also it should be appreciated that the knowledge of pituitary-adrenal hormone relationships to rheumatic disease is the greatest advance in this field of medicine. Never before have such potentialities for the understanding and controlling these diseases existed. I cannot agree with the pessimism occasionally encountered regarding the clinical future. Indeed, there is an inescapable challenge to chemical and medical science to pursue these investigations until there is understanding of rheumatic diseases, and until there are dependable means of treatment.

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