RELATION OF THE ADRENAL CORTEX TO RHEUMATIC DISEASE

A REVIEW OF SOME RECENT INVESTIGATIONS

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For years the literature has contained reports which have suggested that certain rheumatic diseases may be related, in some vague way, to the function of the endocrine glands. Some writers envisaged the possibility of an "endocrine rheumatism" and some even considered, along with other aetiological theories, that rheumatoid arthritis might be elicited through an obscure hormonal imbalance. Such ideas were ill-defined and lacked both experimental and direct clinical support. Recently, however, Hench, Kendall, Slocumb, and Polley, and subsequently others, have demonstrated that an adrenal cortical hormone (cortisone) and a pituitary adrenocorticotrophic hormone (ACTH) exert strikingly beneficial effects on a variety of rheumatic diseases. These observations now serve as strong evidence to link the pathogenesis of certain rheumatic diseases with the function of the endocrine glands, especially the adrenal cortex.

APPLICATION OF ADRENAL CORTICAL FUNCTION TO THE RHEUMATIC DISEASES

The reasoning which eventually led to the discovery that certain hormonal compounds exert powerful anti-rheumatic action was presented in detail by Hench¹. * It has long been known that rheumatoid arthritis is capable of undergoing spontaneous regression and that the course of the disease may be punctuated by spontaneous remissions, partial or complete, temporary or permanent. The disease, therefore, has the inherent capacity of spontaneous reversibility although the potentiality often remains dormant¹. Certain procedures, heretofore apparently unrelated in their mode of action, are known to stimulate, though feebly, this potential reversibility and thereby to induce temporary amelioration of the disease. Such procedures include febrile reactions from foreign proteins, starvation, surgery, and surgical anaesthetics. More potent and more regular antagonists of rheumatoid arthritis are pregnancy, and jaundice from biliary obstruction or hepatitis^{2, 3, 4, 5, 6, 7}. Although the possible mechanism of

* As this article presents an exceptional number of references, we have departed from the usual practice in this Journal. The references will be found in numerical order corresponding to the notes in the text. All titles of articles are given in full.

relief from these various procedures and states appeared diverse and unrelated, Hench speculated that a common *modus operandi* might exist. Further, he was unable to harmonize the microbic theory of aetiology with the powerful ameliorative influence of jaundice and pregnancy, states which are not known to influence favourably the course of proved bacterial or virus infections. If the agent producing articular relief in jaundice were closely related to or identical with the agent responsible for relief in pregnancy, Hench reasoned that the responsible substance must be common to both sexes and was not a unisexual factor. He conjectured that a bisexual hormone, possibly an adrenocortical hormone, might be involved in the curious anti-rheumatic effect of pregnancy.

In September, 1948, Hench, Kendall, Slocumb, and Polley⁸ administered the adrenal cortical hormone, cortisone (Compound E), to a patient with severe rheumatoid arthritis; striking and rapid improvement in the clinical and laboratory features of the disease resulted. In April, 1949, these investigators reported dramatically favourable effects on severe or moderately severe rheumatoid arthritis from cortisone in fourteen patients and from adrenocorticotrophic hormone (ACTH) in two patients. Subsequently it has been found that cortisone and/or ACTH exert a beneficial influence on other rheumatic diseases, including to date acute rheumatic fever, rheumatoid (ankylosing) spondylitis, disseminated lupus erythematosus, periarteritis nodosa, psoriatic arthritis, dermatomyositis, and gout.

Historical Notes on Cortisone and Early Experimental Studies

In 1936 Kendall and his co-workers⁹ reported the isolation of nine separate, but closely related, steroid hormones from extracts of the adrenal cortex. Among these was a compound, later known as Kendall's Compound E, of which the chemical formula was found to be $C_{21}H_{28}O_5$ ^{10, 11}. In the same year an identical substance was also isolated by Wintersteiner and Pfiffner (their Compound F)^{12, 13}, and by Reichstein (his Compound F)¹⁴. In 1938 Mason, Hoehn, and Kendall determined the chemical structure of Compound E to be 17-hydroxy-11-dehydrocorticosterone¹⁵. In 1949 Compound E was renamed cortisone.

The known hormones of the adrenal cortex may be classified broadly according to their principal functions as follows: (1) electrolyte regulating steroids (mineralocorticoids); (2) carbohydrate regulating steroids (gluco-corticoids or glycogenic corticoids); (3) sex-like steroids (principally androgenic steroids). Cortisone belongs to the group of carbohydrate-regulating hormones, along with Compounds A (11-dehydro-corticosterone), B (corticosterone), and F (17-hydroxy-corticosterone). These substances have an oxygen atom attached to the eleventh carbon position in the phenanthrene ring. More specifically, cortisone and Compound F have oxygen atoms at both the eleventh and seventeenth carbon positions, and hence are known as 11-17 oxysteroids; these two substances are the most active of the carbohydrate regulating hormones.

After more than eight years of research, in co-operation with Kendall and co-workers at the Mayo Clinic, partial synthesis of cortisone from a bile acid

(desoxycholic acid) was accomplished in 1946 by L. H. Sarett at the Merck Laboratories¹⁶. Continued research resulted in improvements in the synthesis, and in 1948 sufficient material was accumulated to allow very limited evaluation of the compound. Cortisone is now being prepared and used in the form of its acetate ester (cortisone acetate: 17-hydroxy-11-dehydrocorticosterone-21-acetate). The product is still scarce, but its physiologic properties and clinical applications are being determined at an accelerated rate by a number of investigators.

Prior to its synthetic production, only minute quantities of cortisone were available for research purposes. The scarcity of the naturally-occurring hormone may be appreciated by the fact that one-half ton of beef adrenal gland tissue yielded, on extraction, only 340 mg. of cortisone¹⁷. Yet, in spite of its scarcity, certain important facts regarding its physiologic activity were determined prior to 1948, some of which will be mentioned herein.

Early investigations indicated that cortisone and other adrenal cortical steroids having an oxygen atom at the eleventh carbon position exerted a definite influence on carbohydrate metabolism^{18, 17, 19}. Cortisone given to normal rats (forced fed with a high carbohydrate diet) produced transient hyperglycaemia and glycosuria²⁰. When administered to partially depancreatized animals with intact adrenal glands, it intensified the glycosuria, and when given to partially depancreatized-adrenalectomized animals, glycosuria reappeared^{21, 17, 23}. Because of concomitant increases in excretions of nitrogen and potassium, it was reasoned that cortisone (and other 11-oxysteroids) stimulated gluconeogenesis by manufacturing glucose at the expense of tissue proteins²¹. Later studies, however, suggested that gluconeogenesis may not be accomplished by catabolism of body protein, but by a process of blocking protein synthesis whereby amino acid radicals are diverted to pyruvic acid and glucose (anti-anabolic effect)^{23, 24, 25}. When adrenalectomized^{26, 27} or hypophysectomized²⁸ animals were subjected to phlorhizin and then injected with cortisone an increased excretion of glucose and nitrogen occurred, indicating that the hormone is capable of replacing the gluconeogenic function of the adrenal gland. The hormone was found to counteract effectively the hypoglycaemic effect of insulin^{17, 29, 33} and to promote the deposition of glycogen in the liver and muscles^{30, 18, 31, 32}. In patients with Addison's disease whose electrolyte balance was maintained with desoxycorticosterone, the administration of cortisone corrected the abnormal carbohydrate metabolism; the fasting blood sugar level was raised, the respiratory quotient decreased, and the threshold for hypoglycaemic reactions increased³⁴. In subjects with coexisting Addison's disease and diabetes mellitus, the diabetes was intensified when cortisone was administered in daily doses of 8 to 20 mg.³⁵

Cortisone given to human subjects over long periods has little overall effect on electrolyte metabolism^{36, 37, 38}. At first there may be a negative sodium balance, but later the balance becomes levelled off. According to Thorn, cortisone and its related 11-oxysteroids exert a weak sodium-retaining effect, about one-thirtieth of that produced by desoxycorticosterone. However, under certain conditions, as in the presence of excessive sodium retention induced by desoxycorticosterone,

cortisone (also Compound F) may act in competition and cause increased sodium excretion²³. Cortisone was found to cause increased excretion of potassium and phosphorus in partially depancreatized-adrenalectomized rats²⁵. Its administration to normal subjects and in patients with gout produced increased renal clearance of uric acid resulting in the excretion of large quantities of urates²³. Young rats receiving the hormone exhibited a decrease in the phosphatase activity of the bony epiphyses³⁹.

Cortisone given to young rats suppressed their growth and development, and in both sexes caused marked atrophy of the adrenal and thymus glands⁴⁰. Similar atrophy was noted in the spleen and lymph nodes^{24, 41} which suggested that the hormone might have a regressive effect on certain types of lymphatic tumour⁴². Subsequently it was found that adrenalectomized rats showed an augmented susceptibility to transplanted lymphatic leukaemia, indicating that adrenal secretions might have an inhibitory effect upon the development of this disease⁴³. Heilman and Kendall demonstrated that transplants of a highly malignant mouse tumour (diagnosed as lymphosarcoma) which was transmissible to mice in almost 100 per cent. of instances failed to grow if the recipients received cortisone⁴². Pronounced regression of these tumours, even though well developed, occurred with administration of the hormone. A lysis of fixed lymphoidal tissue, a transient decrease in circulating lymphocytes, and a marked decrease of circulating eosinophils from the blood have been noted during short-period administration of cortisone²³.

Cortisone and other 11-oxysteroids have the capacity of increasing muscle strength and efficiency in adrenalectomized animals^{22, 44, 45}; this effect is not observed in animals with intact adrenal glands. Physiologic resistance to stress and shock is greatly enhanced in adrenalectomized animals when cortisone is administered. Not more than 0.03 mg. of the hormone is required to protect adrenalectomized rats against 25 minimal lethal doses of typhoid vaccine, and the substance is highly effective in protecting such animals against low temperatures³⁹.

Historical Notes on ACTH and Early Experimental Data

Accumulated evidence indicates that the major regulator of adrenal cortical function is the anterior pituitary gland, and that this regulation is achieved through the secretion of adrenocorticotrophic hormone (ACTH). In 1930 it was shown that ablation of the anterior pituitary gland in rats resulted in adrenal cortical atrophy, and that this atrophy could be prevented or corrected by daily homoeo-transplants of anterior pituitary substance⁴⁶. In 1933 Collip⁴⁷ isolated an impure "adrenotropic hormone" which contained adrenocorticotrophic principle in potent amounts. In 1943 a pure form of the hormone, unadulterated by other secretions in the gland, was isolated by Li and his collaborators⁴⁸ from sheep pituitary glands, and by Sayers and co-workers⁴⁹ from swine pituitaries. The hormone so derived was a complex protein substance with a molecular weight of nearly 20,000 and an isoelectric point of approximately 4.7⁴⁸. More recently

it has been demonstrated that the active adrenocorticotrophic principle is contained in a peptide fraction of ACTH⁵⁰.

The major physiologic effects of ACTH are dependent on stimulation of the adrenal cortices to produce steroid hormones. Its administration to animals and humans with intact adrenal glands results in increased secretion of glucocorticoids, some of which are closely allied to cortisone, but also to a lesser degree in increased secretion of other cortical steroids, such as those which influence electrolyte metabolism and androgenic function. Thus, in animals^{51, 52, 53, 54, 55, 56, 33} and human subjects^{57, 58, 59, 38, 23}, the administration of ACTH produces in general the following results: it affects carbohydrate and protein metabolism (inducing hyperglycaemia, glycosuria, and negative nitrogen balance); it alters electrolyte metabolism (inducing increased excretion of potassium and decreased excretion of sodium); it inhibits growth of young animals and produces thymus atrophy; it reduces the alkaline phosphatase content of plasma; it promotes haematologic changes which include falls in total eosinophil and lymphocyte counts, increase in circulating neutrophils, and atrophy of lymph nodes; it causes prompt and pronounced increased excretion of corticosteroids and 17-ketosteroids; it enhances the excretion of uric acid; and it augments anti-hyaluronidase activity. In patients with Addison's disease or in adrenalectomized animals, these effects are not produced.

With administration of ACTH to animals, adrenal cortical hypertrophy may result⁶⁰, and the cholesterol and ascorbic acid contents of the gland are quickly reduced^{61, 62, 63, 64}. A single dose of ACTH may result, within 3 hours, in a 50 per cent. decrease in the gland's cholesterol concentration, and during the period of cholesterol depletion evidences of increased cortical hormone activity are observed. This suggests, but does not prove, that cholesterol may be utilized in the formation of steroid hormones⁶⁵. The relationship between ascorbic acid and the cortical steroids is not established, but the gland's sensitive response to ACTH is now used as a means of bio-assaying the potency of ACTH.

Experimental Data Implicating the Adrenal Cortex in the Pathogenesis of Rheumatic Disease

That the function of the adrenal cortex may be involved in the pathogenesis of certain rheumatic diseases was suggested by Selye and his co-workers in 1944. Rats with intact adrenal glands, when treated with large doses of desoxycorticosterone, occasionally developed joint lesions which were similar histologically to the articular lesions of rheumatic fever⁶⁶. The arthritis was transient and tended to disappear in a few weeks in spite of continued administration of the hormone. While the arthritis was produced in only a small percentage of the animals, other changes of a "rheumatic type", such as arteritis simulating periarteritis nodosa, myocarditis with Aschoff body formation, and encephalitis accompanied by choreiform twitches, occurred quite regularly. In adrenalectomized rats, the articular manifestations developed more frequently and extra-articular lesions were

more pronounced^{66, 67, 68}. Thyroidectomy and exposure to cold also increased the frequency by which experimental arthritis could be provoked with desoxycorticosterone, but to a lesser degree. Selye suggested that adrenalectomy may sensitize the animal to the toxic effects of desoxycorticosterone by removing the endogenous source of gluco-corticoids which may inhibit or oppose the action of such mineralo-corticoids as desoxycorticosterone. Similar lesions in the joints and heart were produced in rats with intact adrenal glands by injecting a crude lyophilized anterior pituitary preparation⁶⁹. Because adrenalectomy prevented these changes, the effects of the preparation were believed to be mediated through the adrenal cortex, possibly by causing an excessive discharge of mineralo-corticoids.

These and other observations led Selye to include rheumatic diseases (rheumatic fever, rheumatoid arthritis, so-called collagen diseases, and gout) among those maladies interpreted by him as "diseases of adaptation"^{70, 69, 66, 71}. According to this theory, the organism normally responds to a variety of stress-provoking agents (emotional tension, infections, intoxications, exposure to cold, etc.) with an increased and balanced corticoid hormone production—a useful "adaptation reaction" which increases resistance in general. Under abnormal conditions, however, there may be an imbalanced elaboration of adrenal cortical hormones with gluco-corticoid production failing to keep pace with the excess out-pouring of mineralo-corticoids⁷². The reasoning leading to this concept was based on the apparent opposing actions of mineralo-corticoid and gluco-corticoid hormones: pre-treatment of animals with desoxycorticosterone tends to cause thymus hypertrophy^{73, 74}, hypoglycaemic response to stress-producing agents,⁷⁵ and aggravation of shock from surgical trauma, while pre-treatment with gluco-corticoids produces opposite effects^{69, 76, 77}.

In November, 1949, Selye⁷² reported observations on the influence of certain anterior pituitary and adrenal cortical hormones on the production and prevention of experimental arthritis. By the local injection of dilute solutions of formaldehyde into the tissues near a joint, acute arthritis and peri-arthritis were produced. When large or repeated doses of formaldehyde were injected, chronic arthritis and peri-arthritis developed. These were self-maintaining proliferative reactions that continued for weeks after stopping the irritant. Microscopically the lesions resembled those found in the "chronic stage of rheumatoid arthritis". This experimental arthritis was intensified if the rats were given either desoxycorticosterone or crude lyophilized anterior pituitary extract for several days before formaldehyde was injected. Conversely, pre-treatment with either cortisone or ACTH almost completely inhibited the development of "formalin arthritis". Furthermore, experimentally produced alarm reactions (forced exercise, exposure to cold, spinal cord transection, starvation) inhibited the development of articular reactions from formaldehyde. The preventive effect of severe stress was interpreted as due to increased endogenous secretion of ACTH and hence of gluco-corticoids. Adrenalectomized animals subjected to similar stresses were not protected from "formalin arthritis".

Deductions were drawn that the inhibitory actions of ACTH, cortisone, and the

alarm reaction on "formalin arthritis" were due to the direct effect of cortisone-like gluco-corticoids upon the injured tissues. Although the mechanism is not known, Selye suggested that it may be related to the anti-hyaluronidase effect of gluco-corticoids or to their anti-histaminic action. Selye cautioned that the anti-arthritic effects of ACTH and cortisone are not specific reactions directed against a hypothetical pathogen, but rather a non-specific effect.

EFFECTS OF CORTISONE AND ACTH ON CERTAIN RHEUMATIC DISEASES

From available information it is estimated that in America up to January 1, 1950, cortisone has been studied in about 160 patients with rheumatic disease, and ACTH in about 175 patients⁷⁸. The majority of these patients have had rheumatoid arthritis. Clinical data from these studies are just beginning to appear in the literature, and hence much of the information included herein is based on reports yet to be published.

Rheumatoid Arthritis

Anti-rheumatic Effects of Cortisone.—Hench, Kendall, Slocumb, and Polley first reported the effects of cortisone on fourteen patients with severe, or moderately severe, rheumatoid arthritis⁸. The duration of the disease in their patients varied from four and a half months to five years, and the erythrocyte sedimentation rates ranged from 108 to 62 mm. in one hour (Westergren method). In nine of the fourteen patients cortisone was given for short periods ranging from 8 to 61 days. Five of the fourteen patients received the compound either continuously or intermittently for periods of 2 to 4 months. In their earlier cases doses of 100 mg. of cortisone were given intramuscularly each day; later 300 mg. were administered on the first day and 100 mg. daily thereafter. All analgesic agents, physical therapy, or other remedies were stopped several days or weeks prior to administration. In each case a prompt and striking improvement in the musculo-skeletal, constitutional, and laboratory manifestations of the disease resulted, and was maintained during the period of administration.

The dramatic response of rheumatoid arthritis to cortisone has been confirmed by Freyberg, Bauer, Holbrook, Rosenberg, and Boland⁷⁹. The experiences of these investigators have been practically uniform and each has observed that the disease in its various manifestations is quickly and greatly improved with administration of the hormone. Boland and Headley⁸⁰ reported clinical observations in eight patients. Five of the eight patients had severe rheumatoid arthritis and were given large doses for short periods (total of 1 g. in divided doses for 8 days). The immediate results were decidedly pronounced improvement in three, pronounced improvement in one, and moderate improvement in one. Three additional patients with less severe rheumatoid arthritis (two with moderate and one with mild disease) were given smaller doses of the drug for longer periods; with daily doses of 50 mg. the symptoms and objective findings were adequately, but not completely, controlled.

A fairly definite pattern of improvement is noted with cortisone administration^{8, 80, 81, 78}. Within a few days (or hours in some cases) there is a marked reduction of stiffness of muscles and joints, lessening of articular aching, tenderness, and pain on motion, and a significant improvement of articular and muscular function.

Usually the first symptoms to subside are muscular and articular stiffness and rest pain. Within 1 to 4 days the patients may have no further desire for acetylsalicylic acid or other analgesics. Next in order of improvement are lessening of joint pain on motion, increased motion, and decreased tenderness of the joints. Reductions in articular swellings are usually slower in appearing and may be not complete, but sometimes swellings and effusions recede rapidly and completely. Mild flexion deformities may be corrected within 7 to 10 days. Muscle strength and joint function may return to a remarkable degree within a few days, despite advanced muscle atrophy and previously restricted joint motion. In early and less severe cases, complete remissions may occur with disappearance of all abnormal physical signs; in cases of longer standing, some articular swelling and slight effusion, together with some tenderness, may persist even with the use of relatively large doses of the hormone. Destructive changes in the cartilage and bone, ankyloses, and ligamentous calcification remain unchanged. Other non-articular features, such as subcutaneous nodules, bursitis, and tenovaginitis, improve or disappear along with the improvement in the joints.

Anti-rheumatic Effects of ACTH.—Hench, Kendall, Slocumb, and Polley⁸ gave ACTH in doses of 100 mg. daily for a period of 12 days to two patients with severe rheumatoid arthritis. Marked clinical improvement, essentially similar qualitatively to that resulting from the use of cortisone, occurred. Striking reductions in stiffness, pain, articular tenderness, and constitutional symptoms were noted within a few days. Side effects, such as a sense of exhaustion, transient gas pains, heaviness in the chest, and moderate elevation (20 to 30 mm.) of blood pressure, were observed. As with cortisone, the beneficial effects were temporary, and both clinical and laboratory manifestations of the disease promptly reverted to their original intensities after withdrawal of the hormone.

The observations made by Hench and his colleagues have been confirmed without exception by others^{82, 83, 23, 84, 85, 78, 81, 86, 87, 88}. Thorn and others²³ treated ten rheumatoid arthritis patients with ACTH in doses of 40 mg. daily for periods ranging from 2 to 14 days. Nine of the ten cases improved promptly and significantly, improvement usually beginning within 12 to 24 hours after the initial injection. Sustained falls in the levels of circulating eosinophils, retention of sodium, and marked increases in 17-ketosteroid excretion occurred which served as evidence for adrenal cortical stimulation. The one patient who failed to improve received ACTH for only 48 hours; the eosinophil count did not fall but there was increased 17-ketosteroid excretion.

Remissions were obtained in each of nine patients with rheumatoid arthritis observed by Rosenberg⁸¹; effective doses ranged between 40 and 100 mg. daily.

Similar results have been observed by Holbrook⁸⁴ in 34 patients, and by Ragan, Grokoest, and Boots⁸⁷ in eight patients; the latter investigators were able to maintain good results with small daily doses (20 to 30 mg.) in two patients. Several of Holbrook's patients treated with daily doses of 40 mg. for 10 to 20 days retained 75 per cent. of the initial improvement for longer than 6 months. In general, those patients with less severe disease experienced longer periods of improvement after the hormone was discontinued.

Effects of Cortisone and ACTH on Constitutional Symptoms.—A striking sense of well-being is exhibited by most patients early in the period of cortisone or ACTH administration^{8, 81, 78, 38}; the degree of mental stimulation varies somewhat with the size of the daily dose given⁸⁰. Some patients, initially depressed and pessimistic, become frankly euphoric. In some the state of euphoria induced seems greater than would be expected from improvement in their physical condition and relief from pain. Other effects noted include loss of "toxic feeling", increased general strength and endurance, and increase in libido in some males. Febrile cases may become afebrile within 24 to 72 hours and remain so during the period of administration. Appetites usually improve rapidly with corresponding increases in food consumption and body weight. Hench and co-workers⁸ noted weight gains in their patients as follows: 21·5 lb. in 10 weeks; 17·5 lb. in 2 months; 19 lb. in 40 days; 15 lb. in 27 days; 7·5 lb. in 26 days.

Effects of Cortisone and ACTH on Usual Laboratory Tests

Erythrocyte sedimentation rates.—Significant decreases in the erythrocyte sedimentation rate occur, usually within a few days after cortisone administration is started; in some patients the decreases occur promptly and rapidly, but in others more slowly. With cortisone in daily doses of 100 mg., the decreases usually continued at the rate of 2 to 4 mm. per day, but in some the correction was more rapid, proceeding with a daily average of 4 to 7 mm.; often rates become normal within 10 to 35 days⁸. With short-term administration of cortisone, decreases in rates varying from 15 to 75 mm. in a period of 8 days may be noted⁸⁰. Even more prompt and more steady decreases result from the administration of large doses of ACTH⁸.

Erythrocyte count and haemoglobin determinations.—When anaemia is present, erythrocyte counts may increase by 500,000 to 1,000,000 cells per c.mm., and haemoglobin determinations may increase by 1·4 to 2·0 g. per 100 cc. within a few weeks⁸. Even with short-term administration, marked improvement in the erythrocyte count and haemoglobin may be noted⁸⁰. Treatment with ACTH results in similar corrections of anaemia.

Leukocyte counts.—Small, but significant, increases in the total number of circulating leukocytes have been noted during protracted administration of cortisone, but no significant changes in the number of lymphocytes or eosinophils occurred during or after administration of the hormone³⁸. Short-term administration may cause significant decreases in lymphocytes and eosinophils²³. When ACTH

was given in doses of 100 mg. daily, complete or almost complete disappearance of circulating eosinophils occurred^{23, 89}.

Articular biopsies.—When these were performed after several weeks of cortisone administration, definite evidences of healing were noted, but the synovial tissues were still not normal; microscopic findings included disappearance of lymphocytic reaction, improvement in the appearance of collagen, and the presence of many fibroblasts⁸.

Electrocardiograms.—Except for slowing of the heart rate, no significant changes have been noted as the result of cortisone administration⁸⁰.

Electroencephalograms.—Changes in the electroencephalographic pattern have been observed with both cortisone and ACTH administration^{80, 87}; full significance of these changes has not yet been reported.

Metabolic and Immunological Effects of Cortisone and ACTH.—Sprague and collaborators³⁸ conducted detailed metabolic studies on patients treated primarily for rheumatoid arthritis with cortisone and ACTH, five of whom were confined to a special metabolic unit for various balance studies. Similar investigations were reported by Ragan and associates⁸⁷ on patients receiving ACTH.

Corticosteroid excretion^{38, 8}.—Urinary concentrations of corticosteroids were increased initially when large doses (100 to 200 mg.) of cortisone were given. With continued administration of 100 mg. daily, the amount excreted remained elevated or declined toward control values. ACTH promoted pronounced corticosteroid excretion. Thirty to 50 per cent. of the total amount excreted consisted of Compound F (17-hydroxycorticosterone) indicating that ACTH stimulates the adrenal cortex to form Compound F rather than cortisone.

17-ketosteroid excretion^{38, 8}.—Administration of cortisone was followed by a prompt and striking fall in urinary 17-ketosteroid values. This suggested that the hormone depressed some functions of the adrenal cortex. Conversely, ACTH caused a prompt and pronounced increase in the excretion of 17-ketosteroids.

Plasma electrolytes^{38, 87}.—Cortisone in doses of 100 mg. daily for 12 to 14 days induced minimal alterations or no changes in the balances for nitrogen, calcium, phosphorus, sodium, potassium, and chloride, and in the concentrations of electrolytes in the extra-cellular fluid as measured in blood plasma. Cortisone in doses of 200 mg. daily for 12 to 18 days regularly induced a negative balance for nitrogen and potassium. The effects of such large doses on excretion of sodium and chloride were variable; the most common were retention of these ions at first, followed later by increased excretion. ACTH in doses of 100 mg. daily for 12 days induced a negative balance for nitrogen and potassium. Initially a marked retention of sodium and chloride occurred, then later these ions were excreted in increased amounts; some lowering of the serum sodium occurred concomitantly.

Urinary total nitrogen^{38, 87}.—Augmentation of nitrogen excretion was slight or absent when the dose of cortisone was 100 mg. daily, and pronounced when the dose was 200 mg. daily. A negative nitrogen balance occurred during ACTH

administration in large doses (100 mg.), but nitrogen excretion sometimes fell to control levels when the daily dose was lowered.

Uric acid in serum and urine^{38, 87}.—Uric acid excretion was only slightly increased with the administration of 100 mg. of cortisone daily. The excretion was moderately increased with ACTH in daily doses of 100 mg. Significant decreases in serum uric acid occurred most commonly with ACTH or cortisone administration when the serum uric acid levels were initially in the upper normal range or above normal.

Creatine and creatinine nitrogen in urine^{38, 87}.—Marked increased creatinuria was found during the early phase of cortisone and ACTH administration. The increased excretion may or may not continue during the period of treatment. Urinary creatinine nitrogen exhibited no changes which could be attributed to ACTH or cortisone.

Carbohydrate tolerance^{80, 38, 87}.—Slight inconstant increases in the fasting blood sugar were observed in some cases during administration of cortisone or ACTH, but the values did not exceed normal range. Carbohydrate tolerance tests were not conspicuously altered although slightly decreased tolerances were noted in a few cases during the period of cortisone administration.

*Glutathione in the blood*⁷⁸.—During the administration of cortisone or ACTH there was no consistent pattern of change in the glutathione of whole blood or of erythrocytes.

*Glucuronic acid and gentisic acid excretion*⁸⁷.—The excretion of neither substance increased during ACTH administration.

Serum proteins^{38, 87, 8}.—The effect of cortisone and ACTH was to increase serum albumin and decrease serum globulin if the pre-treatment values of these substances were abnormal.

*Basal metabolism and respiratory quotient*³⁸.—When the basal metabolism was raised (because of the rheumatoid arthritis and not hyperthyroidism), it became normalized with the administration of either cortisone or ACTH. This resulted apparently from improvement in the rheumatic state. Consistent changes in the respiratory quotient were not observed.

*Sensitized sheep cell agglutination*⁸⁷.—Only one of eight patients showed a fall from the rheumatoid range to the normal range during treatment with ACTH; the one exception had an initially weak positive titre.

*Group A streptococcus agglutination*⁸⁷.—This reaction remained positive in seven of eight patients treated with ACTH; in one instance a positive agglutination changed to a doubtful reaction.

*Serum cholesterol*⁸⁷.—Of seven patients with rheumatoid arthritis, four showed a rise in serum cholesterol, both free and esterified, during ACTH treatment.

*Blood sludging*⁹⁰.—When clinical improvement was greatest during cortisone administration, the degree of blood sludging was significantly decreased in several cases.

Dosage and Schedule of Administration of Cortisone and ACTH.—To accomplish remissions in adults with severe, or moderately severe, rheumatoid arthritis, Hench,

Kendall, Slocumb, and Polley⁸ found that approximately 100 mg. of cortisone daily were required. In their later cases they adhered to a schedule consisting of 300 mg. given on the first day and 100 mg. daily thereafter. In severe cases smaller doses of 25 to 50 mg. were inadequate or ineffective. In moderate and mild cases Boland and Headley^{80, 91} found that doses averaging 50 mg. daily were sufficient to control the clinical manifestations and cause the erythrocyte sedimentation rate to revert to normal; 100 mg. doses given every other day were as effective as 50 mg. doses given daily. In some severe cases, initially brought under control with large doses of cortisone, improvement has been maintained by smaller doses of 50 to 75 mg. given daily, or 100 to 150 mg. given every other day⁹¹. Freyberg⁷⁸ had continued good results in several cases with doses of 100 mg. three times a week. Hench⁹² reported that 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.

With ACTH remissions may be accomplished with daily doses ranging from 20 to 100 mg.^{23, 87, 81, 84}. More effective stimulation of the adrenal cortices appears to be accomplished by injections of hormone in small doses four times daily, than by one large dose per day⁷⁸. After 25 mg. of ACTH have been given four times on the first day, doses of 10 or 15 mg. four times daily usually maintain good remissions, even in severe cases. Ragan and co-workers⁸⁷ held two patients under satisfactory control with doses of 10 or 15 mg. given twice daily. Unfortunately the doses of ACTH employed must vary from time to time according to the potency of individual batches; the milligram dosage of different lots cannot be compared and doses must refer to a biologic standard.

Much more experience is needed before the question of optimal maintenance dosage can be settled. It appears that the dose necessary to produce adequate suppression depends upon a number of variable factors, but particularly on the severity and current activity of the disease process. Because of potential endocrine complications arising from large doses given for prolonged periods, it may be more prudent at times to maintain good but incomplete results with small doses than to strive for complete results with large doses⁷⁸. In the case of cortisone this may be closer to what Hench has referred to as "co-operating with, rather than taking over completely" the function of the adrenal cortex⁹².

Course after Discontinuance of Cortisone and ACTH.—Sustained improvement appears to be dependent upon continued administration, and cessation of the hormones is usually followed by prompt, or fairly prompt, relapse of the disease. In eight out of nine cases reported by Hench, Kendall, Slocumb, and Polley⁸, in which cortisone was discontinued after short-term administration, the symptoms and signs began to return within 2 to 4 days after withdrawal of the compound; the return progressed slowly in six, but rapidly in two cases. The remaining one case retained most of the improvement 5 months after the drug was stopped. In seven of eight cases observed by Boland and Headley⁸⁰ relapse occurred on withdrawal of the medication, and within 4 weeks the clinical and laboratory manifestations returned

to their original intensities. One of their cases retained 75 per cent. of the initial improvement. As with cortisone, withdrawal of ACTH is usually followed by rapid return of symptoms^{8, 87, 23, 81, 78, 84}.

Signs of Hyperadrenalism from Cortisone and ACTH.—Objective clinical signs of hyperadrenalism have occurred in some cases when these hormones have been given for extended periods and in large doses; such signs disappeared when the administration was stopped. With smaller daily doses endocrine changes have not been reported. Because of the many physiologic alterations induced by both cortisone and ACTH, some of which do not have favourable therapeutic implications, signs of endocrine disturbance should be termed “signs of hyperadrenalism” or “other physiologic effects” rather than “toxic reactions”³⁸; the latter term implies a clinically restricted appreciation of the biologic significance of these substances.

Rounding of the facial contour (“moon-like facies”) is one of the earliest signs of hormonal excess; this may or may not be associated with some fuzzy hair growth^{78, 84, 38}. Disturbances in the menstrual cycle, usually in the form of irregular menses or amenorrhoea, may occur with prolonged administration. Transient oedema, usually pretibial, has occurred in a few cases; this has disappeared spontaneously, or when the dose of the drug has been reduced, or when saline diuretics have been administered^{8, 81, 78}. One patient exhibited numerous subcutaneous ecchymoses about the thighs and buttocks during cortisone administration⁸¹. Another patient, a 29-year-old female who was given large doses of cortisone daily for 6 months, developed definite signs of hyperadrenalism characterized by mild acne and hirsutism, rounding of the facial contour, amenorrhoea, and mental depression. The manifestations suggested a mild Cushing’s syndrome, but were reversible and disappeared when cortisone was discontinued⁹³. In a patient with co-existing diabetes mellitus and rheumatoid arthritis, the diabetes was temporarily intensified⁸⁰. During cortisone administration the daily insulin requirement increased from 10 units to between 30 and 50 units while the patient was on a constant measured diet; 3 days after withdrawal the insulin requirement reverted to the pre-cortisone amount of 10 units. Freyberg⁷⁸ has encountered no serious complications in a series of seventeen patients treated with cortisone; treatment was continued in some for as long as 160 days. There appears to be a decidedly greater chance for complications in females than in males, especially during their pre-menopausal years, because of the more complex gonadal functions.

Juvenile Rheumatoid Arthritis (Still’s Disease)

Juvenile rheumatoid arthritis has responded in the same way as the adult form to cortisone and ACTH^{78, 84, 86, 81}. The details of two cases of juvenile rheumatoid arthritis were reported by Elkinton and collaborators⁸⁶. One, a 5-year-old boy, was treated with 25 mg. of ACTH daily for 7 days; within 12 hours he became

afebrile and within 48 hours most of the painful joint swellings had subsided. The other, a 9-year-old girl, was given ACTH intermittently and in varying doses over a period of 152 days. Dramatic clinical improvement resulted during each period of administration, but with daily doses of 50 to 60 mg., signs of hyperadrenalism ensued (acne, oily hair, mild hirsutism, and moon-shaped or Cushing's facies). In Freyberg's experience adequate dosage of these hormones in children depends more on the severity of the disease than on body size⁷⁸. For good anti-rheumatic effects as much may be needed as in an adult, but the metabolic and endocrine complications may be greater in the child because of the larger ratio between hormone dose and body size.

Rheumatoid (Ankylosing) Spondylitis

Results similar to those obtained in peripheral rheumatoid arthritis have been produced by cortisone or ACTH in cases of typical rheumatoid (ankylosing) spondylitis. Temporary remissions were provoked in each of six cases treated by Freyberg with cortisone⁷⁸. Holbrook gave ACTH in doses of 40 mg. daily for 10 to 14 days to four spondylitic patients (three males and one female) and decided improvement occurred in each during the course of administration⁸⁴. One patient retained 75 per cent. of the improvement for three months, whereas the remaining three patients experienced prompt exacerbations when the administration of hormone was stopped.

Rheumatoid Arthritis with Psoriasis and Psoriatic Arthritis

A few patients with rheumatoid arthritis and co-existing psoriasis have been given ACTH or cortisone; the articular response has not differed from that observed in uncomplicated rheumatoid arthritis, and in each instance there has been marked improvement or complete clearing of the skin lesions^{94, 84, 81}. A patient with typical severe psoriatic arthritis and radiographic changes of psoriatic arthropathy was given cortisone in daily doses of 100 mg. for a prolonged period; marked subjective and objective improvement in the joint manifestations resulted together with improvement, but not disappearance of the psoriasis⁹¹.

Acute Rheumatic Fever

Hench and others³⁶ administered cortisone to three adolescent patients with acute rheumatic fever; two were undergoing their first attack and the third was probably having a recurrence. For several days 200 mg. were given daily and then 100 mg. were given daily for a few days. In each patient there was rapid disappearance not only of fever, tachycardia, and polyarthritis, but also of sedimentation rate elevations and electrocardiographic abnormalities. Fever disappeared within one to four and a half days. The joints became symptom-free within 3 to 6 days except for mild metatarsal tenderness which persisted for 8 more days in one case.

Sedimentation rates were refractory for the first 2 to 5 days and then fell rapidly, decreases as great as 100 mm. being noted within periods of 10 to 14 days. Tachycardia disappeared within 3 to 5 days and prolonged P-R intervals in two patients were restored to normal within 7 and 8 days respectively. Weight gains, feeling of well-being, and loss of toxic symptoms were experienced by each patient. No definite evidences of toxicity were noted, but one patient developed mild rounding of the facial contour which subsided after cessation of the hormone. No definite conclusions were drawn as to the effects of cortisone in preventing or lessening chronic sequelae in the heart valves or myocardium. Hope was expressed, however, in view of the markedly beneficial effect of cortisone on skeletal muscles and fibrous tissues, that the compound will exert a similar sparing effect on the cardiac muscles and fibrous valves.

The same investigators³⁶ gave "small doses" of ACTH to a 14-year-old boy with rheumatic fever; fever subsided rapidly, the erythrocyte sedimentation rate fell and the articular manifestations disappeared within 4 days. Thorn and collaborators²³ treated three patients with doses of 40 mg. daily for periods ranging from 8 to 14 days; detailed results were not given but the response was said to be more striking than that obtained with ACTH in rheumatoid arthritis.

Periarteritis Nodosa

Ragan and associates⁹⁵ treated three cases of periarteritis nodosa with ACTH, and in each there was subsidence of the activity. Disappearance or marked improvement of such manifestations as purpuric rashes, pruritis, asthma, periarteritic nodules and eosinophilia resulted. In each instance the disease manifestations recurred when the hormone was discontinued.

Disseminated Lupus Erythematosus

Three patients with acute disseminated lupus erythematosus, observed by Thorn and associates²³, experienced marked clinical improvement during the administration of ACTH in daily doses of 40 mg. Two patients were treated with ACTH by Elkinton and others⁸⁶. One patient given daily doses of 100 mg. became afebrile within 16 hours and the cutaneous lesions cleared within 14 days. The drug was then given in progressively smaller amounts and discontinued after 51 days. Remission remained "fairly complete" 60 days after stopping the hormone. The other patient had severe and apparently terminal disease with multiple visceral changes. Striking improvement, with fall in temperature, clearing of retinopathy, disappearance of pleural effusion, and diminution of the hepato-splenomegaly, resulted from the administration of 75 to 160 mg. of ACTH daily. At about the forty-fourth day of treatment, the patient apparently became refractory to the agent, and the manifestations returned. Despite doses of 200 mg. daily the patient died. In addition to advanced changes of disseminated lupus erythematosus, necropsy revealed normal-sized adrenal glands which were depleted of lipid.

Dermatomyositis

Elkinton and others⁸⁶ treated a severe case of dermatomyositis in a 5-year-old boy with three courses of ACTH. Following cessation of the first two courses, the disease relapsed, but after the third and more prolonged course the disease had remained in complete remission for 117 days (at the time of the report).

Gout

Recent studies have implicated the pituitary-adrenocortical mechanism in gout and gouty arthritis. Robinson and co-workers^{96, 97} found that ACTH given to normal non-gouty subjects resulted in a prompt increase in urate excretion which persisted throughout the injection period and reached its peak on the ninth day; there was no accompanying decrease in the blood urate value as determined by the uricase method. A pronounced drop in urate excretion occurred on the first post-injection day, followed by unusually high values on the second and third post-injection days, after which values did not differ significantly from the pre-injection control period. Similar results were observed by Thorn and others⁹⁸, who could not account for the increase on the basis of accelerated renal excretion alone, and postulated that the hormone must also increase urate production in the normal subject. Administration of ACTH to a patient with latent pre-tophaceous gout and hyperuricaemia resulted in prompt increase in urinary excretion comparable in magnitude to that seen in normal subjects⁹⁸. In contrast to normal subjects, however, there was a concomitant fall in blood urate levels which were less than 50 per cent. of the original value on the fourth day of hormone administration. Certain calculations suggested that ACTH caused increased production of urates as well as increased clearance by the kidney. The effects of colchicine and epinephrine were also studied on a gouty patient during an asymptomatic period; neither substance produced an effect on the urate levels; epinephrine caused the expected sharp drop in the eosinophil count, whereas colchicine had no such effect.

ACTH given during an acute attack of gouty arthritis will promptly produce relief in the acute joint manifestations^{99, 100, 97, 101}. The attack may be suppressed for 24 hours or longer by a single dose of 50 mg. given within 8 hours of the onset. In most instances relief from all manifestations, except slight residual soreness, occurs within a few hours of administration. In some instances a second or third dose is required 6 to 12 hours later. However, the attack usually recurs in the same or other joints when ACTH is withdrawn. Colchicine given during, or immediately after, treatment of acute gouty arthritis with ACTH was found by some¹⁰⁰, but not by others⁸⁴, to prevent a renewal of the attack on ACTH withdrawal.

Robinson, Conn, Block, and Louis⁹⁶ and Hellman⁹⁹ gave ACTH to gouty patients during interval or latent periods between attacks, and then withdrew the hormone. On withdrawal the majority of patients given more than 100 mg. of ACTH during a 24-hour period developed an acute episode of gouty arthritis. The attack so provoked was relieved by further administration of ACTH, but again on withdrawal most patients developed another attack within a few days. This

phenomenon has been interpreted by Wolfson¹⁰⁰ as follows: ACTH withdrawal produces a lack of 11-oxysteroid which appears to precipitate acute gouty arthritis, whereas the induction of a state of 11-oxysteroid excess by administration of ACTH relieves the attack.

Administration of cortisone in large doses (200 to 300 mg.) produced prompt subsidence of objective and subjective manifestations in two cases with acute gouty arthritis studied by Boland and Headley⁹¹; relief occurred within 5 hours in one and within 18 hours in the other. As with ACTH, withdrawal resulted in an acute recurrence of the attacks. In one case the recurrent episode was again suppressed by a second injection of 300 mg. of cortisone and the attack was terminated without further recurrence by giving progressively smaller daily doses over a period of 8 days. They also observed a patient with tophaceous gout whose subacute articular manifestations involving several joints subsided completely in 20 days with the daily administration of 100 mg. of cortisone; concomitant diminution in size of subcutaneous tophi to 10 per cent. of their original dimensions was noted.

Wolfson and associates^{102, 103} observed that the urinary output of 17-ketosteroids was uniformly greatly diminished in gouty patients both during acute attacks and during asymptomatic intervals. Such decreases were not found in patients with non-gouty hyperuricaemia. These findings suggested that in gout there may be either failure of both gonadal or adrenal androgen production or a more obscure disturbance in steroid metabolism. Being unable to explain the very low 17-ketosteroid output by other means, these investigators assumed that biologic androgen activity in gout is maintained by an abnormal androgen of adrenocortical origin which, when metabolized, makes no important contribution to urinary 17-ketosteroids.

REFERENCES

- ¹ Hench, P.S. (1949). "The potential reversibility of rheumatoid arthritis", *Proc. Mayo Clin.*, **24**, 167.
- ² — (1933). "Analgesia accompanying hepatitis and jaundice in cases of chronic arthritis, fibrositis and sciatic pain", *Ibid.*, **8**, 430.
- ³ — (1934). "The analgesic effect of hepatitis and jaundice in chronic arthritis, fibrositis, and sciatic pain", *Ann. intern. Med.*, **7**, 1278.
- ⁴ — (1938). "Effect of jaundice on chronic infectious (atrophic) arthritis and, on primary fibrositis: further observations; attempts to reproduce the phenomenon", *Arch. intern. Med.*, **61**, 451.
- ⁵ — (1938). "Effect of spontaneous jaundice on rheumatoid (atrophic) arthritis; attempts to reproduce the phenomenon", *Brit. med. J.*, **2**, 394.
- ⁶ — (1940). "The advantages of hepatic injury and jaundice in certain conditions, notably the rheumatic diseases", *Med. Clin. N. Amer.*, **24**, 1209.
- ⁷ — (1938). "The ameliorating effect of pregnancy on chronic atrophic (infectious, rheumatoid) arthritis, fibrositis, and intermittent hydrarthrosis", *Proc. Mayo Clin.*, **13**, 161.
- ⁸ —, Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949). "The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: Compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis; preliminary report", *Ibid.*, **24**, 181.
- ⁹ Kendall, E. C., Mason, H. L., Myers, C. S., and Allers, W. D. (1936). "A physiologic and chemical investigation of the suprarenal cortex", *J. biol. Chem.*, **114**, lvii-lviii, May, 1936 (in Soc. Proc.).
- ¹⁰ Mason, H. L., Myers, C. S., and Kendall, E. C. (1936). "Chemical studies on the suprarenal cortex. II. The identification of a substance which possesses the qualitative action of cortin; its conversion into a diketone closely related to androstenedione", *Ibid.*, **116**, 267.
- ¹¹ —, —, — (1936). "The chemistry of crystalline substances isolated from the suprarenal gland", *Ibid.*, **114**, 613.
- ¹² Wintersteiner, O., and Pfiffner, J. J. (1936). "Chemical studies on the adrenal cortex. II. Isolation of several physiologically inactive crystalline compounds from active extracts", *Ibid.*, **111**, 599.
- ¹³ —, — (1936). "Chemical studies on the adrenal cortex. III. Isolation of two new physiologically inactive compounds", *Ibid.*, **116**, 291.

- ¹⁴ Reichstein, T. (1936). "Über Bestandteile der Nebennieren-Rinde VI. Trennungsmethoden sowie Isolierung der Substanzen F.a, H und J (Constituents of the adrenal cortex VI. Methods of separation and isolation of substances Fa, H, and J), *Helv. chim. acta*, **19**, 1107.
- ¹⁵ Mason, H. L., Hoehn, W.M., and Kendall, E. C. (1938). "Chemical studies of the suprarenal cortex. IV. Structures of Compounds C, D, E, F, and G", *J. biol. Chem.*, **124**, 459.
- ¹⁶ Kendall, E. C. (1949). "Some observations on the hormone of the adrenal cortex designated Compound E", *Proc. Mayo Clin.*, **24**, 298.
- ¹⁷ — (1942). "Hormones of the adrenal cortex", *Endocrinology*, **30**, 853.
- ¹⁸ Reinecke, R. M., and Kendall, E. C. (1943). "A comparison of the influence of some crystalline hormones of the adrenal cortex on the deposition of glycogen in the liver", *Ibid.*, **32**, 505.
- ¹⁹ Mason, H. L. (1940). "The chemical nature of the hormones of the adrenal cortex", *Proc. Mayo Clin.*, **15**, 289.
- ²⁰ Ingle, D. J. (1941). "The production of glycosuria in the normal rat by means of 17-hydroxy-11-dehydrocorticosterone", *Endocrinology*, **29**, 649.
- ²¹ Long, C. N. H., Katzin, B., and Fry, E. G. (1940). "The adrenal cortex and carbohydrate metabolism", *Ibid.*, **26**, 309.
- ²² Ingle, D. J. (1940). "Diabetogenic effect of some cortin-like compounds", *Proc. Soc. exp. Biol., N.Y.*, **44**, 176.
- ²³ Thorn, G. W., Bayles, T. B., Massell, B. F., Forsham, P. H., Hill, S. R., Smith, S., and Warren, J. E. (1949). "Studies on the relation of pituitary-adrenal function to rheumatic disease", *New Engl. J. Med.*, **241**, 529.
- ²⁴ Albright, F. (1943). "Cushing's syndrome", The Harvey Lectures, 123-186. The Science Press Printing Co., Lancaster, Pa., U.S.A.
- ²⁵ Ingle, D. J., and Thorn, G. W. (1941). "A comparison of the effects of 11-desoxycorticosterone acetate and 17-hydroxy-11-dehydrocorticosterone in partially depancreatized rats", *Amer. J. Physiol.*, **132**, 670.
- ²⁶ Wells, B. B. (1940). "The influence of crystalline compounds separated from the adrenal cortex on gluconeogenesis", *Proc. Mayo Clin.*, **15**, 294.
- ²⁷ Lewis, R. A., Kuhlman, D., Delbue, C., Koepf, G. F., and Thorn, G. W. (1940). "The effect of the adrenal cortex on carbohydrate metabolism", *Endocrinology*, **27**, 971.
- ²⁸ Wells, B. B., and Kendall, E. C. (1940). "The influence of the adrenal cortex in phlorhizin diabetes", *Proc. Mayo Clin.*, **15**, 565.
- ²⁹ Grattan, J. F., and Jensen, H. (1940). "The effect of the pituitary adrenocorticotrophic hormone and of various adrenal cortical principles on insulin hypoglycemia and liver glycogen", *J. biol. Chem.*, **135**, 511.
- ³⁰ Herring, V. V., and Evans, H. M. (1943). "Effects of purified antero-pituitary hormones on the carbohydrate stores of hypophysectomized rats", *Amer. J. Physiol.*, **140**, 452.
- ³¹ Wang, F. C., and Verzá, F. (1949). "Comparison between glycogenetic property of desoxycorticosterone, 11-dehydro-17-hydroxycorticosterone (Compound E) and adrenal cortical extract", *Ibid.*, **159**, 263.
- ³² Chiu, C. Y., and Needham, D. M. (1949). "Effect of adrenal cortical steroids upon the formation of carbohydrate by rat liver slices", *Nature*, **164**, 790.
- ³³ Ingle, D. J., Sheppard, R., Evans, J. S., and Kuizenga, M. H. (1945). "A comparison of adrenal steroid diabetes and pancreatic diabetes in the rat", *Endocrinology*, **37**, 341.
- ³⁴ Thorn, G. W., Koepf, G. F., Lewis, R. A., and Olsen, E. F. (1940). "Carbohydrate metabolism in Addison's disease", *J. clin. Invest.*, **19**, 813.
- ³⁵ Sprague, R. G., Gastineau, C. F., Mason, H. L., and Power, M. H. (1948). "Effects of synthetic 11-dehydrocorticosterone (Compound A) in a subject with Addison's disease", *Amer. J. Med.*, **4**, 175.
- ³⁶ Hench, P. S., Slocumb, C. H., Barnes, A. R., Smith, H. L., Polley, H. F., and Kendall, E. C. (1949). "The effects of the adrenal cortical hormone 17-hydroxy-11-dehydrocorticosterone (Compound E) on the acute phase of rheumatic fever: preliminary report", *Proc. Mayo Clin.*, **24**, 277.
- ³⁷ Sprague, R. G. Personal communication.
- ³⁸ —, Powers, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1950). "Observations on the physiologic effects of 17-hydroxy-11-dehydrocorticosterone (cortisone) and adrenocorticotrophic hormone (ACTH) in man", *Arch. intern. Med.* (in the press).
- ³⁹ Kendall, E. C. (1941). "The adrenal cortex", *Arch. Path.*, **32**, 474 (in General Review section).
- ⁴⁰ Wells, B. B., and Kendall, E. C. (1940). "The influence of corticosterone and C₁₇-hydroxy-dehydrocorticosterone (Compound E) on somatic growth", *Proc. Mayo Clin.*, **15**, 324.
- ⁴¹ Ingle, D. J., Higgins, G. M., and Kendall, E. C. (1938). "Atrophy of the adrenal cortex in the rat produced by administration of large amounts of cortin", *Anat. Rec.*, **71**, 363.
- ⁴² Heilman, F. R., and Kendall, E. C. (1944). "The influence of 11-dehydro-17-hydroxycorticosterone (Compound E) on the growth of a malignant tumour in the mouse", *Endocrinology*, **34**, 416.
- ⁴³ Murphy, J. B., and Sturm, E. (1944). "The effect of adrenal cortical and pituitary adrenotropic hormones on transplanted leukemia in rats", *Science*, **99**, 303.

- ⁴⁴ Ingle, D. J., and Kuizenga, M. H. (1945). "The relative potency of some adrenal cortical steroids in the muscle-work test", *Endocrinology*, **36**, 218.
- ⁴⁵ —, and Kendall, E. C. (1940). "Influence of amorphous fraction from adrenal cortex on efficiency of muscle", *Proc. Soc. exp. Biol., N.Y.*, **45**, 602.
- ⁴⁶ Smith, P. E. (1930). "Hypophysectomy and a replacement therapy in the rat", *Amer. J. Anat.*, **45**, 205.
- ⁴⁷ Collip, J. B., Anderson, E. M., and Thomson, D. L. (1933). "The adrenotropic hormone of the anterior pituitary lobe", *Lancet*, **2**, 347.
- ⁴⁸ Li, C. H., Evans, H. M., and Simpson, M. E. (1943). "Adrenocorticotrophic hormone", *J. biol. Chem.*, **149**, 413.
- ⁴⁹ Sayers, G., White, A., and Long, C. N. H. (1943). "Preparation and properties of pituitary adrenotropic hormone", *Ibid.*, **149**, 425.
- ⁵⁰ Li, C. H. (1947). "The chemistry of the hormones", *Ann. Rev. Biochem.*, **16**, 291.
- ⁵¹ Gordan, G. S., Li, C. H., and Bennett, L. L. (1946). "Effect of adrenocorticotrophic hormone on urinary nitrogen excretion in normal rat", *Proc. Soc. exp. Biol., N.Y.*, **62**, 103.
- ⁵² Ingle, D. J., Li, C. H., and Evans, H. M. (1946). "Effect of adrenocorticotrophic hormone on urinary excretion of sodium, chloride, potassium, nitrogen, and glucose in normal rats", *Endocrinology*, **39**, 32.
- ⁵³ Evans, H. M., Simpson, M. E., and Li, C. H. (1943). "Inhibiting effect of adrenocorticotrophic hormone on the growth of male rats", *Ibid.*, **33**, 237.
- ⁵⁴ Becks, H., Simpson, M. E., Li, C. H., and Evans, H. M. (1944). "Effects of adrenocorticotrophic hormone (ACTH) on osseous system in normal rats", *Ibid.*, **34**, 305.
- ⁵⁵ Li, C. H., Kalman, C., Evans, H. M., and Simpson, M. E. (1946). "Effect of hypophysectomy and adrenocorticotrophic hormone on alkaline phosphatase of rat plasma", *J. biol. Chem.*, **163**, 715.
- ⁵⁶ Dougherty, T. F., and White, A. (1944). "Influence of hormones on lymphoid tissue structure and function. Role of pituitary adrenotropic hormone in regulation of lymphocytes and other cellular elements of blood", *Endocrinology*, **35**, 1.
- ⁵⁷ Forsham, P. H., Thorn, G. W., Prunty, F. T. G., and Hills, A. G. (1948). "Clinical studies with pituitary adrenocorticotropin", *J. clin. Endocrinol.*, **8**, 15.
- ⁵⁸ Sayers, G., Burns, T. W., Tyler, F. H., Jager, B. V., Schwartz, T. B., Smith, E. L., Samuels, L. T., and Davenport, H. W. (1949). "Metabolic actions and fate of intravenously administered adrenocorticotrophic hormone in man", *Ibid.*, **9**, 593.
- ⁵⁹ Mason, H. L., Power, M. H., Rynearson, E. H., Ciaramelli, L. C., Li, C. H., and Evans, H. M. (1948). "Results of administration of anterior pituitary adrenocorticotrophic hormone to normal human subject", *Ibid.*, **8**, 1.
- ⁶⁰ Sayers, G., and Sayers, M. A. (1946). "Regulation of pituitary adrenocorticotrophic activity", *Fed. Proc.*, **5**, 200.
- ⁶¹ —, Fry, E. G., White, A., and Long, C. N. H. (1944). "Effect of adrenotropic hormone of anterior pituitary on cholesterol content of adrenals with review of literature of adrenal cholesterol", *Yale J. Biol. Med.*, **16**, 361.
- ⁶² —, — (1945). "Regulatory effect of adrenal cortical extract on elaboration of pituitary adrenotropic hormone", *Proc. Soc. exp. Biol., N.Y.*, **60**, 162.
- ⁶³ Carreyett, R. A., Golla, Y. M. L., and Reiss, M. (1945). "Action of gonadotrophic hormone and of pituitary corticotrophic hormone on cholesterol content of adrenals", *J. Physiol.*, **104**, 201.
- ⁶⁴ Sayers, G., Sayers, M. A., Liang, T. Y., and Long, C. N. H. (1946). "Effect of pituitary adrenotropic hormone on cholesterol and ascorbic acid content of adrenal of rat and guinea pig", *Endocrinology*, **38**, 1.
- ⁶⁵ Editorial (1949). "Some aspects of adrenal cortical function and pituitary-adrenal relationships", *Ann. intern. Med.*, **31**, 925.
- ⁶⁶ Selye, H., Sylvester, O., Hall, C. E., and Leblond, C. P. (1944). "Hormonal production of arthritis", *J. Amer. med. Ass.*, **124**, 201.
- ⁶⁷ Pirozynski, W., and Akert, K. (1949). "Polyarthritis und Nebennierenrindenhormone", *Schweiz. med. Wschr.*, **79**, 745.
- ⁶⁸ Hall, O. (1946). M.Sc. thesis. McGill University, Montreal.
- ⁶⁹ Selye, H. (1946). "General adaptation syndrome and diseases of adaptation", *J. clin. Endocrinol.*, **6**, 117.
- ⁷⁰ — (1944). "Role of the hypophysis in the pathogenesis of the diseases of adaptation", *Canadian med. Ass. J.*, **50**, 426.
- ⁷¹ — (1949). "The general adaptation syndrome and the diseases of adaptation", *Textbook of Endocrinology, Acta endocrinol., Montreal*.
- ⁷² — (1949). "Further studies concerning the participation of the adrenal cortex in the pathogenesis of arthritis", *Brit. med. J.*, **4637**, 1129.
- ⁷³ — (1941). "Variations in organ size caused by chronic treatment with adrenal cortical compounds; example of dissociated adaptation to hormone", *J. Anat. Lond.*, **76**, 94.
- ⁷⁴ —, and Boland, E. (1943). "Development and repair of organ changes induced by steroid compounds", *Rev. canad. Biol.*, **2**, 271.

- ⁷⁵ Selye, H. and Dosne, C. (1942). "Physiological significance of compensatory adrenal atrophy", *Endocrinology*, **30**, 581.
- ⁷⁶ —, — (1941). "Influence of traumatic shock on blood sugar of adrenalectomized rats treated with adrenal cortical extract", *Proc. Soc. exp. Biol., N.Y.*, **48**, 532.
- ⁷⁷ —, —, Bassett, L., and Whittaker, J. (1940). "On the therapeutic value of adrenal cortical hormones in traumatic shock and allied conditions", *Canad. med. Ass. J.*, **43**, 1.
- ⁷⁸ Freyberg, R. H. "Effects of cortisone and ACTH in rheumatoid arthritis" (Panel discussion). *Bull. N.Y. Acad. Med.* (In the press.)
- ⁷⁹ Bauer, W., Boland, E. W., Freyberg, R. H., Holbrook, W. P., and Rosenberg, E. F. Discussions, Proceedings Seventh International Congress on Rheumatic Diseases, 1949. (In the press.)
- ⁸⁰ Boland, E. W., and Headley, N. E. (1949). "Effects of cortisone acetate on rheumatoid arthritis", *J. Amer. med. Ass.*, **141**, 301.
- ⁸¹ Rosenberg, E. F. "Rheumatoid arthritis: experiences with cortisone (Compound E), and other adrenal cortical steroids, and pituitary adrenocorticotrophic hormone". (To be published.)
- ⁸² Spies, T. D., and Stone, R. E. (1949). "Relief of the symptoms of acute gout and rheumatoid arthritis by means of pituitary adrenocorticotrophic hormone (ACTH)", *Sth. med. J., Nashville*, **42**, 720.
- ⁸³ Markson, D. E. (1949). "Prolonged treatment of rheumatoid arthritis with pituitary adrenocorticotrophic hormone (ACTH)", *J. Amer. med. Ass.*, **141**, 458.
- ⁸⁴ Holbrook, W. P. Personal communication.
- ⁸⁵ Bauer, W. Personal communication.
- ⁸⁶ Elkinton, J. R., Hunt, A. D., Godfrey, L., McCrory, W. W., Rogerson, A. G., and Stokes, J. (1949). "Effects of pituitary adrenocorticotrophic hormone (ACTH) therapy", *J. Amer. med. Ass.*, **141**, 1273.
- ⁸⁷ Ragan, C., Grokoest, A. W., and Boots, R. H. (1949). "Effect of adrenocorticotrophic hormone (ACTH) on rheumatoid arthritis", *Amer. J. Med.*, **7**, 741.
- ⁸⁸ Spies, T. D., Stone, R. E., Dreizen, S., and Morton, B. F. (1949). "Further studies with pituitary adrenocorticotrophic hormone (ACTH)", *Sth. med. J., Nashville*, **42**, 991.
- ⁸⁹ Bauer, W. (1949). Discussion at the Seventh Internat. Cong. on Rheum. Dis., New York, May 31, 1949.
- ⁹⁰ Freyberg, R. H. Personal communication.
- ⁹¹ Boland, E. W., and Headley, N. E. Unpublished data.
- ⁹² Hench, P. S. Address before New York Academy of Medicine, Jan. 5, 1950—quoted by Freyberg (see reference no. 78).
- ⁹³ —. Personal communication.
- ⁹⁴ —. Personal communication.
- ⁹⁵ Ragan, C. Personal communication.
- ⁹⁶ Robinson, W. D., Conn, J. W., Block, W. D., and Louis, L. H. (1948). "Role of the adrenal cortex in urate metabolism and gout", *J. Lab. clin. Med.*, **33**, 1473.
- ⁹⁷ —, —, —, —, and Katz, J. (1949). "Role of the anterior pituitary and adrenal cortex in urate metabolism and in gout", Seventh Internat. Cong. on Rheum. Dis., May 30-June 3, 1949, New York.
- ⁹⁸ Thorn, G. W.—quoted by Robinson and others (see reference no. 97).
- ⁹⁹ Hellman, L. (1949). "Production of acute gouty arthritis by adrenocorticotropin", *Science*, **109**, 280.
- ¹⁰⁰ Wolfson, W. Q. "The role of the hormones in the pathogenesis and treatment of gout." In *Progress in Clinical Endocrinology*, ed. S. Soskin. New York, Grune and Stratton. (In the press.)
- ¹⁰¹ Margolis, H. M., and Caplan, P. S. (1950). "Treatment of acute gouty arthritis with pituitary adrenocorticotrophic hormone (ACTH)", *J. Amer. med. Ass.*, **142**, 256.
- ¹⁰² Wolfson, W. Q., Guterman, H. S., Levine, R., Cohn, C., Hunt, H. D., and Rosenberg, E. F. (1949). "An endocrine finding apparently characteristic of gout: very low urinary 17-ketosteroid excretion with clinically normal androgenic function", *J. clin. Endocrinol.*, **9**, 497.
- ¹⁰³ —, Hunt, H. D., Levine, R., Guterman, H. S., Cohn, C., Rosenberg, E. F., Huddleston, B., and Kadota, K. (1949). "The transport and excretion of uric acid in man. V. A sex difference in urate metabolism", *Ibid.*, **9**, 749.

Ecorce Surrénale par Rapport à la Maladie Rhumatismale Revue de quelques Investigations Récentes

RÉSUMÉ

1. Application de la fonction surrénale corticale aux maladies rhumatismales:
 - (a) Notes historiques sur le cortisone et les premières études expérimentales. Composés E, F, et Fa. Classification des hormones connues de l'écorce surrénale. Effets du cortisone et de l'hormone adrénocorticotrophique (ACTH) sur animaux et sur hommes.
 - (b) Données expérimentales impliquant l'écorce surrénale dans la pathogénie de la maladie rhumatismale.

2. Effets du cortisone et du ACTH sur certaines maladies rhumatismales:
 - (a) Arthrite rhumatismale:

Effets anti-rhumatiques du cortisone et du ACTH.
 Effets du cortisone et du ACTH sur les symptômes constitutionnels.
 Effets sur les épreuves de laboratoire (sédimentation globulaire, numération des érythrocytes et détermination de l'hémoglobine, numération des leucocytes, biopsies articulaires, électrocardiogrammes, électroencéphalogrammes).
 Effets métaboliques et immunologiques (excrétion corticostéroïde, excrétion des 17-cétostéroïdes, électrolytes du plasma, azote total urinaire, acide urique dans le sérum et dans l'urine, azote de la créatine et de la créatinine dans l'urine, tolérance des hydrates de carbone, glutathion dans le sang, excrétion de l'acide glucuronique et gentisique, protéines sériques, métabolisme de base et coefficient respiratoire, agglutination du sang de mouton sensibilisé, agglutination du streptocoque du groupe A, cholestérol sérique, "blood sludging").
 Posologie et mode d'administration.
 Evolution après l'interruption du traitement.
 Signes objectifs de l'hyperactivité surrénale.
 - (b) Arthrite rhumatismale juvénile (maladie de Still).
 - (c) Spondylite ankylosante.
 - (d) Arthrite rhumatismale avec psoriasis et arthrite psoriasique.
 - (e) Rhumatisme articulaire aigu.
 - (f) Périartérite noueuse.
 - (g) Lupus érythémateux disséminé.
 - (h) Dermatomyosite.
 - (i) Goutte.

L'article est augmenté par une bibliographie épuisante de la littérature, mais beaucoup de renseignements, pas encore publiés, furent communiqués personnellement.

Corteza Suprarrenal con Relacion a la Enfermedad Reumática Revista de Algunas Investigaciones Recientes

RESUMEN

1. Aplicación de la función suprarrenal cortical a las enfermedades reumáticas:
 - (a) Notas históricas sobre el cortisón y primeros estudios experimentales. Compuestos E, F, y F_a. Clasificación de las hormonas conocidas de la corteza suprarrenal. Efectos del cortisón y de la hormona adrenocorticotrófica (ACTH) sobre sujetos animales y humanos.
 - (b) Datos experimentales implicando la corteza suprarrenal en la patogenesis de la enfermedad reumática.
2. Efectos del cortisón y de la ACTH sobre ciertas enfermedades reumáticas:
 - (a) Artritis reumatoide:

Efectos anti-reumáticos del cortisón y de la ACTH.
 Efectos del cortisón y de la ACTH sobre síntomas constitucionales.
 Efectos sobre pruebas de laboratorio (sedimentación globular, recuentos de eritrocitos y determinación de la hemoglobina, recuentos de leucocitos, biopsias articulares, electrocardiogramas, electroencefalogramas).
 Efectos metabólicos e inmunológicos (excreción corticoesteroide, excreción de los 17-cetoesteroides, electrolitos del plasma, nitrógeno urinario total, ácido úrico en el suero y en la orina, tolerancia de los hidratos de carbón, glutatión en la sangre, excreción del ácido glucurónico y gentísico, proteínas séricas, metabolismo de base y el cociente respiratorio, aglutinación de la sangre sensibilizada de oveja, aglutinación del estreptococo del grupo A, colesterol sérico, "blood sludging").
 Dosis y horario de administración.
 Evolución después de la interrupción del tratamiento.
 Indicios objetivos del hiperadrenalismo.
 - (b) Artritis reumatoide juvenil (enfermedad de Still).
 - (c) Espondilitis anquilosante.
 - (d) Artritis reumatoide con psoriasis y artritis psoriática.
 - (e) Reumatismo articular agudo.
 - (f) Periartritis nodosa.
 - (g) Lupus eritematoso diseminado.
 - (h) Dermatomiositis.
 - (i) Gota.

El artículo está completado por una bibliografía minuciosa de la literatura, pero mucha información no publicada aún procede de comunicación personal.