FOREWORD

This volume is a valuable review of the literature of experimental and clinical studies of the effect of the adrenal corticoid and adrenotrophic pituitary hormones in the full range of human disease. The pendulum of opinion in the medical profession has swung from one of complete acceptance of the corticosteroids as a miraculous cure-all to the opposite extreme of complete disapproval as dangerous drugs. But now, the well-balanced belief of the profession is that these hormones have immense and extremely varied clinical usefulness.

Their mode of action and ultimate effect in pathology are by no means elucidated, but a few principles of therapeutic application are now recognizable. In many acute conditions, large doses may be given from the onset with valuable suppressive effect on inflammation, and with little danger of undesirable side effects, provided the term of therapy is measured in days.

In chronic conditions in which the physician has weighed the prognosis without the corticosteroids and decided that the morbidity and fatality to be faced require their prolonged use, in my opinion, the physician and patient should agree that the drugs are to be used without interruption, for years if necessary; until a profound remission of the disease appears to have occurred. Complete discontinuance is contraindicated since such a disease as rheumatoid arthritis may smoulder in a sub-clinical state, only to rebound in a severe exacerbation when even minimal medication is stopped. For example, when arthritis is suppressed, a small dosage is usually strong enough to maintain the suppression, but if this is removed, the smouldering disease flares up in greatly magnified force. This deliberate or ignorant induction of the rebound exacerbation is to be avoided at all costs. At the same time, the physician and patient should know that the dosage is not constant although administration is continuous.

It is advisable in starting the treatment of a chronic disease requiring medication for years, to titrate the benefit of very minimal amounts up to the smallest effective daily dosage. This is the reverse of the method of treating acute conditions in which immediate suppression of the inflammation is desired, and prompt, if graduated, complete hormone withdrawal is planned. In the chronic disease, the dosage will be increased as the disease waxes in severity and decreased as it becomes milder.

Most important in the chronic treatment regimen is the prescription of associated medications required to support biochemical, immunological and physiological homeostasis. These are as follows:

1. Prevention of negative potassium balance and hypokalemia. All the disorders known to result from this may be produced by cortisone medication. One of the chief of these is psychosis. Administration of from 3 to 15 grams (not grains) a day of potassium salts are required.
2. Prevention of cellular catabolism which results in the loss of nitrogen, calcium, potassium and other vital elements may be obtained by the administration of the anabolic sex hormone steroids, testosterone and estradiol or estrones.
3. Abnormal retention of sodium may occur with a dependent edema and hypertension. This can be controlled by a low salt diet and chlorothiazide or related derivatives.
4. Excessive gastric secretion of enzymes and acids which may produce gastric or duodenal ulcers must be neutralized by the usual but well-arranged anti-ulcer regimen: Milk feedings, on a time table by the clock to forestall the occurrence of symptoms; antacids; and effective anticholinergic drugs. In fact, if the patient is on higher dose levels of corticoids, he should routinely receive the full anti-ulcer program, just as if he already had an ulcer.
5. Most important is the anticipation of the spread of either acute or chronic bacterial infections; chest x-rays to detect a dissemination of tuberculosis should be taken at regular intervals. The onset of acute infections should be watched for with unusual alertness and prompt massive antibiotic therapy administered without delay.

The physician must realize that in employing cortisone or ACTH to prevent inflammation with its attendant pain, disability and deforming pathology, he is using an agent which has additional biochemical and physiological effects on all systems in the body. These cannot be ignored; they must be controlled if corticoids are to be used safely.

The multiplicity of the diseases that are presented in this book with the application of the corticoids and ACTH to their treatment is abundant proof of the enormous usage that can be made of these miracle drugs. Each chapter includes a bibliography of the references reviewed, which altogether give a wide survey of this field of therapeutic application.

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CORTICOSTEROIDS IN MEDICAL PRACTICE

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Chapter 1

ACTH AND ADRENOCORTICOSTEROID OUTPUT

ADRENOCORTICOSTEROID OUTPUT

The normal daily adrenocorticosteroid output in man has been estimated to be the equivalent of 12.5 to 40 mg. hydrocortisone per day (1-3). The excretion of hydrocortisone metabolites or 17-hydroxycorticosteroids is about 20 to 30 per cent higher in men than in women (4). Hydrocortisone is the steroid found in highest concentration in human adrenal vein blood and adrenal tissue. Determinations of adrenal vein hydrocortisone levels have indicated the output of hydrocortisone to be about 21 mg. per day (5) and 34 mg. per day (6). The concentration of hydrocortisone in the human adrenal gland is 2.3 to 5.5 micrograms per gram of fresh tissue (7).

Corticosterone, or compound B, is the second most abundant adrenocorticosteroid (8-11). Isotope dilution studies using corticosterone-4-C14 have indicated that the ratio of concentration of hydrocortisone to corticosterone in human plasma is 15 to 1 in normal subjects (8). The ratio of hydrocortisone to corticosterone was 4 to 1 and 13 to 1 in other reports (12, 13). Identification and assay of corticosterone in human plasma by isotope dilution showed the average concentration of corticosterone for twenty normal subjects was 1.1 ± 0.3 microgram per 100 cc. plasma (8). The normal daily secretion of hydrocortisone is thus estimated to be 17 to 29 mg. per day, and of corticosterone 2 to 3 mg. per day (13, 14). Hydrocortisone and compound B make up from 85 to virtually 100 per cent of the total alpha-one-beta-unsaturated-3-ketosteroids in the adrenal venous blood of most species of common laboratory animals (15).

C14 labelled hydrocortisone has been administered intravenously in trace amounts to measure hydrocortisone turnover

rates and production on the basis that the metabolites of the labelled hormones enter equally into the urine with those of non-labelled hydrocortisone (14, 16). When the rates observed during periods of two to four hours were assumed to represent the rate of production throughout twenty-four hours, the rate of hydrocortisone production was estimated to be from 17 to 29 mg. per day, mean 21 mg. per day (14). When total twenty-four hour secretion was measured using C-14 labelled hydrocortisone in 12 quiescent and convalescent patients, a direct measurement of the total C14 content of the urine and the specific gravity of tetrahydrocortisone was determined (16). The average daily secretion of hydrocortisone was about 13.5 mg. in normal subjects with a range of variation of 5 to 28 mg. In six patients with severe active but non-endocrine disease the output was 10 to 32 mg. (average 20 mg.) per day (16). Very low levels of free and conjugated steroids are present in infants and children (17).

Plasma C17-21-hydroxycorticosteroid levels are elevated in pregnancy. Plasma levels of adrenocorticosteroids in pregnant women may reach 400 per cent of the levels in nonpregnant females (18). Similarities between pregnancy and Cushing's syndrome have been noted (19). However, increased adrenocortical activity in pregnancy manifests itself in a response of all sectors of the adrenal cortex (20). The 17-ketosteroids show moderate elevation during the first three months of pregnancy, and subsequently the 17-hydroxycorticoids, glycometabolic activity, and sodium retaining fractions are rapidly augmented (20). A further rise in steroid levels occurs during labor and delivery, reaching a maximum one hour after delivery, but by twenty-four hours post-partum the level is down to that present before active labor (21).

Some individuals have a normal baseline adrenocorticosteroid output but fail to respond with increased output to stress or to ACTH injections (22). When subjected to stress they may have manifestations of adrenal insufficiency. In patients with chronic illnesses the 17-ketosteroid output is not infrequently lowered as compared to healthy subjects (23, 24). Decreased adrenocortical responsiveness to ACTH has been observed in patients debilitated with cancer and other disorders (25, 26). The 17-

ketosteroid response is depressed in debilitated patients undergoing acute stresses, although there may be marked formaldehydogenic increases (27). Urinary adrenocorticosteroid output is usually lowered in chronic hepatic disease, which may be at least partly related to the fact that the liver appears to be the main site of metabolism of the hormones and because other endocrine alterations are not infrequently present in chronic hepatic dysfunction. Excretion of 17-ketosteroids has been noted to be significantly reduced with ageing, particularly the non-11-oxygenated steroids (28). Adrenal insufficiency may occur at times of stress and require small supplements of corticosteroids. Reduced tolerance to stress is more common in the older age groups and in debilitated patients who have had repeated operative procedures (29). The effect of age by itself on adrenal function has been questioned, however (30). Age induces no significant change in eosinophile response to ACTH (31). It has been suggested that the corticosteroids should be administered to elderly patients under circumstances where it is important to increase their general resistance including to protect them from surgical shock (32).

The General Adaptation Syndrome was described by Selye (33). The importance of the hypothalamic-pituitary-adrenal axis is participating in the reaction has been demonstrated (34, 35). Conditions of stress are frequently associated with increased plasma levels of 17-hydroxycorticosteroids (36, 37). The mechanism of such elevation is not definitely known. Cytologic changes in the human adrenal gland in patients dying from conditions associated with acute stress, or after exogenous administration of corticotropin are similar, which supports the view that the adrenal changes in stress are the result of an increase in endogenous corticotropin production (38).

Increased production of ACTH has been attributed to accelerated utilization of adrenal steroids in stress conditions, but there is evidence that the removal rate of hydrocortisone may be normal or decreased in stress. A normal or decelerated rate of cortisol metabolism has been observed in subjects with various diseases (23, 39), and a normal or decreased rate of metabolism of intravenously administered cortisol has been observed in man