CORTISONE (COMPOUND E)

SUMMARY OF ITS CLINICAL USES*

BY

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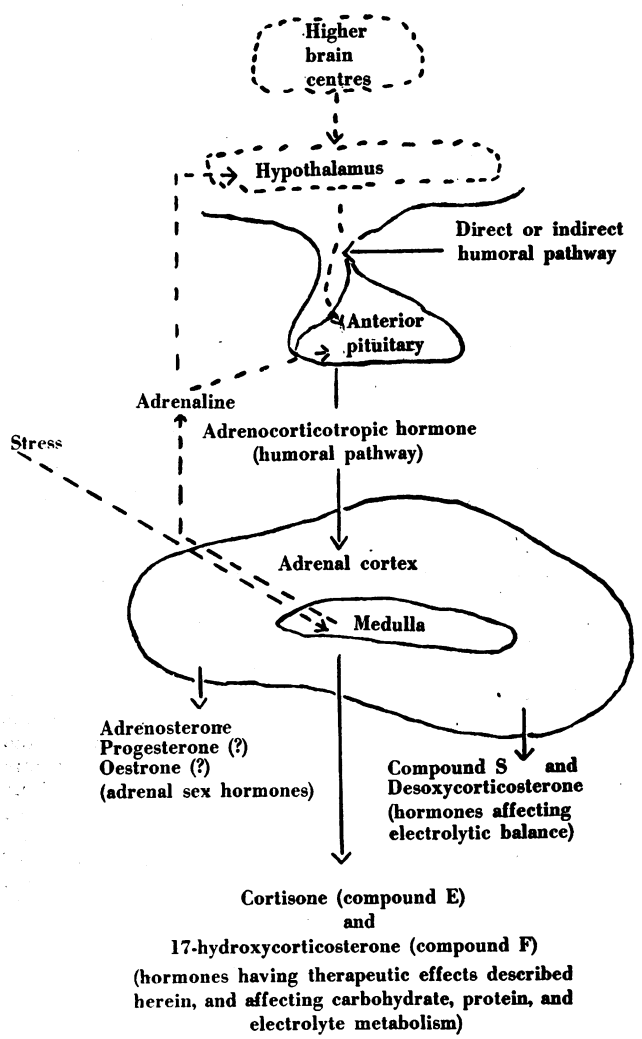
Cortisone is one of the series of crystalline hormonal substances isolated from extracts of the adrenal cortex in the laboratory of Dr. E. C. Kendall, of the Mayo Foundation. This substance, originally named "compound E," was isolated from beef adrenal glands and described by Mason, Myers, and Kendall in 1936. It was also described independently by Reichstein as "substance FA," and by Wintersteiner and Pfiffner as "compound F."

Cortisone was first synthesized from a bile acid in 1946 by Dr. L. H. Sarett, of the Research Laboratories of Merck and Co., Inc. The availability of cortisone in sufficient quantities for clinical use was the result of a practical synthesis developed by the combined efforts of Dr. Kendall and his associates and of Dr. Max Tishler and his associates in the Merck Research Laboratories.

PITUITARY—ADRENAL RELATIONSHIPS



Cortisone (compound E) and 17-hydroxycorticosterone (compound F) (hormones having therapeutic effects described herein, and affecting carbohydrate, protein, and electrolyte metabolism)

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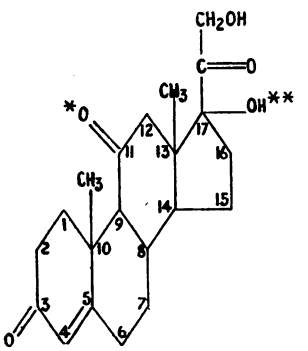
Theoretic Mechanism of Adrenal Secretion of Cortisone and Related Adrenal Steroids

The adrenal cortex upon stimulation elaborates (1) the group of hormones producing the therapeutic effects described herein and affecting carbohydrate, protein, and electrolyte metabolism, such as cortisone and compound F; (2) the group affecting electrolyte balance, such as compound S and desoxycorticosterone; and (3) the adrenal sex hormone adrenosterone, and possibly progesterone and oestrone. The present concept is that the secretion of cortical steroid hormones is mainly or entirely mediated through stimulation of the adrenal cortex by the adrenocorticotropic hormone of the anterior pituitary (see Diagram).

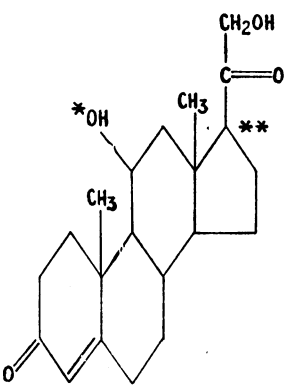
Specificity of the Chemical Structure of Cortisone

From the formula below it will be seen that cortisone has an oxygen atom at position 11* and a hydroxyl group (OH) at position 17**, and that these features differentiate it structurally from the earlier-named corticosterone.

Although the presence of an oxygen atom at position 11 and a hydroxyl group at position 17 are features which are vital to the biological activity of cortisone (and which have required much attention in the synthesis of the hormone),



Cortisone (Kendall's compound E). The chemical name, 17 - hydroxy - 11-dehydrocorticosterone, is based upon points of difference and similarity between the molecular structures of cortisone and corticosterone (Kendall's compound B).



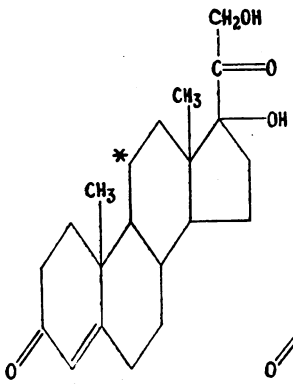
Corticosterone (Kendall's compound B)

it should also be noted that every other atom and configuration of the molecule probably is equally important. This is indicated by the fact that dozens of similar steroids have been prepared and tested for the antirheumatic and other therapeutic activity of cortisone, and that none possesses such activity (with the probable exception of compound F), although chemically each may differ very slightly from cortisone. Examples of a few of these "analogues" are given on the opposite page.

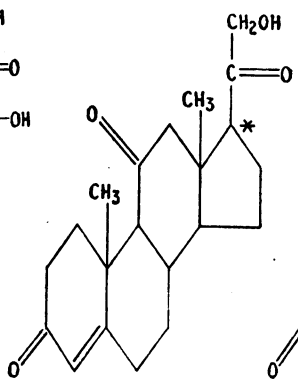
The list could be extended to include many more compounds, now numbering almost fifty, which have been synthesized and tested for cortisone-like activity. As each has been tested and negative results obtained, the remarkable specificity of the cortisone molecule has again been emphasized.

Metabolic Effects

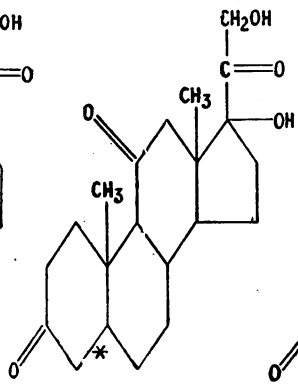
Electrolyte balance is affected in varying degrees in different cases. Retention of sodium and water early in the course of treatment is often observed, especially when high dosage of cortisone has been employed, but is usually followed by spontaneous diuresis on continued



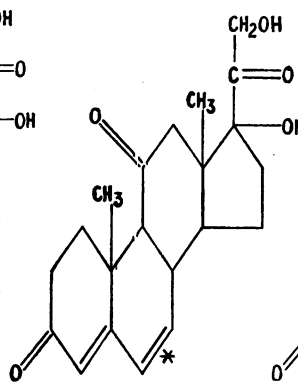
Reichstein's compound S (11-desoxy-17-hydroxycorticosterone, or "desoxycortisone"). *Molecule differs from cortisone only by the absence of an oxygen atom at position 11.



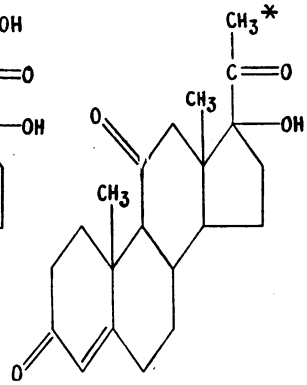
Kendall's compound A (11-dehydrocorticosterone). *Molecule differs from cortisone only by the absence of a hydroxyl group at position 17.



Dihydrocortisone. *Molecule differs from cortisone only by absence of a double bond at position 4, 5 (presence of an extra hydrogen atom).



6, 7 - Dehydrocortisone. *Molecule differs from cortisone only by presence of a double bond at position 6, 7 (absence of a hydrogen atom).



21 - Desoxycortisone. *Molecule differs from cortisone only by the absence of an oxygen atom at position 21.

administration of the hormone or after its discontinuation. In several instances, however, sodium and water retention has been so great as to require lowering the dosage or discontinuing administration of the drug because congestive heart failure with ascites or peripheral or pulmonary oedema developed. Sodium retention can be diminished or avoided by the restriction of sodium intake alone, or together with the use of diuretics during administration of the drug. High dosage of cortisone has caused increased urinary excretion of potassium, with metabolic alkalosis in some cases. In these patients potassium depletion resulting from such loss has produced symptoms of weakness, electrocardiographic changes characteristic of hypopotassaemia (such as lowering of T waves, and depression of the S-T segment and S-T junction), and hypotensibn. This development can be avoided by carefully following the CO_2-combining power, E.C.G., and chloride depletion. If any changes indicating alkalosis are noted, the dosage of cortisone should be reduced, or potassium administered concomitantly with the hormone. Also, it should be noted that in such cases the use of diuretics may provoke a further dangerous diuresis of potassium.

Carbohydrate metabolism may be affected also, in that blood-sugar levels may be increased and the response to insulin decreased. In patients with diabetes mellitus, insulin requirements are increased during administration of the hormone, but revert to their original levels soon after discontinuation of the drug.

Protein metabolism is affected in many patients, especially those receiving high dosage of cortisone. The continued administration of large doses usually produces a negative nitrogen balance, which may be overcome in certain instances by increased food intake. Where reversed albumin–globulin ratios are present, these tend to revert towards normal. Creatinuria is increased, uric acid excretion increased, and changes in the pattern of amino-acid excretion occur.

Studies in animals suggest that cortisone may inhibit the growth of granulation and fibrous tissues. Clinical studies also have provided evidence which suggests that the hormone may retard wound healing. This must be further evaluated, but these data should be considered when surgical procedures are contemplated in patients receiving cortisone, especially patients with ulcerated or inflamed lesions and those who show evidence of hypoproteinaemia, hypovitaminosis, and general malnutrition.

General Physiological or Hormonal Effects

Cortisone is a potent hormonal substance, and definite physiological effects are to be expected from its administration. With high or prolonged dosage, and in certain patients on the recommended dosage, undesired hormonal effects may occur. However, as with other hormones, such effects are reversible and disappear after administration of the substance is discontinued.

In some patients the drug has produced such evidences of hyperadrenalism as rounding of the face, mild hirsutism, acne, striae of the skin, and, in a few instances, amenorrhoea. All these phenomena disappeared after administration was discontinued.

In animal investigations, prolonged administration of large doses of cortisone may cause reduction in the size of the adrenal cortex. In man, muscular weakness and asthenia have been reported for brief periods after treatment was abruptly withdrawn. This suggests that a transient period of adrenal cortical insufficiency may exist when administration of the drug is stopped. In certain patients a temporary reduction of urinary corticoids and 17-ketosteroids is found; a temporary hypoglycaemia and suppression of eosinophil response occasionally occur.

Electroencephalogram.—In several patients an increase of approximately 10% in the frequency of alpha waves has been observed. This finding is said to indicate increased cerebral activity.

Other Physiological Effects

Cortisone has rarely caused a significant increase of blood pressure, but this possibility exists where sodium and water retention occurs. The resting blood pressure in patients with essential hypertension may be decreased. In some cases decrease in prothrombin time has been noted.

Certain mental effects have been reported. Definite improvement in the mental attitude of patients receiving this drug usually occurs, often with acceleration of the alpha waves of the electroencephalogram. In certain instances the increase in psychomotor activity has temporarily produced an exaggerated sense of well-being and, infrequently, a manic state. Conversely, mental depression has been reported in a few cases. Insomnia has been noted in some individuals. In rare instances pre-existent or latent mental derangement, such as schizophrenia, seems to have been intensified or precipitated. In such cases

premonitory symptoms of the psychotic reaction usually occur, such as pronounced insomnia and exaggerated swings of mood.

Clinical Effects in Rheumatoid Arthritis and its Variants

In rheumatoid arthritis and its variants, such as rheumatoid spondylitis (Marie–Strümpell disease), Still's disease, and psoriatic arthritis, the usual pattern of response is, first, diminution in subjective stiffness, usually within 24 to 48 hours, but sometimes within six hours after the initial dose (Table I) : in many cases this symptom is significantly

TABLE I.—*Response of Various Diseases to Cortisone*

Beneficial Effect Often Dramatic	Results Encouraging But Require Further Evaluation	Transient Beneficial Effects Observed	No Beneficial Effects Established
Rheumatoid arthritis	Various allergies: Hay-fever Angioneurotic oedema Drug sensitization Serum sickness	Acute leukaemia (lymphocytic or granulocytic)	Diabetes mellitus (increases insulin requirement)
Rheumatic fever	Acute gouty arthritis	Multiple myeloma	Myasthenia gravis
Rheumatoid spondylitis	Ulcerative colitis	Lymphosarcoma	Cushing's syndrome
Still's disease	Regional enteritis	Hodgkin's disease	Amyotrophic lateral sclerosis
Psoriatic arthritis	Nephrotic syndrome	Chronic lymphatic leukaemia	Multiple sclerosis
Lupus erythematosus (early)	Scleroderma (early)		Progressive muscular dystrophy
Addison's disease	Dermatomyositis		Progressive muscular atrophy
Asthma (status asthmaticus)	Psoriasis		Congestive heart failure (may be detrimental in some cases, but cases secondary to acute carditis may be benefited through effect of cortisone on inflammatory lesions)
Inflammatory eye diseases	Periarteritis nodosa (early)		Chronic myelogenous leukaemia
Exfoliative dermatitis	Pulmonary granulomatosis		Acute monocytic leukaemia
Pemphigus	Alcoholism (?)		Glomerulonephritis (exclusive of nephrotic syndrome)
Panhypopituitarism			Poliomyelitis
			Osteoporosis (may be detrimental?)

or completely relieved within a few days. Next, articular tenderness and pain on motion decrease. Finally, swellings of the joints diminish, sometimes fairly rapidly and completely, but occasionally more slowly and incompletely. In many patients mild soft-tissue deformities of the knees or elbows have disappeared within seven to ten days. An increase in muscle strength has been reported. The extent of return to normal has been limited, as must be expected, by the degree of permanent pathological change present.

The appetite usually improves rapidly, and many patients have described a loss of the feeling of malaise associated with the disease and have experienced a sense of well-being, occasionally within several hours after initial administration of the drug.

When cortisone is discontinued signs and symptoms may begin to reappear within 24 to 48 hours, becoming gradually worse during the following two to four weeks. The degree of relapse varies, and is apparently unrelated to the duration of treatment. In some individuals, however, the greater part of the remission of signs and symptoms achieved after use of the drug has persisted for as long as several weeks or months. If the drug is readministered when manifestations of the disease return, prompt remission is again induced.

Laboratory Findings

Erythrocyte Sedimentation Rate.—Elevated sedimentation rates are decreased, sometimes rapidly, during the administration of cortisone, usually becoming normal within 10 to 35 days. Occasionally, however, the rate does not return to normal, but is definitely reduced. In a few instances, persistently high sedimentation rates may be lowered by temporarily increasing the daily dose of the drug.

Haemoglobin.—Low haemoglobin values tend to increase when cortisone is administered. Increases of 2 g. within several weeks have been observed.

Erythrocytes.—Increases of as much as 1,000,000 red cells per c.mm. of blood have been observed in anaemic patients during cortisone therapy of two weeks' duration or longer.

Serum Protein.—Increased serum-globulin levels and low or reversed albumin–globulin ratios usually return towards normal, in most cases promptly, during treatment, but gradually revert to pretreatment levels when the drug is discontinued.

Arterial Synovial Biopsy.—Findings after several weeks of cortisone therapy included almost complete disappearance of lymphocytic reaction, improvement in appearance of collagen, and the presence of many fibroblasts in more adult form. Though not normal, the synoviae revealed definite evidence of healing.

17-Ketosteroids.—During administration of cortisone, urinary 17-ketosteroid values are initially reduced, but they usually rise again, and to a somewhat higher level. When large doses (e.g., 200 mg. daily) are employed the ketosteroids may remain slightly above the pretreatment level throughout the period of administration.

Corticosteroids.—The urinary concentrations of corticosteroids are initially increased by administration of cortisone and may reach a peak of excretion of about 5 mg. per 24 hours soon after treatment is started. The amount excreted then declines gradually to a fairly constant level, ranging from 1 to 2 mg. per 24 hours, on continued administration of the drug. On discontinuing cortisone therapy following prolonged treatment periods or after the injection of large doses of the drug, both 17-ketosteroid and corticosteroid excretion has been observed to diminish temporarily in certain patients.

Clinical Effects in Acute Rheumatic Fever

Within 24 hours after the initial injection of cortisone patients have usually described a sense of well-being and appeared alert instead of ill and "toxic." Temperatures that had been elevated usually became normal within one to four and a half days. Appetites have usually improved, with resultant gains, reaching 5 to 12 lb. (2.3 to 5.4 kg.) in 18 to 28 days in some cases.

Painful, swollen, and inflamed joints have in most instances become symptom-free after three and a half to six days of treatment with cortisone. In most of the patients with acute rheumatic fever improvement has been maintained for periods of three months or longer following treatment. Several patients with acute rheumatic fever who relapsed after the drug was discontinued responded promptly to another series of injections, and have remained apparently well since discontinuation of the drug a second time. While cortisone has demonstrated its value in curtailing the acute manifestations of rheumatic fever, long-term studies will be necessary to evaluate its effects on the development of cardiac lesions.

Effects on Cardiovascular System

Pulse Rate.—Tachycardia, when present, disappeared in three and a half to five days after treatment was started. Bradycardia, ranging from 44 to 60 beats a minute, accompanied the use of the drug in some cases. The bradycardia persisted while

the young adult patients were receiving 200 mg. a day of cortisone, but disappeared shortly after the dose was reduced to 100 mg. daily.

Blood Pressure.—Significant blood-pressure changes have been observed infrequently during or following treatment of acute rheumatic fever with cortisone.

Electrocardiographic Findings.—In patients with prolonged P-R intervals return to normal or nearly normal limits usually occurred within eight days after the beginning of treatment. Electrocardiograms, made daily, showed no evidence of toxic effects on the heart.

Laboratory Findings

Erythrocyte Sedimentation Rate.—Usually the elevated sedimentation rate became normal within 12 to 18 days after injection of cortisone was begun.

Haemoglobin.—Increase in haemoglobin value by as much as 2.4 g. occurred within three weeks in patients in whom the pretreatment levels were low.

Leucocyte Count.—No characteristic effect on the total number of circulating leucocytes was noted during administration of cortisone, despite rapid clinical improvement and reduction of the erythrocyte sedimentation rate.

Serum Proteins.—In almost every instance administration of cortisone caused a slight increase in the values for serum albumin and a reduction in the values for serum globulin.

Response in Other Diseases

Disseminated Lupus Erythematosus.—Cortisone has produced a temporary beneficial effect in most cases in which treatment was started in the early stages of the disease. Elevated temperatures and sedimentation rates have been lowered, joint symptoms improved, and the skin lesions in certain cases alleviated. The general condition of the patient also has been improved. These effects generally last from a few days to a few weeks, and even longer in some patients. Favourable response cannot be expected in late cases with advanced renal involvement, azotaemia, hypoproteinaemia, retinal haemorrhages, and cachexia. Because of the frequent involvement of the heart and kidneys in this disease, the physician should be particularly watchful for evidence of aggravation of salt and water retention and congestive heart failure in response to cortisone.

Bronchial Asthma.—Cortisone administered to patients in status asthmaticus has in most instances produced relief of the symptoms, and in certain patients has increased the vital capacity. The improved state has lasted from several weeks to several months in many of the cases.

Non-specific Iritis, Iridocyclitis, Uveitis, and Sympathetic Ophthalmia.—Striking improvement during the course of cortisone administration has been reported. Congestion has decreased and vision has improved to some extent. In some cases these benefits occur rapidly, but further investigation is necessary before any conclusions can be drawn concerning the efficacy of cortisone in the treatment of these conditions. Recent reports indicate that local ophthalmic instillation of cortisone (as a 1:4 dilution of the standard formulation in physiological saline solution) may also be effective. (Such instillation should be made at intervals of 30 to 60 minutes throughout the waking hours.)

Skin Conditions.—Cortisone has been tried in a variety of severe skin conditions, including pemphigus, angioneurotic oedema, atopic dermatitis, and exfoliative dermatitis, including cases secondary to drug reactions. In general, its use has resulted in improvement, with rapid subsidence of the inflammatory reaction.

Addison's Disease.—Cortisone has been highly effective in controlling Addison's disease, in conjunction with D.C.A. (desoxycorticosterone acetate) and/or supplementary sodium chloride (for special dosage see below).

Leukaemias and Lymphomas.—In some cases of acute leukaemia, especially in children, there is a temporary response to treatment with cortisone, but relapses are to be expected. Even in those cases in which there is an initial response, refractoriness to cortisone develops during repeated courses of the substance. Chronic lymphatic leukaemia, lymphosarcoma, and Hodgkin's disease also have shown transient involution of neoplastic masses. The peripheral blood picture of chronic lymphatic leukaemia apparently is not altered appreciably. Acute monocytic leukaemia and chronic myeloid leukaemia have shown no response to cortisone therapy in several cases treated.

Other Conditions.—Cortisone has been used in investigations of several other conditions, but the data are still very incomplete and inconclusive. From the information available at present, it appears that cortisone does not produce any significant benefit in chronic gout, myasthenia gravis, amyotrophic lateral sclerosis, or congestive heart failure. It has no appreciable effect on the late structural changes of the rheumatic diseases.

Dosage

With high or prolonged dosage, and in certain patients on the recommended dosage (see below), undesired hormonal effects may occur. The physician planning to use cortisone should have received instruction in its use and should familiarize himself with the published literature before attempting treatment.

The treatment should be given only to patients in hospitals which have adequate facilities operated by trained technicians and under the supervision of a qualified physician. Facilities should be available for electrocardiography and for routine blood determinations, such as blood sugar, carbon-dioxide-combining power, and, where possible, for blood electrolytes. Facilities for laboratory studies must be available during the entire course of treatment.

Although cortisone has now been used in over 3,000 individual cases, the duration of clinical study has been less than two years and only a small number of cases have been observed over this entire period. In no instance has continuous treatment been used for a longer period than eight months. Therefore it must be realized that recommendations are limited by the extent of this experience, and that optimal-dosage schedules are still tentative. The administration of cortisone must be carefully adjusted for each patient and regulated according to the effects observed. Failure to obtain an expected therapeutic response suggests, in the absence of any undesirable effects, the possible need for a temporary increase in dosage.

Dosage in Rheumatoid Arthritis

Initial Dosage.—When a maximal response to cortisone is desired in rheumatoid arthritis in adults, the following schedule is strongly recommended : 100 mg. every eight hours for three doses, then 100 mg. every 12 hours for two doses, followed by 100 mg. every 24 hours for 7 to 14 days (the last can be given as a single injection or as a divided dose of 50 mg. every 12 hours. In some cases it seems that the single injection is better). In all cases the injections should be made deeply into the gluteal muscles, at the outer upper quadrant of the buttock. The optimal dosage for children has not been established, but it seems to be more nearly proportional to the severity of the disease than to body size. A comparatively large dose, or the adult dose, may be necessary and is often well tolerated.

Subsequent Dosage.—When the desired response appears to have been obtained the dosage should be lowered gradually in a stepwise manner. The total daily dose should be reduced by 10 or 15 mg. at two- to three-day intervals until the total daily dose is 50 mg. The schedule may then be changed to 100 mg. every other day (or 100 mg. on Monday and Wednesday, and 100 or 200 mg. on Friday). If at any time during the change-over significant relapse occurs, 100 mg.-a-day dosage must be reverted to until the desired response again appears, before lowering the dosage.

Temporary Increases in Dosage.—If the expected response is not obtained within four to five days after initiating cortisone therapy according to the schedule suggested above, the dosage should be increased to 100 mg. every 12 hours for four doses and then again reduced to 100 mg. daily. If inadequate dosage is employed it is likely that the desired beneficial effect will not be obtained. It is essential for many patients that a temporary increase in dosage, as outlined above, be given in order to provide the greatest relief.

Rest Period.—A rest period of not less than three or four weeks should be allowed between courses of treatment with cortisone in order to permit recovery of adrenal activity. A " course " at full therapeutic dosage is generally considered to extend over a period of two to six weeks, and the total dosage per course should not exceed 3 to 4 g.

Dosage in Rheumatic Fever

Optimal dosage for treatment of rheumatic fever has not been established. In the adult cases treated thus far, 200 mg. of cortisone was injected intramuscularly daily for 10 to 19 days, and, following this, 100 mg. daily for 5 to 27 days.

It is suggested that, as a general practice, courses of treatment be extended over a period of 10 to 14 days, with rest periods of varying duration between the courses (see under " Dosage in Rheumatoid Arthritis "), but it is more important that the natural history of the disease be taken into account and that re-treatment be instituted as indicated by recurrence of signs and symptoms of reactivation of the disease, such as return of fever, increase of sedimentation rate, recurrence of arthralgia, and lengthening of the P-R interval.

Dosage in Other Diseases

For eye and skin conditions and the leukaemias and lymphomas the required dosage seems to be comparable to that outlined for rheumatoid arthritis. Somewhat larger doses may be required initially in bronchial asthma, but the duration of treatment necessary is usually not more than five to ten days. In Addison's disease 25 mg. daily, or less, may be adequate, but supplementary salt or desoxycorticosterone should be given concurrently, as indicated, to maintain normal values of blood electrolytes.

Special Precautions

It must be emphasized most strongly that cortisone is an agent with powerful biological actions. The patient receiving cortisone must be closely watched at all times for the development of unfavourable side-reactions. The most important precautions relative to these are :

1. *Evaluation of Relative Contraindications Before Using Cortisone.*—As in the case of other powerful therapeutic agents having potentially harmful effects, the physician must weigh the advantages of treatment with cortisone against the possible deleterious effects. This consideration is crucial where relative contraindications exist, such as diminished cardiac reserve or congestive heart failure, latent or overt psychotic tendencies, diabetes mellitus, and the debility accompanying advanced cachectic states, uraemia, and senescence.

2. *Restriction of Dietary Sodium Chloride.*—Salt and water retention is a common occurrence after several days of full cortisone dosage. Usually there is a gain of only a few pounds in weight and minimal dependent oedema. This may progress, however, and result in pronounced oedema, including pulmonary oedema, or cardiac enlargement and congestive failure, especially in patients with previously diminished cardiac reserve. Occasionally such symptoms may come on quite suddenly. There may be some elevation of arterial blood pressure. Measurement of fluid intake and output and daily weighing of the patient provide the best indices of fluid retention. When salt and fluid retention occurs the simplest treatment is the low-sodium diet. If sodium intake is kept below 1 g. daily for a few days it is usually possible to prevent or correct fluid retention. In some instances it may be necessary to decrease cortisone dosage or even discontinue it.

3. *Correction of Hypopotassaemia.*—When hypopotassaemia develops, supplementary administration of potassium chloride may be required. It is important to note carefully the discussion under " Metabolic Effects," relative to hypochloraemic-hypopotassaemic metabolic alkalosis.

4. *Control of Hyperglycaemia.*—When a patient with diabetes mellitus is treated for a concurrent disease amenable to cortisone the diabetic status must be followed and regulated with great care. It is usually possible to compensate for the anti-insulin effect of cortisone by administering larger doses of insulin—double the usual requirement may be needed. In treating non-diabetic individuals the physician should be aware of the possibility that cortisone may induce renal glycosuria or hyperglycaemia with glycosuria. In all such cases thus far reported these changes have disappeared soon after cortisone administration was discontinued.

5. *Detection of Early Psychic Disturbances.*—Although the usual psychic reaction to cortisone is a desirable increase in the sense of well-being, an occasional individual will develop pronounced psychic derangements, especially where high dosage has been used for protracted periods, but sometimes early during the course of therapy. These reactions include a wide array of phenomena ranging from pronounced euphoria to frank psychoses. Therefore, treatment should be continued with caution when early signs of such reactions appear. The premonitory symptoms are marked swings of mood, severe insomnia, bad dreams, and increased psychomotor activity.

6. *Supervision of Patient Following Cortisone Therapy.*—After discontinuation of cortisone supervision is essential, for this substance may continue to act for some time after the last injection, or there may be a sudden reappearance of severe manifestations of the disease for which the patient was treated. In a few cases following prolonged high dosage, evidence of a temporary hypo-adrenal state may be observed if treatment is withdrawn abruptly. Weakness and hypoglycaemia may occur, but return of adrenal function may be expected within two weeks.

Theories of the Mechanism of Action of Cortisone

It may be said at the outset that the fundamental nature of the action of cortisone against disease processes is unknown. During the past eighteen months, however, much valuable and intensive work has been directed towards the solution of this problem—a widespread

TABLE II.—*Certain Known (or Probable) Effects of Cortisone*

Metabolic	Interendocrine	Neuromuscular	Immunological and Serological	Cytological	Enzymological
Increases gluconeogenesis	May either depress thyroid activity (probably via diminished pituitary production of thyrotropic hormone) or increase sensitivity of tissues peripherally to thyroid hormone	Restores capacity of muscle for work in adrenalectomized animals	Tends to bring about a restoration of normal A.-G. ratio in disease	Produces lymphopenia (some species) and eosinopenia in peripheral blood	Diminishes hyaluronidase activity
Lowers renal threshold for glucose	Increases insulin requirement. In individuals with normal pancreatic reserve this requirement is adequately met, but in latent or overt diabetes additional insulin must be administered	May cause increased activity in electroencephalogram (increase in frequency of alpha waves) or appearance of abnormal slow rhythms	Diminishes antibody response to typhoid antigen in rabbits	May increase tissue eosinophils and metaplasia of fibroblasts into eosinophils	Probably reduces blood glutathione
Opposes the action of insulin	Relative hypoglycaemia may occur after withdrawal of cortisone	May restore electroencephalographic pattern to normal in Addison's disease	Diminishes or abolishes tuberculin reaction	Inhibits fibroplasia	May be involved in enzyme systems concerned with pigmentation of skin
Increases mobilization and utilization of fat	Restores normal diuretic response to ingested water in Addison's disease	May induce euphoria and increased psychomotor activity	May prevent vascular lesions otherwise resulting from injection of D.C.A. (rats) or heterologous serum (rabbits)	Increases growth of macrophages in tissue culture	Increases arginase in liver and kidney of mice
Increases protein catabolism, urinary nitrogen, and urinary uric acid	May delay or inhibit menstruation, probably via depression of pituitary gonadotropic activity	May precipitate psychotic reaction (probably only in predisposed individuals)	Prevents or reduces tissue reaction to chemical irritants (guinea-pigs)	Stimulates reticulocyte production or release	Increases urinary excretion of uropepsin in patients with Addison's disease
Increases deposition of hepatic glycogen		May increase muscle strength (in rheumatoid arthritis) or may cause muscle weakness (probably only in cases of hypopotassaemia)	May inhibit formation of histamine	May bring about polycythaemia	
May bring about retention of sodium				May increase neutrophils in peripheral blood	
Increases urinary excretion of chloride and potassium				Causes involution of lymphoid tissue and of certain neoplastic tissues	
May increase calcium and phosphorus excretion					

research effort which may be expected to bring about a new concept of the nature of disease itself.

It seems likely that cortisone does not act therapeutically through a single circumscribed mechanism, but that this action must involve the many known physiological properties of the hormone as well as various undiscovered effects of this substance on the chemical processes of organs, tissues, and cells of the normal and the diseased organism. At the present time we have information indicating that (1) cortisone and/or compound F is involved in the metabolism of carbohydrate, protein, and fat; (2) it is necessary to the normal function of certain endocrine organs; (3) it exerts profound effects on neuromuscular metabolism; (4) it has distinct immunological effects; (5) it can bring about remarkable cytological changes; and (6) it is involved in several specific enzyme systems (see Table II).

It is for future research to determine which of these effects, or others, are fundamentally associated with the therapeutic activity of cortisone, and which ones are associated only coincidentally. The tendency to oversimplify the problem must be avoided, since it is clear that the hormone is implicated, directly or indirectly, in a large number of the physiochemical processes of the vertebrate organism.

Looking Ahead

The body of knowledge concerning the exact value of cortisone in the treatment of the variety of diseases discussed above is rapidly growing, as is the understanding of its pharmaco-physiological effects. Steadily increasing supplies of cortisone are becoming available, so that clinical and experimental studies are rapidly expanding in number and scope. So, too, the periods of observation on patients already treated are lengthening, and the results are becoming more measurable. Combined, these factors assure that a more exact appraisal of the effects of cortisone will shortly be possible.

A technical committee of the British Standards Institution has devised simple common names for certain pest-control products. A list of 25 names is being circulated for comment among Government departments, manufacturers, and scientific societies before final publication. In order to pre-empt the use of these names as proprietary names, the list has been lodged with, and approved by, H.M. Patent Office.

STREPTOMYCIN AND NEOMYCIN*

AN ANTIBIOTIC APPROACH TO TUBERCULOSIS

BY

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"This attempt to place between the covers of a book the record of a drug discovered less than five years ago is a daring and unprecedented one. It suggests a wealth of knowledge, established despite the haste of its gathering. It is particularly daring in the instance of tuberculosis, a disease so chronic in its habit that phthisiologists rarely do more than describe its victims as 'apparently' cured, and so multiple in its manifestations that it required the discovery of the tubercle bacillus to unify its many forms beneath a single name."—Walker, Hinshaw, and Barnwell (Waksman, 1949).

Historical

The history of tuberculosis is as old as that of man himself. It was, however, the discovery of the causative agent of this disease, *Mycobacterium tuberculosis*, by Robert Koch that stimulated the search for "cures" of this "white plague" of man. Most of these, ranging from the tuberculin of Koch himself to the much publicized "gold cure" of recent years, led to serious disappointments. The antibiotics, or those compounds of microbial origin that have the capacity of inhibiting and even of destroying in very dilute solutions the growth of other microbes, especially the causative agents of disease, have given new hope for a final solution of this ancient disease. Although most of the antibiotics are not very effective against the acid-fast bacteria, a few have proved to be highly effective against the mycobacteria, including the tuberculosis organism. Side by side with the discovery of antimycobacterial agents of microbial origin, progress has also been made in the use of synthetic compounds which are non-toxic but still active enough to justify their use in chemotherapy.

*A paper to be read at the First International Congress of Internal Medicine, Paris, September 11–14, 1950