1952

Therapeutic use of cortisone in ocular disorders

Damaris Elisabeth Suttle
University of Nebraska Medical Center

THE THERAPEUTIC USE OF CORTISONE IN OCULAR DISORDERS

Damaris Elisabeth Suttle

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

November 30, 1951

Omaha, Nebraska

Outline of Thesis

I. Introduction

A. Statement of Purpose

B. History of the Development of Cortisone

C. Theories of the Action of Cortisone

1. Biochemical

2. Physiological

II. Discussion of the Clinical Use of Cortisone in Ocular Disorders

A. Results of Cortisone Therapy in Specific Ocular Conditions

1. Inflammatory Conditions

2. Degenerative Conditions

3. Hereditary Conditions

4. Miscellaneous Conditions

B. Methods of Treatment with Cortisone

1. Topical vs. Parenteral Treatment

2. Techniques of Topical Treatment

3. Techniques of Parenteral Treatment

C. Problem of Recurrence of Pathology

D. Contraindications to Cortisone Therapy

1. Side Effects

2. Effects upon Associated Systemic Pathology

III. Conclusion: Evaluation of the Use of Cortisone Therapy in Ocular Disorders

A. Conditions in which Cortisone is of Definite Value

B. Preferred Methods of Therapy

The purpose of this paper is to review the literature on the use of cortisone in eye disorders. As far as possible, I have tried to correlate the diseases in which this agent is successfull with the preferrable method of treatment. It was necessary to include the failures of this drug as well as the contraindications so that one reading this paper could gain a fairly good insight into the complete use of this agent in the treatment of eye pathology.

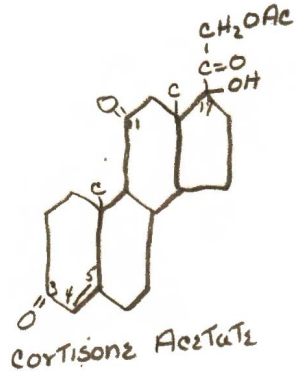
History of the Development of Cortisone

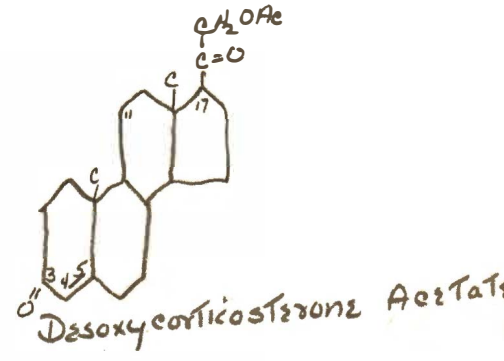
In 1849 Addison demonstrated that the adrenal cortex was essential for life and showed that there was a difference between the action of the adrenal cortex and that of the adrenal medulla. In 1904 epinephrine was first isolated from the adrenal medulla, where it is produced. Investigations of the adrenal cortex carried out during the decade of 1930-1940 by Wintersteiner, Pfiffner and Reichstein resulted in the isolation of no less than 28 crystalline compounds. Of these, only four showed significant physiologic activity when tested in small animals. These compounds were designated by the letters A, B, E, and F. (1) These differed only in the number and position of hydroxyl and ketone groups. In 1941, the National Research Council placed the hormones of the adrenal cortex on the top of its war agenda because of their possible value in aviation medicine and in the treatemet of shock and battle fatigue. (2) By April of 1948, a few grams of cortisone acetate or Compound E were availabel. It was first used on rheumatoid arthritis, but after the announcement that cortisone produced remissions, many clinicians in many different institutions initiated the use of cortisone in many other conditions, including ocular diseases. (3)

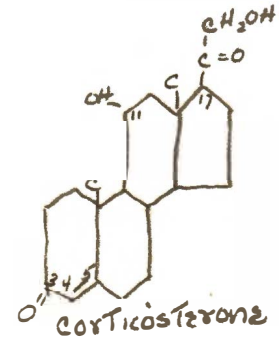
Theories of Action of Cortisone

In contrast to hormones of pituitary origin, and like other hormones extracted from the adrenal gland and the gonads, cortisone is a steroid. Considering that there exists steroid hormones of precisely opposite biologic effects, e. g., estrogens and androgens, and that certain steroids have no direct hormonal effect, e. g., cholesterol, it is a matter of continued wonder that all these compounds have a common structure, a four ring arrangement of some 18 carbon atoms. (4) The varied biologic effects are correlated with various chemical groups attached to certain of these atoms. On the basis of studies to date, it would appear that the antirheumatic properties of steroid compounds are dependent on the presence of the following structural characteristics: a ketone group at carbon 3, either a ketone or a hydroxyl group at carbon 11, a ketone group at carbon 20, hydroxyl groups at C-17 and C-21, and a double bond between carbon atoms 4 and 5. Cortisone and 17-hydrocorticosterone (compound F) are the only known steroids which meet these requirements.

These steroid differences may be simply illustrated by three adrenal hormones, whose structural formulas are given on the next page.







At the upper left is cortisone, whose healing effects in certain ocular diseases will be discussed in this paper. At the upper right is desoxycorticosterone, which has no healing effects whatever on inflammation, but which has been of great clinical use in treating metabolic disturbances of Addison's disease. The chemical differences are at the carbon atoms carrying the numbers 11 and 17. Desoxycorticosterone has no oxygenated groups at 11 and 17, while cortisone has a double-bonded oxygen (ketone) at 11 and a hydroxyl group at 17. Corticosterone, one of the first adrenal hormones worked out by Kendall, is illustrated at the

bottom. This differs from cortisone in having a hydroxyl group at 11 and no oxygen at all at 17. The great biologic differences consequent on these seemingly small chemical ones can be further illustrated by contrasting the effects of cortisone and desoxycorticosterone in the patient with Addison's disease.

Desoxycorticosterone causes the kidney to retain sodium and lose potassium. Cortisone has the same effect but to a far less degree, milligram for milligram of hormone. Desoxycorticosterone has no effect whatever on carbohydrate metabolism; it does not restore the flat glucose tolerance curve often seen in Addison's disease, nor does it prevent hypoglycemic attacks. Cortisone on the other hand, restores normal glucose tolerance in Addison's disease and can prevent hypoglycemia. (6)

In normal subjects prolonged administration of large doses leads to a diabetic state, which usually disappears when therapy is stopped. If this diabetes is uncontrolled, it serves as a second mechanism of excessive urinary loss of potassium. (7)

Again in Addison's disease there are definite cerebral changes, which can be shown by the behavior of the patient and by electroencephalograms. These are not reversed by desoxycorticosterone; they are reversed by cortisone. (8)

So while it can be shown that the chemical formula of cortisone is specifically essential for its biologic activity, little is known of its actual mode of action. Many isolated facts are known about its action, but they have not yet been put together in any pattern. It possesses the ability of depressing the response of tissues to allergic states and of blocking the effect of inflammatory and toxic substances, which in ophthalmology may be particularly important.(9) They do not alter the underlying allergic state, for once treatment is stopped, the allergy continues unchanged and the tissues are again able to respond to the allergen.

Cortisone Therapy in Specific Ocular Disorders

The most striking point in the action of cortisone is its dramatically quick effect in acute inflammatory conditions when the tissue reaction is still largely vascular and lymphatic in nature. Thus, in acute non-granulomatous iritis, when the disease is characterized by ciliary congestion, edema of the iris, and a protein and cellular exudate in the aqueous, all symptoms are quickly controlled in a most amazing manner. (10) If the acute inflammatory reaction can thus be successfully controlled until the attack would normally burn itself out, the symptomatic therapeutic effect appears complete. This is the picture usually observed in acute non-granulomatous iritis, in scleritis, in allergic reactions of the external eye and lids, in early sclerokeratitis, in interstitial keratitis before the stage of necrosis, and in central serous choroiditis. Where acute inflammation is the predominant and almost the only feature, symptomatic cure may be immediate and prompt. On the other hand, in granulomatous disease where the ocular inflammations are characterized by a heavy cellular infiltration of the tissues--such conditions as choroidal exudates, sympathetic ophthalmia, tuberculous uveitis, and virus infections--and where the edema, vascular dilatation, and exudation are secondary to the tissue involvement, the immediate effect of this

agent is limited to control of edema, external inflammation, and vitreous exudation. Acute choroidal exudates, tissue infiltration, and tubercles are not primarily affected. (11) Choroidal exudates become circumscribed and, in the absence of a surrounding inflammatory reaction, gradually grow smaller, and are either finally absorbed or undergo glial change.

In short, in granulomatous uveal disease, the actual effect of cortisone appears to be limited to the control of the exudative and inflammatory phases of the reaction. While inflammation is controlled, when actual healing occurs it is not the result of the adrenocortical hormone action, but rather the result of either the normal factors of resistance or other specific therapy which may have been instituted. Undoubtedly, however, the control of inflammation and edema in some granulomatous diseases may facilitate the healing process.

Experimental studies on the effect of these agents on ocular inflammation, as well as clinical observations, have shown that the therapeutic response is largely on a quantitative basis, commensurate with the amount of the agent used. (12) Thus, in both experimental and clinical inflammations of moderate intensity, the ophthalmic reaction can be completely controlled by the administration of a large dose of cortisone, modified by a moderate dose, or only slightly affected by a minimum dose. However, if in experimental inflammation

the insult to the eye is extreme, be it caused by bacterial infection, irritants, or allergy--even large amounts of cortisone will not control the ensuing reaction.

The action of this agent is not absolute in controlling inflammation. It has very definite limitations and an intense inflammatory reaction may be too severe a test for its capabilities.

In certain inflammatory conditions of the eye, notably secondary glaucoma, optic neuritis, interstitial keratitis, and cloudy corneal grafts, the action of cortisone may be variable.

In secondary glaucoma, there have been reports of 100% cure, (13), 50% cure, and actual development of the condition when iridocyclitis and generalized uveitis was being treated with cortisone. (14) From the cases observed it was the impression that, if the secondary glaucoma was due to an early and active cyclitis, it could usually be controlled. On the other hand, in cases of longer duration where there might be an actual mechanical obstruction at the angle due to inflammatory debris or anterior peripheral synechias, the control of a hypothetical increased ciliary output would have no effect on the tension. It is possible that the occurence of secondary glaucoma complicating parenteral cortisone therapy may be actually related to the hormone therapy, possibly to a sodium chloride retention with

increase in plasma and extracellular fluid volume. If this were true, some tendency to elevated ocular tension might be expected to occur in patients with normal eyes who are receiving cortisone for some non-ocular disease. This was checked and no such elevation was observed, so the solution of this paradox is not yet at hand.

Much more work is needed to clarify the action of cortisone in optic neuritis. If the optic neuritis is secondary to a demyelinizing process, it is difficult to decide whether any apparent improvement is a natural remission or is the result of therapy. Cases of apparent multiple sclerosis have been seen in which the accompanying optic neuritis appeared benefited by the hormone therapy. In cases of optic neuritis due to infection, syphilis, virus disease, and so forth, one would naturally expect a favorable result, and in two such cases a favorable result was obtained. The method of administration here appears quite important. The favorable results were obtained only in cases treated parenterally. Topical treatment, including orbital injection, was not efficacious.

The results in the interstitial keratitis of congenital syphilis reported are somewhat inconsistent, and are not in full accord. The earlier the treatment is started in the disease, the better the results, and topical application of cortisone appears superior to

the parenteral administration. In several early cases, all treated topically, the inflammatory reaction and corneal haziness could be increased or decreased by lessening or increasing the interval between treatment. (15) The favorable results were obtained almost uniformly in early cases, regardless of the presence or absence of vascularization, but continued treatment over a long period was necessary to control the disease finally. Even with continued treatment recurrences were common as the dosage was decreased or treatment terminated too soon. In late cases, both systemic and topical treatment was inefficacious. It seems probable this varying response of interstitial keratitis may be due to the underlying pathology of the disease. In the early stages, the fundamental process is edema and cellular infiltration of the stroma. If treatment is instituted and maintained in this stage, symptomatic relief may be expected. In the later stages actual necrosis occurs in the corneal stroma, with secondary scarring. Here control of an exudative reaction would have little appreciable effect on the clinical picture.

In contrast to the definite response to hormone therapy shown by acute and chronic inflammatory disease, the diseases usually classed as degenerative failed to show any appreciable response to treatment.(16) This included cases of degenerative disease of the cornea, retina, optic nerve, and choroid. The conditions treated were epithelial and endothelial dys-

trophies of the cornea, bullous keratitis, band-shaped keratitis, juvenile and senile macular degeneration, pigmentary degeneration of the retina, diabetic retinopathy, Eales's disease, Coats's disease, retrolental fibroplasia, and malignant exopthalmos. This is indeed what might be expected. Dramatic as is the effect of these agents in inflammatory and exudative disease, they cannot be expected to impart new life to dead and degenerated tissue. Possibly in early cases they might have some effect in the control of a primary edema when such is present in the degenerative process; and it is conceivable that early pigmentary degeneration of the retina might be influenced by the melanophore hormone contained in ACTH, but once actual degeneration has taken place, no real improvement would appear possible.

Of the cases of retinitis pigmentosa that have been treated with cortione, no improvement or only doubtful improvement has been noted. (17)

The cases of Herpes Zoster Ophthalmicus that have been treated with cortisone, have responded very favorably with this therapy. A dramatic response to cortisone was noted in cases of Acne Rasacea Keratoconjunctivitis. Therapy was not successful with vitreous abscess.

Methods of Treatment with Cortisone

It has been demonstrated that cortisone has a definite local action which ACTH has not, since it acts throught stimulation of the adrenal cortex. The present commercial preparation of cortisone is, however, almost completely insoluble in saline, and applied topically, absorption is obviously slight and slow. (18) It is not known whether or notiit acts on the inflamed tissues in its present form, or after some intermediary change. It seems true that in one form or another cortisone acts directly on the tissues. Furthermore, it has been shown that its action is a quantitative one. Therefore, in allergic conjunctival inflammation, in keratitis of on kind or another, in scleritis, and in anterior iritis (when sufficient absorption takes place to affect the iris), the topical application is ideal in that it allows the direct application of a relatively high concentration to a small area, requires a much smaller amount of the agent, permits a protracted period of treatment, and minimiaes the danger of untoward effects. (19) What is most important, experiments have proven that topical use of cortisone gives equal if not better results in anterior inflam .tion than is obtained by the parenteral injection of either ACTH or cortisone. On the other hand, there seems to be no evidence that sufficient cortisone is absorbed after topical application to provoke systemic response. Cortisone applied topically

does not affect the eosinophil count, and any action it may have on deep ocular inflammation is certainly delayed and highly variable. Therefore, in disease of the posterior ocular segment, it appears wiser to administer either ACTH or cortisone parenterally where the experience of all observers indicates it has a profound and widespread systemic action.

So the indications for parenteral and topical administration appear fairly clear. In disease of the conjunctiva, cornea, sclera, or anterior ocular segment, the topical use of cortisone appears preferable. In generalized uveitis, in choiditis, in disease of the posterior ocular segment, the parenteral use of cortisone is indicated.

A favorable response to parenteral injection is rarely noted before 24 to 48 hours. The favorable effects are almost invariably associated with a sharp drop in the circulation eosinophil count. If the eosinophils are not affected, only rarely is a favorable effect on the ocular condition noted.

Cortisone is given in divided doses, 300mg. on the first day, 200 mg. on the second day and 100 mg. on the next seven days. Thereafter it is either abruptly stopped or tapered off to a dosage of 50 mg. per diem. I should not be given in amounts larger than this. However, once the dose has been reduced, it should be increased at any level within these limits if there is evidence of a return of inflammation. If continued as a maintainance dose to prevent recurrence of sumptoms

25 to 50 mg. may be given daily, or intermittent courses of 50 mg. daily. The initial period of sustained treatment is rarely over two weeks.

While under parenteral treatment with cortisone, the patients must be carefully observed for any untoward side effects such as an unusual increase in weight, glycosuria, elevation in blood pressure, and so forth.

Cortisone may be applied topically in suspension either as drops or by subconjunctival injection, or as an ointment.

The present 25 mg./cc. saline suspension of cortisone contains 1.5% benzyl alcohol as the preservative. This suspension is somewhat irritating when instilled directly into the eye. The usual procedure is therefore to dilute it 1:4 with saline for ophthalmic use. The usual procedure is to use one drop every hour throughout the day, and every two hours throughout the night, during the acute stages and as a therapeutic response is obtained, gradually to increase the interval until it can be used twice or three times daily as a maintainance dose. As far as is now known, it can be continued indefinitely without losing its local action or evoking systemic reactions. The use of an eye pad after conjunctival instillation appears definitely to enhance the absorption and therapeutic effect.

When cortisone is given subconjunctivally, the usual procedure is to anesthetize the conjunctiva with o,5% tetracaine hydrochloride, apply a pledget soaked with 10% cocaine, and then inject 0.2 to0.4 cc. of the usual 25 mg./cc. suspension. Further injections are made at another site at intervals of 48 to 72 hours. Two to four such injections are said to be all that are necessary to control acute iritis. Maintainance injections can thereafter be made at weekly intervals in generalized uveitis. (20)

The ointment may be used in the acute stages every three hours throughout the day and immediately before retiring, the eye pad then being applied through the night. This dosage appears to give a therapeutic effect fully equal to the instillation of the suspension every hour during the day and every two hours during the night. As the therapeutic response is obtained, the interval between treatments can be lenghthened.

Of the three methods of topical application of cortisone in the treatment of inflammation of the anterior ocular segment, the ointment appears preferable. It is more easily packaged, the instillation is easier, and the effects appear more constant. The blurring of vision consequent to the ointment base is inconsequential, for the treated eyes usually have little useful vision. The ointment is, moreover, definitely soothing to inflamed eyes.

Problem of Recurrence of Pathology

The incidence of recurrences after apparent complete healing is evidence that this agent acts primarily through the control of acute inflammation and edema, and not by a direct action on the cause of the disease. In short, the use of these agents in ocular disease is essentially symptomatic treatment--when the disease is recurrent or chronic, its use gives, at best, only an inhibition of inflammation and exudation. In some acute and self-limiting diseases, the effect of this agent may simulate a complete symptomatic cure, while in chronic inflammations they may effect only a temporary control of inflammation. Thus, cortisone does not abolish or attack, except indirectly, the underlying pathologic process and pathogenesis of the disease. It does not relieve one from the necessity of searching for the cause of disease and instituting proper specific therapy, where such is possible.

Contraindications to Cortisone Therapy

As the contraindications to cortisone therapy are based on systemic changes, it is obvious that these refer to parenteral cortisone therapy and not to topical therapy. This is true because there seems to be no evidence that sufficient cortisone is absorbed after topical application to provoke systemic response. So the contraindications refer to the parenteral treatment alone.

Cortisone, as a therapeutic agent, shows many side effects when used in large doses or for a prolonged period of time. Following is a discussion of some of the side effects one may look for with cortisone therapy.

One of the characteristic chemical blood findings which has been observed with cortisone therapy is hypopotassemic, hypochloremic alkalosis. This is noted particularly when the dosage is high and the course of treatment is long. It increases the potassium excretion and the changes in the serum chloride and serum ph follow. The presence of this abnormal serum electrolyte pattern is suggested clinically by the development of lethargy, muscular weakness and cardiac irregularities. Early chemical evidence consists of a lowered serum chloride and an elevated carbon dioxide combining power. In order to prevent this, potassium chloride should be administered. Not only does it supply the required potassium and chloride ions but, in addition, its diuretic action reduces water retention,

which generally accompanies adrenal hormone treatment. While hypopotassemia calls for prompt treatment, it should not be overdone for overzealous administration of potassium may prove fatal if an absolute hyper-potassemia develops.

Patients treated with cortisone tend to retain sodium and water, so that edema develops. This is particularly undesirable in situations where congestive heart failure is imminent. So patients should be restricted to a low sodium diet. In spite of these measures, it is occasionally necessary to administer a mercurial in order to force diuresis. (21)

Characteristically, cortisone significantly affects the intermediary metabolism of protein, carbohydrate and fat. The effect most commonly observed clinically is on carbohydrate metabolism. Hyperglycemia and glycosuria accompany tfeatment with this hormone, but it rarely becomes necessary to institute insulin therapy. The glycosuria is in a large measure due to a reduction in renal threshold.

Evidence has been obtained from several sources that following the withdrawal of cortisone there is a temporary functional depression of the adrenal cortex. (22) It is characterized by asthenia and lassitude. This usually lasts from four to seven days, but on occasion in patients who have had prolonged courses of cortisone therapy the adrenal cortical depression may last as long as two weeks. If the insufficiency

is acute, it may prove fatal. Therefore it is important to reduce the dosage gradually.

Cortisone may produce suppression of the thyroid as part of the over-all suppression of the anterior lobe of the pituitary gland--thyroid-stimulating hormone being reduced as well as the production of adrenocorticotropic hormone and gonadotropic hormone (23) The reduction of thyroid activity never reaches serious proportions and may be treated with very small doses of thyroid.

Serious complications arising from disturbances of the gonads are unknown. However, there are certain changes which should be noted. Probably the most common change noted is amenorrhea. This is usually only temporary, lasting throughout the course of treatment, whereas normal menses return two or three months after treatment has been discontinued. In the male there may be a decrease in sexual drive, which occurs only if the treatment is prolonged.

One of the most important changes produced is an alteration in the psychic state. Most commonly this is in the form of euphoria. It develops to some extent in the majority of patients and is a part of the happiness and delight over the disappearance of their disease. It is usually of short duration. In some patients mental depression may appear. This often takes the form of paranoid delusions. Usually the euphoria or the depression will vanish on witholding treatment.

Skin changes may be associated with cortisone treatment. These usually take the form of acne, keratosis pilaris, hirsutism and pigmentation. Inasmuch as these, with the possible exception of the pigmentation, usually disappear following discontinuance of cortisone, no specific measures for their prevention are indicated.

Cushing's syndrome, with rounding of the face, hypertension and purplish abdominal striae, appears with prolonged or intensive therapy. It is always reversible and gradually disappears when treatment is discontinued.

Animal experiments have shown that cortisone interferes with wound healing. (24) Decreased formation of fibroblastic tissue and granulation tissue is observed. Clinically this has not been a serious problem.

The contraindications to cortisone therapy are: hypertension, congestive heart failure, renal insufficiency, peptic ulcer, tuberculosis, syphilis, hirsutism, osteoporosis and arteriosclerosis.

While it has been shown that the use of cortisone will largely control the inflammatory and probably the exudative phases of ocular tuberculosis, there is considerable theoretical evidence at hand which

indicates that the continued use of these agents may have a markedly deterrent effect, and possibly may be contraindicated. It has been shown that the continued use of cortisone in experimental animals fundamentally alters the pathogenesis of the disease, increases the number of tubercles in the lungs after inhalation infection and, instead of decreasing the number of bacilli, actually increases them. (25) Similarly, it is quite possible that cortisone may inhibit the fibrosis around the lesions, which is the essence of bacteriostasis and apparent healing, and thus promote dissemination of the bacilli throughout the eye. Until further information is available, it may be well to use cortisone with considerable caution in ocular tuberculosis.

Summary

Cortisone has a dramatic ability to control the inflammatory and exudative phases of certain ocular diseases, but this ability is not absolute. Allergic conditions of the lids and external eye, inflammations of the cornea, sclera, and uveal tracts are the conditions most favorably affected. Even after apparent complete control, recurrences are not uncommon when administration is terminated. With both parenteral and topical administration, there appears to be a limit to the therapeutic range.

In some conditions the action of cortisone may be irregular. These are secondary glaucoma, optic neuritis, interstitial keratitis and early clouding of corneal grafts.

In other exudative and hemorrhagic diseases, such as Coat's disease, Eales's disease, diabetic retinopathy and malignant exophthalmos, no clear-cut therapeutic effect has yet been demonstrated but there remains the hope they may be of some beneficial effect in early cases. In degenerations, they are without effect.

Parenteral administration of cortisone is the preferred method of treatment in inflammations of the posterior ocular segment. Topical administration of cortisone is preferred in inflammations of the anterior ocular segment. Of the various methods of

topical application now available, the ointment appears most convenient.

Untoward side effects have not been noted after parenteral injection of either ACTh or cortisone in the doses recommended. Patients under such treatment should, however, be carefully watched. No untoward side effects are to be expected after topical treatment.

1. Mason, H. L., Myers, C. S., and Kendall, E. C.: The Chemistry of Crystalline Substances Isolated from the Suprarenal Gland, J. Biol. Chem. 114:613 1936

2. Kendall, E. C.: Cortisone--Its Historic Development and Certain Chemical and Biochemical Aspects, The Merck Report. 59:4 1950

3. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: The Effect of a Hormone of the Adrenal Cortex (17-hydroxy-11-dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis: Preliminary Report. Proc. Staff Meet., Mayo Clinic. 24:181, 1949

4. Sarrett, L. H.: Syllabus on Cortone (Compound E), Merck & Co.,Inc., 1950

5. Scheie, H. G., Tyner, G. S, Buesseler, J. A., and Alfano, J. E., Adrenocorticotropic Hormone (ACTH) and Cortisone in Ophthalmology. A. M. A. Arch. of Ophth. 45:301 1951

6. Thorn, G. W., Senze, W., Prunty, F. T. G., Sarnett, M. D., and Forsham, P. H.: Changes in Urinary Steroid Excretion and Correlated Metabolic Effects During Prolonged Administration Adrenocorticotropic Hormone in Man, Science 105:528, 1947

7. Forsham, P. H., Thorn, G. W., Prunty, F. T. G., Sarnett, M. D, and Hills, A. G.: Clinical Studies with Pituitary Adrenocorticotropin, J. Clin. Endocrinol. 8:15, 1948

8. Sprague, R. G., and others: Observations on the Physiologic Effects of Cortisone and ACTH in Man. Arch. Int. Med. 85:199 1950

9. Thorn, G. W., Forsham, P. H., Prunty, F. T. G., Sarnett, M. D., and Hills, A. G.: A Test for Adrenal Cortical Insufficiency: Response to Pituitary Adrenocorticotropic Hormone. J. A. M. A. 137:1005 1948

10. Blake, E. M., Fasanella, R. M., and Wong, A. S.: ACTH in Glaucoma. Am. J. Ophth. 33:1231. 1950

11. Gordon, D. M., and McLean, J. M.: ACTH in Ophthalmologic Conditions. J. A. M. A. 142: 1271 1950

12. Woods, A. C., and Wood, R.: The Action of ACTH and Cortisone on Experimental Ocular Inflammation. Bull, Johns Hopkins Hosp. 87:482. 1950

13. Reese, A. B., and Blodi, F. C.: Retrolental Fibroplasia. Am. J. Ophth. 34:1. 1951

14. Olson, J. A., Steffensen, E. H., Smith, R. W., Margulis, R. R., and Whitney, E. L.: Use of Adrenocorticotropic Hormone and Cortisone in Ocular Disease. Arch. Ophth. 45:274. 1951

15. Olson, J. A., Steffensen, E. H., Smith, R. W., Margulis, R. R., and Whitney, E. L.: Effect of ACTH on Certain Inflammatory Diseases of the Eye. A Preliminary Report. J. A. M. A. 142:1276 1950

16. Steffensen, E. H., Olson, J. A., Margulis, R. R., Smith, R. W., and Whitney, E. L.: The Experimental Use of Cortisone in Inflammatory Eye Disease. Am. J. Ophth. 33: 1033. 1950

17. Fitzgerald, J. R;.Bellows, J. G., Donegan, J. M., Gamble, R. C., Krause, A. C., Mann, W. A., Pearlman, M. D., and Zekman, T. N.: Early Clinical Results of ACTH and Cortisone Treatment of Ocular Diseases. Arch. Ophth. 45:320. 1951

18. Woods, A. C.: The Present Status of ACTH and Cortisone in Clinical Ophthalmology. A/ J. Ophth. 34:945. 1951

19. Woods, A. C.: Clinical and Experimental Observation on the Use of ACTH and Cortisone in Ocular Inflammatory Disease. Trans. Am. Ophth. Soc. 48:259. 1950

20. Koff, R., Rome, S., Kasper, R., Commons, R. R., Button, R., and Starr, P.: Subconjunctival Injection of Cortisone in Iritis. J. A. M. A. 144:1259. 1950

21. Frawley, T. F.: Recognition and Prevention of the Complications of ACTH and Cortisone Therapy. A. M. A. Arch. Ind. Hygiene & Occup. Med. 3: 587. 1951

22. Sprague, R. G., Power, M. H.,Mason, H. R., Albert, A., Mathieson, D. B., Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, N. F.: Observations on the Physiological Effects of Cortisone and ACTH in Man. Arch. Int. Med. 85:199 1950

23. Hill, S. R.,Jr., Reiss, R. S., Forshma, P. H., and Thorn, G. W.: The Effect of Adreno-corticotropin and Cortisone on Thyroid Function: Thyroid-adrenocortical Interrelationships. J. Clin. Endocrinol. 10:1375. 1950

24. Ragan, C., Howes, E. E., Plotz, C. N., Meyers, K., and Blant, J. W.: Effect of Cortisone on Production of Granulation Tissue in the Rabbit. Proc. Soc. Exper. Bio. & Med. 72:718. 1949

25. Lurie, M., et. al.: The Effect of Cortisone on the Pathogenesis of Tuberculosis. Science. 113:234. 1951