THE CLINICAL USE OF CORTICOTROPIN, CORTISONE AND HYDROCORTISONE IN EYE DISEASE

DAN M. GORDON, M.D.

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By

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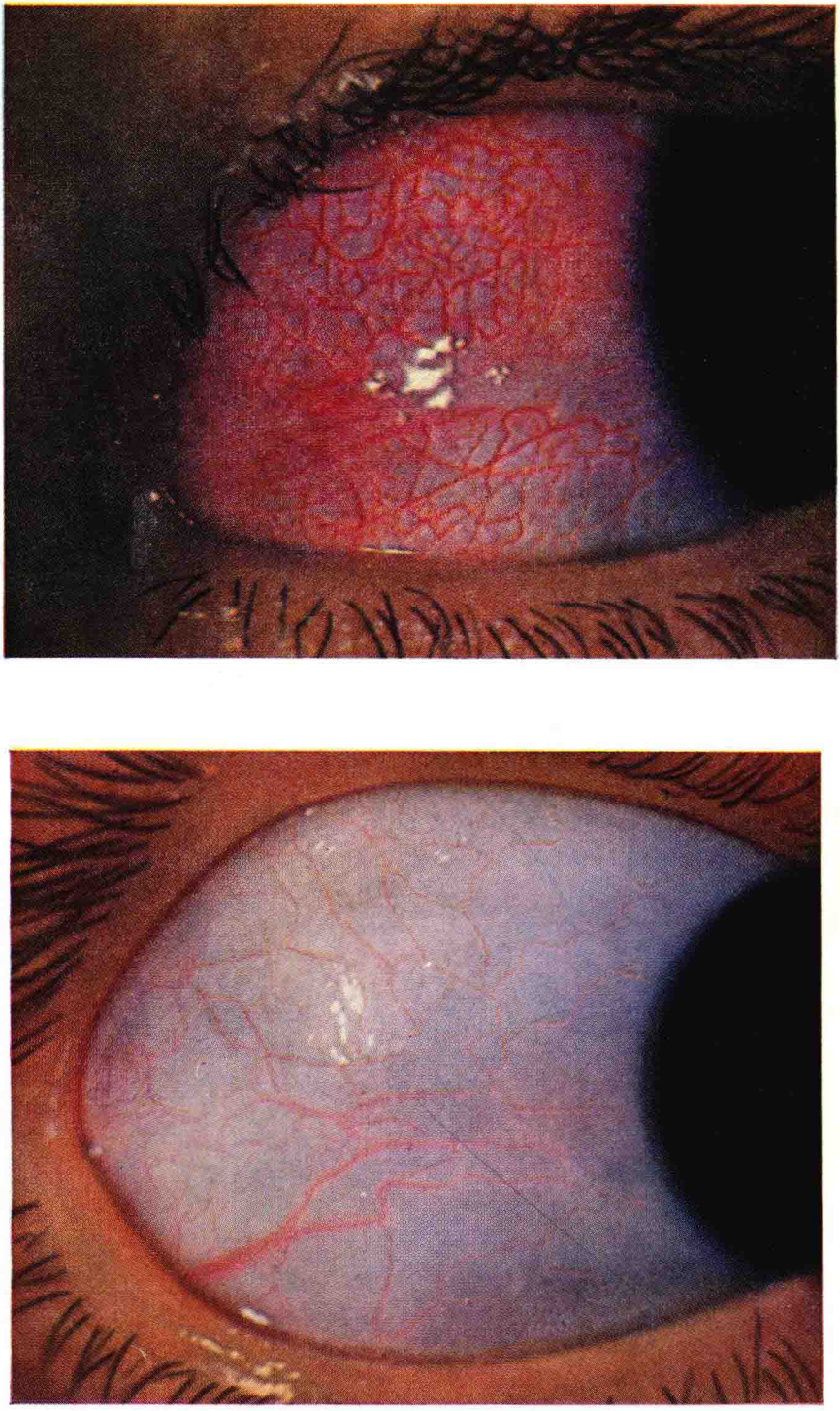

Anti-inflammatory effect of cortisone.
Acute episcleritis treated with topical cortisone; marked reduction of inflammation and injection after about two weeks of therapy.

♦ ♦ ♦ ♦ ♦ ♦ ♦ FOREWORD

THE EXPERIENCES, which form the background of the material presented here, were gained in conjunction with Dr. John M. McLean, head of the department of ophthalmology and Dr. Herbert Koteen of the department of medicine of the New York Hospital–Cornell Medical Center.

This is intended to be a purely clinical presentation in the hope that it will serve as an aid to the practitioner. For that reason, considerable laboratory and pre-clinical experimental material has been omitted, deliberately.

Many ophthalmologists have resisted using Corticotropin, Cortisone and Hydrocortisone systemically. The reasons for this were difficult to discern until I heard a talk by Allen Gregg of the Rockefeller Foundation. He stated that many years ago the Foundation had been asked to investigate medical education in France. It did so and concluded that many changes were necessary. The Foundation was willing to aid in underwriting those changes, only to run into opposition when it attempted to institute them. When investigating the reasons for that opposition they found that the physicians (like people everywhere) could be divided into three groups: the older physicians who were retired or about to retire recognized the need for a change; the younger men did not care what the rules were as long as they were told what rules were in effect; but the great middle group of active practitioners did not want to see the ground rules altered during their practicing days. So it is with the new concept of hormonal-steroid therapy.

♦ ♦ ♦ ♦ ♦ ACKNOWLEDGMENTS

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The bulk of the corticotropin and all of the high potency corticotropin utilized in this work was supplied by the Armour Research Laboratories through the courtesy of Drs. G. W. Bissell and J. Hubata. A small amount was supplied by Parke-Davis & Company, through the courtesy of Dr. E. Vonderheide. All of the hydrocortisone and part of the cortisone were supplied by Merck & Company through the courtesy of Dr. E. Alpert. A large amount of cortisone was also supplied by the Schering Corporation, through the courtesy of Dr. N. Heminway.

D.M.G.

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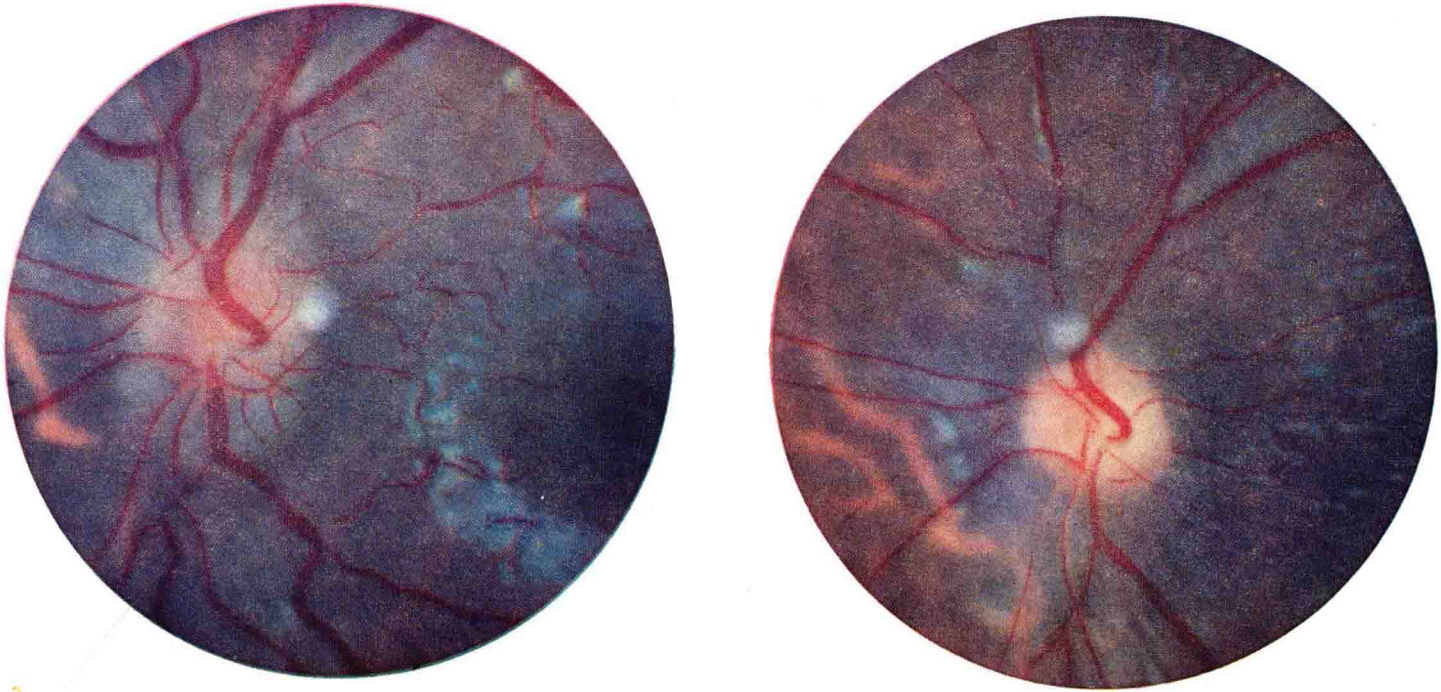

Acute Optic Neuritis, (*Left*) before and (*Right*) after 10 days of intravenous corticotropin (ACTH).

♦ ♦ ♦ ♦ ♦ ♦ INTRODUCTION

In April, 1949, Hench[1] and his colleagues reported on the striking results obtained in the treatment of rheumatoid arthritis (a collogen disease) with the use of 17-hydroxy-11-dehydrocorticosterone (Compound E, Cortisone) and later with the use of the adrenocorticotrophic hormone * (ACTH). Later, Gordon[2] and McLean gave the first report on the use of ACTH in the treatment of various eye diseases.[3, 4, 5, 6, 7, 8, 9, 12] Since that time a considerable amount of information has been gathered relative to the use of hormonal steroid therapy in ophthalmology, as well as throughout the field of medicine.

These hormones have an effect on the regulation of electrolytes, carbohydrates, fat use, proteins and androgens, which cannot be separated from their use, clinically, and which have been detailed by numerous authors.[10, 11]

The supplies of corticotropin (ACTH) and cortisone, at first very limited in amounts, have been increased gradually to the point of general availability. As a result of this, and of the many calls for information pouring in on those who have had any experience in this field, it becomes obvious that some guide for the "bedeviled" ophthalmologist is essential in order that he be led properly round the pitfalls of this new therapy. It is the intent of this paper to lay down some broad outlines of guidance, based on our experiences with a large series of cases, with the knowledge that further experience will bring amendments.

* ACTH is now officially designated as "Corticotropin."

The preparations presently available and of proved therapeutic efficiency are corticotropin (ACTH) for systemic use, cortisone acetate which can be utilized systemically or locally (by topical application or subconjunctival injection) and hydrocortisone.

The Eye Department of the New York Hospital has been conducting an intensive clinical study of various steroids and hormones for over three years. The preparations studied to date are the Melanaphore Hormone, Testosterone, Delta 5 Pregnenolone and 21 Acetoxy-Pregnenolone, Insulin, Cortisone, ACTH, the Somatotrophic Hormone and Compound F (Hydrocortisone).

The work with Melanaphore and Testosterone will be reported separately. The Pregnenolones proved valueless in a variety of ocular conditions. Insulin, both as an eye drop and by subconjunctival injection, was found to be of no value in treating the retinopathy of diabetics.

The present report concerns itself with Cortisone, Corticotropin and Compound F (Hydrocortisone).

MECHANISM

Some knowledge of the pertinent physiology of the anterior pituitary gland and the adrenal glands is requisite to the successful use of these compounds. Unfortunately, space does not permit a complete review. A few pertinent facts will be pointed out. Obviously, cortisone can be used locally by any ophthalmologist; while systemic employment of either hormone may require the aid of a competent internist.

At least six important facts must be borne in mind when employing these preparations: (1) The adrenocorticotrophic hormone * corticotropin (ACTH) has as its chief function the stimulation of the adrenal cortex, which in turn secretes more than 28 different ste-

* Now officially termed "Corticotropin."

roids including cortisone,** under varying conditions. Hence, the adrenocorticotrophic hormone (ACTH) is effective only in the presence of a properly functioning adrenal cortex. (2) The body produces its own adrenal steroids (corticoids). Where these are not present in a quantity sufficient to accomplish the required result, additional steroids must be supplied in amounts greater than the patient's own output, to be of any therapeutic value. Because of these circumstances, if the body is normally producing 100 mgms. of cortisone daily, the administration of 100 mgms. of cortisone will not make available 200 mgms. of cortisone, but a lesser amount. As we are unable to determine the amount of cortisone available to the organism via its own cortices, a certain amount of trial and error is inherent in planning the dosage. When ACTH is employed it should be given in doses large enough to produce adequate amounts of corticoids. The patient's clinical response and the eosinophil counts are of help in determining the dosage. (3) The therapeutic results are dependent upon sufficient quantities of the cortical steroids reaching the sites where needed; and the local tissue response. Hence, that route which is the most effective in transporting the corticoids to the area of utilization is the one of choice, whether systemic, local or two in combination. Failure to achieve a good result would appear to be dependent upon either the amount of steroids reaching the desired area, or upon some (as yet not fully understood) failure of these tissues to respond to the corticoids. From all this it would seem that the action of the cortical steroids (or at least of cortisone) must be on or very near the tissue cells. (4) Each of these compounds (ACTH and cortisone) affects the pituitary and the adrenal glands as well as other organs and glands.

** Cortisone may be a breakdown product of Compound F, rather than a true adrenal hormone.

(5) It seems advisable to propound a "law of therapeutic expectation" in the treatment of any case. Under this law the physician would ask himself, "Just what can I expect to accomplish in this case if I have an optimally efficient preparation available?" Once the rods and cones are destroyed or the optic nerve has atrophied, all of the corticotropin and cortisone in the world will not cause their regrowth. Yet that is exactly what many of us have been asked to do in the first flush of enthusiasm over the advent of a new therapy. (6) It is apparent that cortisone and corticotropin do not affect the causative agents (pathogens); but rather the tissue response to these agents. Hence their applicability to a wide variety of conditions of diverse etiologies * and nature; ranging actually from simple conjunctivitis to pemphigus.

Selye [11] has shown that if formaldehyde is injected into a joint a severe local inflammatory condition is produced. If the area is first pretreated with cortisone and the formaldehyde is then injected, the tissue fails to respond with an inflammation.

Woods [12, 13] has applied a similar experimental procedure in ophthalmology. He and his workers have found that a "satisfactory iritis" was produced in rabbits by injecting infusions of 1:4,000 jequirity seeds into their anterior chambers. When the rabbits were given four days of preliminary treatment with cortisone no such reaction to the jequirity infusion developed. When these rabbits were exposed to additional injections of the jequirity infusion the reactions were suppressed only during the period of continued cortisone treatment, recurring on cessation of the latter. This same suppression can be secured with ACTH.

* The reader is advised to study the three books by Dr. John R. Mote (published by Blakiston & Company) which include all of the papers and discussions of the two ACTH Conferences, to learn more about the actions and diverse uses of ACTH and cortisone.

The analogy here to the effects of corticotropin and cortisone in acute and chronic disease is striking. If an acute disease is treated with either of these preparations during the period when the disease would normally run its course (*i.e.*, until the pathogen died or disappeared) tissue reaction and damage are suppressed and a "cure" results. If the patient is suffering from a chronic or recurrent disease he will be kept, more or less, symptom-free during the period of treatment and for a variable period thereafter. In chronic cases this free period, following treatment may vary from days to months. The reasons for this variability are not understood. There is some relationship to the intensity of treatment (*i.e.*, dosage and length of treatment), and to the intensity of the inflammatory process. Obviously, the longer the remissions which can be induced, the easier it is to "control" the patient on a maintenance schedule of treatment.

This suppression of inflammatory and other reactions may also be harmful, in that a very serious intercurrent condition (occurring usually during treatment) such as a peritonitis, coronary accident, etc., may be masked by the treatment and sensation of well being which the patient enjoys. Recently a man * was treated for a chronic choroiditis. He exhibited definite beneficial response on intravenous corticotropin (ACTH). The day after this treatment was discontinued he complained of gluteal pain. Upon examination he was found to have a well developed cellulitis in this region at the site of an intramuscular injection of cortisone given well over a month before. He had not had any rise in temperature during the period of treatment. Rises in temperature or in pulse rate occurring during treatment should make the physician suspicious of some complication such as pneumonia, peritonitis, coro-

* The author has not had any other such occurrence in his experience.

nary accident, etc., which while apparently not due to the treatment have occurred during its course.

DOSAGE AND RELATED TOPICS

The preparations and their modes of utilization are:

1. *ACTH* (*Corticotropin*)
   (a) Intramuscularly, 25-50 mgm. every six hours.
   (b) Intravenous drip, 25-50 mgm. over eight hours.*
   (c) In long acting vehicle. (High potency preparations—the "gels"). These are the most efficient for ambulatory use, 80-120 units daily in a single injection which is effective at least 24 hours.
2. *Cortisone* (and hydrocortisone)
   (a) Local
      1. Topically as:
         (a) Eye drop (commercially available in 0.5 and 2.5% solutions, *i.e.*, 5 and 25 mgm./cc.).
         (b) Ointment, 15 mgm. per Gram.
      2. Subconjunctival injection, 8⅓ to 25 mgm. (Optimally 8⅓.)
   (b) Systemically**
      (a) Intramuscularly 100-300 mgm. daily in one or two doses.
      (b) Orally. In doses similar to or up to one-third greater than the requisite intramuscular dose.

* Throughout this paper "intravenous ACTH" refers to the "drip."

** In those cases in which corticotropin and cortisone are both effective, clinically about 50% more mgm. of cortisone than ACTH is required. Most of the remarks about cortisone therapy are also applicable to hydrocortisone.