# CLINICAL AND EXPERIMENTAL OBSERVATION ON THE USE OF ACTH AND CORTISONE IN OCULAR INFLAMMATORY DISEASE

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In 1949 Hench, Kendall, Slocomb, and Polley (1) reported from the Mayo Clinic that a hormone of the adrenal cortex (the 17 hydroxy-11 dehydrocorticosterone or Compound E) and the pituitary adrenotrophic hormone (ACTH) had a dramatic though temporary therapeutic effect on rheumatoid arthritis. This discovery has led to a widespread exploratory use of these compounds in a variety of disease conditions and a considerable body of information has now been accumulated (2). It has been shown that there is a marked improvement in rheumatoid arthritis and acute rheumatic fever after the use of these compounds (2,3,4), and that they have likewise an effect in collagen disease such as lupus erythematosis (5,3). All authors, however, stress that symptoms are prone to recur shortly after cessation of therapy and that the side effects may be severe. More recently Harvey and his associates (5) have shown the remarkable action of these agents in controlling the symptomatology of various allergic diseases, notably asthma and allergic rhinitis. It is the purpose of this paper to review briefly the physiologic action of these hormones, the precautions and contraindications for their use, the present ideas of dosage and administration, and to report observations of their effect in certain clinical ocular diseases and experimental ocular inflammations.

Within the last decade significant advances have been made in

*From the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital and University. The cases treated with ACTH were studied and treated in cooperation with the Department of Medicine. The ACTH used in these patients and experimental animals was supplied by Armour and Co. through the courtesy of Dr. John R. Mote. The cortisone used was purchased from a grant from the Public Health Service, National Institute of Health.

our knowledge of the action of the hormones of the adrenal cortex. This information on the physiological action of these compounds has recently been summarized in comprehensive reports (5,6,7). It has been shown that these hormones have widespread metabolic effects and produce profound alterations in body function. Simply stated, the over-all effects fall into three general groups:

1. An electrolyte regulating effect, produced by the so-called "salt" hormones, of which 11-desoxycorticosterone appears the most potent. The 11-17 oxysteroids (Compounds E and F) have only a relatively weak sodium retaining effect. The most important of the metabolic changes in this group are a retention of sodium chloride, an increased excretion of potassium, and an increase in plasma and extracellular fluid volume.

2. The regulation of the carbohydrate, protein, and fat utilization, and control of the lymphoid tissue and circulating eosinophiles. The hormones with these effects are called "S" hormones and the most active ones producing these effects are 17-hydroxy-11-dehydrocorticosterone (Compound E: cortisone) and 17 hydroxycorticosterone (Compound F). The most evident metabolic changes in this group are an increase in the glucose level and the glycogen stores, and increased conversion of protein to carbohydrate (glucogenesis), an increased mobilization of fat and its enhanced utilization, an increase in the renal clearance of uric acid, a lysis of fixed lymphoid tissue, and a depression of the circulating eosinophiles almost to disappearance.

3. An androgenic effect, produced chiefly by the so-called "N" hormones which are believed to exert an effect similar to that of testicular androgens—masculinization, retention of nitrogen, phosphorus, potassium, sodium, and chloride. They are related in structure to testosterone. An excess production of these steroids causes an increased excretion of the 17-ketosteroids.

The pituitary gland secretes, among other hormones, the adrenocorticotrophic hormone or ACTH. The pituitary gland can be stimulated to the production of this hormone from a hypothalamic source, and through the hypothalamus by epinephrine, which is secreted by the adrenal medulla, illustrating the reciprocal action of adrenals and pituitary. Thorn and others have shown that when ACTH is injected parenterally, the normal adrenal cortex responds

with a production of all the various adrenocortico hormones and their increased action can be demonstrated by metabolic studies. While exogenous ACTH stimulates the adrenal cortex, it also suppresses the normal pituitary ACTH mechanism. However, when ACTH therapy is terminated, there is usually a rapid return of the normal adrenal cortex function. Cortisone, on the other hand, is believed to suppress both the pituitary and the adrenal cortex function, even to the point that the glands may become atrophic. With the withdrawal of cortisone therapy there is usually an adrenal cortical deficiency which is much more sustained and marked than is the temporary deficiency evoked by exogenous ACTH. Thus, it is apparent that ACTH can act only when a relatively normal adrenal cortex can respond to the stimulation, while the cortisone can exert its effect with an atrophic adrenal cortex as in Addison's disease.

The prolonged administration of ACTH or cortisone may result in untoward physiological effects. Most important of those is Cushing's syndrome, with the clinical picture of muscle weakness, abnormal distribution of fat with the characteristic facies, hirsutism, hypertension, and amenorrhea. This syndrome was first described by Cushing (8) in 1932 in basophilic tumors of the pituitary gland and is probably related to adrenal cortex hypertrophy.

*Precautions and Contraindications for Clinical Use.* When these agents are administered clinically one of the most immediate subjective changes is the disappearance of pain which appears to herald a reversal in the disease process. Likewise, if the patient was febrile prior to the administration of ACTH or cortisone, there is usually a prompt return of the temperature to normal. The reappearance of pain or fever during the treatment period is an indication for the cessation of treatment until the cause of the recurrence can be evaluated.

Since these hormones may cause a marked change in the electrolyte balance and fluid retention, vascular hypertension and chronic nephritis are contraindications for their use. Similarly, since they have a profound effect on the carbohydrate metabolism, they are contraindicated in patients with a concomitant diabetes. And further, since they produce a substantial alteration in cerebral function, their use in psychotic patients should be guarded.

In general, patients under treatment with ACTH or cortisone should have a low sodium chloride intake. In higher dosages, the fluid balance should be followed. It has been advised that since these agents cause a marked increase in potassium excretion, there should be a high potassium intake.

*Dosage.* There may be considerable variation in the response of different individuals to ACTH and cortisone, depending respectively on the varying sensitivity of the adrenal cortex to stimulation, and to the depressant action of cortisone. The most sensitive objective clue to the adrenal cortex stimulation and to the action of cortisone is the eosinophile count in the peripheral blood. Normally, this is in the neighborhood of 200 cells per cubic millimeter. Under proper stimulation of the adrenal cortex by ACTH or by the parenteral injection of cortisone, it may be decreased from 50 percent to a complete disappearance of the eosinophiles. The eosinophile count is the most satisfactory "rough and ready" index of a proper response. The uric and creatin ratio and the urinary excretion of the 17 ketosteroids are also indices of adrenal cortical stimulation, but are of little practical value in assessing adequate dosage.

The optimum dosage of both ACTH and cortisone is as yet undetermined. It is likewise unknown how long treatment should be continued to obtain the maximum results. It is possible that smaller doses than those outlined below will prove efficacious as more experience is accumulated. At present one must carefully follow the progress of the disease and the evidence of adrenal stimulation in each individual, as a wide range of dosage may be necessary from patient to patient. Once beneficial results are obtained, the improvement can usually be maintained with smaller doses. There appears to be a relationship between the effect on circulating eosinophiles and the clinical results. If the dose of ACTH is too rapidly reduced eosinophiles reappear and symptoms may immediately recur.

In general, ACTH was given the first 3-4 days in doses of 80-100 mgms. (Armour) per diem, in divided doses q. 6 hours. Thereafter, the dose was tapered to 80, 60, 40, and finally to 20 mgms. per diem. Infants were given proportionately smaller doses. The minimum period of treatment with ACTH was 10 days in a patient

with sympathetic ophthalmia where a brilliant result was obtained, up to a maximum of 47 and 49 days in two patients with respectively disciform degeneration and sympathetic ophthalmia. The average period of treatment with ACTH was 24 days.

Cortisone was given in the dosage suggested in the February, 1950, brochure of Merck and Co.—300 mgms. for the first day, 200 mgms. on the second day, and thereafter 100 mgms. per diem for a period of 7-14 days. No untoward side effects were noted in any of the patients treated with the above dosages.

*Local Treatment.* In hospital patients one drop of undiluted cortisone suspension, 1 c.c./25 mgms., was instilled in the eye q. 1 hr. during the day and q. 2 hrs. during the night. This caused mild transient irritation which passed in a few minutes. In ambulant patients the instillation was q. 1 hrs. throughout the day and irregularly during the night. In two patients it was necessary to dilute the 1 c.c/25 mgms. 1:4 on account of local irritation.

*Ancillary Studies.* All patients who received systemic treatment had daily total eosinophile counts by the Thorn and Forsham technique. In several patients with a demonstrable hypersensitivity to either tuberculin, bacterial antigens, or drugs, the cutaneous reactions to the specific allergen were determined before and after treatment.

*ACTH and Cortisone in Ocular Disease.* There is only occasional mention of the effect of these hormones on ocular inflammations. Elkinton (3) reports the complete clearing of a hemorrhagic retinopathy in a case of generalized collagen disease treated with ACTH, Mann and Markson (9) report a case of iritis and episcleritis which cleared completely on ACTH therapy. Olsen (10) and his associates report seven cases of inflammatory ocular disease treated with ACTH in total dosages of 182-432 mgms., with a marked control of the inflammatory symptoms. Gordon and McLean (11) report six cases of various forms of ocular disease treated with ACTH in total dosages of from 75 to 525 mgms. In the inflammatory cases there was a dramatic response. In a later communication (12) McLean reported that his further experiences in a total of about 40 cases confirmed his preliminary observations—in inflammatory ocular disease there was a remarkable control of the exudation and inflammation and this improvement occurred

synchronously with a fall in the circulating eosinophiles. Jones and Meyer (13), have reported an experimental study in which they showed that the subconjunctival use of cortisone inhibits the vascularization of the cornea which follows alkali burns, indicating a peripheral and local action of cortisone (Compound E). Except for these isolated observations, the ophthalmological literature is as yet almost barren of reports on the clinical use of these hormones.

### THE USE OF ACTH AND CORTISONE ON CLINICAL OCULAR DISEASE

In August of 1949, Dr. A. McGehee Harvey, at the instigation of Dr. William Marr treated a case of nongranulomatous iritis associated with an early rheumatoid arthritis with ACTH (Case 1). The immediate results in this case were so dramatic that as further supplies of ACTH and cortisone became available, other patients with various forms of ocular disease on the ophthalmological and medical wards of the hospital have been treated. The purpose of this paper is to report the results in these cases and certain experiments in animals which were stimulated by the clinical observations. I am indebted to Drs. William Marr, Angus MacLean, and William C. Owens for their permission to include their private patients.

ACTH and cortisone have been administered parenterally in the treatment of fourteen patients with various ocular disorders. Cortisone has been used topically in the eye in the treatment of eight additional patients.

*Parenteral Administration of ACTH and Cortisone.* The cases treated parenterally fall into two groups: those which showed no change in the eyes after such treatment, and those which showed a marked, often dramatic effect.

The five cases in the first group are shown in Table 1. One was a case of advanced, syphilitic interstitial keratitis with necrosis and ectasia of the cornea. This patient had been previously treated with subconjunctival penicillin, and the active stage of inflammation controlled. The second was a case of Cogan's syndrome (nonsyphilitic interstitial keratitis with vertigo and deafness); the third a case of unilateral advanced juvenile Coat's disease, and the last two cases were retrolental fibroplasia. The treatment of

TABLE I. SYSTEMIC TREATMENT WITH ACTH AND CORTISONE: UNIMPROVED*

| *Patient* | *Diagnosis* | *Treatment* | *Result* |
|---|---|---|---|
| 507475 | Syphilitic Interstitial Keratitis | ACTH | No improvement (patient with corneal necrosis treated in non-inflammatory stage) |
| 527767 | Juvenile Coat's Disease | ACTH | No improvement |
| 532320 | Cogan's syndrome (Non-syphilitic keratitis with audio-vestibular involvement) | Cortisone | No improvement |
| A74384 | Retrolental Fibroplasia | ACTH | No improvement |
| A75782 | Retrolental Fibroplasia | ACTH | Some subsidence in subretinal edema; progression of gliosis |

*Encouraging results have been observed in one case of advanced sympathetic ophthalmia treated locally with cortisone.

two cases of keratitis was entirely exploratory. There was little evidence of active inflammation but the exact pathogenesis of the disease was undetermined, and there was a possibility of an allergic background. Treatment with ACTH and cortisone was therefore justified. The reason underlying the treatment of the Coat's disease and the retrolental fibroplasia patients was that a remarkable subsidence of subretinal edema has been noted in several cases of central serous retinopathy and it seemed reasonable to explore the possibility of such absorption in retrolental fibroplasia. No effects of any kind directly attributable to the ACTH or cortisone were observed in any of these five cases, although in one case of retrolental fibroplasia there appeared to be a decrease in the subretinal edema, accompanied, however, by an increase in the gliosis (14).

The cases in the second group are shown in Table 2. They in-

TABLE 2. SYSTEMIC TREATMENT WITH ACTH AND CORTISONE: IMPROVEMENT

| *Patient* | *Diagnosis* | *Treatment* | *Result* |
|---|---|---|---|
| 511411 | Nongranulomatous iritis. Recurrence after 7 months | ACTH Cortisone | Prompt recovery. Recurrence in 7 months; prompt recovery. |
| 507475 | Disciform degeneration of macula secondary to subretinal hemorrhage. Bilateral. Central serous retinopathy, right. | ACTH | Improvement in right vision from 20/70 to 20/30. Decrease in paracentral scotomata. |
| 523479 | Sympathetic ophthalmia. Atropine sensitivity. | ACTH | Clearing of all inflammation. Right vision rose from 4/200 to 20/30. Blocking of atropine sensitivity. |
| 525991 | Sympathetic ophthalmia. | ACTH | Clearing of all inflammation. Vision rose from 20/50 to 20/15. |
| 532752 | Tuberculous (?) sclerokeratitis. Atropine sensitivity. | ACTH | Clearing of all ocular inflammation. Blocking of atropine sensitivity. |
| 533134 | Tuberculous choroiditis. Secondary glaucoma. | Cortisone | Clearing of vitreous, subsidence of subretinal edema. Control of secondary glaucoma. |
| 534114 | Nongranulomatous cyclitis. Central serous retinopathy (bilateral). | Cortisone | Subsidence of subretinal edema in 4 days. Vision in each eye rose from 20/70 to 20/30. |
| 534258 | Tuberculous uveitis. Secondary glaucoma. | Cortisone | Clearing of vitreous and increase in vision in 4 days. Immediate relapse after cessation of treatment. Very slight change in eosinophile count. |
| 262058 | Tuberculous uveitis. Secondary glaucoma. | ACTH | Complete clearing of all external inflammation. Vision rose from fingers to 20/100. Control of secondary glaucoma. |

clude one case of nongranulomatous iritis, one case of bilateral disciform degeneration of the macula, two cases of sympathetic ophthalmia, three cases of probable tuberculous uveitis, one case of probable tuberculous kerato-iritis with marked atropine sensitivity, and one case of recurrent nongranulomatous cyclitis with central serous retinopathy. The results observed in these nine cases were so instructive that brief mention of each case should be made.

*Case 1* (511441): *Recurrent unilateral nongranulomatous iritis associated with rheumatoid arthritis.* The patient was first seen in an attack of 3 weeks' duration and vision was reduced to 20/70. General symptomatic treatment, including nonspecific protein therapy, had been unavailing. Treatment with ACTH was followed by prompt relief of inflammation 12 hours after starting treatment. Vision rose to 20/30 within 5 days and to 20/20 within two weeks. The total dosage of ACTH was 514 mgms. There was a complete remission for 7 months when the iritis recurred. Examination at this time showed marked cutaneous hypersensitivity to four strains of the subgroup A of the Beta streptococci. Patient was then put on cortisone therapy. After 5 days' treatment, corresponding with a fall in the circulating eosinophiles, all evidence of inflammation in the eye disappeared and vision advanced to 20/15.

*Case 2* (507475): *Disciform degeneration of the macula, secondary to macular hemorrhage 8 years previously in right eye and 2 years previously in left eye.* On admission, right eye showed marked subretinal edema in macular area with retinal atrophy. Left eye showed a similar picture with an overgrowth of glial tissue and yellowish crystals over the lesions (Figs. 1 and 2). Visual fields showed absolute scotoma above and below the point of fixation in the right eye and a large central scotoma in the left eye (Fig. 3). Vision on admission was right, 20/70, left, 20/200. After 47 days' treatment with ACTH, the subretinal edema in the right eye subsided and vision rose to 20/30. In the left eye the subretinal edema subsided and the yellowish crystals below the lesion disappeared. Vision remained at 20/200. Figs. 4 and 5 show the right and left eyes at the end of treatment. The visual fields in the right eye showed a disappearance of the upper scotoma and shrinking of the lower scotoma; in the left eye the central scotoma decreased in size (Fig. 6). The total dosage of ACTH was 2,228 mgms. over a 47-day period.

*Case 3* (523479): *Sympathetic ophthalmia;* a 66-year-old woman with a full-blown sympathetic ophthalmia of one-week duration following a cataract extraction in the right eye seven weeks previously. On admission correct vision was 4/100 in the right eye and the vitreous was so cloudy the fundus could not be visualized. Corrected vision in the

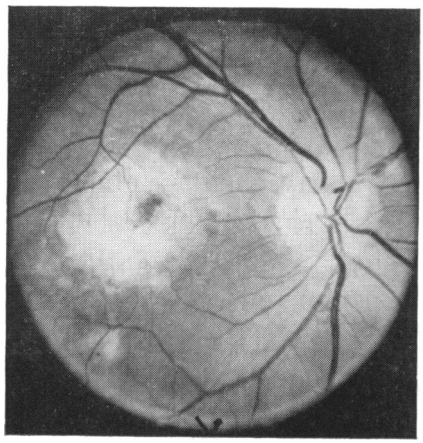

FIGURE 1. RIGHT FUNDUS, CASE 2, PRETREATMENT

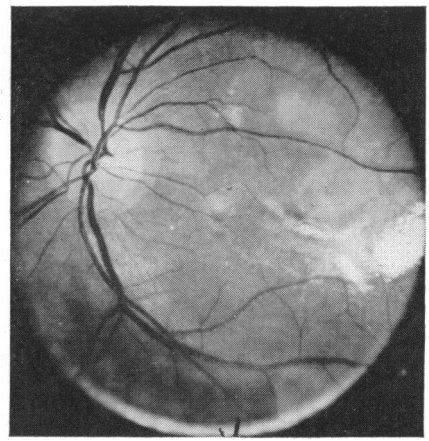

FIGURE 2. LEFT FUNDUS, CASE 2, PRETREATMENT

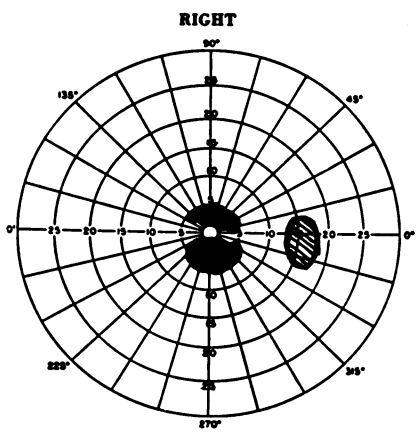


FIGURE 3. VISUAL FIELDS, CASE 2, PRETREATMENT

left eye was 20/200. There was a dense nuclear cataract in the left eye. An atropine sensitivity had developed four days prior to admission and atropine had been discontinued. There was an immediate favorable response to ACTH therapy with a clearing of the vitreous in the right eye and a subsidence of inflammation. After five days' treatment atropine was again given and was tolerated without reaction for nine days. After 10 days treatment, corrected vision was right, 20/50, left, 20/200. When the dose of ACTH was reduced to 10 mgms. per diem there was a recurrence both of ocular inflammation and the atropine sensitivity. With an increase in the dosage of ACTH the inflammation

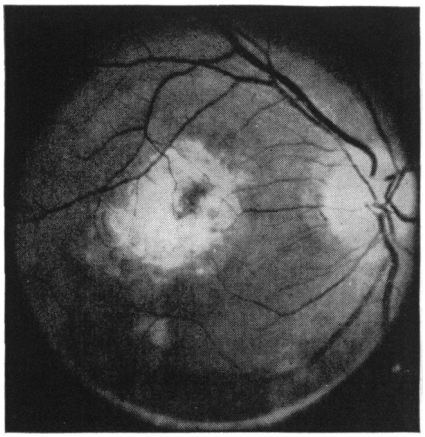

FIGURE 4. RIGHT FUNDUS, CASE 2, POSTTREATMENT

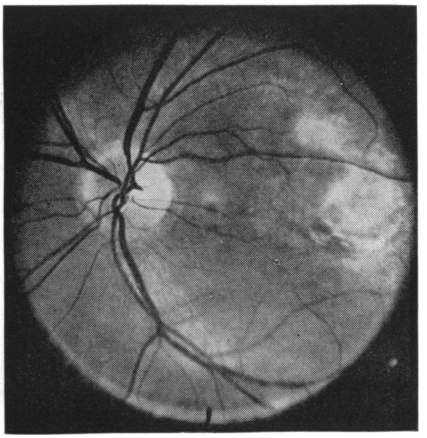

FIGURE 5. LEFT FUNDUS, CASE 2, POSTTREATMENT

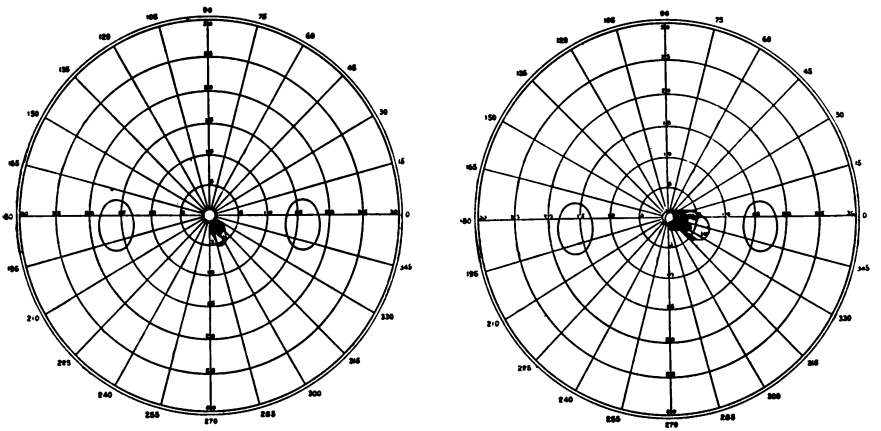

FIGURE 6. VISUAL FIELDS, CASE 2, POSTTREATMENT

again subsided. After 42 days' treatment the supply of ACTH temporarily gave out and the patient was five days without treatment. Synchronous with this, a second exacerbation of the inflammation occurred. With a resumption of the ACTH, the inflammation again subsided. The dosage of ACTH was then gradually reduced, and after seven days' further treatment was discontinued. There was again a subsidence of the inflammatory reaction, which did not return with termination of treatment. At discharge, right corrected vision was 20/30, and left corrected vision 20/100. This has been maintained to date over a period of five months. Fig. 7 shows graphically the relation

of treatment to inflammation and vision in the right eye. Figs. 8 and 9 show the external appearance of the right and left eye on admission, and Figs. 10 and 11 show the appearance of the eyes on discharge. The total dosage of ACTH was 3,240 mgms. over a 49-day period.

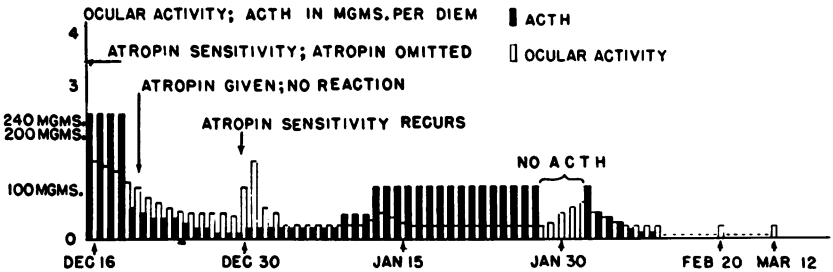


FIGURE 7. RELATIONSHIP OF TREATMENT TO OCULAR ACTIVITY, CASE 3

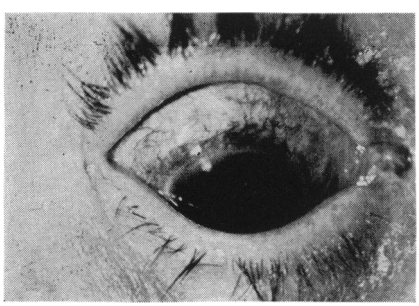

FIGURE 8. RIGHT (EXCITING) EYE, CASE 3, PRETREATMENT

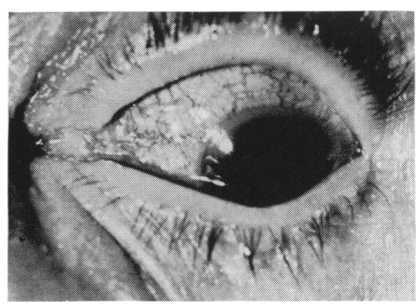

FIGURE 9. LEFT (SYMPATHIZING) EYE, CASE 3, PRETREATMENT

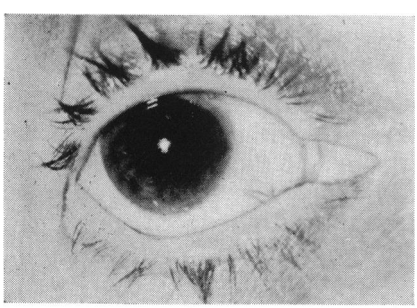

FIGURE 10. RIGHT (EXCITING) EYE, CASE 3, POSTTREATMENT

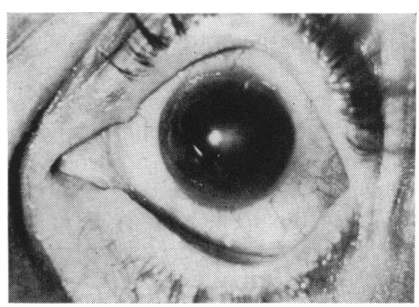

FIGURE 11. LEFT (SYMPATHIZING) EYE, CASE 3, POSTTREATMENT

*Case 4* (525991): *Sympathetic ophthalmia;*[1] a 62-year-old woman with sympathetic ophthalmia of the left eye following an iridencleisis of the right eye four weeks previously. On admission the right vision was hand movements and the left vision 20/50. There was an immediate favorable response to ACTH therapy; the inflammation steadily subsided in both eyes and vision improved, and at the end of ten days' treatment right vision was 8/200 and left vision 20/30. After discharge the improvement continued and four months later vision was 8+ 8/200 and left 20/15.[2]

*Case 5* (532752): *Tuberculous kerato-uveitis and atropine sensitivity;* a 42-year-old woman with a recurrent tuberculous kerato-uveitis, the present attack being of five months' duration, complicated by violent dermatitis due to atropine sensitivity. On admission the eye was violently inflamed with edema of the corneal epithelium and elevated tension. Vision was limited to light perception. No accurate examination was possible on account of the induration and edema of the lids. The patient was violently sensitive to tuberculin and to two strains of streptococci and gave a marked reaction to the atropine patch test. There was an immediate favorable response to ACTH therapy. The atropine dermatitis rapidly cleared, the induration of the lids subsided, the examination of the eye, which was now possible, showed residual pericorneal congestion and a corneal infiltrate. After one week's treatment the patient was challenged with atropine, to which she now showed only a minimal reaction on a patch test. She was likewise challenged to tuberculin and now showed a 10x10 erythema to 0.01 mgms. of tuberculin, to which she had before showed a violent erythema, with induration and necrosis. She showed no reaction to the strains of streptococci to which she had formerly been sensitive. On discharge after 16 days of treatment, all trace of dermatitis had disappeared, the eye was entirely white and free of inflammation, and vision had risen to 20/100. There was some capsular clouding of the lens. The total dosage was 1,360 mgms. over a 16-day period. One month later the eye was still entirely free of inflammation and vision had risen to 20/50.

*Case 6* (533134): *Tuberculous choroiditis and secondary glaucoma;* a 17-year-old boy with a unilateral tuberculous choroiditis of four months' duration, with some involvement of the anterior uvea. On admission, vision was 3/200 and the media were so cloudy no fundus details could be visualized. There was a whitish reflex above. Tension varied between 35 and 40 mm. Cortisone therapy was followed by a marked clearing of

[1] The ACTH used in this case was supplied by G. S. Searle and Co., through the courtesy of Dr. Ira Winter.

[2] Five months after the patient was discharged from the hospital, she had a sudden attack of acute glaucoma in the left eye. There were, however, no associated evidences of a sympathetic inflammation or uveitis.

the vitreous and a gradual fall of tension to normal. After completion of the course of cortisone therapy over 10 days, the outlines of the disc could be seen. A large circumscribed exudate was visible in the upper fundus and the macula showed evidence of degeneration. Vision had risen to 15/200. The patient was discharged to his physician for streptomycin and promizole therapy. The total dosage of cortisone was 1,280 mgms. over a 10-day period.

*Case 7* (534114): *Non-granulomatous irido-cyclitis with central serous retinopathy;* a 52-year-old woman with a history of rheumatoid arthritis over 18 years and recurrent attacks of bilateral iridocyclitis with central serous retinopathy over one year. On admission the arthritis was inactive, with minimal crippling residua. The eyes were free of inflammation but vision was reduced to 20/70 in each eye, and ophthalmoscopic examination showed an elevation of about two diopters in each macula, with a blurred reflex. There were bilateral paracentral scotomata. Cortisone was given in the usual dosage over a 10-day period. There was an almost complete subsidence of the macular edema, and corrected vision rose to 20/30 (+4) and 20/30 in the right and left eyes. The central scotoma disappeared to the point that only small multiple relative scotoma could be detected with a 1/6 degree target.

*Case 8* (534258): *Chorioretinitis (tuberculous);* a 21-year-old white female with evidence of an old, inactive, pulmonary tuberculosis. The right eye was blind from an old uveitis and secondary detachment of the retina. The left eye had become violently inflamed two days before admission.

On admission the left eye showed an active, generalized uveitis with vision reduced to 20/50. The medical survey was negative except for evidences of an old pulmonary tuberculosis and tuberculin hypersensitivity. Patient was placed on streptomycin and promizole therapy, from which the first beneficial effects could not be expected before two weeks of treatment. During the first week, the vitreous continued to cloud, the vision fell to 5/200, and the eye went into secondary glaucoma with a tension around 50 mm. Cortisone was then given intramuscularly. It had only a moderate depressant effect on the circulating eosinophiles. After three days of treatment the eye improved somewhat. The tension fell to normal and vision improved to 20/70. After eleven days of treatment cortisone was discontinued. During the period of treatment it continued to have only slight effect on the circulating eosinophiles. Immediately on discontinuing the cortisone the eye again became inflamed. Vision fell, and tension rose to 40-50 mm. Cortisone was then given topically over an eight-day period, during which time all of the external inflammation disappeared. The tension dropped to normal but there was no change in the vitreous clouding. The patient was now given a second course of intramuscular cortisone but again with no effect on the circulating eosinophiles and with no resulting clearing of

the vitreous. The eye remained white and free of inflammation with normal tension. At the end of the fourth week, the eye began to improve and the vitreous to clear—an effect believed due to the streptomycin and promizole.

*Case 9* (262058): a 27-year-old colored woman with a history of recurrent enlargement of the parotid gland over eight years, with an epitrochlear, axillary and hilar adenopathy. Biopsy of the glands had been variously reported as sarcoid and later as caseous tuberculosis. The right eye had a uveitis of one year's duration, with secondary glaucoma. Before treatment, right eye showed violent pericorneal congestion, heavy mutton-fat keratic deposits, a positive aqueous ray with a thickened edematous iris without nodules. There were heavy clouds in the vitreous. The tension varied between 19 and 40 mm. Vision was hand movements. After six days' treatment with ACTH all ciliary congestion faded and the aqueous ray became negative. Tension remained elevated for ten days and then fell to normal. Vision rose to 20/100. There was some clearing of the vitreous.

*The Topical Use of Cortisone.*[3] Inasmuch as cortisone appears to be the most potent of the hormones produced through stimulation of the adrenal cortex by ACTH, and the parenteral injection of exogenous cortisone produces an effect quite similar to that produced by ACTH, the question immediately arises if cortisone instilled locally in the eye would have any effect on ocular inflammation or overgrowth of lymphoid tissue. The local use of cortisone would have immense advantages, if any such peripheral therapeutic action could be demonstrated. These advantages are, first, that much smaller amounts of the hormone would be required, and, second, that the depressant action of exogenous cortisone on the adrenal cortex might be avoided. Third, any effect obtained by local treatment might be more permanent, since the normal secretion of cortisone by the adrenal cortex might not be seriously interfered with by the instillation of small amounts of exogenous cortisone. That cortisone locally might have an effect on ocular inflammation is indicated by the experiments of Jones and Meyer.

The few cases in which cortisone has been used locally are shown in Table 3. A brief description of these cases and the results obtained follow.

[3] Merck and Co. have recently made available an ophthalmologic preparation of cortisone, in buffered solution with a preservative. This preparation was made available through the courtesy of Dr. J. M. Carlisle.

TABLE 3. LOCAL USE OF CORTISONE

| *Patient* | *Diagnosis* | *Treatment* | *Result* |
|---|---|---|---|
| 534258 | Tuberculous uveitis. Secondary glaucoma. | Cortisone locally | Local use of cortisone controlled all evidence of external inflammation and glaucoma. No effect on vitreous clouding. |
| 536264 | Vernal catarrh | Cortisone systemically for 2 days—locally for 12 days | Marked regression of lymphoid follicles. Control of inflammation. Clearing of corneae. Vision rose from H.M. to 20/100 and 20/40 (−). |
| Ambulant S.S. | Nongranulomatous iritis. Secondary glaucoma. | Cortisone locally | Clearing of all external inflammation. No effect on vitreous clouding. Control of tension from 70 mm. to 15 mm. |
| 148260 | Sclerokeratitis | Cortisone locally | Control of external inflammation. |
| 117384 | Pemphigus (?) | Cortisone locally | Marked temporary (?) improvement |
| 548152 | Alkali burn of cornea | Cortisone locally 36 hours after injury | Control of symblephara and vascularization of cornea. No effect on corneal clouding. |
| 538178 | Nongranulomatous iritis | Cortisone locally | Complete control of all external inflammation in 72 hours. Vision rose from 20/70 to 20/20. |
| 538999 | Sympathetic ophthalmia | Cortisone locally | Complete clearing of all inflammation. No improvement in vision. |

*Case 10* (534258): This has already been reported as Case 8 treated systemically. Immediately following the first course of parenteral cortisone, there was an immediate relapse of external inflammation and exudation in the vitreous. Cortisone was now instilled locally for a period of eight days. Within twelve hours there was a complete clearing of all external inflammation and a control of intra-ocular tension, but there was no effect on the vitreous clouding or any improvement in vision. The local use of cortisone had little effect on the circulating eosinophiles, the only change observed being a fall from 577 to 400. In the effort to clear the vitreous, a second course of cortisone was given parenterally. However, this again produced no changes in the circulating eosinophile count and no effect on the eye. The observations in this patient suggested that, while the local instillation of cortisone in the conjunctival sac controlled the ciliary congestion, it had no effect on the vitreous clouding.

*Case 11* (536264): *Vernal catarrh.* In April, 1944, an 18-year-old male Negro with a family history of tuberculosis developed a bilateral conjunctivitis, characterized by the formation of huge follicles in the palpebral conjunctiva and vascularization and infiltration of the corneae. There had been some improvement in November, followed by an exacerbation which continued up to the time of admittance in May of 1950. Exhaustive studies in other clinics, including biopsy, animal inoculation, and cultures, had not revealed any etiological factor. There were many eosinophiles in the conjunctival discharge. Biopsy of a follicle showed lymphoid hyperplasia with a surrounding zone of eosinophiles—the histological picture of vernal catarrh. On admittance the corneae were completely opaque and heavily vascularized. The palpebral conjunctivae were the sites of massive follicular hypertrophy.

The patient was given 300 mgms. of cortisone parenterally on the first day, and 200 mgms. on the second day. There was a marked drop in the circulating eosinophiles and a slight improvement in the subjective picture. The intramuscular injection of cortisone was discontinued, and the local instillation of the hormone in the conjunctival sac substituted. Within 12 hours there was a marked objective improvement and within 8 days the cornea cleared to the extent the irides could be clearly seen. The follicles rapidly diminished in size. Vision rose from hand movements in each eye to right 12/200 and left 20/100. Cortisone therapy was terminated after 14 days' treatment. At this time right vision was 20/100 and left vision was 20/40. The patient was then given beta irradiation to clear the remaining follicles and the corneal vascularization. Figs. 12 and 13 show the appearance of the right eye before and after cortisone therapy, and Figs. 14 and 15 the appearance of the left eye before and after cortisone therapy was discontinued.

*Case 12: S.S. Ambulant;* a 40-year-old white woman with an active granulomatous uveitis of 4 months' duration with a secondary glau-

coma, the ocular tension measuring 70 mm. The etiology of the uveitis had not been established. Efforts to control the tension by paracentesis had been without success. Local cortisone therapy was begun May 12. Within three days the pericorneal congestion had subsided, the eye whitened, and the tension fell to 15 mm. The aqueous flare which had formerly been positive was entirely negative. Heavy vitreous veils were unaffected and vision remained unchanged at 10/400.

*Case 13* (148260): a 50-year-old white female with a long history of tuberculous sclerokeratitis, who had shown marked improvement after two courses of streptomycin and promizole. A low-grade intermittent scleritis with some edema of the lids persisted in spite of intense antibiotic and sulfone therapy. Cortisone 166/25 mgms. was given with an immediate subjective improvement, but was followed by an irritation conjunctivitis. The cortisone was then diluted 1:3 and was now tolerated without reaction. Within four days there was a marked improvement in the inflammatory symptoms with subsidence of the lid edema.

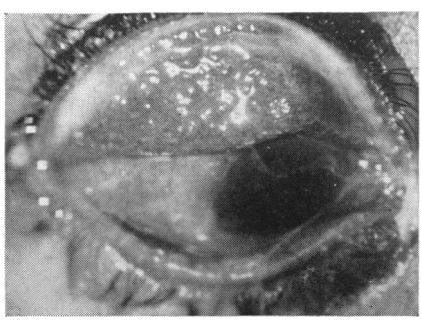

FIGURE 12. RIGHT EYE, CASE 11, PRETREATMENT

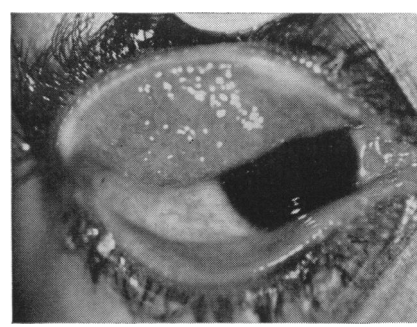

FIGURE 13. RIGHT EYE, CASE 11, POSTTREATMENT

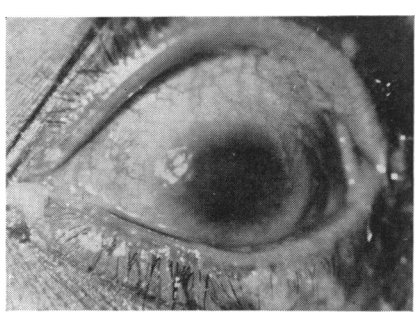

FIGURE 14. LEFT EYE, CASE 11, PRETREATMENT

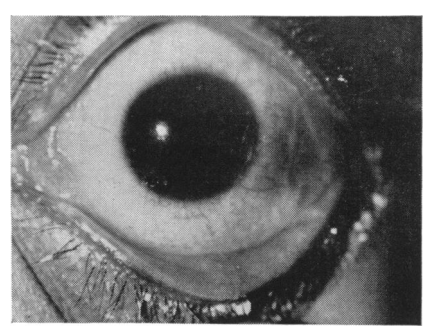

FIGURE 15. LEFT EYE, CASE 11, POSTTREATMENT

*Case 14* (117384): a 70-year-old white woman with an old history of rheumatoid arthritis had an uneventful extraction of a left cataract in 1947. Following removal of the sutures an endophthalmitis developed which was controlled by antibiotics and sulfones. Later a secondary glaucoma developed which was controlled by operation, a full 20/20 vision resulting. In January, 1950, the eye developed a keratoconjunctivitis with degeneration of the corneal epithelium and loss of all corneal sensitivity. Animal inoculations, cultures, and conjunctival scrapings were all negative. Antibiotic and sulfone therapy had no effect in this picture. The inflammation steadily progressed, with an overgrowth of lymphoid tissue over the cornea and the formation of symblephara above and below, and obliteration of the cul-de-sacs. The picture exactly resembled an ocular pemphigus. Beta ray therapy had no effect. Local cortisone was started on May 15. Within 48 hours there was a marked improvement, the acute inflammation disappearing and the lymphoid overgrowth on the cornea regressing. There was little or no change in the symblephara. Synchronous with this there was a dramatic improvement in the arthritic symptoms.

*Case 15* (548152): a 34-year-old white woman with an unimportant past history sustained an alkali burn of her face, head, and both eyes from a can of "Drano," to which she had added hot water. When admitted to the Wilmer Institute three days later her vision was reduced to 10/50 in the right eye and 10/70 in the left eye. There was bilateral chemosis and blanching of the exposed bulbar congestion. The corneae were hazy, and symblephara were forming in the left lower conjunctival sac. There was some clouding of the anterior capsule of each lens and strongly positive aqueous flare. It was felt the prognosis was poor.

The patient was placed on local cortisone therapy, the only other therapy being breaking the symblephara with a glass rod and the early use of the conformer. Cortisone therapy was started on May 12 and continued for 12 days. The chemosis subsided completely. There was no vascularization of the corneae and the symblephara did not reform. The cornea clouded somewhat, and a descemetocele, which ultimately ruptured, developed in the left eye.

*Case 16* (538178): a 37-year-old farmer with a history of an attack of acute iritis in the left eye in 1947. The past medical history was negative, except for arthritis symptoms of 3 weeks' duration. The left eye had been inflamed for one month and for two weeks had been the site of an active nongranulomatous iritis. On admission there was violent pericorneal congestion and marked ciliary tenderness. The pupil was dilated under a mydriatic, the iris was thickened with a blurring of the normal patterns and markings. There were no nodules of synechiae. Slit-lamp examination showed the remains of fibrin in the anterior chamber. There were no keratic deposits, but the aqueous ray was strongly positive. Vision was 20/70. Cortisone was given locally. After

three days' treatment all ciliary tenderness disappeared, the eye became white and free of inflammation, the aqueous ray was almost imperceptible and corrected vision rose to 20/20. After three days of treatment the eosinophile count fell to 32, after 6 days to 0, and returned to 133.3 after treatment was discontinued.

*Case 17* (538999): *Sympathetic ophthalmia;* a 76-year-old white female with a sympathetic ophthalmia of three and one-half months' duration, following a cataract extraction on the left eye. The exciting eye had not been enucleated. There had been a partial remission of the inflammation of the left eye followed by a violent exacerbation of about two weeks' duration. When first seen both eyes were violently inflamed, with marked ciliary tenderness and pain. The tension was normal and the cornea was grossly clear. Vision in the right eye was reduced to light perception and projection. There was advanced capsular clouding of the lens, with advanced posterior cortical opacities. There were large keratic deposits and a strongly positive aqueous flare. The left eye was in phthysis with questionable light perception. There were heavy keratic deposits and a strongly positive aqueous flare.

The patient was placed on cortisone topically in the usual dosage. This was the only treatment. Within 48 hours all ciliary tenderness and pain had disappeared and the ciliary congestion was much improved. After four days' treatment there was only a trace of ciliary congestion, and after 11 days' treatment the eyes were white and free of any external evidence of inflammation. The aqueous flare was still positive in both eyes. The greasy deposits in the posterior surface of the corneae had absorbed. There was no change in vision. The eosinophile count fell from 206 to 133 after 4 days' treatment with cortisone topically.

An over-all survey of these cases reveals certain interesting findings. First, the beneficial effects of the adrenal cortex hormones on ocular disease appear primarily to be a control of the inflammatory and exudative phases. When these agents are administered parenterally, these beneficial effects are manifested by a clearing of circumcorneal congestion, clearing of the vitreous, circumscriptions of exudates, and disappearance of subretinal edema. The beneficial results were invariably accompanied by a marked drop in the eosinophile count, often to the point of complete suppression.

When cortisone is given locally by instillation in the conjunctival sac, there again appears to be a subsidence of external inflammation, and of exudation with a resulting control of secondary glaucoma. From the meager evidence at hand, it seems possible

that the local instillation of cortisone has little appreciable effect on exudation in the vitreous.

In the majority of the conditions in which the blocking effect on inflammation was observed there was some reason to suspect an allergic factor or background for the inflammatory reaction. Nongranulomatous iritis is currently believed to be a phenomenon due to bacterial hypersensitivity. In tuberculous disease the inflammatory phase is dependent upon a hypersensitivity of the tissues to tuberculo-protein, and in sympathetic ophthalmia there is sound reason to believe that hypersensitivity to uveal pigment is a part of the symptoms complex. Harvey and his coworkers have clearly demonstrated that these agents are capable of blocking the clinical symptomology of various other allergic diseases, as asthma, nasal polyps, and drug-hypersensitivity reactions. In the exploration of the question of how these agents act on acute ocular inflammation and edema, it seemed pertinent first to investigate experimentally their effect on recognized allergic inflammatory ophthalmic reactions. The details of the various experiments on the influence of the systemic administration of ACTH and cortisone and the local use of cortisone on ocular inflammation will be reported in detail elsewhere. They are reported here only in summary. These experiments were done in collaboration with my associate, Dr. Ronald M. Wood.

## THE EXPERIMENTAL ACTION OF ACTH AND CORTISONE ON OCULAR INFLAMMATION

Three basic experimental, anaphylactic, and allergic ocular reactions are recognized. 1) The anaphylactic reaction due to sensitization and intoxication with protein agents, first described by Nicolle and Abt (15) in 1908. 2) The allergic "opthalmic" reaction due to sensitization and intoxication with bacterial antigens, first described by Derick and Swift (16) in 1929. 3) The focal reaction, long recognized clinically, and described experimentally in tuberculous eyes after the systemic injection of tuberculin by Woods and Burky in 1943 (17). The influence of ACTH and cortisone on these three reactions was investigated experimentally in rabbits.

*Experiment I: Protein Hypersensitivity; Parenteral Use of ACTH and Cortisone.* A series of six rabbits were sensitized to horse serum in

the usual manner, serum titers of from 1:3200 to 1:12,800 resulting. Two rabbits were left untreated as controls, two others were treated with cortisone, and two with ACTH for a period of four days prior to intoxication and four days after intoxication. After the four days' preliminary treatment, all rabbits, controls and treated, were given an intoxicating injection of horse serum in the anterior chamber. The cutaneous sensitivity was determined before and after treatment. The results of this experiment are shown graphically in Fig. 16. The control animals showed a prompt and violent ophthalmic reaction. One of

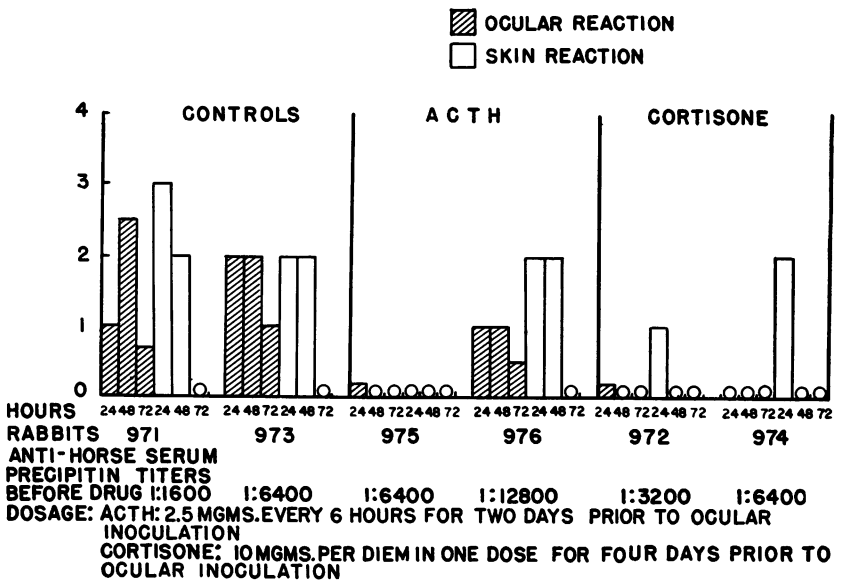


FIGURE 16. EFFECT OF CORTISONE AND ACTH IN INFLAMMATORY PHASE OF OPHTHALMIC PROTEIN REACTION

the rabbits treated with ACTH showed no reaction, while the second ACTH-treated rabbit showed a mild reaction. Both rabbits treated with cortisone showed a complete blocking of the anaphylactic ocular reaction. The cutaneous reaction was affected to a lesser degree than the reactions in the eye. One month after cessation of treatment, all rabbits were again given both anterior chamber and intracutaneous injections of horse serum, and all rabbits now reacted with marked and equal ophthalmic and cutaneous inflammation, all blocking effects of the ACTH and cortisone having completely disappeared. The precipitin titers in the blood serum were not altered by the administration of the ACTH or cortisone.

*Experiment II: Quantitative Relationship of Treatment to Blocking*

*Action.* A series of rabbits was sensitized to horse serum. Four rabbits were left untreated as controls, four animals received 10 mgms. of cortisone for 4 days prior to anterior chamber injection and for 4 days thereafter. Four others received 5 mgms. per diem in a similar manner, and 4 received 2.5 mgms. After 4 days' treatment all rabbits were given anterior chamber injections of horse serum. The untreated controls reacted in the usual manner with a violent reaction. The four receiving 10 mgms. per diem showed an almost complete blocking of the inflammatory reaction. The four receiving 5 mgms. per diem showed a similar blocking, but not as complete as the rabbits receiving the larger amounts. The rabbits receiving 2.5 mgms. per diem showed only a partial blocking. These results are shown graphically in Fig. 17. Quite

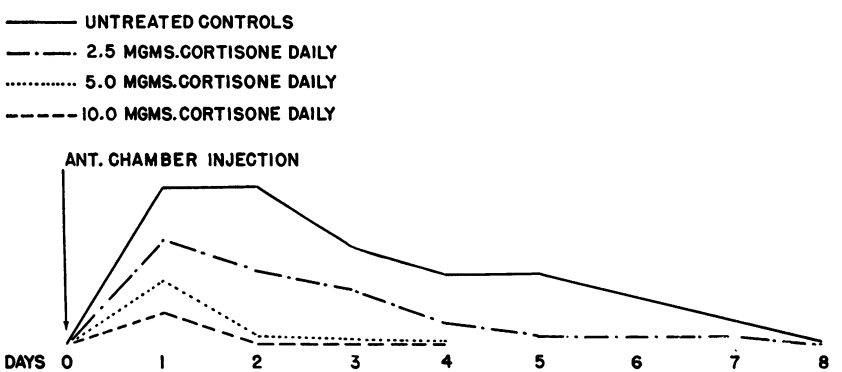


FIGURE 17. QUANTITATIVE RELATIONSHIP OF TREATMENT TO BLOCKING EFFECT

evidently the degree of blocking effect on the inflammatory reaction is proportional to the amount of cortisone administered.

*Experiment III: Bacterial Hypersensitivity.* A series of normal rabbits was sensitized to killed Beta streptococci in the usual manner, all developing marked cutaneous reactions. Two rabbits were left untreated as controls, and three were given cortisone for 4 days prior to intoxication and for 7 days after intoxication. After the four days' preliminary treatment with cortisone, all rabbits were given an intoxicating anterior chamber injection of the bacterial antigen. Within 24 hours the controls developed an acute iritis with pericorneal injection, clouding of the cornea, inflammation and edema of the iris and fibrin in the anterior chamber. This reaction was of 5 to 9 days' duration. The cortisone-treated rabbits behaved quite differently. In one animal there was no reaction of any kind to the intoxicating anterior chamber injection, in the second there was a minimal transient traumatic reaction, while the third, the most sensitive of the group, showed

a weak ophthalmic reaction of 3 days' duration. The cutaneous reactivity to the bacterial antigen was slightly suppressed, but definitely to a lesser extent than the ophthalmic reaction. These results are shown graphically in Fig. 18.

One month after cessation of treatment, all rabbits, both controls and those formerly treated, were tested again with anterior chamber and intracutaneous injections of the bacterial antigen. Marked and equal reactions were found both in the controls and the formerly treated animals, all blocking action of the cortisone having disappeared.

*Experiment IV: The Focal Reaction.* A series of rabbits was rendered immune-allergic by the systemic injection of virulent human tubercle bacilli. After well-marked cutaneous hypersensitivity to P.P.D. had developed, all rabbits were given a second injection of living bacilli in the anterior chamber, all eyes showing a transient reaction to the tuberculin in the inoculum. After 3 weeks, signs of early ocular tuberculosis were present in all eyes. The animals were then divided into three groups of six rabbits each. One group was left untreated as controls, the second group was treated with ACTH, and the third group with cortisone. After 4 days' treatment, all rabbits were given a shocking dose of 100 mgms. old tuberculin subcutaneously. The controls now showed a violent focal reaction in the diseased eyes. Two of the rabbits treated with ACTH showed a moderate focal reaction, while four showed either a minimal traumatic reaction or no reaction of any kind. One of the rabbits treated with cortisone showed a minimal focal reaction, while in five animals there was no reaction of any kind. ACTH was discontinued 4 days after this first shocking dose of tuberculin was given, but cortisone treatment was continued in the Group III rabbits. A second shocking dose was given all animals 5 weeks later. The controls again all reacted violently. Three of the rabbits formerly treated with ACTH now showed focal ocular reactions, two of the rabbits still receiving cortisone showed minimal traumatic reactions, while the others showed no ocular reaction of any kind. Cortisone was now discontinued in the Group III rabbits. Two weeks later all rabbits were given a third shocking dose of tuberculin. All rabbits, both controls and formerly treated animals, now showed acute and equal ophthalmic reactions, all blocking effect of the ACTH and cortisone having disappeared 5 and 2 weeks, respectively, after discontinuing treatment. These results are shown graphically in Fig. 19.

One peculiar finding was noted in the animals treated with cortisone. The number and size of the tubercles in the iris continued to increase, but as long as the cortisone treatment was continued, there was a complete absence of any external inflammation, the picture being that of a progressive tuberculosis in an eye totally devoid of any inflammatory reaction.

From these experiments it is evident that both ACTH and cortisone

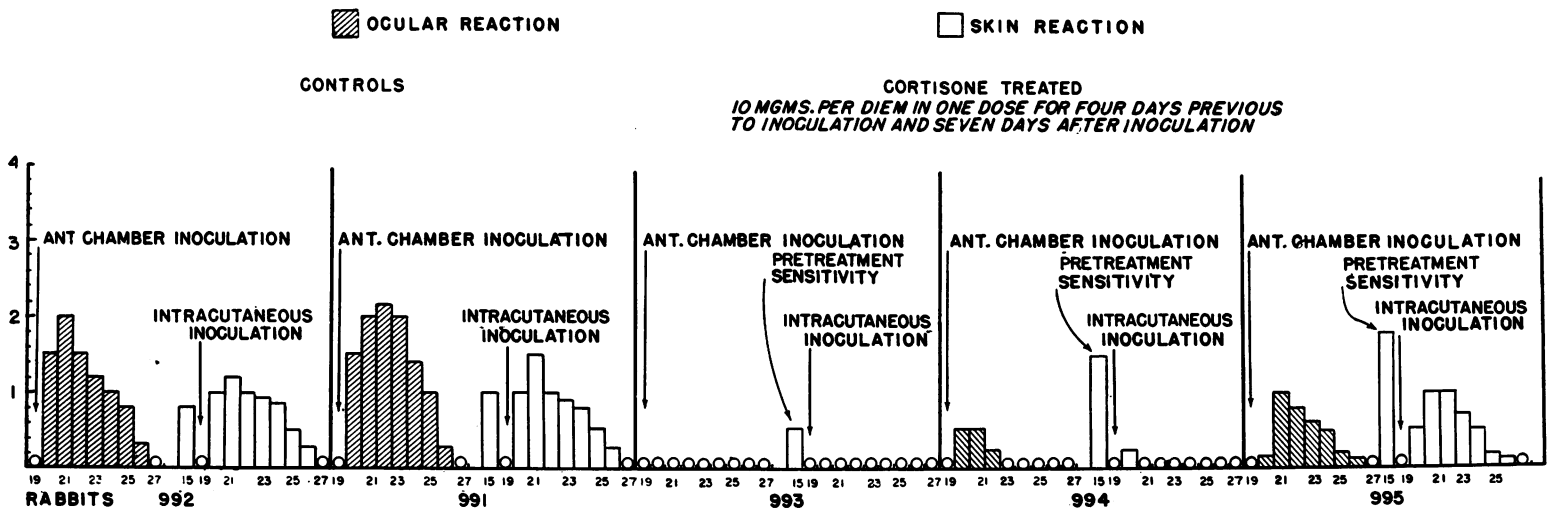


FIGURE 18. EFFECT OF CORTISONE ON INFLAMMATORY PHASE OF OPHTHALMIC PROTEIN REACTION

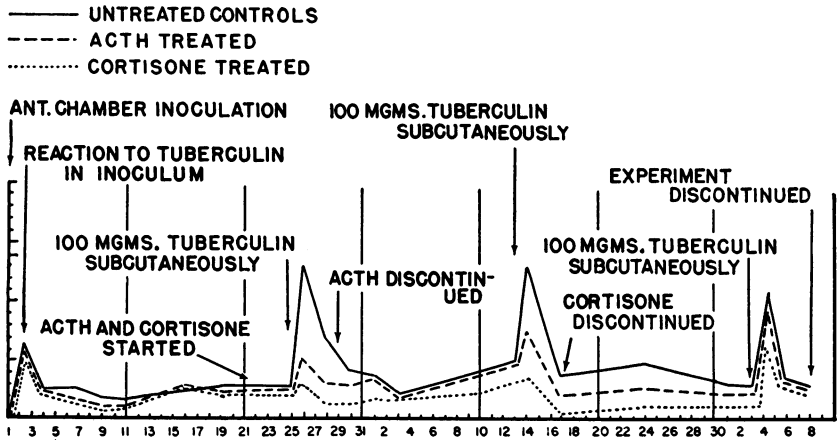


FIGURE 19. EFFECT OF CORTISONE ON INFLAMMATORY PHASE OF LOCAL REACTION TO TUBERCULIN

can either completely or partially block the inflammatory and exudative phase of the protein anaphylactic of the bacterial allergic reaction, and can also block focal reactions to tuberculin in tuberculous eyes. These agents, however, did not appear to alter the underlying hypersensitive state, the animals reacting to the specific antigen in the usual manner after the hormones were discontinued.

Obviously the next point to determine was if these agents had a similar blocking effect on ocular inflammation unrelated to a hypersensitive state. This question was explored by determining the effect of systemic injection of ACTH and cortisone in the inflammatory reaction which follows the injection of such irritants as glycerin and jequirity in the anterior chamber.

*Experiment VA: Ocular Inflammation Secondary to Glycerin.* In 1931, Seegal and Seegal (18), in the course of experiments on local tissue hypersensitiveness, showed that the introduction of such irritants as glycerin in the anterior chamber produced a transient iritis. Five rabbits were given 4-day preliminary treatment with cortisone and then given an anterior chamber injection of the proper amount of glycerin. Cortisone was continued for a further period of 4 days. Five untreated rabbits were similarly inoculated as controls. All of the control rabbits showed a moderate iritis of three days' duration. Of the treated rabbits, one showed a minor traumatic reaction, while the remaining four showed no iritis of any kind, the only change noted being a minor clouding of the lower half of the cornea, due apparently to a disturbance of the endothelium. This was shown likewise by all the controls. These results are shown graphically in Fig. 20.

*Experiment VB: Ocular Inflammation Secondary to Jequirity.* It has been known for many years that infusion of jequirity seeds instilled in the conjunctival sac produce a violent inflammatory reaction. An infusion of jequirity was therefore prepared and 0.1 c.c. of various dilutions was injected in the anterior chamber of the eyes of a series of normal rabbits. It was found that strengths greater than 1:500 produced an inflammatory reaction so violent that necrosis developed and many of the eyes perforated. Infusions of 1:1000 to 1:4000 produced a

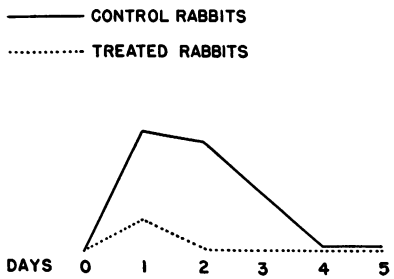


FIGURE 20. EFFECT OF CORTISONE ON INFLAMMATION SECONDARY TO GLYCOSIS IN ANTERIOR CHAMBER

satisfactory iritis of several days' duration. A series of 6 rabbits were then given 4 days' preliminary treatment with cortisone and then an anterior chamber injection of 0.1 c.c. of a 1:4000 dilution of jequirity infusion. Treatment was continued 4 days after the jequirity injection. Six untreated rabbits were given a similar anterior chamber injection of jequirity infusion. The treated rabbits showed no reaction to the jequirity injection, while the untreated controls showed a mild transient iritis, which faded on the second day. On the third day all rabbits were given a second anterior chamber injection of 0.1 c.c. of a 1:2000 infusion. Again the treated rabbits showed no reaction of any kind, while the controls now showed a well-marked iritis. The inflammatory reaction produced by the injection of jequirity in the anterior chamber was completely blocked by systemic treatment with cortisone. The results are shown graphically in Fig. 21.

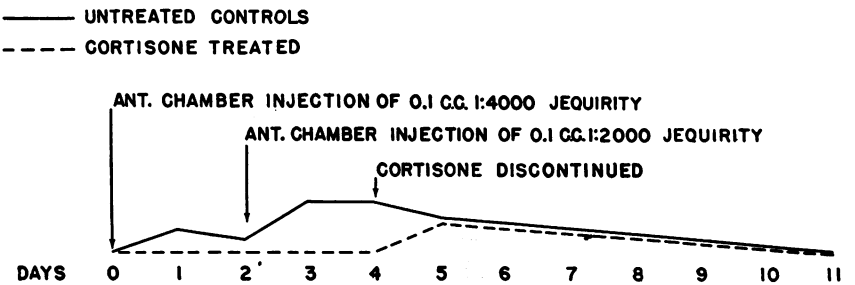


FIGURE 21. BLOCKING EFFECT OF SYSTEMIC CORTISONE TREATMENT ON JEQUIRITY INFLAMMATION

LOCAL INJECTION OF CORTISONE

*Experiment VIA: Protein Hypersensitivity.* A series of rabbits was sensitized to horse serum in the usual manner, titers of 1:1600 to 1:3200+ developing in the blood serum. Four rabbits were now injected in the anterior chamber of the right eye with a 0.1 c.c. of horse serum and 1.25 mgms. of cortisone. In the left eye they were given 0.1 c.c. of horse serum and 0.25 mgms. of cortisone. Four other sensitized rabbits were given 0.1 c.c. of horse serum alone in the anterior chamber, as controls. The controls developed a violent inflammatory reaction characterized by pericorneal inflammation, clouding of the cornea, inflammation of the iris, and a fibrous exudate in the anterior chamber. Two of the eyes injected with 1.25 mgms. of cortisone and horse serum in the anterior chamber showed no reaction of any kind, one showed a minor traumatic reaction, while the fourth, a highly sensitive rabbit, showed a definite reaction of moderate intensity. One of the eyes receiving 0.25 mgms. cortisone in the anterior chamber showed

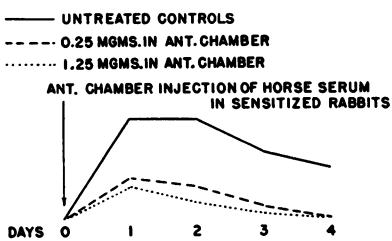


FIGURE 22. BLOCKING EFFECT OF LOCAL CORTISONE ON ANAPHYLACTIC INFLAMMATION

no reaction; one a minor traumatic reaction; one a very mild anaphylactic reaction; the fourth (the same rabbit which showed a reaction in the fellow eye after the injection of 1.25 mgms.) showed a moderately severe anaphylactic reaction. These results are shown graphically in Fig. 22. The local injection of 1.25 mgms. of cortisone in the anterior chamber effectively blocked the inflammatory phase of the protein reaction in three of four animals so tested, and decreased the severity of the reaction in the fourth animal. The injection of 0.25 mgms. had a similar, but weaker, blocking action.

*Experiment VIB: Jequirity Inflammation.* Six normal animals were given an anterior chamber injection in an eye of 1.25 mgms. of cortisone and 0.1 c.c. of a 1:4000 jequirity infusion. Two days later they were given a second anterior chamber injection in both eyes of 1.25 mgms. of cortisone and 0.1 c.c. of a 1:2000 jequirity infusion. Six control rabbits were given similar anterior chamber injections of jequirity infusions alone. The control rabbits reacted with a mild transient iritis to the first injection, and with a more marked inflammatory reaction to the second injection. The rabbits receiving cortisone with the jequirity

injections showed no reaction of any kind in the infected eyes. These results are shown graphically in Fig. 23.

To determine how long the protection against jequirity inflammation would last, three rabbits were given an anterior chamber injection of 1.25 mgms. of cortisone alone. Three days later they were given 0.1 c.c. of a 1:2000 jequirity infusion. All three rabbits showed a moderate inflammatory reaction. Quite evidently the blocking effect of the previous cortisone injections had disappeared.

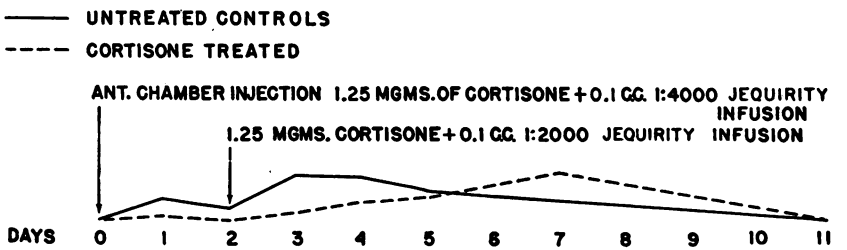


FIGURE 23. BLOCKING EFFECT OF LOCAL CORTISONE ON JEQUIRITY INFLAMMATION

## COMMENT

The clinical observations here reported are quite similar to those reported by other observers and indicate that ACTH and cortisone have a profound effect on the inflammatory and exudative phases of ocular disease. It is further evident from the cases treated systemically, all of which showed a concurrent fall in the circulating eosinophile count, that this blocking effect on ocular inflammation paralleled evidences of increased adrenal cortex activity. The accumulating evidence also indicates that cortisone instilled locally in the conjunctival sac has a peripheral action, and has a quite similar effect on ocular inflammation. Two questions immediately arise. 1) How do these agents act; through what mechanism do they exert this remarkable effect? 2) What is the place of these agents in ocular therapeutics?

Inasmuch as ACTH and cortisone have a similar effect in blocking the symptomatic manifestations of certain allergic diseases (Harvey *et al.*), and also block ocular inflammation which may be dependent upon an allergic background, one might at first suspect that they alter in some way the allergic reaction. This supposition is borne out by the experiments here reported in which the inflam-

matory phase of the experimental anaphylactic ocular reaction, of the similar bacterial hypersensitive reaction, and of the focal reaction of bacterial allergy were completely or partially blocked. However, despite these demonstrations it appears that their fundamental action is not on the allergic reaction per se, but that they function independently of the hypersensitive state. The evidence in favor of this is, first, that the antibody titer of the serum of the experimental animals is completely unaffected; second, that, when the experimental animals are reexamined two to three weeks after the cessation of treatment when the effects of these hormones have worn off, the underlying hypersensitive state is found undisturbed, and the eyes and skin of these animals again react to contact with the specific antigen in the usual manner. It might, of course, be argued that in some way—through an alteration in the permeability of the cell membrane, through some action on complement, through an antihistaminic action, or by some as yet undetected and unsuspected mechanism—they temporarily inhibit the antigen-antibody reaction. There is, however, no evidence in favor of this, and considerable evidence against such a supposition. It is shown here that in normal animals these agents can block the ocular inflammatory reaction due to irritants—an inflammation quite independent of the allergic reaction. Further, as yet unreported experiments by Landau and his coworkers (19) have shown that these agents will not protect experimental guinea pigs against histamine shock and death, and that strips of intestinal muscle from sensitized guinea pigs treated with ACTH, react to contact with the specific antigen in the Dale phenomenon, quite as readily as do strips of intestinal muscle from sensitized untreated animals. Therefore it seems fairly evident that the effect of these agents on the hypersensitive state is confined to blocking the inflammatory and exudative phases of the allergic reaction, and it is probable that this action in blocking allergic inflammation is quite identical with their action in blocking nonallergic inflammation due to irritants.

If this reasoning is correct, the immediate question is how these agents block the inflammatory reaction. Obviously one would suspect some action on the mesenchymal cells, the connective tissue of the vascular and lymphatic systems. This would explain not only

the blocking effect of these agents on inflammation and exudation, but also their favorable effect on collagenous disease. But how they act on mesenchymal tissue is not apparent. One might suspect some action on capillary or cell permeability or some anti-enzymatic action. There is, however, no evidence as yet in favor of such suppositions, and it is obvious that the question requires much further investigation.

It was interesting that in the experiments here reported, the inflammation-blocking effect of these adrenal cortex hormones could be more effectively demonstrated in the eye than in the skin. This may well be due to the fact that the eye with its rich vascular and nervous tissues, completely encapsulated in the sclerocorneal envelope, is a capital place to observe and follow isolated inflammatory reactions, and is much more selective than such a cosmopolitan structure as the skin. The high hyaluronic acid content of the vitreous and cornea may also influence the picture.

What are the practical therapeutic applications of this form of therapy in ophthalmology? It is not altogether clear which agent is preferable for systemic use in the control of clinical ocular inflammation, although the balance seems to tip the scale in favor of ACTH. The optimum dosage and method of treatment are still to be determined. The evidence from the treatment of rheumatoid arthritis indicates the beneficial effect may be only temporary in most instances. In Case 1, here reported, there was a severe recurrence of the iritis seven months after cessation of treatment with ACTH, and in all the experimental rabbits in which the inflammatory phase of the anaphylactic, bacterial hypersensitivity, and focal reactions was completely or partially blocked, the eyes and skin were again normally reactive when brought into contact with the specific antigen two to three weeks after the cessation of treatment. Thus it would appear that at best only a temporary beneficial effect can be anticipated. If these agents are to have any permanent place in ocular therapy, it seems probable they will be most valuable in conditions which are in their very nature self-limiting. Notable among such diseases are nongranulomatous iritis, allergic keratitis, and sympathetic ophthalmia. Somewhat similar would be a tuberculous uveitis with an acute inflammatory phase secondary to tissue hypersensitivity. If, in these conditions,

the inflammatory, exudative, destructive phase of the lesion can be blocked sufficiently long for the normal defense mechanism of the body to take up the task of overcoming the infection, or for appropriate therapeutic measures—antibiotic and chemotherapy, desensitization, and so on—to be instituted and accomplish their effect, then these agents may have a tremendous field in ocular therapeutics.

The possibility of local use of cortisone in the eye is most interesting, and for ophthalmologists is the most encouraging development. At present, judging from the small amount of clinical and experimental data available, it would appear that cortisone topically may have an immense field of usefulness in controlling external ocular inflammatory reactions. Whether, when instilled in the conjunctival sac, it will have any effect on deep uveal inflammation remains to be determined. Anterior chamber injection, which appears efficacious in animals, is probably impossible in clinical cases. If the topical administration does prove of value, such a finding will go a long way to solving the economic question of its use. It was most interesting that several patients, notably patient 16, in whom cortisone was used topically showed a marked drop in the eosinophile count, while in others only a slight or no effect was observed. Considerably more data will be needed to determine if a drop in the eosinophile count has any relation to the therapeutic action of cortisone used topically.

The ultimate side effects of these agents are as yet unknown. It must be remembered that they are about the most powerful hormones yet produced and may cause disastrous side effects. It is by no means clear how long the adrenal cortex can tolerate stimulation with ACTH or how damaging the depressant action on the adrenal cortex of exogenous cortisone may ultimately prove to be. These are only a few of the problems confronting workers in this field.

It would seem wise for the present to be conservative and to content ourselves with the assurance that while these adrenal cortex hormones offer a new and powerful weapon to control certain types of ocular inflammation, and have opened vistas of possible therapeutic application, they should not yet be regarded as accepted or proven therapeutic agents. Until more is known of their action, of the proper dosage, of the methods of treatment, of the ultimate

results produced, of the occurrence of side effects, both ACTH and cortisone had best be excluded from the accepted therapeutic armamentorium of ophthalmologists, and regarded only as exploratory agents. When employed therapeutically their use should be limited to those conditions where the severity of the ocular picture, and the meager knowledge already accumulated, warrant their use.

SUMMARY

1. ACTH and cortisone given systemically have a profound effect in the control of ocular inflammation and exudation in the ocular humors.

2. Cortisone administered locally in the conjunctival sac has a similar effect on external ocular inflammation, the beneficial effects being uniformly observed after two to four days of intensive treatment. It has not yet been demonstrated that cortisone given topically has any effect on exudation in the vitreous.

3. The optimum method of treatment, either systemically or topically, has yet to be determined.

4. Experimental studies confirm the clinical observations. ACTH, administered systemically, and cortisone, systemically or topically, block in the eye the inflammatory and exudative phases of the anaphylactic protein reaction, of the bacterial allergic reaction, and the focal reaction produced by the subcutaneous injection of tuberculin.

5. Both ACTH and cortisone given systemically appear to depress temporarily the cutaneous reactions incident to drug allergy, bacterial and tuberculin hypersensitivity.

6. Cortisone given either topically or systemically blocks the inflammatory reaction produced by such agents as glycerin and jequirity.

7. While ACTH and cortisone block the inflammatory and exudative phases of the anaphylactic and allergic reaction, the evidence so far at hand indicates they have no effect on the underlying hypersensitive state.

8. The mode of action of ACTH and cortisone is as yet undetermined. It seems probable that they act in some way on the mesenchymal tissues.

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## *DISCUSSION*

DR. JOHN M. MCLEAN. It is both a pleasure and a privilege to be asked to open the discussion of this paper by Dr. Woods in a new and fascinating field. He has pointed out that the cost and scarcity of these agents preclude their present widespread use in ocular therapy. I should also like to emphasize that these are extremely potent weapons and by no means without danger of either both immediate and possibly long-term side effects about which much remains to be learned. Although they are not ready for general therapeutic use, particularly in ophthalmology, these substances do open new approaches to therapy and new notions of some of the mechanisms and concepts of disease processes. I would also like to add a word of caution regarding their evaluation therapeutically because, as has been well demonstrated, the subjective results are much less reliable than the objective results. These agents produce in many patients a definite euphoria, and patients who are being treated, because of this euphoria as well as their enthusiasm and hope for results from a startling new agent, are very prone to be overenthusiastic in their estimation of the changes produced.

Up to the present, at the New York Hospital we have treated over 40 assorted cases of eye disease parenterally, and 30 cases topically, with ACTH and cortisone, and a few with subconjunctival cortisone. In general, our clinical results parallel those described by Dr. Woods. I will not review them here, except to point out two situations in which our results differ from Dr. Woods. We have had two cases of sympathetic ophthalmia, one definitely proven by histological study of the enucleated inciting eye, and the other a clinical diagnosis without histological material. Both cases are of longer duration than Dr. Woods' cases, one over three months and the other over four months after the beginning of the disease process before treatment was started; in both cases our results have not shown the spectacular improvement which you have just seen in the two early cases reported.

The other difference is in our experience with secondary glaucoma in various forms of uveitis. Dr. Woods has shown you improvement in secondary glaucoma in those with active uveitis, and we confidently expected that if we could get the active uveitis to subside the secondary glaucoma would improve with it. Much to our surprise and disappointment in several cases the reverse has been the situation. We have not only seen exacerbation of secondary glaucoma under ACTH therapy, but we have seen secondary glaucoma develop when it was not there before ACTH therapy. This is not true in the majority of cases, but it apparently can be true, and we are forced to the conclusion that the secondary glaucoma was either accelerated or produced by this treatment, possibly through the mechanism of electrolyte imbalance or

fluid retention, which can be severe systemically with patients under this form of treatment. If the local use turns out to be efficient, and our experience in this respect has been confined to cortisone—it has not seemed very logical to use ACTH locally—if, as we are beginning to believe in suitable cases, the local use will work out well, it promises not only to be much safer but economically much more feasible.

A big problem in the clinical use of these agents is the problem of relapses. We have an idea that, in those cases which require systemic therapy to produce an improvement in an intraocular lesion, a means of tapering off treatment without prompt relapse may be first a gradually decreasing systemic dosage and subsequently decreasing topical use. Exactly as Dr. Woods has reported, we also have found that this type of clinical treatment is most effective in fresh or acute inflammatory disease, and it seems to be able to hold the severe disruptive forms of inflammation in check while the bodily defenses are being sufficiently mobilized to take over.

Another important phase in evaluating the effects of these agents is the question of possible coincidental improvement in self-limited acute conditions. In a number of cases we have tried to test that possibility, in the improving phase, by abruptly discontinuing therapy for a few days, concluding that, if there was an immediate and severe recurrence of the inflammatory process which again subsides promptly when the ACTH or cortisone is resumed, it is presumptive evidence that the improvement shown is response to the agent and not coincidence.

As to the mechanism involved, I am sure I have no more idea than Dr. Woods has, and probably less, as to how these things work. It has been suggested that the mechanism is basically the so-called alarm reaction of Selye, and in that regard it may parallel foreign protein shock. It has been suggested that it blocks allergic response. Dr. Woods has elaborated on that subject and clearly shown that is not the main mechanism; but it does seem clear that, whatever the mechanism may be, these agents are able, at least for a significant time, to suppress the cellular and tissue response to inflammatory stimuli.

In closing this discussion I would like to emphasize the major importance of this contribution of Dr. Woods toward our knowledge not only of eventual better therapies in severe eye disease, but also toward our further evaluation of the mechanism of these processes.

DR. LUDWIG VON SALLMANN. We are all fascinated by the various experimental approaches of Dr. Woods to study the mechanism of cortisone and ACTH on the eye. We have learned from him that local effects of nonspecific nature are apparently one mechanism, or what is the most important mechanism, in achieving the results obtained. Dr. Woods referred to the work of Jones and Meyer on vascularization of the cornea by using cortisone locally when an injurious agent as sodium

hydroxide was injected into the cornea. The continuation of this work in the last months has led to a study on the process of wound healing under local nonspecific-effect of cortisone in the monkey eye. We hoped that the application of cortisone would influence the fibroblastic response of the scleral tissue, but we were unable to find any difference between the eyes which were treated with cortisone and the control eyes; our hope that these agents will be useful in making fistulizing operations more successful has failed so far. ACTH and cortisone were used in the Eye Institute in about 15 patients systemically and cortisone in about 20 patients locally. Treatment has not been successful so far in two patients with advanced sympathetic ophthalmia but the nature of the lesion has not been anatomically proven. We have had no good results in cases with chronic uveitis except for one or two patients. Thus our results are less favorable than those reported by Dr. Woods. The local treatment was given by subconjunctival injection of 0.05 c.c. of undiluted cortisone suspension and it was followed by no unfavorable response or pain. We were impressed with the improvement of corneal conditions, which consisted in deep infiltration of the cornea of various types, the disciform type, and others of unknown etiology. Patients with phlyctenular keratoconjunctivitis of both eyes showed clear-cut improvement in the eye treated with cortisone, but there were relapses, as you would expect from what Dr. Woods has said. In two instances the subconjunctival injection of cortisone was, in our hands, more successful than instillation of the diluted compound in cases of vernal conjunctivitis.

Dr. Alan C. Woods. The discussion has brought up several important points. I was especially interested in what Dr. McLean said about the failure to control secondary glaucoma. There may be various explanations for this. Obviously these agents could only control a rise in tension due to exudation and could have no effect on an elevated tension due to organic changes. Our cases in which glaucoma was controlled were treated with relatively larger doses of cortisone, which has only a very weak salt-retaining action. If ACTH is given, there is a production of all the hormones, including those with a salt-retaining effect. Thus with ACTH one would expect a greater retention of sodium chloride and fluid than one would with cortisone.

I think there is another explanation for our different results with sympathetic ophthalmia. The two cases here reported were only of one week's duration. Dr. McLean's cases were not early cases. One other case is now under treatment. The patient had a cataract extraction in November and apparently in February the second eye developed sympathetic ophthalmia, which for awhile did fairly well. In the latter part of May there was a violent exacerbation. The acute inflammation completely cleared under topical cortisone therapy.

Another question is that of dosage. I was interested in analyzing the dosage given by Dr. McLean. His average dose was 500 to 600 mgms. We have used larger doses; our average being 1,500 mgms. while some cases received 3,000 mgms. We have been able to show experimentally that the clinical result is proportional to the amount of these agents given. It is quite possible that smaller amounts would have produced an equally good effect. The good results, however, always parallel a fall in the circulating eosinophiles, which is evidence of an increased adrenocortical activity.

Dr. McLean also spoke about tapering off treatment. When you give ACTH you depress the normal pituitary mechanism, but, when you stop it, there is a prompt recovery of the pituitary mechanism which secretes the adrenocortico-stimulating hormones. Exogenous cortisone on the other hand has a markedly depressing action on the adrenal cortex. Thus exogenous cortisone must be given in large amounts, first, to make up for the amount lost by suppression of the normal adrenal cortex activity and, secondly, an additional amount to get a therapeutic effect. If too much is given one may get such a depressing effect that the gland may be atrophied. As Dr. McLean pointed out, if we can substitute the local cortisone for systemic treatment we may be able to give smaller amounts and avoid this depressing action of systemically administered cortisone.

I think the discussion clearly illustrates a point I tried to bring out: we are still in the exploratory phase of the use of these agents; nobody yet knows the best treatment, whether it should be constant, should be tapered off, or given in intermittent courses. Until we can solve those questions I do not think we can regard this as other than an exploratory agent.