COMMUNICATIONS

USES AND LIMITATIONS OF ACTH AND CORTISONE IN OPHTHALMOLOGY*†

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IN 1949 Hench and his associates at the Mayo Clinic published their paper on the dramatic effects of cortisone and ACTH on the subjective symptomatology of rheumatoid arthritis. Shortly thereafter it was noted by several observers that these agents had a similar effect on the acute non-granulomatous iritis so often associated with rheumatoid arthritis. Although these substances were then in scant supply and only a few cases of ocular disease could be treated, it soon became evident that they had a remarkable effect on various ocular inflammations. There was no information then available on the therapeutic range or limitations of these hormones, of the proper dosage or methods of administration, or of the mechanism through which they exerted their effect. A great deal was known, however, of their general physiological action, and certain definite contraindications to their use were recognized, although by no means all.

Ophthalmologists were therefore confronted with a four-fold problem which may be summarized as follows:

(1) To determine the therapeutic range and limitations of these agents in ophthalmology, *i.e.*, to ascertain to what extent these hormones have a favourable clinical therapeutic action, and in what ocular conditions they are effective.

(2) To determine the proper dosages and optimum methods of administration in ophthalmic disease.

(3) To determine the range of the therapeutic and inhibitory effect of these hormones on various experimental ocular lesions and to explore the mechanism of their action.

(4) In the light of clinical and experimental investigations, to determine the ocular conditions wherein hormonal therapy might have a deleterious effect and be specifically contraindicated.

As these substances became more abundant, ophthalmologists addressed themselves to these problems with enthusiasm. On the first two points, in the short period of 2 years, a great mass of valuable and informative material has been collected. On the last two points there is still much to be learned.

The early clinical investigations by ophthalmologists were chiefly of the "hit or miss" and "trial and error" type, with case reports bristling with photographic evidence of the remarkable therapeutic results obtained. These early isolated reports were gradually followed by comprehensive studies from

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the various established clinics and the material now available makes a formidable and remarkably uniform total. The purpose of this report, therefore, is to assemble the information already obtained, and to point out what has been established, and what requires further investigation.

I. Therapeutic Range and Limitations of ACTH and Cortisone

In the seventh Gifford Memorial Lecture (Woods, 1951a), the paucity of the then existing reports was pointed out. The material of this lecture comprised a series of cases treated in the New York Hospital and made available through the courtesy of Dr. John McLean (McLean and others, 1951), and a similar series treated in the Wilmer Institute. A study of these cases, 397 in all, permitted certain broad conclusions.

A number of other reports have since appeared in the literature, notably those of Leopold and others (1951; 142 cases), Olson and others (1951; 55 cases), Scheie and others (1951; 121 cases), Mosher (1951; 33 cases), Fitzgerald and others (1951; reporting 196 patients from the various Chicago clinics), Duke-Elder and others (1951; 416 cases), and other equally valuable reports including Hogan and others (1951), Agatston (1951), Gordon and others (1951), and Potter (1951).

With minor differences in terminology and in the incidence of favourable results, these reports all confirm the general conclusions reported in the Gifford Lecture, which were the following:

(a) In certain inflammatory conditions of the eye, especially those affecting the cornea, uveal tract, and external eye, the parenteral administration of ACTH or cortisone, or the topical administration of cortisone, is followed in a high percentage of cases by a dramatic control of the inflammatory and exudative phases of disease. These agents do not affect the cause of the disease but rather influence the reaction of tissues to the cause or to the irritant.

(b) In many diseases favourably influenced there is a definite tendency for the inflammation to recur after cessation of treatment.

(c) In certain oedematous and inflammatory conditions, especially secondary glaucoma, inflammations of the retina and optic nerve, and oedematous corneal grafts, and also probably in syphilitic interstitial keratitis, the action of ACTH and cortisone is variable and cannot be accurately predicted.

(d) In some haemorrhagic and exudative conditions (Coats's disease, Eales's disease, malignant exophthalmos, diabetic retinopathy, and retrolental fibroplasia) no consistent therapeutic results have as yet been demonstrated.

(e) In degenerative disease, whether of the cornea, retina, or uveal tract, these agents are totally ineffective.

The material now available from other investigators and from our own further experiences at the Wilmer Institute, where the number of cases treated is now more than double that reported in the earlier paper, permits the elucidation and definition of broad general principles for the use of these agents in ophthalmic disease. The favourable action and limitations of ACTH and cortisone, as indicated by the information available at present, may be summarized as follows.

(1) EXTERNAL DISEASES.—Inflammations of the external eye result either from allergic, toxic, or physical trauma, or from a degenerative process, or are evidence of an exogenous or endogenous infection. The therapeutic range of cortisone or ACTH in external ocular inflammations varies greatly according to the cause of the ocular disease.

In acute non-bacterial inflammations of the external eye, the action of cortisone or ACTH is usually spectacular. Here the inflammation secondary to the physical, allergic, or toxic trauma is in itself the harmful reaction, and, if severe, long-enduring, or repeated, ultimately produces actual damage to the cells and organic change in the eye. Hormonal therapy, either parenteral or topical, usually controls the inflammation and exudation secondary to physical or toxic trauma, interposes a shield between the cells and the irritant, and facilitates prompt recovery without residual damage.

Allergic reactions in the eye are usually acute insults and are self-limiting. They may, however, appear chronic when they result from a hypersensitivity to bacterial antigens and when intoxication arises from a chronic focus of infection. In the acute type—an allergic conjunctivitis, vernal catarrh, phlyctenular keratoconjunctivitis, episcleritis, etc.—if cortisone or ACTH therapy is continued over the natural life of the reaction, the control of inflammation and exudation may simulate a complete cure. Within 24 to 48 hrs of the institution of treatment, the eyes become white and free of inflammation, and, if the reaction has burned out when cortisone or ACTH is discontinued after 6–10 days, the eyes remain free of symptoms until the allergic insult is repeated. In the chronic type, where the body is apparently unable to free itself of the intoxicating allergen, a similar suppression of inflammation is experienced, but unless steps are taken to remove the intoxicating allergen or to desensitize the patient, there will be an almost immediate return of inflammation when treatment is withdrawn. However, it is in the allergic reactions that cortisone and ACTH reach their highest usefulness. In over 90 per cent. of external allergic inflammations the use of these agents gives almost complete symptomatic relief, and if properly continued, complete control of the acute attacks. The availability of hormonal therapy and the resultant symptomatic cures do not relieve the ophthalmologist of the duty of determining, if possible, the cause of the allergic intoxication and of taking proper steps to remove it. Otherwise, acute attacks will recur on a renewal of the stimulus and in the chronic type the recurrence will often be immediate on cessation of treatment.

One form of external allergic reaction, contact dermatitis, requires special mention. Dermatologists are almost unanimous in reporting that the parenteral use of cortisone or ACTH, or the topical use of cortisone, has no effect whatsoever on contact dermatitis or drug allergy. On the other hand, Carey and others (1950) have reported that the intensive ACTH or cortisone treatment of patients with skin eruptions secondary to drug allergy usually results in prompt and complete control of the dermatitis but with a marked tendency for recurrence after termination of treatment. The question is of especial interest to ophthalmologists since they so frequently encounter a hypersensitivity to atropine and other alkaloids commonly used in the eye. There is little in the literature on this subject. Our experience has been not only that vigorous parenteral ACTH treatment is followed by a prompt subsidence of the lid dermatitis, but also that atropine or the offending alkaloid can usually be used again without reaction as long as the hormonal

treatment is continued. A similar but less intense effect may be obtained by cortisone applied topically in the conjunctival sac. While it is difficult to attribute the subsidence of the dermatitis to this therapy, the fact that the patient can be challenged with the alkaloid without reaction while under hormonal treatment, indicates a cause and effect relationship.

It has been stated that cortisone is without effect in degenerative disease. While it has no therapeutic action on the underlying condition, topical cortisone is nevertheless of value in controlling the inflammation and irritation secondary to a degenerative keratitis. Thus in a band-keratitis with calcium carbonate and phosphate crystals beneath the epithelium and occasional erosion through the epithelium, the photophobia, conjunctivitis, and irritation can often be successfully controlled by the instillation of cortisone ointment in the conjunctival sac. Unless an active underlying granulomatous uveitis is present, there is no contraindication to the prolonged use of topical cortisone, and it frequently gives symptomatic relief which can only doubtfully be obtained by any other means.

In exogenous or endogenous infections, the action of cortisone or ACTH at best is limited to a control of the inflammatory reaction. These hormones have no antibiotic or antiseptic action and do not affect the invading organisms which cause the inflammation. Further, their ability to control inflammation is in inverse proportion to the severity of the stimulus. If the infecting organisms are of high toxicity, and especially if they produce tissue destruction or necrosis, the inflammatory reaction may be well beyond the therapeutic range of either cortisone or ACTH. Any therapeutic action they have in bacterial infections is, therefore, limited in scope and related to the severity of the inflammatory stimulus. In minor infections, they may give symptomatic relief, but if the infecting organism is not destroyed by the natural factors of resistance or some form of therapy, the bacteria continue to grow and cortisone or ACTH only masks the symptoms. Thus, while cortisone and ACTH are useful agents in a bacterial conjunctivitis or in infected corneal ulcers in so far as they reduce inflammation and pain, their use carries the risk of masking symptoms and inducing a false sense of security.

In deep-seated endogenous infections of the cornea, an additional question arises. In many instances the inflammatory, neo-vascularizing and fibroblastic processes which accompany a keratitis are defensive and reparative phenomena. Obviously they should not be suppressed unless other adequate specific therapy is available.

This principle is well exemplified by a case of abscess of the cornea. On admission there was conjunctival inflammation, marked chemosis and beginning vascularization of the cornea. The patient was placed immediately on hormonal therapy with a partial clearing of the external inflammatory reaction and a subsidence of the chemosis. There was no change in the picture of the abscess itself, which if anything progressed. After one week of treatment the causative organism had been isolated and its sensitivity to antibiotics and sulphones determined. Specific therapy was followed by a prompt regression and healing of the abscess. The same principle is also exemplified by the interstitial keratitis of congenital syphilis. In the early stages of infiltration, hormonal therapy is followed by a clearing of the interstitial infiltrates and an inhibition of vascularization. It is far from clear, however, if this inhibition of neo-vascularization is desirable, for prolonged hormonal therapy is then required to maintain control of the disease, and after cessation of treatment recurrences are frequent (*vide infra*, Section IV, Contraindications).

The underlying principle in the use of ACTH and cortisone in external ocular disease is that, in acute inflammation from allergic or physical trauma, ACTH or cortisone will

shield and protect the tissue from the resultant toxin or irritant, and so prevent the inflammatory reaction. Since allergic or physical trauma is usually self-limiting, treatment throughout the natural life of the tissue reaction may simulate a complete cure. If the inflammation results from bacterial infection, the use of these agents should always be accompanied by proper antibiotic or chemotherapy to destroy the infecting organisms. In chronic or deep-seated external ocular infections, not only should the use of ACTH or cortisone be accompanied by appropriate therapy directed at the cause of the disease, but the question whether the inflammatory or vascularization phenomena are defensive and reparative reactions should also be considered before hormonal therapy is instituted.

(2) UVEAL DISEASE.—In evaluating the action of the adrenal cortical hormones on uveitis, the fundamental differences between non-granulomatous and granulomatous uveitis and between acute and chronic uveal inflammation must be kept clearly in mind.

Non-granulomatous uveitis is believed to be either a hypersensitivity phenomenon, the reaction of the sensitized uveal tract to allergic insult, or the result of acute physical or toxic trauma. The usual causes are either a bacterial hypersensitivity resulting from a former infection or a reaction from operative or other trauma. It is characterized clinically by acute inflammation, oedema, and sometimes by a fibrinous exudate, without primary organic changes in the tissues. The insult is usually acute and the tissue reaction limited. A severe attack may produce organic damage, but as a rule the early attacks clear without residua and organic damage occurs only upon repeated attacks. In the chronic allergic type, where the body is unable to free itself from the intoxicating allergen, the tissue reaction may be prolonged until the hypersensitive state is exhausted or burned out. Histologically, the reaction is characterized by oedema, serous exudation, and diffuse lymphocytic infiltration (Biegel, 1951). Classical examples in the anterior uvea are the acute iritis so often associated with rheumatoid arthritis or old gonococcal infections, and non-infectious post-operative cyclitis. A similar example in the posterior uvea would be the intense subretinal oedema and vitreous exudation seen as part of the focal ocular tuberculin reaction.

Granulomatous uveitis is believed to be caused by the actual invasion of the uveal tract by the living organisms which cause granulomatous disease, and is therefore essentially a chronic infection. The recognized granulomatous ocular diseases are tuberculosis, syphilis, brucellosis, and viral and fungal infections, but there are probably many other unrecognized causes. Clinically, granulomatous uveitis is characterized by low-grade chronic inflammation, nodular infiltration of the tissues, with gradually developing organic changes, tissue destruction, and replacement by fibrous tissue. Histologically the cellular infiltration is usually with epithelioid and macrophagic cells, large mononuclears, and fibroblasts. Classical clinical examples would be a chronic tuberculous uveitis in an individual with low sensitivity to tuberculin, or the chronic diffuse choroiditis of early syphilis.

In the classical forms of non-granulomatous and granulomatous uveitis, the two types of inflammation (the acute, intense inflammation caused by the hypersensitivity reaction and the chronic comparatively low-grade inflammation caused by infection) can be readily differentiated. Non-granulomatous uveitis is usually easily recognized in the acute stage, although often, in the chronic types or after repeated acute attacks with resultant tissue damage, the picture may closely simulate that of granulomatous uveitis. The chief diagnostic difficulty is the confused picture often shown by granulomatous uveitis. There is no reason why

organisms causing typical granulomatous changes in the tissue may not at the same time produce a bacterial type of hypersensitivity. Once such a hypersensitivity is established, a resultant allergic reaction will be evoked by various fractions of the bacterial antigen. This certainly occurs in tuberculosis and quite probably in other granulomatous diseases. Thus in the same eye we have the picture of a non-granulomatous reaction superimposed on a granulomatous focus. In highly sensitized tissue the allergic reaction may be so intense as to mask the true granulomatous nature of the underlying disease. In other cases the dual return of the reaction may be quite evident—violent external inflammation associated with typical granulomatous changes in the anterior uvea, or the very common picture of a massive choroidal exudate surrounded by a zone of subretinal oedema.

The importance of this concept of two types of inflammation occurring in the same eye is paramount in evaluating the value of hormonal therapy in granulomatous uveitis. The adrenal cortex hormones suppress the inflammatory and exudative reactions whether due to allergy, irritants, physical trauma, or bacterial infection. In evaluating the therapeutic effect of an agent one must consider what is suppressed and the value of such suppression. Since different concepts of the aetiology of uveitis are held in different clinics, and varying terminology and diagnostic criteria are often employed, it is somewhat difficult to evaluate the results reported in the literature. However, when due allowances are made for these variables, an analysis of the reports gives a remarkably uniform and consistent result.

(a) *Non-Granulomatous Uveitis*.—In the classical acute inflammations of the anterior uvea, whether due to allergic insult or to a post-operative reaction without infection, ACTH and cortisone exert their most dramatic and consistent effects. In approximately 80 per cent. of acute endogenous iritis a prompt favourable reaction is noted within 48 hrs, varying from improvement to complete subsidence of ciliary congestion and oedema of the iris, and the disappearance of cells and fibrin from the anterior chamber. If treatment is continued thereafter during the natural life of the disease or tissue reaction, this improvement may simulate a complete cure. In the post-operative type without infection, both ACTH and cortisone have a profound effect in controlling both pain and inflammation.

In the so-called chronic form of non-granulomatous iritis or iridocyclitis, the reported results were not so spectacular. A favourable reaction, varying from improvement to complete subsidence of inflammation, is observed in approximately 60 per cent. of the cases. However, unless the offending allergen or underlying infection is eradicated, there is a tendency for the inflammation to return after cessation of treatment.

Non-granulomatous disease of the posterior uvea is variously termed non-granulomatous choroiditis, acute choroiditis, acute diffuse choroiditis, acute exudative choroiditis, etc. In its typical acute form, it is characterized by intense generalized oedema of the choroid and clouding of the vitreous, usually without heavy organized opacities. The more chronic form is characterized by ill-defined exudates with surrounding subretinal oedema. These ill-defined exudates may be non-granulomatous foci where the cellular infiltration is most intense, or they may be true granulomatous lesions and the surrounding oedema an allergic tissue reaction due to a bacterial hypersensitivity to the invading organisms responsible for the basic granulomatous disease—a non-granulomatous process superimposed on a granulomatous one.

In the acute oedematous form without exudation, or where any ill-defined exudates are merely foci of increased cellular infiltration, the use of ACTH and cortisone is usually followed by a complete regression of all objective symptomatology, and if adequate treatment is maintained over the natural life of the reaction this may simulate a complete cure. However, if the ill-defined exudates are actually granulomatous foci with a secondary

allergic reaction about them, the action of ACTH and cortisone may be limited to control of the subretinal oedema, circumscription of the exudate, and clearing of the vitreous. In such cases, unless other therapeutic procedures have controlled the basic disease process, recurrences are frequent when the hormone therapy is stopped. The various reports indicate that a favourable reaction, circumscription of exudates, and clearing of the vitreous, may likewise be expected in approximately 80 per cent. of the treated cases. Almost all observers agree that to obtain a favourable result in posterior-uveal diseases more prolonged and intensive treatment is required than in the anterior form.

There appears to be considerable difference of opinion in the various reports on the incidence of recurrences of acute uveal inflammation after hormone therapy. This probably is due to variations in the periods of observation after treatment. A study of the Wilmer Institute cases, where the period of observation in the early cases is now almost 2 years, indicates that in notoriously recurrent types of uveal disease (such as acute non-granulomatous iritis associated with rheumatoid arthritis), if specific therapy directed at the cause is not instituted or is not successful, recurrences after primary control of the inflammation by ACTH or cortisone therapy occur with the same regularity as before treatment.

(b) *Granulomatous Uveitis*.—Granulomatous inflammation of the anterior uvea is usually called chronic uveitis, and characterized by chronic low-grade inflammation, and organic changes in the iris and ciliary body, with secondary corneal and lens changes. It may smoulder for months or years and may undergo exacerbations with periods of acute inflammation which are probably local hypersensitive reactions. If hormonal therapy is used during an acute exacerbation, a favourable immediate result in control of inflammation and pain will usually ensue. If it be used in the chronic phase when the low-grade inflammation is predominantly due to infection, the response may be less striking and recurrences quite prompt and frequent after treatment is terminated. Organic changes and nodules in the iris are not usually affected; if they appear to regress, this is almost certainly due to a subsidence of the inflammatory reaction and to the disappearance of inflammatory cells and is not related to a specific action of the adrenal cortex hormones on the cause of the granulomatous disease. The experience of various investigators indicates that some control of inflammation occurs in approximately 60 per cent. of cases of chronic granulomatous uveitis but that relapses are frequent.

Granulomatous disease of the posterior uvea is called, amongst other designations, granulomatous choroiditis, chronic choroiditis, focal choroiditis, chronic exudative choroiditis, circumscribed plastic choroiditis, and deep fog-like choroiditis. Whatever name it may be given, it is essentially an exudative disease with tissue destruction. It is not readily amenable to ACTH or cortisone therapy, an apparently favourable result having been reported in only about one-third of the cases, where it is usually limited to circumscription of the exudates, control of any surrounding subretinal oedema, and some clearing of the vitreous—control, in short, of the secondary non-granulomatous allergic reactions. If the exudates gradually absorb without gliosis, such absorption should not be considered a cure. It may be due to the suppression of the inflammatory and cellular reaction of infection, to the natural forces of resistance, or to some other form of therapy, but not necessarily to a specific action by the hormones themselves on the cause of the disease.

Recurrences of exudative or granulomatous choroiditis after cessation of hormonal therapy are frequent. How frequent they are one cannot say, for the different terminology used in various reports and the absence of the exact data of treatment make accurate analysis impossible. To judge from a consulting practice, where one sees generally the worst cases, severe recurrences appear to be the rule rather than the exception.

In granulomatous uveitis hormonal therapy may be a two-edged sword. The adrenal cortex hormones tend to suppress inflammation and exudation, whether due to a hypersensitive reaction or to infection. On the one hand, the inflammatory reaction due to

allergy is violent and may be destructive, and its suppression is thus desirable. On the other hand, the inflammation due to chronic infection is low-grade and may be considered as a reparative phenomenon. The question in granulomatous uveitis, therefore, is how to use hormonal therapy to control a destructive allergic inflammation, yet not to interfere with the reparative processes accompanying the inflammation of infection. There is no clear answer. Until the situation is clarified by further study the wisest rule to adopt is that ACTH or cortisone should not be used in granulomatous uveitis unless there is clinical evidence of a serious secondary allergic inflammation, when their use should always be guarded, never prolonged, and if possible always accompanied by specific antibiotic or chemotherapy.

Two types of granulomatous uveitis require special mention. These are sarcoidosis and sympathetic ophthalmia. The early attempts to control ocular complications of sarcoidosis with the parenteral use of ACTH or cortisone, or the topical use of cortisone were as a rule disappointing, although occasional favourable results were reported. Comparatively recently it has been shown that under intensive intravenous ACTH therapy the mediastinal, cutaneous, and ocular lesions of sarcoidosis melt away, but only to recur promptly when treatment is terminated. The eye, however, offers a unique opportunity for a sustained therapy which may possibly control the disease. In the Wilmer Institute several proven cases of ocular sarcoidosis were treated intensively with intravenous ACTH and a dramatic resolution of the lesions ensued (Schulman, 1951), but there was prompt recurrence after cessation of treatment. The disease was again brought under control by intravenous ACTH therapy, and thereafter the patients were given continued and sustained treatment with topical cortisone ointment in the conjunctival sac. During the period of observation (now as long as 8 months in one case) there have been no ocular recurrences. What the end result will be is unpredictable, but in view of the gravity of the disease and the lack of any other form of therapy, these attempts appear justified.

Haik and others (1951) have recently assembled and analysed the results of ACTH and cortisone therapy in 72 cases of sympathetic ophthalmia. Regardless of the severity or duration of the disease, an immediately favourable result was obtained in 47 (64 per cent.) of the cases. After termination of therapy, eighteen relapsed, but the disease was again brought under control by further treatment. In early cases, the favourable results were even more striking, approximately 80 per cent. being controlled, a significantly higher percentage than that achieved thus far by any other form of treatment. Moreover, it appears quite possible that the failure rate might have been still further lowered if intensive intravenous ACTH therapy had been used in the unsuccessful cases. Although sympathetic ophthalmia is a long drawn-out disease, it is ultimately self-limiting, and it therefore appears that prolonged treatment over the natural life of the disease may be necessary. Certainly, when the gravity of the disease is considered, patients who do not respond to the usual parenteral therapy may be treated with intravenous ACTH with proper precautions, and may later receive sustained treatment with topical cortisone.

INFLAMMATIONS OF THE NERVE AND RETINA.—It is almost impossible to evaluate the reports of favourable action of ACTH and cortisone in optic neuritis. A number of observers have reported remarkable improvement in optic and retrobulbar neuritis after the use of these agents and other reports are entirely negative. The authors reporting favourable results have all recognized that many forms of optic neuritis, whether due to demyelinating disease, syphilis, or other undetermined causes, have a natural tendency to sudden and spontaneous remission. Therefore, in any individual case, it is difficult, indeed often impossible, to state whether an observed improvement occurs *post hoc* or *propter hoc*. The general clinical impression appears to be that a favourable resolution of optic neuritis is noted in over one-half of the cases treated with ACTH or cortisone and that this result is related to the therapy. Until the exact aetiology of optic neuritis is better understood, and the mechanism of the action of these hormones in disease is finally established, it will probably be impossible to relate the improvement definitely to

the therapy. The present indications, on the basis of the information available, are that the use of these agents is indicated in optic and retrobulbar neuritis, certainly as a trial procedure.

In central serous retinopathy, if treatment is instituted before degenerative changes have occurred in the retina, the results of ACTH or cortisone therapy appear remarkably good, subjective and objective improvement usually beginning after 2 to 3 days' treatment, with subsidence of the central serous exudation within 7 to 10 days. Recurrences after cessation of treatment, however, are not uncommon.

In acute exudative retinitis (Coats's disease), which may be either an acute exudative disease in the external retina, or a subretinal haemorrhagic reaction, there is some equivocal evidence that in the early stages of the exudation before detachment and gliosis have occurred, ACTH or cortisone may check the remorseless course of the disease. However, a consistently favourable reaction has not yet been demonstrated. Only a few such cases have been treated, and failures appear to be more frequent than successes. Further investigation of the action of ACTH or cortisone in the exudative type of Coats's disease is justified.

In other forms of retinopathy (the various haemorrhagic types, diabetic retinopathy, atherosclerotic, and arteriolar-sclerotic retinopathies, Eales's disease, leukaemic retinitis, etc.) the use of these agents has given uniformly disappointing results. A large number of diabetic retinopathies have been treated with topical cortisone with no real improvement. It has been demonstrated that parenteral treatment with ACTH and cortisone is possible in diabetics if the insulin intake is properly increased and the patients are kept under adequate control. In a few cases of diabetic retinopathy treated under this regime the results have again been disappointing, any visual improvement observed probably being due to a spontaneous absorption of vitreous haemorrhage rather than to any alteration in the retinopathy. While undoubtedly many more cases of this tragic disease will be so treated, there is little reason to hope that more favourable results will be obtained.

(3) MISCELLANEOUS OCULAR DISEASE.—There are several ocular diseases in which there has been or is still considerable difference of opinion concerning the therapeutic action of ACTH and cortisone. Chief of such conditions are the exophthalmos of Graves's disease, cloudy corneal grafts, secondary glaucoma, and retrolental fibroplasia.

Exophthalmos or Graves's Disease.—There are only a few reports of treated cases in this category. Fitzgerald and others (1951) report two cases in which a conspicuously favourable result ensued, but other reporters (including McLean, Woods, and Scheie, and their co-workers) have observed no effect. Experimentally, Smelser and Ozanico (1951) have shown that ACTH and cortisone have no effect on the experimental exophthalmos of guinea-pigs. The rationale of hormonal therapy in thyrotropic exophthalmos appears to be the proven fact that there is a marked increase in the water volume of the orbit and the unproven assumption that the use of these agents decreases capillary permeability. Since the results reported to date are directly contradictory, further exploration is indicated.

Keratoplasty.—A number of cases of corneal grafts, with early clouding and vascularization, have been treated with topical or parenteral cortisone or with ACTH. Treatment with these agents was usually instituted from the second to the fifth week after operation and after clouding or vascularization of the graft had appeared. When treatment was instituted within the first 3 days after clouding was observed, a clearing of the graft and inhibition of vascularization was noted in 50 per cent. of cases, and what threatened to be an unfavourable result was transformed into a favourable one. Topical cortisone appears to be the treatment of choice, and treatment must be instituted before the changes are established and irreversible. Maumenee (1951) has recently published experiments indicating that delayed clouding of the graft may be related to an allergic reaction to the donor graft by the recipient. There are experimental studies indicating that cortisone

inhibits neo-vascularization of the cornea (see below). In view of this experimental work and the favourable clinical results reported, the topical use of cortisone in early clouding and vascularization of corneal grafts appears fully justified. Though treatment should be instituted early it should probably be delayed until 2 weeks after operation in order not to interfere with the firm union of the graft.

Secondary Glaucoma.—Here the action of ACTH and cortisone appears quite unpredictable. Blake and his associates (1950) have reported four cases of secondary glaucoma in which the tension was controlled by the use of ACTH. Other observers have noted that in some patients the use of these hormones is followed by a control of tension, that in others it is unaffected, and that in some the parenteral use of ACTH or cortisone has been followed by the development of a secondary glaucoma. Tillett (1952) has recently reported a study which indicated that in patients with normal eyes the ocular tension is quite unaffected by parenteral ACTH. The explanation of these conflicting results may be that when the secondary glaucoma results from acute inflammation or exudation, the control of such inflammation or exudation may restore a normal balance; but if it is due to organic changes or to blocking of the angle by inflammatory debris, the hormones will have no effect. From the clinical viewpoint there appears to be little reason for the use of ACTH or cortisone in secondary glaucoma unless there is active ocular inflammation.

Retrolental Fibroplasia.—Reese and Blodi (1951) have argued that retrolental fibroplasia is essentially an angioplastic or angiomatous process, although in some cases the early dilatation of the retinal vessels may be absent; they pointed out that many of the infants showed skin angiomata, that the adrenal-pituitary axis is not well developed in early infancy, that ACTH appears in the placenta only in the last 3 months of pregnancy, that the premature birth deprives the infant of ACTH, and that premature infants show a deficiency of 17-ketosteroids in the urine—all indicating a relative ACTH deficiency. It was therefore logical to postulate that the angiomatous disease, retrolental fibroplasia, might be related to an ACTH deficiency. In their first communication they reported on fourteen premature infants with retrolental fibroplasia who were treated with large doses of ACTH. In all of them progression of the disease was inhibited, whereas in three out of five untreated controls the disease progressed. More recently (Reese and others, 1951) they have reported their further experiences. They divide the acute phase of the disease into five stages and point out that if treatment is to be successful, it must be instituted in Stage I or II. In thirty cases in these categories treated with ACTH, success was attained in sixteen and failure or indeterminate results occurred in fourteen. In 36 similar untreated control cases, however, there was spontaneous regression in 25, and progression of the disease in only eleven. Combining their two series, they found no statistical difference in the progress of the disease in the treated and untreated cases, and have therefore concluded that ACTH has no effect on the course of the disease. This observation agrees with that of the majority of the other observers*, although Coston (1951) and Scheie and others (1951) reported isolated successes. Since ACTH therapy in premature infants is attended by a high mortality and morbidity, and all the weight of evidence is against such treatment having any therapeutic value, no further exploration of its use in retrolental fibroplasia appears justified.

(4) *DEGENERATIVE DISEASE.*—In the recent Gifford Lecture (Woods, 1951a) the statement was made that in degenerative disease, whether of the cornea, retina, or uveal tract, these agents are totally without effect. In the strict sense, this is undoubtedly true, but the statement requires some explanation and amplification.

Degenerative disease of the eye may in some instances be secondary to inflammation or exudation, and the resultant visual loss may be due to both the oedematous and the degenerative factors. A control of the oedematous or inflammatory phase may therefore give a subjective visual improvement, and at

* See discussion on Dr. Reese's paper, *Trans. Sect. Ophthal. Amer. med. Ass.*, 1951. In the press.

the same time check the progression of the secondary degeneration. For example, in central serous retinitis, an incipient macular degeneration may be secondary to the localized subretinal oedema. A control of the serous retinitis may therefore result in restoring the retina to its proper position and so improve vision and check the progress of the macular degeneration. The retinal degeneration which has already taken place, however, will remain unaffected. Essential degenerations (corneal dystrophies, juvenile or senile macular degeneration, hyaline degeneration, familial retinal degeneration, and degeneration secondary to haemorrhage) are totally unaffected by the adrenocortical hormones. Pigmentary degeneration of the retina, and fibrinoid degeneration of the connective tissue, are two conditions which merit special mention.

A number of cases of pigmentary degeneration of the retina have been treated by parenteral injections of ACTH or cortisone, and by the topical use of cortisone. Careful efforts have been made to detect any actual improvement by following the visual acuity, the light sense, and the visual fields. Some moderately encouraging results have been recorded in a few cases by McLean and others (1951) and in one by Olson and others (1951). Steffensen and Kukora (1951) have reported slight improvement in visual fields, visual acuity, and biophotometric readings in nine out of fourteen patients receiving parenteral ACTH or cortisone therapy. However, an almost equal improvement was noted in four out of seven patients receiving "intermedia", a contaminant of ACTH. Except for these occasional cases, the results have been almost consistently disappointing and a study of the cases in which improvement was noted yields no convincing evidence that there was any true organic regression or even inhibition of the degenerative disease. When the fluctuations in vision, visual fields, and light sense which occur under placebo treatment and even in untreated cases are considered, together with the subjective emotional reactions in patients with a disease they are naturally reluctant to admit is hopeless, it seems impossible to attribute the occasionally reported improvement to the hormone therapy. Even if a slight improvement was causally related to cortisone treatment, continued parenteral therapy would probably be necessary to sustain it. Until new and more convincing evidence is presented, it is probable that ACTH and cortisone will take their place with the many other forms of treatment which have unsuccessfully been tried in pigmentary retinal degeneration.

Fibrinoid degeneration of the connective tissue and myxomatous swelling of the ground substance is, more or less, a common denominator in the various collagen diseases. It was in the so-called "collagen diseases", rheumatoid arthritis, acute rheumatic fever, essential polyangiitis (periarteritis nodosa), acute disseminated lupus erythematosus, that the remarkable therapeutic action of ACTH and cortisone was first noticed and in which these agents reach their maximum usefulness.

The connective tissue system consists of cellular elements (fibroblasts), fibrillar elements (collagen, reticulin, elastin), and an interfibrillary amorphous ground or cement substance (a colloid, hyaluronic acid, and mucopolysaccharides). The reaction of the connective tissue system to trauma, be it physical, bacterial, or allergic, may be either proliferative (keloid) or degenerative (fibrinoid degeneration). While the other vascular and granulomatous changes of the various collagen diseases may differ, they all have the common denominator of fibrinoid degeneration with straightening and thickening of the fibres, and an increase in their optical refractivity and apparent friability. In an excellent article, Stillerman (1951) has recently reviewed the ocular manifestations of the various diffuse collagen diseases

and has pointed out that the common factors of vascular change and fibrinoid degeneration may account for both the systemic and the ocular findings. In many of the ocular complications the connective tissue changes may be secondary, but in others, such as scleromalacia perforans and the conjunctival nodules of erythema multiforme, they may be primary. Stillerman then suggests that other ocular degenerative diseases of unknown aetiology (Mooren's ulcer, marginal corneal dystrophy, keratoconus, progressive myopia, etc.) may in truth represent a degeneration of the cellular, fibrillary, or interfibrillary components of the connective tissue, and, like other collagen diseases, be susceptible to the action of ACTH or cortisone. Duke-Elder and others (1951) reported three cases of Mooren's ulcer treated with cortisone with questionable symptomatic improvement in two instances. We have noted remarkable regression of rheumatoid nodules in the sclera, but there is as yet no evidence of any action in sclero-malacia perforans, keratoconus, or marginal dystrophies. Further exploration of these possibilities is indicated.

II. Dosage and Methods of Administration

The methods of parenteral administration of ACTH and cortisone have been elaborately reported and are well known. They may be summarized as follows:

ACTH is given either by intramuscular injection or by intravenous infusion. If given by intramuscular injection the initial dose is usually from 80 to 120 mg. daily in divided doses. It may be given in saline or ACTHAR vehicle, or in ACTHAR gel. If in saline, the injections should be not less than 6 hrs apart; if in long-acting ACTHAR vehicle or gel, the injections are usually given at 12-hr. intervals. After the first day the amount given may be increased, maintained, or decreased, according to the therapeutic and eosinophil response. If a favourable response is obtained, the dose is usually decreased from 120 mg. daily, first to 80, then to 60, 40, and finally 20 mg., being increased again if there is an exacerbation of the ocular inflammation. Maintenance doses of 20 to 30 mg. daily, or intermittent courses, can be given over a considerable period with the usual precautions.

ACTH is given intravenously in a glucose drip, usually over an 8-hr. period once daily; it is from eight to twelve times as effective when given intravenously as when given intramuscularly, for the destruction of the ACTH by proteolytic enzymes in the muscle is avoided. For most conditions 20 mg. ACTH is a full daily intravenous dose. In ocular sarcoidosis or resistant sympathetic ophthalmia, larger doses, up to 40 mg. daily, may be required to elicit a satisfactory therapeutic result. Again, as a satisfactory result is obtained, the dose is gradually decreased and tapered off over a 10 to 20-day period.

The parenteral and oral dosage of cortisone is well established. It is usually given in divided doses in a total dosage of 300 mg. the first day, 200 mg. the second day, and 100 mg. daily thereafter over a 7 to 14-day period and then gradually tapered off, a maintenance daily dose being from 30 to 50 mg. The injections are usually given twice daily and oral cortisone every 6 hrs. At the conclusion of oral or parenteral cortisone therapy, ACTH is often given over a 2 to 3-day period to stimulate the adrenal cortex and so overcome the depressing action of the exogenous cortisone.

When both ACTH and cortisone were first used clinically by parenteral injection, rather elaborate laboratory studies were carried out in order to detect and avoid toxic reactions. As experience with these agents has increased, these studies have

become simplified. Daily weight and blood pressure determinations should be done and the fasting blood sugar determined at the onset of treatment and every 4 to 6 days thereafter. The urine should be carefully followed for any evidence of glycosuria. Daily eosinophil counts are done as an index of the general physiologic response, and the daily dosage of the hormone is adjusted on this basis and on the therapeutic response. The eosinophil response is more constant with ACTH than with cortisone. To compensate for a possible potassium loss, 3 g. potassium chloride daily may be given during ACTH or cortisone therapy.

The most interesting method of treatment for ophthalmologists is the topical administration of cortisone. It has been abundantly shown by a number of investigators that cortisone administered topically in the eye has a therapeutic effect in anterior ocular diseases quite equal and indeed superior to that obtained by parenteral injection. This same local action has also been demonstrated experimentally. The effect is noted within a few hours and is obviously quite independent of any general physiologic action. Even when the topical administration is prolonged over months, no general physiologic reactions are observed, and only rarely is the eosinophil count affected, even though the therapeutic effect be marked. Relatively small amounts of cortisone topically are needed to obtain the maximum therapeutic effect. The topical use therefore permits prolonged, even indefinite treatment, requires no precautions or general laboratory studies to avoid side-effects, and affords great economy.

Cortisone topically may be given by instillation as a collyrium, as an ointment, or by subconjunctival injection. Koff and others (1950) have advocated the subconjunctival use, on the grounds that an equal therapeutic effect is obtained, treatment only every 1 to 3 weeks is required, and a minimum of local reaction occurs. On the other hand, Mosher (1951) has reported distinctly poorer results with subconjunctival injection than with topical instillation, and Leopold and others (1951) have reported mild, but definite local reactions. Leopold's studies on the permeability of the cornea to cortisone indicate no marked increase in absorption when cortisone is given by the subconjunctival route. The author has had better results with instillation into the conjunctival sac, and slight though the trauma of subconjunctival administration may be, it is avoided by conjunctival administration.

If given as a collyrium, the usual commercial preparation (25 mg./ml.) is diluted with saline 1: 5, thus reducing the concentration of benzyl-alcohol which is used as a preservative (1.5 per cent.) to a point where it produces no ocular irritation. An ophthalmic suspension has now been prepared* in a buffered phosphate solution with 1: 5,000 zephherin as the preservative. This is entirely non-irritant and permits the use of the collyrium in the full 25 mg./ml. strength if so desired, thus making very frequent application less necessary. This strength, or a 1: 2 dilution, is usually given every 1 to 2 hrs during the acute stages of ocular inflammation or until a satisfactory response is obtained and thereafter the interval is lengthened. The eye is best kept under an eye-pad to prevent the washing away of the insoluble steroid. A maintenance dose is usually 1 drop every 12 hrs.

An especially happy method for the topical application of cortisone is the use of an ophthalmic ointment. It is readily packaged, easily applied by the patient, permits slow and steady absorption, obviates the need of an eye-pad, and avoids the loss of cortisone which is washed out by the tears and coagulates along the lashes when it is used as a collyrium. To avoid the competition of a mineral-oil

* By Merck and Co.

base, in which cortisone is slightly soluble, it may be prepared in an aquaphor or lanolin base. A concentration of 10 to 15 mg./g. appears sufficient for the usual case, although it may be used in the concentration 25 mg./g. in acute cases. Preparations weaker than 10 mg./g. appear ineffective. Applied every 3 to 4 hrs, it has a therapeutic effect equal to that of the collyrium applied every hour. The blurring of vision which results from the use of an ointment is not usually troublesome, for, when it is used through the day, the treated eyes are usually so acutely inflamed that the blurring of vision is not noticed, and when it is used as a maintenance therapy in non-inflamed eyes, it need be used only once in 24 hrs just before retiring. The ophthalmic ointment is now available commercially.

In disease of the posterior ocular segment, choroiditis, endophthalmitis, and generalized uveitis, the parenteral administration of ACTH or cortisone or oral cortisone are undoubtedly the methods of choice. The effects of the two agents are about equal. Intravenous ACTH is indicated in patients in whom there is either no therapeutic response to ACTH or cortisone parenterally, or no eosinophil response to ACTH intramuscularly.

The topical use of cortisone, either as an ointment or as a collyrium, is the method of choice in all external diseases and in inflammation of the anterior ocular segment, giving results equal if not superior to the parenterally administered ACTH or cortisone. However, if anterior uveal inflammation does not yield to topical therapy, parenteral administration should be tried. The topical administration has the advantages of absence of side-effects, obviates the need of the usual examinations made when the hormones are used parenterally, and permits prolonged use, easy application, and economy. Further, when generalized uveitis or disease of the posterior ocular segment is once controlled by parenteral ACTH or cortisone, the improvement can often be maintained by the topical use of cortisone ointment.

III. Effect of the Adreno-Cortical Hormones on Ocular Reactions and Disease in Experimental Animals

Despite extensive investigations by immunologists, clinicians, physiologists, and chemists, the mechanism whereby ACTH and cortisone exert their dramatic effect on inflammation is as yet undetermined. There are, however, certain experimental observations of their effect on ocular reactions and disease which throw considerable light on their mode of action, and are of particular interest to clinical ophthalmologists. The experimental ocular conditions on which the effect of these hormones has been studied are the ocular inflammations caused by the various hypersensitivity reactions, by irritants and by infection, the capillary permeability of the eye, wound healing and neo-vascularization in the cornea, and the development of tuberculous lesions in the eye. These studies may be summarized as follows:

(1) EFFECT ON OCULAR INFLAMMATION

(a) *Inflammation due to Hypersensitivity Reaction.*—There are three recognized anaphylactic and allergic reactions which can readily be evoked in the eyes of experimental animals:

(i) *Anaphylactic Reaction.*—This is due to sensitization and intoxication with protein agents, horse serum being the protein commonly used; it was first described by Nicolle

and Abt (1908). After sensitization of the animal by the proper systemic injection of horse serum, the injection of small amounts of horse serum into the anterior chamber produces an intense non-granulomatous iritis, characterized histologically by oedema and lymphocytic infiltration of the uveal tract. This iritis is transient, lasting for 4 days or more and then usually subsiding without residua.

(ii) *Allergic "Ophthalmic Reaction"*.—This is due to sensitization and intoxication with bacterial antigens; it was first described by Derick and Swift (1929). Usually the animal is sensitized by repeated intracutaneous injections of living α -streptococci, or killed β -streptococci. After sensitization has been obtained, the injections of minute quantities of the homologous specific antigen into the anterior chamber produces a non-granulomatous iritis of some 3 to 14 days' duration. In highly sensitized animals this may be accompanied by clouding and vascularization of the cornea.

(iii) *Focal Reaction to Tuberculin*.—This is shown by eyes with tuberculous disease after the systemic injection of an excessive dose of tuberculin, and the reaction has long been recognized clinically. It was produced and described in experimental animals by Woods and Burky (1943). If immune-allergic rabbits with a restrained secondary ocular tuberculosis are given a systemic injection of 100 mg. old tuberculin, the quiescent diseased eyes flare up within 24 to 48 hrs with a typical non-granulomatous iritis which persists for 2 to 4 days and then fades.

It was found that when sensitized animals in these three categories were treated with parenteral ACTH or cortisone for a 4-day period before the anterior-chamber injection, and for 4 days afterwards, the ocular reactions were partially or completely suppressed, the injected eyes of the treated animals showing either a minimal reaction or none to the anterior-chamber injection of the specific antigen and to the parenteral injection of tuberculin. It was further found that if cortisone was injected into the anterior chamber at the same time as the specific antigen was given, the reaction could be suppressed by this means alone. The degree of suppression shown after either parenteral or topical treatment was proportional to two factors—the amount of the hormone given, and the degree of hypersensitivity shown by the experimental animal. In these various experiments the cutaneous reactions to horse serum, α - or β -streptococci, and tuberculin were likewise partially or completely suppressed by the parenterally administered ACTH or cortisone. However, the underlying tissue hypersensitivity was not disturbed, for when treatment was discontinued and the eyes or skin of the sensitized animals were later re-injected with the specific antigen, they reacted quite as briskly as the untreated controls.

(b) *Inflammation due to Irritants*.—Seegal and Seegal (1931), in the course of experiments on local tissue hypersensitivity, showed that the introduction into the anterior chamber of such irritants as glycerin or iodine produced a transient iritis. A similar iritis can be produced by staphylococcus toxin, and a more intense iritis, which may actually be accompanied by corneal necrosis and perforation of the globe, by jequirity (Woods and Wood, 1952a). If the animals were parenterally treated with ACTH or cortisone 4 days before the anterior-chamber injection and for 5 days after it, the iritis produced by glycerin or staphylococcus toxin could be completely inhibited. A similar suppression was observed when the test animals were treated with cortisone injected into the anterior chamber at the same time as the irritant. Again it was found that the degree of suppression, from mild to absolute, was quantitatively related to the amount of the hormone administered.

When jequirity infusions of sufficient strength to produce necrosis were used, neither the parenteral administration of ACTH or cortisone, nor the anterior-

chamber injection of cortisone had any effect on the resulting lesions (Woods and Wood, 1952a). When weaker infusions were used, the inflammation shown by the controls was partially or completely suppressed both by parenteral ACTH or cortisone, and by topical cortisone, the degree of suppression varying with the degree of the insult, *i.e.*, the strength of the jequirity infusion used.

(c) *Inflammation due to Infection.*—In the experiment on the suppression of the focal reaction to tuberculin by the parenteral administration of cortisone, it was found that when treatment with parenteral cortisone was continued for 3 weeks after the focal reaction in the eye had subsided, the eyes of the treated rabbits became white and free from visible inflammation, although the tubercles on the iris continued unchanged or even increased slightly. Thus, for a short period, treatment with cortisone produced the peculiar picture of white non-inflamed eyes with an active tuberculosis (Woods and Wood, 1950).

In the experiment on the effect of hormonal therapy on the development of ocular tuberculosis, it was found that ACTH, cortisone, and Compound F, administered parenterally, suppressed all inflammation in the inoculated eyes for a period of 5 to 6 weeks after inoculation. During this period the organisms quite evidently propagated, for myriad tubercles later developed after this prolonged incubation period and the lesions were found swarming with bacilli. It thus appeared evident that in these experimental animals the adrenal cortex hormones inhibited the inflammatory reaction due to infection with *Mycobacterium tuberculosis*. Incomplete experiments, as yet unreported, indicate that this suppression of the inflammation of infection is not limited to tuberculosis but also occur in infections with other organisms. This accords with the clinical findings that hormonal therapy suppresses such inflammatory reactions.

From this group of experiments it was concluded that the ability of ACTH and cortisone to control inflammation was not limited to the inflammation secondary to hypersensitivity reactions but also extended to inflammation produced by irritants and infection. Since small amounts of cortisone injected into the eye immediately suppressed the inflammatory response produced either by the hypersensitivity reaction or by irritants, it was apparent that the cortisone acted locally at the cell level, and that its action was independent of any general physiological change. It did not affect the underlying antigen-antibody reaction, but in some unexplained way actually shielded the cells, lessened the toxic effect of the allergic reaction, irritant, or bacterial toxin, and so prevented the inflammatory response. Its ability to control inflammation was only relative, however, and failed in the presence of too powerful an insult.

(2) *CAPILLARY PERMEABILITY.*—If a decrease in capillary permeability were produced by ACTH or cortisone, this would go far in explaining their inhibitory effect on inflammation and exudation. The various studies of capillary fragility in collagen diseases (Harrogate Conference, 1951) indicate that capillary fragility as tested by suction devices is decreased after ACTH or cortisone therapy. Similarly, Armstrong and Irons (1951) reported studies on the protein content of the vesicles in a patient with scleroderma, indicating that after treatment with ACTH or cortisone, it fell markedly until it

approached that of a transudate. This they interpreted as evidence of decrease in capillary permeability.

Two methods have been employed to determine the permeability of the capillaries of the eye: to assay the passage of protein across the ciliary blood-aqueous barrier, and to assay the passage of fluorescein.

It is well known that, after repeated punctures of the anterior chamber in normal animals, the regenerated aqueous has a much higher protein content than the original aqueous, which indicates an increase in permeability of the capillaries at the ciliary barrier. Irvine and Irvine (1951) studied the protein content of the first and second aqueous of animals under treatment with cortisone, and found that the increased protein content of the second aqueous was not affected by such treatment. They concluded that in the normal rabbit, under the conditions of their experiment, cortisone had no effect on capillary permeability.

The action of cortisone in inhibiting the passage of fluorescein across the ciliary blood-aqueous barrier was first studied by Leopold and others (1951), who found that treatment of a normal animal with cortisone had no inhibitory effect on the passage of intravenously injected fluorescein into the aqueous, indicating that such treatment did not decrease the capillary permeability of a normal rabbit for molecules the size of fluorescein.

Cook and MacDonald (1951), working on human patients, found that treatment with cortisone did not influence the passage of fluorescein into the anterior chamber of non-inflamed eyes. However, in eyes inflamed from various ocular diseases, where the passage of fluorescein into the anterior chamber was greatly increased, treatment with cortisone reduced it to the normal level. They concluded that while cortisone had no effect on the capillary permeability of the normal human eye, it played an important role in the reduction of an increased capillary permeability associated with inflammation. This agrees with the observation of Biegel (1951) that, in the anaphylactic uveitis produced by sensitization and intoxication with horse serum, cortisone effected a marked inhibitory effect on the exudation. Further investigation of this important question seems to be desirable.

(3) WOUND HEALING.—The various general studies of Ragan and others (1949), and Spain and others (1950), clearly indicate that treatment of the experimental animal with cortisone interferes with new fibroblast formation but not with granulation tissue already formed. The evidence of an effect on epithelialization is somewhat conflicting. In the eye, the question of wound healing has been especially investigated by Friedenwald (1951), Leopold and others (1951), Newell and Dixon (1951), and Ashton and Cook (1951).

Friedenwald studied the effect of treatment with cortisone on the mitosis rate of corneal epithelium and found no difference in the mitosis of the corneal epithelial cells of treated rats from that in controls. Leopold and others (1951) found that rabbits treated with cortisone showed slight delay in epithelialization of the cornea after standard trephine wounds. They observed no gross clinical difference in the healing rate of stromal wounds in the treated and control rabbits, but histological studies of

the eyes showed there to be definitely less granulation tissue in the treated eyes than in the controls. They made no observations on endothelial regeneration. Newell and Dixon studied the effect of subconjunctival cortisone on the healing of full corneal grafts. They found no evidence that cortisone had any significant influence on the normal rapid proliferation of corneal epithelium. There was a marked difference in the stromal healing. In the untreated controls after the third day, leucocytes and eosinophils began to disappear, and proliferating keratoblasts migrated between the wound margins, displaced the epithelium, and formed cellular connective tissue. In the treated eyes leucocytes persisted up to the eighth day, keratoblastic proliferation was minimal, and as late as the eleventh day the wound was filled only with epithelium and fibrin. These workers definitely noted that endothelial cells in the grafts were absent in many sections and fragmented in others, and that fibrin filled the posterior edges of the wound.

Ashton and Cook investigated the effect of cortisone on perforating corneal wounds. In an exceptionally well-illustrated paper they showed that cortisone inhibited the fibrinous coagulum, cellular infiltration, and fibroblastic repair. Like Newell and Dixon they observed fragmentation of the endothelium, and in addition an inhibition of endothelial regeneration. The inhibition of both the stromal and endothelial repair was related to the quantity of cortisone administered, being moderate with small doses, where repair was still adequate, and marked with large doses, where repair might be completely inhibited. Just how cortisone inhibits the fibroblastic reaction is much of a mystery. Steen (1951), who has studied the effect of cortisone on tissue cultures, found that cortisone added to tissue cultures in concentrations up to 25 times that of the usual therapeutic levels, had no effect whatsoever on the fibroblastic growth of chick embryos.

It is doubtful, however, if these well-established experimental findings have any marked clinical significance. Ashton and Cook do not state the amount of cortisone administered in order to obtain complete inhibition of repair. It is quite probable that the amount so administered was well in excess of the usual amount given clinically. Certainly both general surgeons and ophthalmologists have repeatedly operated on patients under ACTH or cortisone therapy and have consistently observed no undue retardation in the healing of cutaneous or corneal wounds.

(4) NEO-VASCULARIZATION.—Jones and Meyer (1950) reported that cortisone applied topically had a marked inhibitory action on the neo-vascularization which so regularly followed caustic burns of the cornea. Quite recently this finding has been fully confirmed by Ashton, Cook, and Langham (1951), and also by Lister and Greaves (1951). The first group of workers determined the effect of both subconjunctival and parenteral cortisone on the vascularization and corneal oedema produced by injection of a solution of alloxan into the anterior chamber. They found that such injections reduced and delayed the neo-vascularization, but did not completely inhibit it. The degree of inhibition was much greater when cortisone was administered subconjunctivally. Similarly, they found that subconjunctival cortisone had a

marked effect in inhibiting oedema, opacification, and increased thickness of the cornea, where parenteral cortisone had no such effect. Lister and Greaves found that cortisone, either subconjunctival or parenteral, inhibited the vascularization that follows thermal burns of the cornea.

There is no exact evidence of the process whereby cortisone inhibits neovascularization. The most plausible explanation so far available is that the phenomenon may be concerned with the inhibition of endothelial proliferation first noticed by Newell and Dixon and confirmed by Ashton and Cook.

(5) CORTISONE AND OCULAR TUBERCULOSIS.—There is considerable evidence that treatment of experimental animals with cortisone may radically alter the course and possibly the pathogenesis of systemic tuberculous lesions. Michael and his co-workers (1950) and Spain, Molomut, and Haber (1950) reported experiments indicating that treatment with cortisone depressed the natural resistance to infection possessed by tuberculosis-resistant rats. Later Lurie and others (1951) showed that, in rabbits with a pulmonary tuberculosis produced by inhalation of bacilli, the whole course of the ensuing lesions was radically altered by treatment with cortisone, with caseous foci in the tubercles and a great increase in the numbers of the bacilli in the lesions. A series of experiments recently reported from the Wilmer Institute (Woods and Wood, 1952b) indicates that in the eye the entire course and type of the tuberculous lesions can be altered for the worse by treating the animals either with topical or parenteral cortisone, or with parenteral Compound F. These experiments were briefly as follows:

Ocular tuberculosis runs a radically different course in the normal and in the immune-allergic rabbit. In the normal, non-immune rabbit there is a minimal reaction to the anterior-chamber injection of tubercle bacilli; thereafter there is an incubation period, followed by the development of hard tubercles. A high degree of reactivity to tuberculin then develops in the diseased eye, and simultaneously a stage of acute inflammation. Thereafter, the tubercles soften, necrosis and caseation follow, the eyes go into buphthalmos, and within 6 to 8 weeks the majority of them rupture (Fig. 1).

FIG. 1.—Ocular tuberculosis in untreated normal control, showing buphthalmos and rupture of globe, 60 days after inoculation.

On histological examination the eyes show large caseous tubercles with tissue destruction (Figs 2 and 3).

FIG. 2.—Ocular tuberculosis in untreated normal control, showing necrosis and caseous tubercles of iris, 60 days after inoculation.

FIG. 3.—Ocular tuberculosis in untreated normal control, showing caseous tubercle of ciliary body, 60 days after inoculation.

In immune-allergic rabbits the picture is radically different. There is an initial inflammatory reaction in the eyes to the tuberculo-protein in the inoculum. This fades in 3 to 7 days, and there is then an incubation period of varying time, after which the eyes develop a restrained tuberculous disease (Fig. 4, opposite). Acute inflammation, necrosis, caseation, buphthalmos, or rupture of the globe are rarely if ever observed, and within 3 to 5 months the eyes become quiet with variable residual scarring. On histological examination only minimal healed granulomatous lesions are found (Figs 5 and 6, opposite).

FIG. 4.—Ocular tuberculosis in untreated immune-allergic control, showing restrained, healing tubercles of iris, 90 days after inoculation.

FIG. 5.—Ocular tuberculosis in untreated immune-allergic control, showing nondescript granulomatous lesion of iris, 90 days after inoculation.

FIG. 6.—Ocular tuberculosis in untreated immune-allergic control, showing nondescript granulomatous lesion of iris, 90 days after inoculation.

When immune-allergic rabbits were treated with parenteral or topical cortisone, or with parenteral Compound F, over a 50 to 58-day period from the time of inoculation, the development of visible lesions was inhibited over a 20 to 48-day period while the controls developed lesions in 10 to 14 days (Fig. 7).

FIG. 7.—Diagram illustrating course of ocular tuberculosis in immune-allergic rabbits.

After this prolonged incubation period, the eyes of the treated animals developed lesions quite similar to the controls. When treatment was stopped after 50 to 58 days, showers of soft tubercles developed on the iris and in the cornea (Fig. 8), and on bacterial stains these were found to be swarming with bacilli.

FIG. 8.—Cortisone-treated immune-allergic rabbit. Soft tubercles of iris occurring 3 days after cessation of treatment.

Thereafter the eyes developed necrosis, caseation, and buphthalmos (Fig. 9, opposite), and some of them ruptured. The whole picture of the disease was radically changed and the eyes of the immune-allergic rabbits assumed the pattern observed in the eyes of the normal non-immune rabbit (Figs 10 and 11, opposite).

FIG. 9.—Cortisone-treated immune-allergic rabbit, showing buphthalmos, necrosis, and caseation of globe, 32 days after cessation of treatment.

FIG. 10.—Cortisone-treated immune-allergic rabbit, showing caseous tubercle of ciliary body after cessation of treatment.

FIG. 11.—Cortisone-treated immune-allergic rabbit, showing necrosis and caseation of iris after cessation of treatment.

A study of these animals indicates that this changed picture in the immune-allergic rabbits was not due to a loss of their immune status, but was probably related to an inhibition of phagocytosis and fibrosis, and possibly to the depression by the cortisone of the animals' own adrenal cortex with a consequent adreno-cortical hormone deficiency when the exogenous cortisone was withdrawn. Immune-allergic rabbits similarly treated with ACTH did not develop this changed picture of tuberculous disease. A possible explanation for the failure of ACTH-treated rabbits to develop this rebound phenomenon may be that such rabbits maintained their adrenal hypertrophy for the 100-day period of observation after cessation of treatment, and were thus probably not deprived of the protective influence of their own cortisone.

These findings in the eye are quite in accord with those of other investigators of systemic tuberculosis. They are also, in general, quite similar to those of Turner and Hollander (1950) in experimental syphilis; instead of the usual circumscribed, indurated lesions observed in the untreated controls, rabbits treated with cortisone developed large, boggy, non-ulcerative lesions which were swarming with treponemata. When treatment was stopped there was a sharp rebound phenomenon, with spread and violent accentuation of the disease.

These experiments appear to have a particular clinical significance. Unless it can later be proved that the administration of streptomycin and *para*-amino-salicylic acid or other newer agents (nydrazidoe, etc.) at the same time as cortisone therapy prevents such recurrences and rebound phenomena in tuberculous eyes, it would be wise to assume that cortisone therapy should be severely restricted in any case of proved or suspected ocular tuberculosis.

(6) ABSORPTION OF CORTISONE BY THE EYE.—When the effect of topical cortisone on ocular inflammation was first observed it was difficult to understand just how a substance as insoluble as cortisone acetate could be absorbed from the conjunctival sac. That it did penetrate into the eye was clearly attested by its effect on non-granulomatous iritis. Leopold and his co-workers studied the question experimentally and analysed the aqueous for its cortisone content after instillation of cortisone suspension into the conjunctival sac and after both subconjunctival and retrobulbar injection. They found that all methods of application resulted in penetration of cortisone into the aqueous, and that subconjunctival injection was only slightly superior to the instillation of a collyrium into the conjunctival sac.

In the course of experiments on the effect of topically applied cortisone on the various hypersensitive reactions, we noticed a curious phenomenon. After the anterior-chamber injection, the chalky crystalline suspension of the cortisone acetate was clearly visible as a flocculent mass; within 24 to 36 hrs all trace of it had disappeared, but ACTH injected into the anterior chamber was only slowly absorbed over a period of several days. However, when cortisone acetate is given subconjunctivally, the crystals can readily be seen

beneath the conjunctiva for about a week. It seems probable that cortisone in the anterior chamber or in the conjunctival sac undergoes some chemical alteration making it readily soluble and easily absorbed. Just what this change is remains a complete mystery. Did the cortisone change into Compound F in the eye?

A recent observation by Steen (1951) may be of great importance. In the course of his experiments on the growth of mesoderm in tissue cultures with cortisone, Steen observed that in the presence of living cells, the insoluble cortisone acetate combined with glucose to form a new and soluble compound which may be cortisone-glucoside. The similarity of cortisone in the anterior chamber of a living eye to the conditions of Steen's experiments is striking. Perhaps Steen has found a solution for the puzzling question of absorption of cortisone by the eye. This is certainly an interesting field for further investigation.

IV. Contraindications for Adreno-Cortical Hormones in Ophthalmology

When ACTH and cortisone were first used clinically, a great mass of information on their general physiologic action had already been accumulated. It was known that the thirty or more adrenal cortex hormones had three main fields of action:

(a) "salt" hormones with an electrolyte-regulating effect, the most important action being retention of sodium chloride, increased excretion of potassium, and increased plasma and extra-cellular fluid volume,

(b) "S" hormones, which influence carbohydrate, fat, and protein utilization, cause a lysis of fixed lymphoid tissue, and depress the circulating eosinophils,

(c) "N" hormones, related in structure to testosterone, which cause androgenic effects, hirsutism, masculinization, etc.

The various recognized adreno-cortical hormones all fall roughly into one of the above groups, although there is a distinct over-lap in their action. Thus cortisone, an "S" hormone, is most active in causing an increase in the glucose level, in glycogen stores, and in glucogenesis, but has also a weak salt-regulating effect. ACTH, which produces a general stimulation of the adrenal cortex, has a much more wide-spread action and may produce all three effects.

The prolonged clinical use of either ACTH or cortisone may produce untoward physiological side-effects, retention of salt and water with a resulting hypertension, relatively insulin-resistant hyperglycaemia, Cushing's syndrome with the characteristic facies, hirsutism, amenorrhea, etc., and even alterations in cerebral function. Their use therefore is contraindicated in patients with hypertension, nephritis, diabetes, and various psychoses, but it has been found that the normal individual has sufficient pancreatic reserve to cope with the hyperglycaemia, and under proper control, with some increase in the insulin dosage, both ACTH and cortisone may be administered to diabetics.

It is now known that, in addition to their unexplained action on the collagen diseases, these hormones also have an inhibitory action on inflammation, exudation, neo-vascularization, and the fibroblastic reaction, and various warnings and speculations have been advanced regarding their final effect in certain infectious diseases. Thus Armstrong and Irons (1951) warned that

when the inflammatory reaction has a defensive action, that is when infection exists in the inflamed tissue, the action of ACTH and/or cortisone can be clearly deleterious.

Similarly, in the discussion of Olson's paper in June, 1950, Swan stated

much remains to be determined about the dosage and side-effects, and the possibility of delayed or indirect effects has scarcely been investigated.

The validity of these warnings is now becoming apparent. In deep infections of the cornea and in granulomatous disease of the uveal tract, the essence of infection is the invasion of the tissues by the exciting micro-organisms, with resulting damage to the cells by bacterial toxins or by a secondary allergic reaction to bacterial antigens. The essence of resistance or healing is bacteriostasis with immobilization of the invading organisms, followed either by their destruction through phagocytosis or their encapsulation by a fibroblastic reaction. The final tissue repair is by fibrosis.

Experimental evidence indicates that when ACTH and cortisone suppress inflammation they do so irrespective of whether it is due to the hypersensitivity reaction, to irritants, or to infection. In some unknown manner they place a shield between the noxious agent and the cell. In so suppressing the inflammation secondary to infection, the accompanying mobilization of phagocytic cells and fibroblasts is likewise suppressed. Thus the fibroblastic reaction and neo-vascularization are impaired and healing is delayed. It has been shown experimentally that treatment with cortisone may radically alter the entire pattern of tuberculous ocular disease, and it seems probable that the suppression of phagocytosis and fibrosis is intimately concerned in the reversal of the picture from a restrained process to a destructive one.

There appears to be considerable evidence that the inhibition of neo-vascularization, fibrosis, and phagocytosis by hormonal therapy has an adverse effect in clinical ocular disease. At a recent meeting of the Study Section of the National Institutes of Health and the American Venereal Disease Association in Washington, D.C. (April, 1951), it was clearly brought out by several speakers that when cortisone was properly used in the early stages of the interstitial keratitis of congenital syphilis, its use was followed by a prompt relief of all inflammation, a clearing of the interstitial corneal infiltrates, and a prevention of the vascularization phenomena. These immediate results in early cases are incontestable. However, if the keratitis has advanced to the stage of corneal necrosis before treatment is started, the use of cortisone has little or no effect, and treatment at this stage may actually retard the final healing of the keratitis by inhibiting vascularization and fibrosis. A study of some of the early treated cases indicated

that prolonged treatment may be necessary to prevent immediate recurrences; how long is as yet undetermined. In the Wilmer Institute series are several cases which have been under treatment for a year or longer; while under local cortisone treatment the eyes remain white and free of inflammation, but, if a minimum of treatment is stopped, the eyes again exhibit evidences of returning inflammation within 72 hrs. In these cases the stimulus for inflammation, whatever it may be, is still present. Other experimental studies (Chesney and Woods, 1944) have also shown that an immunity of the cornea to reinoculation with *Treponemata pallida* accompanies the development of the vascularization cycle, and it has been suggested that the vascularization *per se* is responsible for such immunity. It therefore may well be that the inhibition of vascularization in the cornea in interstitial keratitis is not desirable from the viewpoint of local healing or of preventing recurrences. Indeed syphilologists and ophthalmologists doubt whether cortisone therapy in interstitial keratitis is a justifiable procedure (Woods, 1951b).

The high incidence of recurrences of granulomatous uveitis after apparent primary control of the disease by adrenal cortex hormone therapy has already been mentioned. In many of these cases there is a notable absence of the usual glial scars. It is well recognized that a large percentage of such granulomatous uveitis is tuberculous, various investigators placing the incidence from 10 to 40 per cent., while some German authorities believe it to be still higher. In tuberculous eyes many of the recurrences observed after the termination of hormone therapy may be rebound phenomena such as occur in experimental animals. No histological material from patients is yet available for study to confirm this supposition, but clinical evidence supports the idea that such phenomena do occur in man. Two patients at the Wilmer Institute suffering from undoubted tuberculous choroiditis, were both treated energetically with cortisone to control the choroidal inflammation and exudation, and at the same time they were given streptomycin with either promizole or *para*-amino-salicylic acid as the adjuvant. In both there was an immediate satisfactory circumscription of the exudates and clearing of the vitreous, with resolution of the lesions and absorption and disappearance of the exudates. The patients were discharged after about 42 to 60 days of treatment with streptomycin and the adjuvant. Within one week one patient returned with a violent exacerbation around the original lesion, and within 6 weeks the second patient returned in the same condition. Fortunately, in both instances, the disease was again controlled by prolonged streptomycin and adjuvant therapy. It seems probable that in both the violent recurrences were rebound phenomena, here probably delayed by the streptomycin and adjuvant therapy. Reasoning from experimental results, one may assume that inhibition of phagocytosis and fibrosis by cortisone may have been intimately related to the prompt recurrences.

Whether the inhibition of inflammation, phagocytosis, and fibrosis by hormonal therapy operates adversely in other forms of granulomatous uveitis (those due to *Brucella*, fungi, *treponemata*, viruses, etc.) remains an open

question. In the meantime, the moral of the present clinical and experimental observations seems clear. When tissues are actually infected with pathogenic organisms the inflammatory reaction to infection is a defensive mechanism. It should not be interfered with or inhibited unless there is reason to believe that the infection will be overcome by the natural factors of resistance, or by specific chemotherapeutic or antibiotic measures, or unless there is a secondary hypersensitive reaction which in itself threatens destruction of vision. In such cases, ACTH or cortisone may be given to control both the subjective symptomatology of the disease and the secondary allergic inflammation around the lesions. However, if there is no promise of natural or induced recovery and the secondary allergic reaction is not unduly threatening, then the natural pattern of the disease had best not be disturbed by ACTH or cortisone therapy. If such patients are so treated without proper adjuvant therapy such treatment must be guarded, otherwise the patient may be deprived of the normal inflammatory defence mechanism. This is certainly true in tuberculosis, probably so in syphilis, and possibly so in other chronic infections of the eye. In such granulomatous infections ACTH or cortisone should either not be used at all, or, if employed to control an alarming secondary allergic reaction, their use should be guarded, never prolonged, and recognized as a calculated risk.

Comment

The remarkable action of the adreno-cortical hormones on ocular inflammation was greeted by ophthalmologists with almost incredulous enthusiasm. As this enthusiasm has gradually subsided and more information has been obtained, understanding of the actual therapeutic application of these hormones, of their limitations, and of the contraindications for their use is taking shape. There is still much to be investigated in certain specific conditions, but the broad principles of their therapeutic action are becoming clear. They are not curative agents; their action is limited to a control of the exudative and inflammatory phases of disease, and even here their therapeutic range is limited. The salient question to be considered before they are used is whether the control of inflammation, with all its accompanying phenomena, is a desirable aim? In many cases, notably allergic reactions, the answer is an unequivocal "Yes"; in others, notably uveal tuberculosis, it is usually an equally positive "No"; in a large group of chronic infections it remains an open question. In this last group these hormones will usually give early symptomatic relief, but against this favourable action must be weighed the attendant disadvantages: inhibition of fibrosis, phagocytosis, and neo-vascularization. If specific therapeutic procedures are available to compensate for the loss of these reparative phenomena, then the symptomatic relief these hormones afford may well be a blessed thing for both patient and ophthalmologist. On the other hand, if no adequate accessory therapeutic procedures are available, then the natural pattern of the disease and defence mechanism had better not be unduly disturbed.

How these hormones control exudation and inflammation is still a fascinating mystery. It now seems clear that their action in this respect is quite independent of any general physiological influence they may exert, and that they act at the cell level. That they may act through depressing the local permeability of the capillaries is a pleasant thought, but the evidence in favour of such a supposition is still far from convincing, and, though such depression of capillary permeability may enter into the picture, it is probably far from being the entire story. L. W. Kinsell, at a recent conference sponsored by Merck and Co., suggested three possibilities:

- (1) That these hormones act by freeing lysins from eosinophils, large mononuclears, and other cells.
- (2) That they act at the level of the cell membrane, placing a block between the toxin and the cell protoplasm.
- (3) That they act within the cell, from some action on an enzyme system.

Turner and Hollander (1950) suggest that the local changes produced by these hormones are based primarily on an alteration of the mucopolysaccharides of the ground substance which is manifested by an accumulation of hyaluronic acid and suppression of chondroitin sulphate.

Certainly the true answer is not yet apparent. Perhaps, for the time being, we had best temporize and accept the all-embracing but somewhat meaningless explanation that they act at the cell level through some as yet unknown action upon the mesenchymal tissue.

Summary

(1) ACTH and cortisone have a definite but limited role in ophthalmic therapeutics. Their favourable action is limited to the control of inflammation and exudation. They have no antibiotic or chemotherapeutic effect, and act not on the cause of disease but on the reaction of the tissues to a cause or irritant.

(2) When ocular inflammation is the result of acute trauma—allergic, toxic, or physical—the reaction of the tissues is usually self-limiting, and the control of inflammation over the natural life of the tissue reaction may simulate a complete cure. These hormones therefore find their highest usefulness in allergic reactions of the external eye and non-granulomatous inflammations of the uveal tract.

(3) In chronic granulomatous uveitis, the effect of these hormones is not so spectacular. Recurrences after cessation of treatment are frequent.

(4) When employed to suppress the inflammatory reaction due to chronic infection of the tissues, their use should always be accompanied by specific antibiotic or chemotherapeutic procedures to eliminate the basic underlying infection.

(5) They have no effect in the usual degenerative diseases of the eye. There is a possibility, however, that they may be effective in ocular disease related to fibrinoid degeneration.

(6) The use of cortisone, and probably of ACTH, is usually contra-indicated in any form of ocular tuberculosis; the hormones should be used with great caution in chronic granulomatous infections.

(7) In disease of the external eye and anterior ocular segment, the treatment of choice is the topical use of cortisone, either as an ointment or as a collyrium.

(8) In disease of the posterior ocular segment, parenteral ACTH or cortisone is preferable. In severe resistant cases, intravenous ACTH may be indicated.

(9) Experimental studies, using various ocular reactions as the indices, have shown that :

(i) Topical or parenteral cortisone and parenteral ACTH will:

- (a) suppress various recognized ocular hypersensitivity reactions,
- (b) suppress ocular reactions due to irritants,
- (c) suppress inflammation due to infection,
- (d) inhibit neo-vascularization of the cornea,
- (e) reduce fibroplastic activity in the stroma of the cornea and regeneration of the corneal endothelium;

(ii) Cortisone and Compound F will radically alter the pathogenesis of ocular tuberculosis, changing the picture in the immune-allergic rabbit from a restrained fibrotic process into a necrotizing caseating destructive lesion.

(10) The mechanism of the therapeutic action of ACTH and cortisone in ocular disease is as yet undetermined. The present indications are that it is due to a direct action of the adreno-cortical hormones on the mesenchymal fraction of the inflamed tissue.

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