COMMUNICATIONS

THE CLINICAL VALUE OF CORTISONE AND ACTH IN OCULAR DISEASE

A Preliminary Assessment for the Medical Research Council

BY

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SUFFICIENT has now been written in a literature already large and rapidly growing, and at the same time readily accessible, to make it unnecessary here to summarize the story of the isolation of the potent steroids elaborated in the adrenal cortex and the dramatic results of their application to a number of pathological conditions, particularly the collagenous, allergic, and lymphatic diseases. The object of this paper is to provide an assessment of the clinical value of these substances in the restricted field of ophthalmology, so far as this is possible at this early stage, the material on which it is based being derived partly from the literature and partly from the experiences of a team of investigators in Great Britain whose activities have been correlated by the Medical Research Council.

It will be sufficient to say in parenthesis that while of recent years a considerable amount of work has been done on the chemistry of the steroid substances elaborated by the adrenal cortex, particularly by Wintersteiner and Pfiffner (1935), Mason and his colleagues (1936–40), and Kendall (1940), the interest in this work was considerably increased by the demonstration of their clinical effect upon patients suffering from adrenal disorders such as Addison's disease (see, for example, Sprague and others, 1948–49; Thorn and others, 1949); it was again increased, on this occasion to a much more dramatic extent, by the revolutionary results published by Hench and his associates (1949–50) on their use in the treatment of patients suffering from rheumatoid arthritis at the Mayo Clinic. The widespread effects thus obtained depend essentially on those steroid hormones elaborated by the adrenal cortex which have an oxygen atom attached to the 11th carbon atom of the parent steroid nucleus (the C-11 oxygenated steroids) of which the most potent is cortisone (17-hydroxy-11-dehydrocorticosterone or compound E). This substance itself may be given to produce these effects, or somewhat

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similar clinical responses may be obtained by stimulating the adrenal cortex to elaborate an unusual amount of active steroids by the administration of the pituitary adrenocorticotrophic hormone, ACTH (see Hechter, 1950; Mason, 1950).

METABOLIC ASPECTS.—It would not be expected that substances so powerful would fail to exercise profound disturbances on the metabolism of the body: a knowledge of their “side-effects” is therefore of importance. In the first place the prolonged administration of cortisone depresses the normal adrenal function even to the extent of causing atrophy of the gland, while exogenous ACTH similarly depresses the normal elaboration of this substance by the pituitary gland, an effect, however, which is usually rapidly made good when the administration of the hormone ceases. During the administration of either substance the main metabolic consequences are as follow (see, for example, Sprague, Power, and Mason, 1950; Mote, 1951):

(1) An impairment of the carbohydrate tolerance so that glycosuria may be induced or diabetes rendered more symptomatically pronounced. It is interesting that in the adaptation syndrome induced by large doses of adrenocortical extract, Pentini and Fornaro (1950) found an increase of glucose in the aqueous humour which was inhibited by the administration of ACTH.

(2) An alteration in protein metabolism involving increased breakdown and impaired resynthesis, together with an increased renal excretion of nitrogen as uric acid and creatinine.

(3) An increased mobilization and utilization of fat leading to the characteristic “moon-face”.

(4) A disturbance in the distribution of electrolytes and water, the most important manifestations of which are an increased excretion of potassium leading to a deficiency of this substance in the blood, and a retention of sodium and water resulting in an increase in the volume of the plasma and extracellular tissue-fluid.

(5) A lysis of fixed lymphatic tissue together with a diminution of circulating eosinophil cells.

(6) Complementary effects on the other endocrine organs may become apparent, mainly androgenic in nature, changes which on prolonged administration may simulate Cushing's syndrome associated with basophil pituitary tumours.

(7) Finally, mental effects, characteristically euphoria during the administration of these hormones followed by depression on their sudden cessation, may sometimes become obvious.

THERAPEUTIC ACTION.—The mechanism by which these substances exert their powerful therapeutic action is yet unknown, but some of the most obvious effects on the inflammatory process have been established: capillary permeability, for example, is decreased, cellular exudation is reduced, the formation of granulation tissue, the

fibroblastic reaction in healing, and the formation of new vessels are inhibited. At which level these effects occur is again unknown; presumably, however, the hormone becomes effective at the tissue-level where the inflammatory responses to irritation are (within limits) temporarily blocked. In the eye, this inhibition affects not only the ocular inflammatory response to direct organismal infection (Leopold and others, 1951) or anaphylactic or allergic reactions arising therefrom (Woods, 1950; Biegel, 1951), but also to non-bacterial irritants injected into the eye, such as glycerine or jequirity (Woods, 1950), or talc (Bourquin, 1951). It is to be remembered that the hormone is in no sense bactericidal, and it has been amply demonstrated, particularly in the eye, that it has no effect on the hypersensitive state, for although it blocks the inflammatory evidences of an anaphylactic or allergic reaction, once it is withdrawn the ocular tissues react in their previous hypersensitive manner if contact with the specific antigen is re-established (Woods, 1950, with the ocular reaction to tuberculin; Biegel, 1951, with horse serum uveitis in rabbits).

While thus profoundly affecting the reaction of mesenchymal tissues to irritants, organismal and otherwise, *cortisone does not affect the cause of any disease process but merely provides susceptible tissues with a temporary protection against it*, so that the tissue-cells, rendered more resistant to injury, are allowed to function normally in an environment which had become grossly abnormal: in Hench's picturesque words, it acts as a fire-shield but neither puts out the fire nor acts as a carpenter to repair the fire's damage. The effect is thus limited—a fact which is not yet generally recognized—to the blocking of the pathological evidences of inflammation so long as the administration of the hormone is continued; on its withdrawal the disease forthwith resumes its natural course, and it is without effect on the structural damage to the tissues previously caused by disease.

It is true that in an organ composed of tissues so delicate as the eye, in which the maintenance of optical transparency is a necessity for function, the inhibition of an inflammatory reaction may be of the first importance even when considered as an emergency measure, but it has not been established that, particularly in the presence of organismal infection, the inhibition of the tissue-response to injury—essentially protective in its function—is always without disadvantage or even danger. There is evidence, for example, that the resistance to tuberculous infection may be lessened and the spread of tuberculosis may be facilitated by the suppression of fibrosis while the causal organism still lives (see, for example, Woods, 1951; Lurie and others, 1951). *The ideal therapeutics is the control of the deleterious aspects of the inflammatory response until such time as the infective or other causal agent is eliminated by other means.* Thus

the acute exudative manifestations of a gonococcal iridocyclitis can be held in check until the infection is controlled by antibiotics and the eye may thus escape unscathed; but, unfortunately, this is an ideal rarely attainable.

In certain respects the response to cortisone resembles that to fever therapy by "protein shock" and, indeed, there is evidence that the latter method of therapeutics acts by stimulating the adrenal cortex to secrete steroids (Olson and others, 1950; Arendshorst and Falls, 1950).

Ophthalmic Experiences with Cortisone and ACTH

Although numerous papers on the clinical effect of cortisone and ACTH in ophthalmological diseases have appeared, many of them are of comparatively little value, suffering as they do from paucity of material, from lack of or inadequacy of clinical detail and controls, and—perhaps most important of all—from absence of follow-up observations. Most of the follow-up histories in the literature do not exceed a few months: some of them are measured in days. In view of the short time these drugs have been available and the relatively small quantities in which they can as yet be obtained, this is, of course, to some extent unavoidable, while the dramatic nature of some of the results obtained, and the enthusiasm this apparent revolution in therapeutics has excited, have undoubtedly—and rightly—served as a stimulus to early publication. It may be worth while, however, to summarize the present position and to assemble the evidence now available, since it is becoming obvious that there is general unanimity over certain broad considerations concerning the methods of administration of these substances in ophthalmic conditions, their suitability in some, their unsuitability in others, and their limitations in all types of ocular disease. It must be emphasized, however, that even in those conditions wherein the value or uselessness of cortisone has been most readily agreed upon, any such assessment at the present time must be considered provisional and perhaps premature.

For the purposes of this assessment, those papers available in the ophthalmic literature, some ninety in all referring to approximately 1,500 cases, have been collated; but particular attention has been paid to reports from five centres whence the most comprehensive reports have emerged—

Baltimore (a series of 117 cases, 69 treated topically with cortisone and 48 systemically, with either cortisone or ACTH, Woods, 1951);

New York (315 cases, 198 treated topically, 109 systemically, and 8 by a combination of the two methods, Gordon and McLean, 1950; McLean, Gordon, and Koteen, 1951);

Philadelphia (265 cases: 142 cases, Leopold and others, 1951; and 123, Scheie and others, 1951);

Chicago (198 cases treated locally and systemically, Fitzgerald and others, 1951);

Dublin (143 cases, mostly treated topically, Lavery and others, 1951).

These results have been compared with our own series of 416 cases reported elsewhere in this issue (Duke-Elder and others, 1951), and the results have been compared—in all, an assessment of approximately 1,900 cases. In quite a large number of conditions there is little statistical difference in the results observed, and since the results obtained at different clinics supplement each other in the number of cases of different conditions treated and in methods of administration, the general picture is of considerable value.

METHODS OF ADMINISTRATION

In the treatment of ocular disease, cortisone may be administered in two ways—locally or by systemic injection; ACTH, of course, inasmuch as it acts by stimulating the adrenal cortex, is of value only as a systemic injection.

The question of the relative value of the local and systemic treatment of diseases of the eye with cortisone is most satisfactorily answered by those who have been in a position to assess the effects of each in large numbers of patients. Both Woods (1951) and McLean and others (1951), who, between them, have reported on 142 cases treated systemically and 255 treated locally, are in general agreement that there is little difference between the two methods of administration in diseases affecting structures to which cortisone administered locally can readily be brought into contact in sufficient concentration to have a therapeutic effect. On the whole, local treatment seems to be preferable in diseases of the conjunctiva, sclera, cornea, and the anterior segment of the uveal tract. In diseases of the posterior segment of the eye (or in generalized uveitis), systemic treatment is indicated. Our own experience amply confirms the relatively negative effect of local treatment in the latter class of case. Assuming that the greater part of the cortisone administered locally becomes available to the anterior segment of the eye, the greater efficiency of local treatment is not surprising, since in terms of ocular weight compared with total body weight, the concentration of hormone in the usual doses employed should be many hundred times greater than the amount that can safely be made available by systemic therapy.

Apart from therapeutic efficiency, local administration has the considerable practical value of having no demonstrable systemic reactions or ill-effects, so that patients can receive relatively large doses over an indefinite period without fear of complications, and can be treated without the constant clinical control or hospitalization

advisable during systemic treatment, apart from the obvious economic advantage that this treatment requires very much smaller quantities of a drug which is both scarce and expensive. Longer, safer, cheaper, and ambulant treatment is thus attained.

LOCAL TREATMENT.—As supplied commercially, cortisone acetate is almost completely insoluble in saline; on subconjunctival injection the material can be seen to remain *in situ* from 5 to 10 days and sometimes up to 14 days. It is difficult to imagine that the relatively insoluble hormone can be absorbed into the eye in any quantity, but its local action is undoubted and may be very rapidly clinically apparent: whether it exerts these effects by direct absorption or by the intermediary of break-down products, is unknown. The work of Steen (1951), reported in a subsequent paper in this issue, on the behaviour of cortisone in tissue-cultures suggests that the latter assumption may prove to be correct.

That active material does penetrate into the eye has been proved by Leopold and others (1951) in rabbits, using alkali 2, 3, 5, triphenyl tetrazolium chloride as a reagent which produces a red colour in the presence of the active sterol. These workers found that the best penetration into the aqueous as tested by this means was obtained by subconjunctival injection; the instillation of drops was not so effective, but the penetration obtained thereby could be improved by the addition of a wetting agent such as zephiran. It is to be noted that active material was apparent in the vitreous after retrobulbar injection.

The tissue-reaction following the injection of cortisone was studied by the same authors. Histological studies carried out at varying periods after subconjunctival and retrobulbar injection showed that it was minimal in degree—no greater in fact than was obtained after an injection of saline. Similarly, an injection of cortisone into the anterior chamber or the vitreous body in rabbits produced no deleterious effects apart from mild evidences of irritation (Leopold and others, 1951; Bourquin, 1951).

In this connection it may not be without interest to note that a transient *irritative or allergic reaction* to the local administration of cortisone has been noted by a few observers (McLean and others, 1951; Dubois-Poulsen, 1950; Bourquin, 1951). In our series of 416 cases, two showed an irritative reaction to cortisone injected subconjunctivally: in one (cyclitis) there was considerable chemosis on the fifth injection, and in the other (superficial punctate keratitis) the reaction was violent and the conjunctiva threatened to slough.

Local treatment may be made available by the following methods:

(1) *Drops.*—The undiluted commercial (Merck) suspension (25 mg. per ml. saline suspension of cortisone acetate with 1.5 per cent. benzyl alcohol as a preservative) may cause some transient irritation when instilled into the eye, particularly if it is inflamed. The usual collyrium therefore

recommended is a 1:4 dilution of the commercial preparation in saline. In our experience there would seem to be little or no clinical advantage in using the undiluted preparation, a finding confirmed by Woods (1951) (who used a 25 per cent. concentration) and McLean and his co-workers (1951) (a 10 to 20 per cent. concentration). In our clinical work we have employed as a routine a buffered diluent to make a 1:4 solution; this is completely non-irritant even if the undiluted suspension is used. Its composition (suggested by A. C. Woods) is as follows, in quantity sufficient to make 1,000 ml.:

Sodium acid phosphate with one molecule water	...	4.6 g.
Sodium phosphate anhydrous		4.7 g.
Sodium chloride		4.8 g.
Benzalkonium chloride		1:5,000 q.s.

Merck and Co. have prepared for experimental use a special ophthalmic suspension in a similar buffered phosphate vehicle with 1:5,000 alkoninium hydrochloride added as preservative. This would appear to be soothing rather than irritative to an inflamed eye (Woods, 1951).

Initially in an acute case the recommended dosage is one drop every hour throughout the day and every 2 hours throughout the night; as symptoms subside the frequency of dosage is decreased to 3 or 4 times during the day and irregularly through the night. The application of an eye-pad after instillation possibly enhances absorption. The disadvantage of this method is the disturbance caused by frequency of the applications.

(2) *Ointment*.—To obviate this frequency various ointments have been supplied by Merck and Co. The first was a simple cortisone acetate ointment (25 mg. per g.) in a vaseline base; subsequent bases employed have been lanolin and aquaphor which are said to give better clinical results (Woods, 1951; Fitzgerald and others, 1951). In view of the insolubility of the acetate, similar ointments using the more soluble cortisone-21-hemisuccinate have been tried, but experiments on animals have shown that these are only about one-half as efficacious as the acetate despite the relative insolubility of the latter (Woods, 1951).

We have had no opportunity of using these ointments but they have been employed elsewhere on a considerable scale (for example, by Woods, 1951; Lavery and others, 1951; Arruga, 1951). It would seem that, in addition to the avoidance of the nuisance of repeated instillation, the effect is equal to, if not more constant than, that of drops. The routine recommended by Woods (1951) in the acute stage is 3-hourly applications during the day and immediately before retiring, an eye-pad being applied during the night, and the intervals being lengthened as a therapeutic response is obtained.

(3) *Subconjunctival Injection*.—In our experience this is the method of choice for the treatment of intra-ocular inflammations affecting the anterior segment. After local anaesthetization, an injection of 0.2 to 0.4 ml. of the commercial suspension (25 mg. per ml. cortisone acetate) is made well behind the limbus and repeated at 2 to 4 days' intervals at other sites. Maintenance doses can be repeated at weekly or longer intervals.

(4) *Retrobulbar Injection*.—Such injections in comparable doses have been tried in the hope that they would similarly affect inflammatory diseases of the posterior segment. They have sometimes been found to produce a considerable reaction (ten cases, Leopold and others, 1951); at other times they have been readily borne (Offret and Forest, 1950). We have found little disturbance with *intra-tenon injections*, but the relative efficiency of the two methods of administration is somewhat academic since neither is of great clinical value.

(5) *Intracameral Injection*.—This method has been less frequently employed, but it has been found that the injection of 0.3 ml. of the commercial suspension into the anterior chamber after withdrawal of the aqueous is without irritative or other deleterious effects (Offret and Forest, 1950–51): sometimes the cortisone disappears rapidly within a few hours, and at other times the suspension remains visible in the anterior chamber for 7 days.

SYSTEMIC TREATMENT.—In ocular affections this type of therapy—indicated particularly in diseases of the posterior segment of the eye—follows general lines. There seems to be little difference between the effects of cortisone and ACTH so far as their action on pathological processes in the eye is concerned, although, according to Woods (1951), the initial effect of the latter may be evident earlier (within 12 hours) than that of the former (24 to 48 hours).

A full course of cortisone may be taken to average the parenteral injection of 300 mg. on the first day, 200 mg. on the second day, and 100 mg. on the next 7 days, to be followed, if necessary, by maintenance doses, sometimes advisedly given as intermittent courses, of 50 mg. daily which can well be administered by mouth. Such subsequent dosage can be increased, if necessary, to control a recrudescence of symptoms.

ACTH is usually commenced with a daily dose of 100 to 120 mg. which must be divided into 6-hourly periods owing to the rapid destruction of the hormone. Depending on the therapeutic response obtained and the systemic reaction excited, this may (occasionally) be increased initially to 200 mg., or (more usually) after the first 3 days may be reduced to 80, 60, 40, and finally 25 mg. daily, the final dose being maintained, or if necessary increased, to control the condition.

In view of the widespread metabolic effects which we have already noted after the administration of these hormones, it follows that large or long continued parenteral dosage should only be undertaken with care and under close clinical supervision lest the balance between noxious metabolic effects on the one hand and the adequate control of an inflammatory process on the other become precarious or be dangerously upset. The most simple and practical criterion whereon to base a clinical appreciation of the effectiveness of these hormones is the fall in the blood-eosinophil count: a diminution of these cells indicates the activity of the hormones, and their disappearance should lead to further enquiry. In general, the

eosinophil count should show a diminution of approximately 50 per cent. until the disease is under control: if, despite such a drop, the inflammatory symptoms of the disease are unaffected, the general view is that the treatment can as well be discontinued. During treatment, a watch should be maintained for evidence of glycosuria, hypertension, cardiac changes, fluid retention, or mental changes. During long-term therapy, tissue-atrophy may be prevented by the administration of testosterone, glycosuria or diabetic acidosis by insulin, oedema by a very low intake of sodium chloride in the diet, and hypopotassemia and metabolic alkalosis by the administration of potassium.

Contraindications to the systemic administration of cortisone or ACTH except under rigorous control are diabetes, hypertension, chronic nephritis, and psychotic states. Thus in diabetes insulin has usually to be increased but treatment may be carefully continued (Woods, 1951); in hypertension occlusion of a retinal artery with loss of vision has occurred (Frenkel and others, 1951); and several experiences of trouble with the mentally unstable have been recorded. Fortunately, however, the fact that local administration is effective in many ocular diseases simplifies greatly the problem of the complications which may occur during systemic therapy.

Results of Treatment in Various Types of Ocular Disease

I. INFLAMMATORY DISEASES OF THE EYE

A survey of the literature and experience with our own cases make it clear that certain general principles characterize the response of inflammatory diseases of the eye to treatment by cortisone.

In the *initial acute phase* of ocular inflammation, symptomatic relief is early and obvious, while the congestive and exudative phenomena characteristic of the inflammatory reaction can frequently be temporarily controlled in a manner which, in its rapidity and effectiveness, is so dramatic that it is equalled by no other therapeutic agent at our disposal. This blanketing of the inflammatory response, however, lasts only so long as the treatment continues. If the disease has a short natural course, therefore, the results may be excellent, and if the cause of the inflammation, whether organismal, allergic, metabolic, or otherwise, can be eliminated before the cessation of treatment, this method of therapy is undoubtedly an ideal adjuvant to measures directed against the specific aetiology. If, however, this is not possible and the cause of the inflammation persists, a relapse is almost certain to occur on the cessation of treatment, so that the final stage appears to be little altered from what would have been expected if cortisone had never been given, except that the tissue-damage due to the acute phases of the

inflammation may be eliminated. It is important, however, that on further treatment such relapses tend to respond, as did the initial condition, although larger doses of the hormone are usually necessary for their control.

In *chronic inflammations*, much the same type of response is evident, for here the active exudative phenomena are again controlled, but, on the whole, the inflammatory process tends to persist even during treatment, although at a lower grade of activity. Again, on the withdrawal of treatment, the eye tends to return to its initial state. Where chronic disease has left organic sequelae (adhesions, organized exudates, etc.), these are unaffected.

In all cases, the reaction to cortisone is not absolute in its nature, nor is it characterized by an all-or-nothing response. In each individual the therapeutic effect depends on:

- (1) the severity of the inflammatory process,
- (2) the size of the dose of hormone,
- (3) the reaction of the individual to the hormone.

In most cases of early inflammation, the clinical evidences may be brought rapidly under control, but if the injury to the tissues is extreme, cortisone will not necessarily eliminate the inflammatory response although it may greatly modify it. We shall see that the same graded response is evident in the pathological studies reported in later pages in this Journal. However, a remission of the inflammatory reaction during an acute phase is of particular importance in the eye, for it may mean the difference between the possibility of continued function and blindness.

Small doses, in terms of either quantity or frequency, may only modify the clinical evidences of inflammation, while in the same disease or in the same case, larger doses may block the inflammation entirely.

Individuals vary in their response to both local and general treatment, even although the disease is apparently very similar. A particular type of inflammation may, on the whole, show a markedly favourable response to cortisone, but in occasional cases no relief is obtained. The reason for this is not clear. Moreover, attempts to relate the response to the aetiology of an inflammatory process have so far led to no very determinate conclusions. In a general study of the material available, one thing is particularly impressive—early inflammation gives the best response no matter what its aetiology.

There is no question that this blanketing of the acute exudative phases of inflammation does occur and that the amelioration must be attributed to cortisone. In clinical medicine controls are notoriously difficult to arrange, but in ophthalmic medicine the difficulty is more readily overcome. Thus we have seen that a first

attack of acute iridocyclitis can almost invariably be aborted. But among our observations, in cases of bilateral iridocyclitis wherein the two eyes were equally affected, the local treatment of one has been followed by its rapid resolution, while its fellow, treated similarly apart from the administration of cortisone, has behaved in the torpid way characteristic of this disease. In bilateral cases when the worse eye alone has received this treatment it has promptly become the better. Finally, a condition which wrought havoc with one eye on a previous occasion has been seen to be aborted in the fellow eye which, before treatment, gave every clinical indication of running an identical course.

Thus, in one case associated with diffuse articular disease of the Marie-Strümpell type, one eye had 18 months previously suffered a severe attack of generalized uveitis with a gelatinous exudate filling the anterior chamber and a complete exudative detachment of the retina with resultant blindness. The other eye became affected in an exactly similar way with an acute exudative uveitis, and at the stage when the anterior chamber became full of the same type of gelatinous exudate, cortisone was administered, with the result that within 3 weeks the eye was quiet and giving rise to no anxiety. The drama of a similar comparison was observed in a case of sarcoidosis: one eye had been excised three years previously; the other, starting with a similar severe granulomatous iridocyclitis, was quiet with 6/9 vision within 4 weeks of beginning cortisone treatment and has remained without relapse for 10 months.†

(A) Intra-Ocular Inflammations

(1) UVEITIS

(a) IRIDOCYCLITIS (ANTERIOR UVEITIS).—Of all intra-ocular inflammations most experience has been obtained with iridocyclitis.

Apart from the special categories of uveal inflammation described below, 291 cases are available in the literature of iridocyclitis, with which 145 of our own can be compared (Rome and others, 1950; Desvignes and others, 1950; Dubois-Poulsen, 1950; Hartmann and others, 1950; Harvey and others, 1950; Mann and Markson, 1950; Steffensen and others, 1950-51; Spies and Stone, 1950; Koff and others, 1950; Michaud and Forestier, 1950; Calamandrei and Ferrata, 1950; Ferrata and Calamandrei, 1950; Posner, 1950; Moutinho, 1950; Henderson and Hollenhorst, 1950-51; Offret and Forest, 1950-51; Woods, 1950-51; Olson and others, 1950-51; Arruga, 1951; McLean and others, 1951; Lavery and others, 1951; Scheie and others, 1951; Mosher, 1951; Fitzgerald and others, 1951; Leopold and others, 1951; Barrios and Barrière, 1951; Werner and Lavery, 1951; Jensen and Ward, 1951; Brückner, 1951; Hogan and others, 1951; Bernasconi Cramer and others, 1951; Engelman and others, 1951).

Acute Iridocyclitis.—This gives the most dramatically favourable response of all intra-ocular inflammations, and it may be said in general that in this disease cortisone is more effective in temporarily reducing clinical symptoms and signs than any method of therapy known to-day. It would seem to matter little whether the treatment is by systemic or local administration. On the whole, local treatment would seem to be better, and in our experience subconjunctival

injection is the most effective method of therapy. Only occasionally has it been found that systemic treatment has been effective where local treatment has failed (Steffensen and others, 1951). If treatment is begun in the early stages of the disease, few cases show no response. Of all the cases of acute iridocyclitis reported in the literature (252) only some 12 per cent. were classified as failures, while a further 12 per cent. relapsed after cessation of treatment. In our series, the response in a first attack of acute iridocyclitis was invariably good (21); in a second or in subsequent attacks (33) the same degree of resolution was not so frequent, but practically all cases showed some degree of improvement (rapid in 20, slight in 9), and only four failed to show any response. In 42 subacute cases the response was more variable: ten showed rapid improvement, 26 slight improvement with accentuated resolution, and six no response. Of the entire series of 96 cases of acute and subacute iridocyclitis only 16.4 per cent. were complete therapeutic failures.

In cases brought under control in this way at an early stage of the malady, the relief of the subjective symptoms of pain, photophobia, and lacrimation is sometimes rapid, occasionally occurring within a few hours but more usually within 24. Soon thereafter, frequently from 24–48 hours from beginning the treatment, the objective signs of inflammation tend to disappear—ciliary injection, oedema of the iris, aqueous flare, cells in the anterior chamber, fresh keratic precipitates, and even fine dust-like opacities in the anterior part of the vitreous. Severe haemorrhagic or fibrinous accumulations in the anterior chamber may fade away with a quite astonishing rapidity, and in a purely exudative case, symptomatic cure may appear to be complete after two or three subconjunctival injections given at 3 to 5 days' interval. The immediate effect, however, is limited to the disappearance of these exudative manifestations, and any granulomatous reactions—heavy cellular infiltration or gross exudative deposits in the tissues—remain.

Chronic Iridocyclitis.—This has received much less attention.

Only 39 cases are recorded (Dubois-Poulsen, 1950; Koff and others, 1950; Olson and others, 1950–51; Bernasconi Cramer and others, 1951; Arruga, 1951; Mosher, 1951; Fitzgerald and others, 1951). Our own series comprised thirty cases.

In this condition the response is very much less dramatic. In the usual case, although any active exudative evidences are lessened the disease tends to remain active or at any rate resumes its activity when the treatment is stopped, while such organized evidences of inflammation as posterior synechiae, organized keratic precipitates, old vitreous opacities, or pathological changes in the cornea or lens are quite unaffected.

Among specific forms of iridocyclitis, the GONOCOCCAL type seems to

respond very well, as also do SYPHILITIC cases. The RHEUMATIC types, forty of which are reported in the literature, show no difference from those of other aetiology in their clinical behaviour, although in this series relapses are more common and rise to a proportion of 25 per cent. with a short after-history of a few months. In general, the response seems to be less determined by a particular aetiology than by the duration or recurrent habit of the ocular inflammation. One case of LEPROTIC IRIDOCYCLITIS in our series showed a rapid subsidence of exudative phenomena although corneal opacities remained unchanged.

Recurrent Hypopyon Iridocyclitis.—The literature is somewhat barren in reports of this disease. One case suffered a rapid recurrence (Dubois-Poulsen, 1950) and a second failed to respond (Barrios and Barrière, 1951). Two cases in our series improved rapidly, the hypopyon in each case disappearing promptly. In two cases of Behçet's syndrome, however, no response was obtained.

Hypertensive Iridocyclitis.—This presents special problems. In the literature there are varying reports, and of the 26 cases of which the records are adequate seven did not respond to treatment. Thus some authors (Blake and others, 1950; Desvignes and others, 1950; Michaud and Forestier, 1950; Dubois-Poulsen, 1950; Henderson and Hollenhorst, 1950–51; Olson and others, 1950–51; Trope, 1951; Barrios and Barrière, 1951; Hogan and others, 1951) have found that cortisone is particularly effective in reducing the ocular tension in such cases. Others have found that approximately equal numbers of cases are relieved and unaffected (Woods, 1950–51; McLean and others, 1951). Our experience, which includes fifteen cases, has been that, if the hypertension is due to acute exudative phenomena, the pressure in the eye usually falls, at least temporarily, coincidently with the subsidence of the exudative phase of the inflammation; if, however, more permanent organized changes have become established, or if the angle of the anterior chamber is gonioscopically blocked, a fall in the tension is rarely apparent. In early cases of the former type, therefore, local cortisone is a very effective method of controlling this complication.

The development of hypertension as a complication of systemic treatment with cortisone has also been noted in cases of iridocyclitis. The precipitation of secondary glaucoma in this way, for example, was found by McLean and others (1951) in three out of thirteen cases of iridocyclitis, and in four out of twenty cases of general uveitis, four of which required surgical intervention. It is interesting that such a complication is much more rarely found when local treatment is employed. Thus McLean only encountered one such case in 27 thus treated. It is not clear why the systemic administration of cortisone should occasionally produce a secondary glaucoma, but it may be, as suggested by Woods (1950–51), that the complication is connected with the upset in the electrolytic balance caused by the hormone; more observations, however, are required with more fully detailed clinical (including gonioscopic) observations before the extent of this possible danger can be assessed.

(b) GENERAL UVEITIS.—The literature on general uveitis is much less extensive. Local treatment has been reported in 51 cases (Moutinho, 1950; Theodore, 1950; Henderson and Hollenhorst, 1950–51; Offret and Forest, 1950–51; Woods, 1950–51; McLean and others, 1951; Mosher, 1951; Moutinho and Basto, 1951), and

general treatment in 57 (Henderson and Hollenhorst, 1950-51; Woods, 1950-51; McLean and others, 1951; Scheie and others, 1951; Fitzgerald and others, 1951). The local treatment has included the instillation of drops, and injections subconjunctivally and retrobulbarly or into the anterior chamber. In the literature generally there is again little difference between the results of general and local treatment, the failures amounting to about 25 per cent. in each case. In our small series of four cases, the results were equivocal.

In general terms, in acute cases of generalized uveitis a remission may be achieved but this is usually incomplete. Even so, however, a disaster which may permanently incapacitate the eye may be thus averted. Chronic diffuse uveitis responds poorly. It is true that the exudative signs may be alleviated during treatment, but the disease persists, any remission is incomplete, and although a relapse with exudative features may be successfully quietened, the disease returns promptly to its original state after the cessation of therapy. The most favourable prognosis in this type of case would seem to be when systemic treatment is possible over a long period. In one such very recalcitrant case of ours complete resolution (apart from a few remnants of a dense cloud of vitreous opacities and a circumscribed complicated cataract) seems to have been attained after systemic treatment which was persisted in for 9 months.

Sarcoidosis.—Sones and his collaborators (1951) found in two cases of severe and widespread sarcoidosis that cortisone therapy produced a marked and steady regression of the lesions together with an amelioration of symptoms. The effect of such treatment on the ocular manifestations of this disease has been varied. Steffensen and others (1951), Mosher (1951), and Leopold and others (1951), together reported six cases treated locally: three improved and three remained unaffected. In our series three patients received local treatment, two of whom improved slightly and one dramatically.

The more chronic exudative forms of uveitis such as *Harada's disease* (Scheie and others, 1951; Leopold and others, 1951) or the *Vogt-Koyanagi syndrome* (Leopold and others, 1951) have invariably failed to respond to either local or systemic treatment.

Sympathetic Uveitis.—Seventeen cases of sympathetic ophthalmitis are reported as having been treated locally (Desvignes and others, 1950; Woods, 1950-51; Arruga, 1951; Mosher, 1951; Werner and Lavery, 1951; McLean and others, 1951; Lavery and others, 1951; Leopold and others, 1951), including three by intracameral injection (Offret and Forest, 1950-51); and 27 have been treated systemically (Harvey and others, 1950; Joseph and others, 1950; Hartmann and others, 1950; Howard and others, 1950; Woods, 1950-51; Offret and Forest, 1950-51; Vesterdal, 1951; Laws and Howard, 1951; McLean and others, 1951; Lavery and

others, 1951; Fitzgerald, and others 1951). To these our own series adds a further fifteen cases treated mostly by subconjunctival injection. It is important to remember that in the great majority of these cases the presence of a true sympathetic inflammation has not been histologically proved for this summary includes all those wherein evidences of an iridocyclitis with corneal precipitates developed in the other eye after an injury or operation to its fellow.

The anxiety caused by this type of case is too well known to require remark, and the tendency—quite rightly—up to the present time is to advise removal of the injured eye if it seems liable to cause trouble to its fellow. In general, it would appear that if cortisone is administered at an early stage when inflammatory evidences in the sympathizing eye have lately appeared, a complete cure (*so far as the available histories extend*) may be looked for in a comparatively short period varying from 5 days to 6 weeks. If, however, the disease is first treated in its later stages when the inflammatory process has become fully established, irritable phenomena may be controlled but inflammatory activity persists and relapses tend to occur on the cessation of treatment: established infiltration of the uveal tissue is, as usual, not dispersed. While an expression of opinion is dangerous on the basis of some sixty cases and rash without much longer follow-up histories, preliminary impressions lead to the hope that, if this disease is treated in its early stages, cortisone treatment may be capable of revolutionizing a prognosis which has almost invariably been gloomy. At any rate, even at this early date, we have already retained, so far with impunity, more than one eye which has received a perforating injury which, in pre-cortisone days, we should undoubtedly have excised.

(c) FOCAL CHOROIDITIS.—The literature reports a considerable number of cases of focal choroiditis, 51 treated locally (Woods, 1950–51; Arruga, 1951; Mosher, 1951; Guinan, 1951; Werner and Lavery, 1951; Barrios and Barrière, 1951; McLean and others, 1951; Lavery and others, 1951; Leopold and others, 1951; Scheie and others, 1951), and 77 treated generally (Hartmann and others, 1950; Steffensen and others, 1951; Offret and Forest, 1950–51; Henderson and Hollenhorst, 1950–51; Woods, 1950–51; Scheie and others, 1951; Fitzgerald and others, 1951; Lavery and others, 1951; Leopold and others, 1951). To these our own series adds eight cases treated locally.

It is obvious that the response of lesions in the choroid is very much less good than that of inflammations of the anterior segment of the eye, and it is also without doubt that in the former disease general treatment is more effective than local. With the systemic method of therapy, 25 per cent. of cases are recorded as failures; with local therapy, 40 per cent. It is noteworthy that, among the available methods of local treatment, retrobulbar injection seems to

have no greater efficacy than subconjunctival injections (Offret and Forest, 1950-51; Leopold and others, 1951).

In general terms, early cases of focal choroiditis show an initial favourable response with systemic treatment in the sense that the local exudative phenomena disappear in one or two weeks instead of several, and that the processes of repair start sooner. The surrounding oedema is controlled, keratic precipitates may disappear in a few days, and although the clearing of a haze in the vitreous has occasionally been recorded as being dramatic, the more usual effect in this respect is neither rapid nor particularly good; a functionless scarred area, however, remains. On the cessation of treatment relapses are by no means uncommon, when fresh haemorrhages and areas of oedema or even an extension of the inflammatory area may occur. Chronic choroidal lesions, on the other hand, are completely unaltered with any method of administration.

(2) RETINAL AND NEURAL INFLAMMATIONS

Inflammations of the uveal tract, particularly those affecting the anterior segment, tend to respond favourably to cortisone when treatment is instituted at an early stage, but inflammations affecting the retina and optic nerve appear to be more recalcitrant.

(a) CENTRAL SEROUS RETINOPATHY.—This condition, of both angio-spastic and allergic origin, has received, on the whole, favourable reports in the literature. Woods (1950-51), Olson and others (1950-51), and Fitzgerald and others (1951) treated seven cases systemically, all with favourable results, but the two failures reported by Scheie and others (1951) would indicate that this is not by any means invariable. So far as local treatment is concerned, Barrios and Barrière (1951) and McLean and others (1951) reported prompt and satisfactory recovery with a resolution of the oedema and a shrinkage of the central scotoma. Our series contains four such cases treated by subconjunctival injection, and our impression therefrom is that such prompt and complete resolution is by no means the rule. Some response is usually obtained, particularly if treatment is commenced in the early stages, but it must be remembered that such an evolution is frequently seen without cortisone therapy. Of the four cases, one relapsed subsequently, and the pigmentary changes in old cases were unaffected.

(b) LUPUS ERYTHEMATOSUS.—In one case, Ferriman and Wilsdon (1950) found that systemic treatment led to a rapid disappearance of the characteristic haemorrhages and exudates.

(c) OPTIC NEURITIS AND RETROBULBAR NEURITIS.—The number of cases of neuritis of the optic nerve in the literature is not large: eighteen treated systemically (Olson and others, 1950-51; Arruga, 1951; Scheie and others, 1951; McLean, and others, 1951; Fitzgerald and others, 1951), and locally by subconjunctival and retrobulbar injection (Woods, 1950-51; Arruga, 1951; McLean and others, 1951; Leopold and others, 1951). These figures include the demyelinating diseases; several cases associated with DISSEMINATED SCLEROSIS have been treated with variable results, and in one case of DEVIC'S DISEASE in our series, no effect was apparent.

Such cases are notoriously difficult to evaluate. On the whole, the results of local injection seem to be poor (80 per cent. failures). Judging from the published results, some 25 per cent. of cases failed to respond to general treatment. In a disease the prognosis of which is so unpredictable and which has so great a tendency to spontaneous resolution, this cannot be said to be a satisfactory figure. The fact, however, that systemic treatment may on occasion have a favourable effect seems demonstrated in a case treated (with ACTH) by McLean and others, wherein a remission followed the commencement of treatment, a relapse immediately occurred on its cessation and improvement again followed the resumption of treatment. Here again, more observations are required before any assessment can be made.

(d) **RETINAL PERIPHLEBITIS AND VITREOUS HAEMORRHAGES.**—Most of the twelve cases reported fall into the category of EALES' DISEASE (Offret and Forest, 1950–51; Barrios and Barrière, 1951; Brückner, 1951; Arruga, 1951; McLean and others, 1951; Lavery and others, 1951; Mosher, 1951). Both with local and general treatment the results have been uniformly bad, an experience which is confirmed in our own series.

(B) Extra-Ocular Inflammations

(1) KERATITIS.

It may be said in general that nearly all cases of keratitis respond favourably to the local administration of cortisone if treatment is commenced at an early stage before gross cellular infiltration has occurred or tissue necrosis has taken place; once necrosis has given place to fibrous formation, such treatment is without effect, although a recession of vascularization may bring about some temporary subjective relief to symptoms. In these cases topical therapy has generally been employed in preference to systemic therapy, a choice which appears to be wise; and in diseases limited to the cornea, the instillation of drops appears on the whole to be more effective than subconjunctival injections. Drops or ointment, or a combination of both, seem to be the method of choice.

(a) **NON-SPECIFIC ULCERS.**—These, including the traumatic type, have responded capriciously. Of forty cases of ulcers and other inflammatory superficial conditions reported in the literature, 25 per cent. have been said to represent therapeutic failures (Woods, 1950–51; Leopold and others, 1951; McLean and others, 1951; Lavery and others, 1951; Fitzgerald and others, 1951). On the whole, however, it can be said that the results have been more favourable than could reasonably have been expected without the intervention of hormone therapy, although a sufficient analysis of the response of individual types of cases has not yet been made.

(b) **MARGINAL ULCERS.**—These, on the other hand, have as a rule cleared up rapidly, altogether twenty cases being recorded (Steffensen and others, 1951; Arruga, 1951; Mosher, 1951; Brückner, 1951; Scheie and others, 1951; Fitzgerald and others, 1951; Leopold and others, 1951). Occasionally the response has been said to be dramatic (Scheie and others, 1951), but the histories available are not of sufficient duration to allow any conclusions to be drawn as to the permanency of healing and it is noteworthy that only temporary subjective improvement can be said to have

been obtained in the two cases included in our series. Any assessment of the response of this condition must await longer after-histories.

(c) DEEP ULCERS OF THE HYPOPYON TYPE and CORNEAL ABSCESSSES have received less attention. Three cases in the literature have been reported on favourably by Desvignes and others (1950) and unfavourably by Arruga (1951) and by McLean and others (1951) respectively. Our own experience is more extensive and, on the whole, more favourable. Of fourteen cases, ten responded well without relapses and showed more rapid healing than would have otherwise been expected; three showed an equivocal result, and only one no response.

It is to be noted that in ulcerative processes of the cornea there is occasionally a mention of what would seem to be *delayed epithelial healing*, for while the activity of an ulcerative process has been controlled, epithelialization has been apparently delayed, and staining with fluorescein has persisted longer than would have been expected, to disappear promptly on the cessation of treatment. Two such cases were encountered in our series. This question will be discussed again in a later paper (Duke-Elder and Ashton, 1951) but it may be noted here that any inhibition of epithelialization appears to be sporadic in its incidence and temporary in its duration. This effect would not seem to be a serious contraindication to cortisone therapy.

(d) PHLYCTENULAR DISEASE.—As would be expected from an essentially allergic condition, this responds well to local treatment by cortisone. Of 41 cases recorded in the literature only two were failures (Steffensen and others, 1951; Barrios and Barrière, 1951; Thygeson and Fritz, 1951; Arruga, 1951; Scheie and others, 1951; Fitzgerald and others, 1951; Leopold and others, 1951; McLean and others, 1951), and in the two cases included in our series a rapid and dramatic subsidence of activity was seen. Particularly when it affects the cornea, this condition without doubt constitutes an indication for treatment by cortisone, but in established cases a lessening of the infiltration and of the vascularization of fascicular corneal ulcers, without the disappearance of scars, is all that can be expected. Here again, longer after-histories will be necessary to assess the significance of relapses.

(e) ROSACEA.—Judged from the few reports available, rosacea keratitis would seem to respond to cortisone as happily as phlyctenular keratitis, whether the hormone is administered locally or systemically. Six cases are recorded in the literature, all of which were improved and (within the limits of the short histories available) only one relapsed: the improvement in some of them has been called spectacular (Lepri, 1950; Steffensen and others, 1951; Olson and others, 1950–51; Fitzgerald and others, 1951). Our series includes twelve cases, all treated by drops with uniformly good short-term results. There was a rapid diminution of the infiltration and congestion and, although relapses occurred in

some, these were readily controlled by further treatment. It would seem that in this disease the preliminary assessment would be justified that cortisone is the treatment of choice from the symptomatic point of view; but in a condition of this type long case histories extending over many years are necessary before any final opinion can safely be given. The keratitis will almost certainly relapse eventually if the constitutional factors determining its activity persist; how far such relapses will be tided over by cortisone must remain a question for the future. It is obvious, however, that in a recalcitrant disease of this type, so prone to involve symptomatic and functional disability of a very severe nature in the eye, such control, even though temporary, will be an inestimable boon.

(f) SUPERFICIAL PUNCTATE KERATITIS.—This is reported on by several authors: in a total of twelve cases, eight are said to have responded well, three relapsed and one was unimproved (Steffensen and others, 1951; Arruga, 1951; Mosher, 1951; McLean and others, 1951; Scheie and others, 1951; Lavery and others, 1951). Here again, the follow-up histories are short. In our own short series of three cases no dramatic response was ever observed. This condition obviously requires further investigation before its suitability for cortisone therapy can be assessed.

(g) HERPETIC AND METAHERPETIC KERATITIS.—Fifteen cases of *dendritic ulcer* have been reported (Steffensen and others, 1951; Olson and others, 1950–51; Brückner, 1951; Lerner, 1951; McLean and others, 1951; Leopold and others, 1951; Fitzgerald and others, 1951). Of these, a considerable proportion (60 per cent.) is said to have done well, occasionally dramatically so (Fitzgerald and others, 1951). In our series of seven cases this finding was by no means substantiated, and on the whole our experience would indicate that cortisone is relatively useless in this condition, relapses tending to occur in those few cases wherein a temporary improvement was obtained. This depressing experience finds a parallel in the absence of any favourable therapeutic effect found by Leopold and his co-workers (1951) and by Hallett and others (1951) in experimentally produced lesions of this type in rabbits. Our experience of metaherpetic keratitis has been similar, but Scheie and others (1951) reported two cases, one of which showed a good and the other a questionable response. Further observations are required before any assessment can be made in this type of infection.

(h) HERPES ZOSTER.—This condition, on the other hand, whether affecting the cornea alone or associated with an iridocyclitis, has on the whole given a better response. In the literature eight cases are available which have received local treatment and four which have received systemic treatment (Harvey and others, 1950; Olson and others, 1950–51; Arruga, 1951; Brückner, 1951; Barrios and Barrière, 1951; Leopold and others, 1951; Lavery and others, 1951; Fitzgerald and others, 1951). With each method of treatment 25 per cent. of the cases showed recurrences of the active inflammatory signs, and 25 per cent. failed to respond. With general treatment by ACTH, Olson and others (1950–51) found that a patient was rendered asymptomatic with a complete disappearance of

pain in an early case within four hours. In our small series of four cases, all of which had kerato-iridocyclitis, a similarly rapid improvement was obtained particularly in the early stages of the disease. The general impression gathered is that this malady certainly constitutes an indication for cortisone treatment provided it is undertaken early.

(i) EPIDEMIC KERATO-CONJUNCTIVITIS.—This condition is represented in our series by one case. It was of three months' duration, was characterized by a severe conjunctivitis, a profuse keratitis of the nummular type and a subacute iridocyclitis with keratic precipitates. It had been very resistant to treatment which had included penicillin, aureomycin and chloramphenicol, but all signs of active inflammation rapidly resolved after subconjunctival injections of cortisone leaving attenuated corneal nebulæ.

(j) DISCIFORM KERATITIS.—This condition also responds well to local cortisone, probably better than to any other type of treatment. Six authors have reported on this disease (Steffensen and others, 1950-51; Arruga, 1951; Brückner, 1951; Mosher, 1951; Lavery and others, 1951; Scheie and others, 1951), and the results have generally been remarkably good.

This has been substantiated by our series of nine cases. Early cases improved subjectively and objectively, opacities in the exudative stage, before tissue necrosis or fibrosis had developed, dwindled, but old scarred lesions were unaffected; relapses tended to occur after the cessation of treatment unless this were maintained for a considerable time. If, however, the disease is brought under treatment with cortisone drops before it is far advanced, and the treatment is continued until the eye is quiet, it would seem that its usually prolonged duration is shortened and the residual disabling opacity is considerably lessened.

(k) TRACHOMATOUS ULCERS AND PANNUS.—These have been reported on favourably by Arruga (1951) who used local treatment in three cases. In one case of old-standing trachomatous pannus included in our series there was a marked reduction of the vascularity with considerable relief of symptoms which was maintained over some months, but a long history is not available.

(l) SYPHILITIC INTERSTITIAL KERATITIS.—If treated early in its course, this disease is one of the definite indications for cortisone treatment. Local therapy seems to be more effective than general; indeed, the effectivity of topical treatment has been demonstrated after the failure of systemic treatment (McLean and others, 1951). The literature has records of 44 cases thus treated, with 20 per cent. failures and 10 per cent. recurrences (Steffensen and others, 1950-51; Woods, 1950-51; Arruga, 1951; Offret and Forest, 1951; Horne, 1951; Werner and Lavery, 1951; Simpson and others, 1951; McLean and others, 1951; Lavery and others, 1951; Scheie and others, 1951; Leopold and others, 1951), while with general treatment the failures recorded amount to nearly 50 per cent. (Geddes and McCall, 1950; Woods, 1950-51; Olson and others, 1950-51; McLean and others, 1951; Scheie and others, 1951; Fitzgerald and others, 1951). Our series of nineteen cases generally confirms this experience.

In the early stages of the disease the results are excellent, particularly when drops (or ointment) are employed. Subjective symptoms disappear

with extraordinary rapidity with a profound psychological effect for good, and during the early phases corneal oedema diminishes and corneal transparency is often maintained. Indeed, as was remarked by Woods (1951), the symptoms, both subjective and objective, can be seen to wax and wane with the cessation and renewal of the administration of cortisone. Relapses thus tend to occur rapidly if treatment is stopped at an early stage, and it would seem that the ideal course to adopt in the treatment of this disease is to control the symptoms by local therapy and thereafter to give intermittent courses for some considerable time in order to anticipate recrudescences of the inflammation. Whether this will be necessary throughout the normal natural period of the disease of some 12 months or more will become apparent in the future. Sufficient length of follow-up observations of this type is not available for a decision yet to be made whether in this way the clinical evidence of syphilitic interstitial keratitis can be largely eliminated, but it would seem at least possible that if the disease is kept under control from a sufficiently early stage, such a favourable conclusion may be obtained in at least some cases. In more advanced cases, even where considerable corneal infiltration is apparent, a marked clearing of the opacities and lessening of the vascularization may be obtained during the first 4 weeks of treatment. On the other hand, in long established disease, the results are much less dramatic or entirely negative. If tissue necrosis has become responsible for an opacity, no effect is obtained with cortisone apart from transient symptomatic relief, a temporary lessening of the inflammatory symptoms and some emptying and regression of vascularization.

(*m*) DEEP KERATITIS.—Non-specific deep keratitis and kerato-iritis have received little attention in the literature but our studies include a series of 26 cases. The results on the whole were good so far as the acute inflammatory and exudative phenomena were concerned, and occasionally an early case cleared up leaving no scarring or a residual nebula so slight that considerable credit must be given to this therapeutic agent. On the other hand, in more advanced cases, consolidated scars showed no improvement although vascularization, particularly of the superficial type, tended to decrease. In this disease, however, several relapses were noted some months after the cessation of treatment and it is of interest that 2 cases developed a secondary glaucoma during the administration of the hormone.

(*n*) SCLEROSING KERATITIS AND SCLERO-KERATITIS.—These have received uniformly good reports in the literature with local treatment by cortisone, even when, as in ten cases, the aetiology has been tuberculous or apparently so (Moutinho, 1950; Steffensen and others, 1950-51; Arruga, 1951; Barrios and Barrière, 1951; Offret and Forest, 1951; Scheie and others, 1951). In our own series of eight cases the response has been somewhat similar to that of most types of deep keratitis. The acute inflammatory phase is almost invariably controlled; in early cases complete control may seem to have been attained, but relapses tend to occur with monotonous regularity on the cessation of treatment, and no effect whatever has been obtained upon established scars.

(o) **MOOREN'S ULCER**.—Lavery and others (1951) reported a case which showed no response, a conclusion substantiated by the negative results obtained in the three cases in our series, although in two of these subjective relief and a regression of vascularization occurred.

(p) **CORNEAL SCARS**.—These are relatively unaffected by cortisone. It is noteworthy that Brückner (1951) found that a recent scar perforated shortly after the institution of local treatment, while Fitzgerald and others (1951) found little value in the treatment of unstable corneal scars.

(2) SCLERAL AND EPISCLERAL INFLAMMATIONS

(a) **EPISCLERITIS**.—This is reported as almost invariably responding well to treatment with cortisone—thirty cases treated locally (Moutinho, 1950; Jensen and Ward, 1951; Arruga, 1951; Barrios and Barrière, 1951; McLean and others, 1951; Lavery and others, 1951; Scheie and others, 1951; Leopold and others, 1951; Fitzgerald and others, 1951), and seven cases treated systemically (Mann and Markson, 1950; Calamandrei and Ferrata, 1950; Mundy and others, 1951; Fitzgerald and others, 1951).

(b) **SCLERITIS**.—Here the response has been less uniformly good. There were 15 per cent. of failures in 28 cases treated locally (Moutinho, 1950; Moutinho and Basto, 1951; Werner and Lavery, 1951; McLean and others, 1951; Lavery and others, 1951; Mosher, 1951; Fitzgerald and others, 1951; Leopold and others, 1951), and with general treatment three cases, reported by Henderson and Hollenhorst (1950–51) and Olson and others (1950–51), relapsed. Our experience of sixteen cases shows results which are more variable and capricious than the literature would suggest. Cases with a rheumatic aetiology mostly showed a marked immediate improvement, occasionally, however, confined to the subjective symptoms; relapses were prone to occur, and 20 per cent. of cases of scleritis showed no response. It is probable that, at any rate so far as local treatment is concerned, this method of therapy is better than any other available, is usually dramatic when the inflammation is superficial, but is by no means so effective in the deeper types of disease, particularly when metabolic disturbances are widespread.

(3) CONJUNCTIVITIS

(a) **CHRONIC CONJUNCTIVITIS**.—Of the 34 cases treated locally which are reported in the literature, the majority has been reported as showing considerable and sometimes marked improvement (Arruga, 1951; Jensen and Ward, 1951; McLean and others, 1951; Scheie and others, 1951; Fitzgerald and others, 1951; Leopold and others, 1951); some 12 per cent. of the chronic cases, however, either

showed no improvement or relapsed. In our series, two cases of chronic conjunctivitis were treated by drops, one with a good and one with a bad result. Eight cases have been labelled as allergic conjunctivitis (Moutinho, 1950; Moutinho and Basto, 1951); these have all been reported as cured, and of the three allergic types in our series, all responded rapidly and well, one case, for example, which had persisted for one year, being "cured" in three days.

(b) FOLLICULAR CONJUNCTIVITIS.—Lavery and others (1951) reported marked improvement in one case treated locally.

(c) SPRING CATARRH.—This condition comes into a category of its own. Of 28 cases treated locally (Moutinho, 1950; Steffensen and others, 1950–51; Henderson and Hollenhorst, 1950–51; Olson and others, 1950–51; Arruga, 1951; Rossi, 1951; Mosher, 1951; Barrios and Barrière, 1951; Moutinho and Basto, 1951; Leopold and others, 1951; McLean and others, 1951; Scheie and others, 1951), only one was said to have been unimproved while the remainder showed an unusually good response, but 25 per cent. relapsed in a short time. A similarly good immediate response, using general treatment, was obtained in one case each by Harvey and others (1950) and Hogan and others (1951); but one of these rapidly relapsed. In our single case, which had a history of 2 years, the immediate response to drops was dramatic. It would seem that in this condition the instillation of cortisone relieves the immediate symptoms of itching and irritation more dramatically than any other medicament and that it rapidly diminishes the exuberance of the vegetations; but it appears likely that the continuance of treatment to a modified degree is necessary during practically the whole season in which the symptoms are liable to recur. It is not yet known, of course, how a case thus treated will behave in a subsequent year; the probability is that a repetition of treatment will be necessary.

(d) ERYTHEMA MULTIFORME EXUDATIVUM affecting the conjunctiva (STEVENS-JOHNSON DISEASE) has been treated locally by Bleier and Schwartz (1951), Scheie and others (1951), and Leopold and others (1951), with no response except in one case which showed some improvement. In one of our cases treated topically, no response whatever to the instillation of drops was apparent; but in one very severe case which was treated systemically as well as with drops, the ocular conditions improved although the affections of other mucous membranes remained unchanged.

(e) OCULAR PEMPHIGUS.—This cannot be said to respond dramatically, but the reports in the literature are somewhat varied. Of four cases treated locally, three showed no response to treatment while one was noted as showing improvement (Werner and Lavery, 1951; Lavery and others, 1951; Leopold and others, 1951). Fitzgerald and others (1951)

described a case which showed no response to local treatment but was promptly cured on the administration of ACTH. Cannon and others (1951) reported a series of seven cases treated systemically; two died, three showed some improvement though the disease remained active, and in the two others a temporary improvement was rapidly followed by a relapse. In our series, three cases received local treatment by the instillation of drops for a relatively short period (14 days), but none showed any response. Two were treated systemically with the same negative result, and of these one died after 3½ months' treatment. On the whole, it may be that isolated cases respond to systemic treatment, but the response appears usually to be partial and temporary; in general, the results of cortisone therapy so far obtained in this disease are disappointing.

(f) ECZEMATOUS CONDITIONS OF THE LIDS.—These have been reported on by Brückner (1951), who used local cortisone with good results, and by Hogan and others (1951) who obtained a temporary improvement in a case treated systemically.

(g) ATROPINE AND DRUG IRRITATIONS.—These have received a considerable amount of attention. The literature shows a series of thirteen cases treated locally with one recorded failure (Woods, 1950–51; Arruga, 1951; McLean and others, 1951; Leopold and others, 1951), and four cases treated systemically with invariable success (Carey and others, 1950; Howard and others, 1950). Our experience has been by no means so uniformly successful; 25 cases were all treated locally by drops, the majority of them showing irritation to atropine. Of nineteen such cases, six showed a subsidence of the allergic reaction, in 3 the reaction was controlled for a time but recurred during cortisone treatment, in four no effect was evident, and the remaining six developed atropine irritation during treatment by cortisone. Irritation to hyoscine reacted in much the same way, and equally equivocal results were observed in irritation to albucid and penicillin. In view of the known effect, sometimes dramatic in degree, of cortisone upon allergic reactions, the equivocal nature of our results in the local allergic reactions to drugs of the conjunctiva and palpebral skin is both surprising and disappointing.

II. DEGENERATIVE CONDITIONS

It may be said at once that, while many inflammatory ocular diseases show, at the least, a good immediate response to treatment by cortisone, particularly in their earlier stages, degenerative conditions show a monotonous absence of improvement; any good effect of the treatment would appear to be an incidental and usually transient amelioration of irritative symptoms in a few degenerations affecting the outer eye.

(A) Degenerative Conditions of the Inner Eye

(1) **PRIMARY PIGMENTARY DEGENERATION OF THE RETINA (RETINITIS PIGMENTOSA).**—This has been treated systemically in twelve cases by Olson and others (1950–51) and McLean and others (1951), and locally in sixty cases by Arruga (1951), Barrios and Barrière (1951), and McLean and others (1951). Apart from one questionable case, the results were uniformly bad.

(2) **ANGIOID STREAKS** were treated systemically by Olson and others (1950–51) without result.

(3) **CHOROIDERAEMIA.**—A similar negative result was reported by McLean and others (1951) in three cases.

(4) **MYOPIC CHORIO-RETINAL DEGENERATION.**—No response was seen in a case treated locally by Arruga (1951).

(5) **TAY-SACHS DISEASE.**—Scheie and others (1951) found no response to systemic treatment in one case.

(6) **SENILE AND EXUDATIVE MACULAR DEGENERATION** has similarly given uniformly disappointing results in the 21 cases reported in the literature (Olson and others, 1950–51; Arruga, 1951; Fitzgerald and others, 1951; McLean and others, 1951; Leopold and others, 1951), an experience paralleled by the eight cases in our own series. In the exudative types at their early stages, there may have been some evidence of absorption leading to some visual improvement of a temporary nature in three cases, but the general picture is depressing.

(7) **OPTIC ATROPHY.**—Of three cases which received systemic treatment (Olson and others, 1950–51; McLean and others, 1951) none showed any response.

(8) **CATARACT.**—Patients who were undergoing systemic treatment with cortisone or ACTH for other conditions and who also had cataract were studied by McLean and others (1951), who observed no therapeutic effect on the lens in any of them.

(B) Degenerative Conditions of the Outer Eye

Corneal degenerations offer a similarly disappointing picture.

(1) **BULLOUS KERATITIS.**—An improvement was noted in only two cases out of nine (Mosher, 1951; McLean and others, 1951).

(2) **RECURRENT EROSIONS.**—A good result was obtained by McLean and others (1951) in two cases.

(3) **FILAMENTARY KERATITIS.**—Arruga (1951) found no improvement, and McLean and others (1951) reported prompt clearing in one case; in our one case a good effect was noted with treatment by drops, but a relapse occurred immediately the treatment was stopped.

(4) GROENOUW'S DYSTROPHY.—No response was observed by Arruga (1951).

(5) FUCHS' DYSTROPHY.—A temporary response was seen in two cases out of sixteen (McLean and others, 1951; Fitzgerald and others, 1951).

(6) BAND-SHAPED KERATITIS.—One case was reported by Scheie and others (1951) to have shown no improvement, and a temporary slight improvement was seen in one case in our series.

(7) EXPOSURE KERATITIS, due to cicatrization following lupus, was found by Fitzgerald and others (1951) to improve on local treatment.

(8) OTHER MISCELLANEOUS DEGENERATIONS OF THE CORNEA.—Various other conditions were recorded as unimproved (Steffensen and others, 1950-51; Woods, 1950-51; Lavery and others, 1951; Leopold and others, 1951).

III. POST-OPERATIVE AND TRAUMATIC INFLAMMATIONS

The inflammatory response of the tissues of the eye to local trauma, post-operative or otherwise, would seem to be a legitimate field for the exploitation of cortisone; and so it has turned out to be. Its use in such cases, however, has been tempered by the finding of experimental and clinical observers that the healing process has been delayed not only in its acute exudative phases but also in the fibroblastic activities of tissue-repair after the exhibition of this hormone. This subject will be discussed more fully in a later paper (Duke-Elder and Ashton, 1951) and, although there is no doubt that while this repression of reparative activity is marked in such highly vascularized tissues as the skin or bone, experimental work has shown that such an effect is less obvious in the eye, particularly in the avascular cornea. It would indeed appear that effective, although not so exuberant, healing occurs in corneal wounds in experimental animals under the influence of cortisone. Reasoning from the inhibitory effect evident in other tissues, the opinion has been usually stressed that cortisone should not be given for some days after operation when satisfactory healing has probably established itself, but it seems questionable whether the effect is of sufficient magnitude to preclude its use in small doses in this type of case. This view is borne out by the fact that several authors have reported successful and uncomplicated healing in operations conducted while the patient has been under cortisone therapy for the control of an acute or subacute inflammatory disease, the remission in the inflammatory symptoms often allowing surgical intervention to be successfully undertaken in cases which would otherwise have given rise to anxiety (Henderson and Hollenhorst, 1950-51; Hogan and others, 1951; Fitzgerald and others, 1951).

(1) POST-OPERATIVE KERATITIS, including striate keratitis and other oedematous conditions of the cornea, has invariably been said to clear well with local treatment by cortisone drops (Steffensen and others, 1950-51; Arruga, 1951; Offret and Forest, 1950-51). This experience is confirmed in our series of cases; it is interesting that a violent chemosis after an operation for strabismus disappeared within 5 days.

(2) POST-OPERATIVE AND POST-TRAUMATIC UVEITIS.—Reports are available in the literature of 37 cases of post-operative uveitis treated by local methods (Desvignes and others, 1950; Michaud and Forestier, 1950; Woods, 1950-51; Lavery and others, 1951; Mosher, 1951; Trope, 1951; Arruga, 1951; Werner and Lavery, 1951; Leopold and others, 1951; Scheie and others, 1951; Fitzgerald and others, 1951), and of 22 cases treated systemically (Theodore, 1950; Lippmann, 1950; Woods, 1950-51; Olson and others, 1950-51; Scheie and others, 1951; Fitzgerald and others, 1951); to these may be added our observations on 34 further cases treated by drops or subconjunctival injections.

On the whole, the results, although variable, are good in this type of case. About 25 per cent. of cases have shown little or no response, but most demonstrate an initial improvement. This applies equally when the inflammation is a simple post-traumatic reaction and when it appears to be due to the presence of lens substance in the eye after an extracapsular extraction of cataract or to a phako-anaphylactic reaction.

It is indeed probable that in cases of persistent irritation after an injury or operation, cortisone treatment (perhaps preferably given as an ointment) is a most effective therapeutic measure. In several cases in our series, a post-operative iridocyclitis which showed little or no amelioration to the usual methods of treatment, quietened rapidly and resolved, even in such unpromising subjects as diabetics. And in cases of perforating injury, where the appearance of aqueous flare, cells in the anterior chamber, and keratic precipitates associated with progressive signs of inflammation in the injured eye would normally have led to its excision, the timely exhibition of cortisone by drops or subconjunctival injection led to the prompt subsidence of inflammatory signs and allowed the retention of the eye without harm to its fellow.

(3) POST-OPERATIVE AND POST-TRAUMATIC INTRA-OCULAR INFECTIONS.—These conditions have received less attention. The literature contains the reports of eight such cases (Hartmann and others, 1950; Olson and others, 1950-51; Fitzgerald and others, 1951), and our experience includes five. On the whole, it may be said that cortisone is frequently capable of holding the acute inflammatory evidences in check until the infection is overcome by antibiotics, in which case the eye may retain its function. If, however, the infection remains uncontrolled, the prognosis is usually bad. Thus in a case of vitreous abscess reported by Olson and others (1950-51), the inflammation was controlled initially but a subsequent relapse necessitated the eventual excision of the eye.

(4) CORNEAL GRAFTS.—A considerable amount of attention has been given to the possible value of cortisone in the early post-operative period of corneal grafts. It is well known that in certain cases, particularly when the graft is applied to a heavily vascularized or densely opaque cornea, the graft may tend to become hazy and to be invaded by new vessels from the second to the sixth post-operative week. It has been suggested that cortisone might have an inhibitory effect on any mutual intolerance based on an allergy-antibody reaction between the host cornea and the graft and might in this way exercise some effect in reducing opacification and inhibiting vascularization. Surgeons have hitherto delayed the exhibition of cortisone for some days after the operation in case the hormone interfered with the healing of the graft.

In the literature nineteen cases of this type have been reported: in nine a successful result has been claimed; in seven (three of which were treated parenterally) the treatment is said to have been without effect; in the remainder, the results were indeterminate (Hartmann and others, 1950; Woods, 1950-51; Offret and Forest, 1951; Scheie and others, 1951). In the six cases in our own series a subsidence of inflammatory signs and a tendency for early opacification to clear were noted after treatment by cortisone, and in three of them the progress of vascularization of the graft seemed to have been checked; in none could the effect be said to be dramatic, but only one of the six cases showed no apparent response. It would seem on the whole (although an evaluation of such treatment is difficult and at this stage probably dangerous) that the topical exhibition of cortisone, either by drops or by ointment, is sufficiently encouraging in cases wherein cloudiness and vascularization of the graft seem imminent to make such treatment worth while.

(5) BLOOD-STAINING OF THE CORNEA.—One case was treated locally by Fitzgerald and others (1951) with strikingly good results.

(6) POST-RADIATIONAL X-RAY CONJUNCTIVITIS AND IRITIS.—In our series of cases this condition showed a rapid improvement; a similarly rapid relief of subjective symptoms together with a resolution of an iritis within 5 days followed the instillation of cortisone drops in a case of radiational inflammation following *radium therapy* given for an ethmoid carcinoma.

(7) CHEMICAL INJURIES.—A number of chemical injuries mainly affecting the cornea has been reported in the literature; the results have been variable and not very conclusive.

Lime Burns.—Among nine cases treated locally reported in the literature (Trope, 1951; Werner and Lavery, 1951; Lavery and others, 1951; Leopold and others, 1951), seven are said to have improved and two to have shown no response to treatment. Our own single case, which was treated topically, showed no significant improvement.

Acid Burns.—One case reported by Lavery and others (1951) which was treated topically showed no beneficial result.

Alkali Burns.—Among four cases reported by McLean and others (1951) and Lavery and others (1951), local treatment was said to produce an improvement in two, but had no effect in the remaining two.

Silver Nitrate Burns.—One case was reported by Fitzgerald and others (1951) to have improved; one treated by us showed relief of the congestion but no other marked effect.

Mustard-Gas Burns.—Two cases were found by Scheie and others (1951) to be unimproved; in our one case there was rapid initial improvement with healing of the ulcers, but a relapse occurred 10 days after cessation of treatment.

IV. MISCELLANEOUS CONDITIONS

(1) **DIABETIC RETINITIS.**—This has been treated locally in thirty cases (Woods, 1950–51; Arruga, 1951; McLean and others, 1951) without any good result. Woods subjected one case to systemic treatment with a questionable result. Systemic treatment in diabetes has obviously to be very carefully controlled, but on the whole it would seem that there is little prospect of inhibiting the exudative phenomena in the retina in this disease.

(2) **COATS' DISEASE.**—In view of the exudative nature of this disease, two cases were treated systemically by Woods (1950–51), and two in our series were treated by subconjunctival injections. In none was any effect obtained.

(3) **CENTRAL RETINAL VENOUS THROMBOSIS.**—One case has been treated systemically (Fitzgerald and others, 1951), and two by retrobulbar injections (Arruga, 1951; Barrios and Barrière, 1951). None showed any good effect.

(4) **RETROLENTAL FIBROPLASIA.**—Much interest has been taken in the effect of cortisone in this condition. Systemic treatment has been attempted in thirty cases (Woods, 1950–51; Reese and Blondi, 1951; McLean and others, 1951; Scheie and others, 1951; Fitzgerald and others, 1951), mainly by ACTH. Local therapy with cortisone has been found to be without effect in three cases reported by Fitzgerald and others (1951) and in two in our series.

In assessing the value of treatment by ACTH in this disease it is interesting that in fourteen cases Reese and Blondi found uniformly good results, in the sense that the progress of the disease stopped. Scheie and his colleagues, in five cases, concluded that two were arrested and three unaffected, while all other observers have reported negative results. The treatment has been given on the theory that the pituitary gland is not fully developed at birth and ACTH appears in the mother's placenta only in the last 3 months of a normal pregnancy. It is obvious, therefore, that a premature infant might suffer from a deficiency in cortical hormone and, indeed, a deficiency of steroids has been found in the urine which can be

remedied by stimulating the adrenal cortex with exogenous ACTH. It must be remembered, however, that the clinical appearances described as retrolental fibroplasia probably do not constitute a single uniform disease-entity; moreover, it is well known that many cases progress to a certain point and then stop spontaneously. It may have been that the uniform success reported from New York is explicable on the supposition either that this group formed an atypical type of case or that it was of a non-progressive nature. However this may be, it is obvious that further work must be done on this subject before any definite opinion can be expressed.

(5) GLAUCOMA.—A few cases of primary glaucoma have been treated systemically by cortisone or ACTH, both of the simple and congestive variety (Blake and others, 1950; Olson and others, 1950–51). None of them showed any response. Similarly, negative results using local treatment were obtained by Barrios and Barrière (1951) and by Fitzgerald and others (1951), who found no response in a case of secondary glaucoma due to a hypermature lens. In our series, a similar negative result followed local treatment of a case developing secondarily to a dislocation of the lens. Fitzgerald and others (1951) also recorded a failure in a case of secondary glaucoma following retinal venous thrombosis treated systemically. The very different response in secondary glaucoma associated with iridocyclitis has already been noted.

(6) SJÖGREN'S SYNDROME.—Of three cases of Sjögren's syndrome treated by Offret and Forest (1950), Frenkel and others (1951), and Fitzgerald and others (1951), one is said to have shown a temporary improvement followed by a relapse, the other two showed no effect. The result in a single case in our series treated by local injection must be classed as negative.

(7) EXOPHTHALMIC CONDITIONS.—The pathology of exophthalmos associated with pituitary-thyroid disturbances, with its marked oedema and exudation, has suggested to several workers that the condition might be amenable to cortisone therapy. Scheie and others (1951) found that a case of thyrotoxic exophthalmos was unaffected by systemic treatment, a result corroborated by Woods (1950–51) in a case of thyrotropic exophthalmos (exophthalmic ophthalmoplegia). Cole (1951), on the other hand, in a case of the latter disease following thyroidectomy, found a rapid reduction of 8 mm. in the exophthalmos within a period of one week with ACTH. Local treatment has been tried in this latter condition by Woods (1950–51) and by Fitzgerald and others (1951) in three cases; the results were all indeterminate, although the chemosis became less apparent. The material available is not yet sufficient to allow any definite conclusion, but it is obvious that the hormone does not act as a panacea in this disease although Cole's report would suggest that ACTH might legitimately be given a trial in serious cases.

(8) NEOPLASMS.—Olson and others (1950–51) treated a carcinoma of the limbus, at a stage when it was not definitely diagnosed, with cortisone, and this was followed by an apparent improvement due to diminution of the vascularization. A conjunctival granuloma was treated by drops in our series without effect.

(9) **NEOPLASTIC DISEASE OF THE RETICULAR SYSTEM.**—We have already indicated that an atrophy of lymphatic tissue occurred as one of the metabolic results of the continued administration of cortisone or ACTH. This observation has led a number of authors to explore the possibility that these substances might control the various manifestations of leukaemia or neoplastic conditions of the reticular system. A few papers deal with this question from the point of view of general medicine, particularly those by Pearson, Eliel, and their collaborators (1949–51), who have extended their observations to over seventy patients. It would appear that these hormones have some palliative value in chronic lymphatic leukaemia, and in some types of lymphosarcoma and multiple myeloma, while a slight temporary improvement has been observed in Hodgkin's disease. In all cases, the response to hormone therapy apparently develops with some rapidity but the remission tends to be temporary. No response has been obtained in chronic myelogenous leukaemia, acute monocytic leukaemia or in a variety of sarcomata. Nothing has so far been published on the manifestations of these diseases as applied particularly to the eye, but presumably the same principles will obtain.

Summary

IN view of the frequency with which the eye is affected by acute inflammatory processes, and of its susceptibility to permanent functional damage as a result thereof, cortisone therapy is peculiarly effective in ophthalmology, its value being considerably enhanced by the ease and safety of local treatment.

The general clinical effect of cortisone in ocular diseases may be summarized, as far as this is possible at the present early stage in our knowledge, by saying that it temporarily blocks the exudative phases of inflammation whether bacterial, anaphylactic, allergic, or traumatic in origin, and that it inhibits fibroblastic formation in the stage of tissue-repair without in itself influencing the cause of the responsible disease. It is without effect on the organized sequelae of inflammatory disease or on degenerative conditions affecting the eye.

Of the therapeutic methods available, local treatment, particularly by drops or ointment, is indicated in external diseases of the eye, and by drops, ointment, subconjunctival, or, if necessary, intra-cameral injections, in intra-ocular inflammatory conditions of the anterior segment of the eye; systemic therapy is indicated in diseases affecting the posterior segment.

(1) The following conditions usually, but not invariably, respond well to cortisone, the degree of response being proportional to the early commencement of therapy, and to the degree of severity of the inflammation:

With Local Therapy

acute and subacute iridocyclitis (infective, allergic or post-traumatic),

sympathetic ophthalmitis,
 infective superficial keratitis,
 early deep keratitis (including zoster and other viral types),
 syphilitic interstitial keratitis,
 episcleritis,
 phlyctenular kerato-conjunctivitis,
 rosacea keratitis,
 spring catarrh.

With Systemic Therapy

acute and subacute generalized uveitis,
 early focal choroiditis.

- (2) The following conditions respond indifferently or irregularly:
 chronic iridocyclitis,
 chronic choroiditis,
 chronic general uveitis,
 scleritis,
 irritation to atropine and other drugs,
 superficial corneal degenerations,
 chemical injuries.
- (3) The following conditions show no response:
 Mooren's ulcer,
 corneal scars,
 pemphigus,
 Stevens-Johnson's syndrome,
 dystrophic conditions of the cornea (Groenouw's, Fuchs', band-shaped keratitis, etc.),
 mustard-gas keratitis,
 Sjögren's syndrome,
 Coats' disease,
 central retinal venous thrombosis,
 periphlebitis retinae (Eales' disease),
 primary pigmentary degeneration of the retina,
 pigmentary macular degeneration,
 primary glaucoma,
 cataract,
 optic atrophy,
 degenerative ocular conditions generally.
- (4) More observations are required to allow any assessment in the following conditions:
 dendritic herpetic ulcers,
 superficial punctate keratitis,
 epidemic kerato-conjunctivitis,
 sclerosing keratitis,
 central serous retinopathy,
 exudative macular retinopathy,
 optic neuritis,

retrolental fibroplasia,
reticuloses,
exophthalmic conditions,
early pathological changes in corneal grafts.

The main gaps in our present knowledge are the absence of adequate after-histories, the most useful methods whereby to combat, if possible, the deleterious effects of the more chronic types of inflammatory disease, and the most efficient techniques wherewith to forestall relapses when aetiological factors remain operative over considerable periods of time.

Cortisone therapy cannot justifiably be said to cure any ocular disease; while the use of this hormone may be of immense advantage in temporarily blocking the acute evidences of inflammatory processes or subacute exudative phenomena and thus preventing the occurrence of damage to the eye which may on occasion be catastrophic, its action is confined to the time during which it is administered and shortly thereafter, and its use can in no sense replace specific aetiological treatment. If cortisone treatment alone be relied upon as a method of therapy, the factor dominating the prognosis of practically every case is the occurrence of relapses. Thus the value of this hormone in ophthalmology is limited, but within its restrictions it is great, particularly if the cause of the malady is eradicable or the inflammation self-limiting. There is no value in its haphazard administration in every recalcitrant disease affecting the eye, particularly if it is used as a substitute for diagnosis and therapy directed against the aetiology.

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