

# CORTISONE IN THE TREATMENT OF SYPHILITIC EYE DISEASE\*

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The effect which cortisone will produce in an acutely inflamed eye was first noticed by Hench and his co-workers (1949 ; 1950a, b), whilst using the drug to treat patients with rheumatoid arthritis, some of whom also had attacks of iritis. The pain and inflammatory signs of congestion and exudation were much more rapidly relieved than had ever previously been the case in these conditions. Within a very short period this observation led to a trial of cortisone, first by systemic application, and later by topical use in a wide range of ophthalmic conditions. Reports covering a large series of cases which have appeared in the literature are well reviewed and summarized by Woods (1950 ; 1951a, b) and Duke-Elder (1951).

## LOCAL EFFECTS OF CORTISONE

The effect of cortisone on tissues in an inflammatory state, or exhibiting an allergic reaction, is to control the inflammatory and exudative phase of the disease. It will reduce the amount of vascular congestion, and where capillary permeability of vessel walls is increased by disease, will restore it to normal levels (Cook and Macdonald, 1951).

The effect of this is to reduce the amount of exudation into the tissues. Experimental evidence by Spain and others (1950) indicates that cortisone inhibits the early stages of fibrosis in a healing process and also inhibits phagocytosis and new vessel formation (Ashton, Cook, and Langham, 1951).

Clinically, the effect can be seen when cortisone is used on an inflamed eye. The amount of congestion is reduced, making the eye "white" within 2 or 3 days or sooner, and the patient experiences a dramatic relief of symptoms. The effect, however, is not permanent. If the drug is stopped before the condition treated has run its full course, a "relapse" will occur and all the original inflammatory signs will reappear. Hence it seems that cortisone must be continued throughout the natural life of the condition treated, and it is essential that other

concurrent therapy, appropriate to the case, must also be applied. Cortisone is in no sense a bactericidal drug and, indeed, unless the primary source of infection can be stamped out, will inhibit the body's natural methods of defence against bacteria. This has been demonstrated in rabbits with tuberculous eye disease, where in spite of cortisone or because of it, the tuberculosis became uncontrolled and the eyes rapidly degenerated (Woods, 1952).

Diseases of the anterior segment of the eye respond to topical application of cortisone, that is by drops, ointment, or sub-conjunctival injection. Leopold and others (1951) found that after topical application by these methods cortisone is present within the aqueous humour, the greatest concentration of all being obtained after sub-conjunctival injection.

Topical application gives as good results as systemic administration in anterior segment disease (Woods, 1950 ; 1951a, b ; Mclean and others, 1951). It has the advantage that the patient is not exposed to the side-effects of systemic therapy, and that the treatment can if necessary be continued over a long period. Less cortisone is used in topical than in systemic therapy ; the most economical method being by sub-conjunctival injection, less than 1 ml. being required every few days.

## TOPICAL ADMINISTRATION

**Drops** (5 mg. to 1 ml.).—Cortisone is supplied as a suspension of 25 mg. cortisone acetate in 1 ml. normal saline, with 1.5 per cent. benzyl alcohol added as a preservative.

This suspension is used in a 1 : 5 dilution, since if used at full strength the drops irritate the eye. Drops are used every 2 hrs for the first 24–48 hrs, then every 4 hrs, and later in a so-called maintenance dose, twice daily.

**Ointment.**—This is prepared by distributing the cortisone in a lanoline base in a strength of 10mg./g. According to Woods (1952) strengths of less than this are not so effective. Ointment is used every 4 hrs initially, the application being gradually reduced to twice daily.

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**Sub-Conjunctival Injections.**—These contain 0.4 ml. of the standard saline suspension; each injection thus contains 10 mg. cortisone. This is injected under the bulbar conjunctiva where it produces a white chalky deposit which will slowly absorb over a period of up to 7 days, when another injection is indicated. These injections are not suitable for use over a prolonged period; sub-conjunctival fibrosis is produced at each injection site and after about six injections have been given it becomes technically difficult to obtain further satisfactory sub-conjunctival deposits of cortisone. Our own experience indicates that ointment will give as good results as sub-conjunctival injections.

**Retro-Bulbar Injections.**—0.4 ml. standard saline suspension is injected with a long retro-bulbar needle into the retro-ocular space. It was hoped that this method would be suitable in treating diseases of the posterior segment but it has failed in our hands to give satisfactory results and has now been abandoned.

#### SYSTEMIC ADMINISTRATION

Systemic administration of cortisone can be carried out by giving tablets by mouth, or by intramuscular injection of the standard saline suspension. The dosage in both methods is 200 mg. (in four divided doses 6-hrly) over the first 24 hrs, 100 mg. (in four divided doses 6-hrly) over the second 24 hrs, and 50 mg. (in two divided doses daily) subsequently for about 10 days.

A count of circulating eosinophils in the blood can be used to gauge whether the dosage is effective during the first 2 days; a fall of 50 per cent. in the count should be obtained (Duke-Elder, 1951). The dosage of cortisone may have to be increased or decreased according to the level of the count. The subsequent level of the eosinophil count over the rest of the period does not bear any relation to the adequacy of the dosage.

This is better judged by watching for a satisfactory response in the clinical condition.

Systemic application is used in diseases of the posterior segment, e.g. retro-bulbar neuritis, papillitis, and choroiditis, and in such conditions topical application has little effect. When using the drug systemically for ocular lesions due to syphilis, the possible effect of the cortisone on the general syphilis has, of course, to be considered (Horne, 1952).

#### INTERSTITIAL KERATITIS

The typical local effect of cortisone is well seen in early cases of interstitial keratitis, in which the sensitivity to light, acute discomfort, and redness of the eye are relieved in a remarkable way. It is a striking feature that the misery which patients normally experience for weeks is completely relieved by cortisone.

Our series includes 28 cases of interstitial keratitis in congenital syphilis, and it is in this field of ocular syphilitic disease that cortisone has been used most extensively. Interstitial keratitis is a disease process which also involves the anterior uveal

tract, in addition to the cornea. In 700 cases described by Spicer (1924), all but 6 per cent. had anterior uveitis, in addition to keratitis.

The earliest signs of the disease, seen by examination with a slit-lamp microscope, include a slight oedema of the endothelium of the cornea and discrete precipitates in the corneal stroma. These are followed in a few days by the typical progressive stage, with marked photophobia, watering, pain, and vascular congestion around the cornea, which rapidly becomes hazy, giving the typical ground glass appearance. According to Spicer, this haze comprises:

- (1) surface haze, produced by epithelial oedema, giving an irregular dull appearance to the surface of the cornea.
- (2) haze in the corneal stroma proper, produced by oedema and cellular infiltration, mainly of lymphocytes, into the spaces between the individual cells comprising the corneal lamellae.
- (3) deep haze on the endothelial or posterior layer of the cornea, composed of oedema and deposits of cells and debris.

This stage is followed by a rapid invasion of the cornea by blood vessels, which spread inwards from the periphery, producing the well-known "salmon patch". It continues for 3–4 months and is accompanied by acute discomfort. During this stage, a necrosis of corneal cells and exudates occurs, and polymorphonuclear leucocytes and phagocytic cells appear. A phagocytosis of necrosed tissue and a clearing of the corneal opacity then begins. The final stage is one of retrogression, in which the patient experiences relief from his symptoms. The blood vessels begin to close off, the corneal opacities clear, and there is a process of fibroblastic proliferation of cells from the invading vascular tissue, and a proliferation of the fixed corneal cells. This is the stage of repair and may be prolonged for several months, or as long as 2 years. The closed-off blood vessels remain as permanent threads of fibrous tissue in the cornea and have been seen as long as 50 years after the attack. The extent of visual recovery is often extremely good, even after the most severe reactions. Recurrences, though relatively rare, can occur many years after the initial attack.

Here then is a self-limiting condition, characterized by exudation, congestion, and new vessel formation, and, later on, by fibrosis in the cornea and anterior uveal tract. It is known that cortisone will reduce all these stages of inflammation. This is, in fact, observed clinically when the drug is used in these cases, and the disease process is radically altered from its previously known clinical picture.

Cortisone will relieve the distressing symptoms of photophobia and pain, and will rapidly reduce the congestion of the acutely inflamed eye, so that the patient under treatment is relatively very comfortable.

In cases treated by us in the early stages, that is, during the progressive stage of corneal haze before corneal vascularization has appeared, the disease has been halted; and in six cases we have seen the opacity begin to clear, without any vascularization occurring. The opacity clears quickly at first, because in this early stage much of it is due to oedema. If cortisone is stopped too soon in these cases, or if dosage is inadequate to control the reaction, a typical relapse occurs. It seems impossible to say when cortisone should be stopped in these cases in which cure is simulated and the physical signs are suppressed. The only method seems to be by trial and error, stopping treatment and watching for a reappearance of photophobia and redness. Recurrences are easily controlled by a re-application of cortisone, and in our experience it has been necessary to keep on the treatment for 3-4 months.

Most of our cases were in the stage of vascularization when treatment was begun. The effects of cortisone in this stage are variable. Symptomatic relief is obtained within a week, or sooner, and a gradual halt is called to further vascularization. When treatment is commenced in this stage it takes longer to bring cases under control, depending upon the amount of corneal vascularization present, and it may take two weeks before the eye is quiet. Here again it is difficult to say how long to continue cortisone.

Some of the cases relapsed whilst on treatment, probably because of inadequate dosage, or because the cortisone itself was insufficient to control a severe reaction. When this occurs, if a change is made from sub-conjunctival injection to drops or ointment, the case will respond more satisfactorily. It seems necessary to prolong treatment for at least 3 months, and three of our cases were kept on treatment for 12 months before the eyes would remain permanently quiet.

One case had a bilateral interstitial keratitis of 10 weeks' duration, and each cornea was completely vascularized, except for a small, central, corneal opacity dense yellowish-white in colour, the so-called central gumma (Spicer, 1921). Both eyes were treated with two sub-conjunctival injections, during the first 2 weeks, and then with ointment for 7 months. Symptomatic relief was obtained in 10 days, and after 8 weeks the corneal vascularization disappeared. No relapse occurred on stopping the

treatment. Although this case would possibly have settled in due course without cortisone, I think the corneal scarring was less than might have been the case without the drug.

In one case of old interstitial keratitis of 6 months' standing, which was in the final stages of repair after disappearance of the corneal vessels, cortisone had no effect at all.

The most important part of the treatment is still the concurrent local and general therapy. Local treatment consists of atropine drops to the eye given every 4 hours and must be continued throughout, and after, treatment with cortisone. The general treatment has consisted of a heavy course of intramuscular penicillin, one million units daily over a 10-day period, followed by a course of arsenic and bismuth.

It does not, therefore, appear that the actual length of time of treatment is reduced by the use of cortisone, but I think that the corneal scarring will be less and the visual results will be better in many cases. This is the final criterion by which the value of cortisone will have to be judged. Cases will require observation over a much longer period to assess the fear expressed by Woods that cortisone may prove to be of no value at all in the treatment of interstitial keratitis. From observation of our own cases, some of which have been watched for 18 months, these fears have not yet been substantiated. While it is always difficult to assess the results of a new treatment applied to a self-limiting condition which undergoes a natural resolution, I am quite sure that, clinically, the cases we have treated have had a much less stormy course because of the treatment, and that they are very much better for having had cortisone.

The majority of our cases were treated as in-patients during the first 2 weeks, with intensive penicillin and frequent cortisone applications. When the condition is under control, cases can well be treated as out-patients. Atropine and cortisone ointment are both used 4-hrly until the condition is quiet, and thereafter twice daily. This is not a rigid rule; if the case does not respond quickly enough to ointment, then 2-hrly drops can be used, or the effect can be tried of sub-conjunctival injections at 7-day intervals.

Where permanent corneal opacities remain after an attack of interstitial keratitis, particularly affecting the central area of the cornea, the operation of corneal grafting is eminently suitable, provided the condition is stationary. The corneal opacities can clear even up to 2 years from the start of the attack, so that grafting need not be considered until this interval has gone by. Grafting has been

carried out, notably by Paufigue (1949) and Paufigue and others (1948), in the earlier stages of interstitial keratitis where the Wassermann reaction is positive. With the reduction in the amount of the corneal scarring which occurs in cases treated with cortisone, corneal grafting might not be so often indicated.

The type of case at present requiring grafting is that in which both eyes are badly scarred and the corneae are free from active disease and vascularization. Also there should be no defects, so far as it is possible to determine, in the deeper structures of the eye, such as posterior synechiae, optic atrophy, or disease of the retina and choroid.

#### IRIDOCYCLITIS

Secondary syphilitic iridocyclitis is characterized by its acute onset and the severity of the inflammatory and exudative signs. A profuse exudate into the anterior chamber occurs, with rapid formation of adhesions between the iris and the underlying lens of the eye. If not rapidly controlled, these changes constitute a serious menace to the patient's vision.

Our series includes sixteen cases of acute iridocyclitis, but none of these were proved to be due to syphilis. Treatment with cortisone brought about a rapid reduction in the amount of exudate with subsequent improvement in vision. Topical application gave as good results as systemic application, with none of the risks of side-effects. Since iridocyclitis is a self-limiting condition, in which coincident anti-syphilitic treatment can be actively applied, cortisone is a useful adjuvant to treatment. This type of case does well without cortisone therapy but where the severity of the exudative features threatens vision, cortisone reduces this risk. Duke-Elder (1951), in an analysis of cases reported in the literature, quotes 80 per cent. as successfully treated.

I have not seen a case of Jarisch-Herxheimer reaction leading to an acute flare-up of an iritis or interstitial keratitis, but it is likely that in such a case topical cortisone therapy would reduce the severity of the exudative features whilst concurrent therapy is still continued.

In chronic iridocyclitis cortisone gives inconsistent results. In general, results are not good because the underlying cause cannot be found, and the natural history of the condition is prolonged and subject to recurrences. Short courses of cortisone alleviate the symptoms and signs during the period of application but, as might be expected, relapses and recurrences are common when the drug is withdrawn. It remains to be seen whether long

courses of cortisone, topically applied, may be of some benefit in these cases, or whether, in the end, it will prove a disadvantage, or even, as Woods (1952) suggests, a positive danger.

#### CHOROIDITIS

Since this is a disease of the posterior segment of the eye, topical therapy is ineffective in controlling it, and systemic cortisone is necessary. Many cases of this condition, in its focal form, have been reported in the literature, and we have treated six. If treated in an early stage, some cases appear to resolve quickly, but those in a later stage with permanent damage to the choroid and retina are not affected by the administration of cortisone.

#### RETRO-BULBAR NEURITIS AND PAPILLITIS

According to Woods (1951a) the value of cortisone in these conditions is difficult to determine since many of these cases undergo spontaneous remission. It is possible that systemic cortisone would reduce the amount of exudate and swelling in the optic nerve and congested, inflamed tissue, but it would not prevent damage, by toxins, of the optic nerve fibres.

#### SUMMARY

In cases of ocular inflammation of syphilitic origin, the possible benefits of cortisone therapy must be set against the possible effects which systemic cortisone might have on the general syphilis.

It cannot be stressed too strongly that cortisone has not *cured* any condition in which it has been used. It is an adjuvant only to other general and local therapy, which must be actively applied. From the point of view of syphilitic eye disease, this concurrent therapy is possible, since the basic cause of the eye condition is known. Unfortunately, in many other ophthalmic conditions treated, this information is not so easily forth-coming.

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## DISCUSSION

DR. ROBERT LEES expressed his appreciation of Dr. Ashworth's lecture, and complimented him on his lucid exposition of the work that had been done. It was an impressive statement that two hundred cases of eye diseases treated by cortisone had been observed by Dr. Ashworth. He would like to take the opportunity of expressing his own warm appreciation of the cooperation he had received from the ophthalmologists of the Royal Eye Hospital in Manchester and also from the venereologists who had referred cases for treatment.

He emphasized Hench's dictum regarding cortisone :

It did not put out the fire, but acted as a fire-guard ; nor did it act as a carpenter repairing fire damage, it simply protected susceptible tissues from the damage which might be caused by the disease process, whether infective, anaphylactic, or traumatic.

In their present problem cortisone did not cure congenital syphilis nor its ocular manifestations, nor did it remove the damage already caused by interstitial keratitis and other eye inflammations, but it did protect the very vulnerable tissues of the eye from damage while measures were taken to combat the fundamental cause. The problem was two-fold :

- (a) to treat the disease congenital syphilis ;
- (b) to protect the eye from damage.

It was very dramatic to observe the rapid relief of symptoms in early cases under cortisone treatment, but this relief was obtained much more readily if treatment was started very early in the course of the eye disease ; it was less striking or did not occur if the ocular damage was already extensive. The effect of cortisone in relapses was prompt and usually complete ; calming of the inflammation resulted if treatment was begun at an early stage. The improvement in the eye appeared to be proportional to the degree of vascularization and in inverse ratio to the amount of fibrous tissue formation.

The most dramatic case he had observed was that of a child aged 3½ whose mother brought him to hospital in the belief that he had "sand in the eyes". Cortisone and specific treatment was begun within 3 days of the onset of symptoms ; the redness, pain, and photophobia cleared away in another 3 days and there was no damage to the eye.

But even in cases which might be regarded as almost hopeless, some degree of recovery might be secured, and further advance of the disease process might be pre-

vented. This was illustrated by a girl aged 13 who had been treated by her own doctor with a variety of drops and ointments for about 10 weeks. Both eyes were very seriously damaged by extensive vascularization and infiltration of the cornea, with keratitis punctata and no useful vision. After 6 months treatment, this girl was able to attend an ordinary school ; there was some opacity in both corneae, but even these seemed to be clearing slowly.

Several patients had had concomitant effusion in the knees and this might occur also in relapses. No attempt had been made to treat the joint condition by cortisone.

The specific treatment of inherited syphilis had been started from the time of clinical diagnosis, and in no case had he felt that there was an exacerbation of the eye condition, such as might be feared if there was a Herxheimer reaction. Treatment was begun with penicillin in high dosage, giving a child of 3 to 4 stones weight penicillin procaine 600,000 units, and penicillin G. in saline 500,000 units daily for a period of 14 days. This was followed by prolonged use of arsenical drugs and bismuth.

Many of these patients appeared ill—they were pale and below average weight, and lacked energy and vitality. Many improved considerably after a prolonged period of complete rest in bed, which made it easier to ensure that the eyes were rested also and that reading, visits to the cinema, and gazing at "T.V." were avoided. At a later stage a period in a convalescent hospital or a holiday at the seaside was very beneficial.

The serological results were, as might be expected, quite inconclusive, though there was usually a gradual fall in the titre of positive reactions.

The result in respect of vision could not be assessed until the cases had been observed much longer, but he felt strongly that if only the condition was diagnosed early there would be minimal damage to the eyes and results would be much better than in the pre-cortisone era. The ideal management, in his view, was early diagnosis, active treatment of syphilis, and the use of cortisone as long as there was any suspicion of active inflammation in the eye.

Prolonged observation in which the ophthalmologist and venereologist cooperated was necessary, and at least 2 years should be allowed to elapse before a final review of such cases was attempted.