removed relapses are prone to occur if the treatment is stopped.

It was noted above that the local use of cortisone produced disappointing results in scleritis. It seems to us that for this condition it is necessary to give cortisone parenterally. This suggestion is supported by the fact that a case of scleritis (not described in this paper), associated with rheumatoid arthritis which was being treated (by Professor Henry Moore and Dr. Mervyn Abrahamson) with intramuscular injections of 100 mg. of cortisone daily, cleared up completely in five days. The scleritis had previously been resistant to the accepted forms of treatment. On withdrawal of the cortisone, both the rheumatoid arthritis and the scleritis relapsed, but were again controlled upon the reinstitution of the treatment.

Summary

Cortisone has been used in the treatment of a variety of eye conditions (143 cases in all), mostly administered by subconjunctival injection or in the form of drops. Interstitial keratitis was particularly benefited, and iridocyclitis also improved rapidly in most cases. Treatment of two cases of sympathetic ophthalmia with systemic cortisone was successful. It is concluded that cortisone is very valuable in the control of allergic reactions in the eye, but has no effect on any underlying disease which may be the basic condition.

We express our thanks to our ophthalmological colleagues who gave us access to their cases for the purpose of this investigation.

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TOPICAL CORTISONE IN TREATMENT OF SYPHILITIC OCULAR DISEASE

BY

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Jones and Meyer (1950), Woods and Wood (1950), and Leopold *et al.* (1951) have studied the action of A.C.T.H. and cortisone on experimental ocular inflammation. Reports of clinical trials in ocular diseases with A.C.T.H. have been made by Blake *et al.* (1950), Gordon and McLean (1950), Mann and Markson (1950), McLean (1950), and Olson *et al.* (1950); with A.C.T.H. and cortisone by Harvey *et al.* (1950) and Woods (1950); and with cortisone by Henderson (1950), Henderson and Hollenhorst (1950), Fitzgerald *et al.* (1951), Leopold *et al.* (1951), Olsen *et al.* (1951), Scheie *et al.* (1951), Steffensen *et al.* (1951), and Thygeson and Fritz (1951).

The indications for the use of these hormones were discussed by these authors in the light of their relatively short experience, and all were agreed on the dramatic effects in various inflammatory and exudative conditions of the eye, especially in those in which hypersensitivity plays a part. It appeared that the earlier the hormone was administered in the course of the disease the more dramatic and beneficial were the results. After the end

of treatment relapses occurred in some conditions, but readministration of the hormone controlled them.

Woods (1950) described the effect of topical cortisone as being as dramatic in some cases as when cortisone was used parenterally, and summarized its advantages as being: "(1) That much smaller amounts of the hormone are required, (2) that the depressant action of exogenous cortisone on the adrenal cortex might be avoided, and (3) that any effect obtained by local treatment might be more permanent, since the normal secretion of cortisone by the adrenal cortex might not be seriously interfered with by the instillation of small amounts of exogenous cortisone." He instilled one drop of cortisone suspension (25 mg./ml.) into the eye every hour during the day and every two hours during the night, but had to dilute the suspension 1:4 in two out of eight cases on account of local irritation. Harvey *et al.* (1950) found that in most of their 12 cases local instillation of cortisone was just as effective as parenteral administration of either A.C.T.H. or cortisone, but that the former method did not influence vitreous exudation or changes in the posterior uveal tract.

Steffensen *et al.* (1951) listed the conditions responding to the instillation of cortisone among 24 cases of "anterior-segment" eye disease. Thygeson and Fritz (1951) treated 14 cases of phlyctenular keratoconjunctivitis successfully with cortisone instilled into the eye or injected subconjunctivally. Leopold *et al.* (1951) listed the conditions responding to cortisone administered parenterally, by local instillation, and by subconjunctival and retrobulbar injection, based on the treatment of 142 eyes.

As most cases of inflammatory and exudative ocular disease in patients with syphilis behave as if they were manifestations of "hypersensitivity," A.C.T.H. and cortisone would be expected to be of value in their management, but the literature on the use of these hormones in syphilitic ocular disease is small. Fitzgerald *et al.* (1951) reported rapid improvement (and no relapse after four months' observation) with parenteral cortisone in a case of acute syphilitic granulomatous uveitis. Reports on cases of interstitial keratitis have been made by Woods (1950) (one case, advanced and with corneal necrosis); Fitzgerald *et al.* (1951) (one case, with chronic non-granulomatous uveitis); Leopold *et al.* (1951) (four cases, no details given); Olsen *et al.* (1951) (one case, "atypical"); and Scheie (1951) (three cases, one of which was advanced with the "salmon patch" type of vascularization).

It is difficult from these reports to assess the results in interstitial keratitis in view of the small number of cases, the differing methods of administration of the hormone, and the limited data provided, but the results on the whole were disappointing. Greater success appeared to be obtained when the hormone was used early in the course of the disease and for a prolonged period.

Clinical Trial

In this investigation cortisone has been used in five cases of syphilitic ocular disease. All the patients were admitted to hospital for treatment. The drug was used topically in a strength of 5 mg./ml. of normal saline, one drop being instilled three-hourly day and night (except where otherwise stated). Only brief clinical details are given, as the objects of this communication are (1) to confirm the beneficial effects of topical cortisone; (2) to indicate that it has an application in ocular

conditions associated with syphilis; and (3) to draw attention to the needs of some of those ocular conditions in which relatively small doses of cortisone give excellent results—an important matter at this time, when only a limited supply of the hormone is available.

Case 1. Acquired Syphilis

The patient, a man aged 42, probably acquired syphilis in 1945. He developed bilateral acute iridocyclitis at the beginning of September, 1950, his blood Wassermann reaction being positive. He was first seen on October 3, when no other clinical evidence of syphilis was found, and x-ray examination of the chest revealed no disease. The positive W.R. was confirmed. The cerebrospinal fluid was normal.

Between October 3 and December 6 the patient was treated (in hospital, with the exception of one period of six days) with atropine instillations and local hot bathing, two separate courses of 10,000,000 units of penicillin, weekly injections of neoarsphenamine and bismuth, and five periods of artificial fever induced by graded doses of T.A.B. vaccine. Apart from one or two transient improvements, the ocular condition deteriorated, pain and photophobia persisted, there was gross impairment of vision in both eyes, and the patient was quite incapacitated and very depressed.

All systemic and local treatment was stopped on December 6, and, as local sensitivity to atropine had developed, "lachesine E.3" was substituted for atropine. (This would appear to have been unnecessary in the light of the experience of Woods (1950), who found in one case that sensitivity to atropine was controlled by cortisone.) Saline drops were instilled three-hourly for three days, with no change in the local condition, and on December 9 cortisone was substituted, one drop being instilled in each eye three-hourly. Within 12 hours discomfort in the eyes was almost completely relieved and vision had begun to improve strikingly. Within two days there was obvious rapid regression of the inflammatory changes, and four days after starting cortisone vision was 6/9 in each eye. The psychological change in the patient was equally dramatic. The cortisone was reduced to six drops in 24 hours on December 16. On the 18th no residual inflammatory or exudative changes could be detected. Cortisone and lachesine were stopped, and the patient was discharged from hospital on December 20.

Antisyphilitic treatment was restarted. The blood W.R. was negative on December 28, and has been negative on several occasions since, supporting the probability that the infection was recent in origin. The eyes have remained normal up to the patient's last visit on April 3, 1951.

Case 2. Congenital Syphilis

A man aged 27 developed acute interstitial keratitis in the right eye at the beginning of February, 1950. He was first seen on March 3. His blood W.R. was strongly positive, and Hutchinsonian incisors were present. He was admitted to hospital and treated with local atropine and hot bathing, penicillin (10,000,000 units), artificial fever (eight rigors induced by intravenous T.A.B. vaccine), then a further course of penicillin (10,000,000 units). At the end of this treatment there was considerable improvement in the eye; it had begun during the fever therapy, but there were still signs of activity eight weeks after the onset of symptoms. The man was observed at intervals as an out-patient, and the eye was first noted to be perfectly clear on April 18.

He remained free of symptoms until about the middle of December, when he developed acute interstitial keratitis in the left eye. He was not seen until January 11, 1951, when there was gross vascularization of the cornea and considerable interstitial and deep corneal opacity; there were dilated vessels on the iris, but no definite keratitis punctata was seen.

He was readmitted to hospital, and topical cortisone was started on January 12, one drop three-hourly. Pain and

photophobia were relieved over the course of a few days, but improvement in vision was slower. By January 17 the eye was clearing rapidly (vision 6/60), and on January 29, when cortisone was stopped, no evidence of disease could be found. (This was approximately six weeks after the onset of the attack, the previous attack in the other eye having lasted nearly three months.)

He was discharged from hospital on February 5, and was kept under observation as an out-patient. While in the ward he was given a course of penicillin, and this has been followed by weekly injections of bismuth. There had been no recurrence up to the time of his last visit on March 16. He has defaulted since then (as he had done in the past), but it can therefore be assumed that at least he has had no recurrence of acute symptoms.

Case 3. Congenital Syphilis

A boy aged 12 had inflammation of both eyes for three weeks before reporting on January 9, 1951. He was found to have acute bilateral iridocyclitis with early interstitial keratitis. His blood W.R. was strongly positive, and he had active periostitis of left arm. He was practically blind, and showed the personality changes typical of such cases. He was admitted to hospital, and topical cortisone, one drop three-hourly, was started on January 10. Next day there was marked improvement in vision, almost complete relief of pain and photophobia, considerable clearing of the anterior chamber and circumcorneal injection, and a corresponding change in personality—he was now alert, co-operative, and cheery.

There was progressive improvement, and on January 22 the eye was almost white; there was no evidence of interstitial keratitis, but still some keratitis punctata. Cortisone was stopped and the condition remained stationary. Cortisone was restarted on February 15, after which there was further improvement, until, when it was stopped again on March 7, the only signs of activity were a few cells in the anterior chamber of the right eye. Vision in the right eye was 6/12, and in the left 6/9.

He was discharged from hospital on March 15, when there was again a slight exudate in both anterior chambers, and continued to be observed as an out-patient. While in the ward he had received 10,000,000 units of penicillin, and this was followed by weekly injections of bismuth, which he is still receiving as an out-patient. On March 29 there was still a slight exudate in both anterior chambers, and cortisone was restarted, one drop being instilled three times daily.

Case 4. Congenital Syphilis

A youth aged 17 developed iridocyclitis and acute interstitial keratitis in the left eye and painless effusion in the left knee-joint at the end of December, 1947. He was first seen on February 3, 1948. His blood W.R. was strongly positive and Hutchinsonian incisors were present. He was admitted to hospital and treated with local atropine and hot bathing, penicillin, arsenic, and bismuth. The condition subsided slowly over several months, but it was not until September that no evidence of activity was noted. Treatment was continued with courses of arsenic and bismuth until July, 1949, and a further course of penicillin was given in January, 1950. The blood W.R. remained positive.

He was free of symptoms until March 13, 1951, when he developed inflammation of the right eye. He was found to have an exudate in the anterior chamber, keratitis punctata, and deep vascularization of the cornea with patchy opacities.

He was admitted to hospital on March 16, and topical cortisone was started immediately, one drop three-hourly. For the first four days a suspension of 25 mg./ml. was used, and the immediate response (relief of symptoms, clearing of anterior chamber, and circumcorneal injection) appeared to be even more dramatic than in the other cases. The usual suspension (5 mg./ml.) was then substi-

tuted, and improvement continued. On March 29 there was still some deep vascularization of the cornea and a slight deep corneal haze, but no other signs of activity. Cortisone was stopped, and he was discharged from the ward on April 2. A week later there was still no sign of activity, and vision was 6/18. (In the left eye, the site of the previous attack, vision was only 4/60.)

On April 13, while symptoms were not present, vision was still 6/18 in the right eye, and there was no significant change in the cornea; there were slight conjunctival and ciliary injection and cells in the anterior chamber. The administration of further cortisone was contemplated to control these recent inflammatory changes. No anti-syphilitic treatment had been given up to this time.

Case 5. Congenital Syphilis

A man aged 28 developed acute iridocyclitis in his right eye while in the Army in April, 1941, and was subsequently discharged with the diagnosis of congenital syphilis. Recurrences in the right eye appeared in 1945, 1949, and March, 1950, all treated elsewhere. Each attack lasted for several months in spite of treatment (which had included arsenic and bismuth, penicillin, and artificial fever), and had resulted in progressive deterioration of vision. It was stated that the attack started in March, 1950, and had never completely subsided, but flared up about three weeks before first being seen on December 12.

On examination then the right eye showed active iridocyclitis with marked circumcorneal injection. There was evidence of previous damage with posterior synechiae, but signs of active or healed interstitial keratitis were not seen. The left eye also showed evidence of old healed iritis, but no signs of recent activity. The patient complained of photophobia and irritation in the eye, and marked blurring of vision. The blood W.R. was still positive, and, although no definite confirmatory evidence of congenital syphilis could be found, the balance was in favour of this diagnosis rather than that of acquired syphilis. X-ray examination of the chest revealed no evidence of disease.

He was admitted on December 7. Atropine was instilled twice daily, and saline drops three-hourly. No other local or systemic treatment was given. Topical cortisone was substituted on December 9, one drop being instilled three-hourly. There was almost complete relief of photophobia and irritation within 12 hours, and vision began to improve. The circumcorneal injection and other evidence of activity were still slowly subsiding two weeks after cortisone was begun, but the condition was not yet by any means completely quiescent. At this point the possibility of the condition being tuberculous in origin was considered, and the case passed out of my care.

Discussion

These five cases show the effectiveness of topically applied cortisone, even in very small quantities, in inflammatory and exudative ocular conditions associated with syphilis, acquired and congenital. It is of course difficult to assess the effects of treatment in conditions which are in any event self-limiting, but in the cases recorded the results could fairly be described as striking, and in two of them there had been previous attacks for comparison. Most dramatic were the almost immediate relief of pain and photophobia and the improvement in vision. These are of great importance especially in young patients with congenital syphilis, when the often prolonged and severe symptoms, and sometimes temporary blindness, may result in permanent psychological damage and sometimes a characteristic facial appearance.

The effect of topical cortisone on the iridocyclitis was similar to that described by other observers, and in the acute cases resolution was obtained without any signifi-

cant permanent residual pathological changes. In the three cases in which acute interstitial keratitis was present the results were also good, and scarring will probably be minimal. In two of these three cases the attack was of very recent onset, however, and in neither had the typical "salmon patches" developed.

It should be borne in mind that cortisone is not "curative," but appears merely to inhibit the inflammatory and exudative reactions typical of this type of hypersensitivity, and relapses may therefore be expected on withdrawal of the hormone as long as the hypersensitive state persists, as was found in Cases 3 and 4. Treatment may therefore have to be prolonged, or be repeated, and must also be directed against the underlying disease—syphilis. Nevertheless, the application of cortisone during such hypersensitive episodes will help to prevent the permanent pathological changes in the eye which up to the present it has been difficult to avoid, and which result in varying degrees of permanent impairment of vision:

Summary

The beneficial effect of the topical application of cortisone in five cases of syphilitic ocular disease (iridocyclitis and interstitial keratitis) is described. The cortisone was used as a suspension (5 mg. per ml. of normal saline), one drop being instilled three-hourly.

I am indebted to Mr. G. W. Black, Mr. J. Foster, Mr. J. Sherne, and Mr. P. Wilson for their collaboration in the treatment of the cases. The cortisone used in the treatment of one case was made available through the Medical Research Council and is part of a gift to the Council by Merck and Co. (North America), New York, U.S.A.

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An interesting case of human foetal malformation is described in the *Report of the Sudan Medical Service for 1948*, page 50. A stillborn, approximately full-term monster of the type known as ischiopagus, weighing 10 lb., was received from Dongola. "The peculiarly interesting feature of this monster was that one of its component individuals was male and the other female. These monsters are extremely rare, and in all previous examples the two component individuals have always been of the same sex. The occurrence of both sexes in this one indicates that it must have arisen from the fusion of binovular twins during development."