

- Horne, G. O. (1952). *British Journal of Venereal Diseases*, 28, 106.
- Leopold, I. H., Purnell, J. F., Cannon, E. J., Steinmetz, C. G., and McDonald, P. R. (1951). *Amer. J. Ophthalm.*, 34, 361.
- McLean, J. M., Gordon, D. M., and Koteen, H. (1951). *Trans. Amer. Acad. Ophthalm. Otolaryng.*, 55, 565.
- Paufique, L. (1949). *Trans. ophthalm. Soc. U.K.*, 69, 67.
- , Sourdille, G. P., and Offret, P. (1948). "Les greffes de la cornée." Masson, Paris.
- Spain, D. M., Molomut, N., and Haber, A. (1950). *Science*, 112, 335.
- Spicer, W. T. H. (1924). *British Journal of Ophthalmology*. "Parenchymatous Keratitis : Interstitial Keratitis : Uveitis Anterior." Monograph Supplement No. 1.
- Woods, A. C. (1950). *Amer. J. Ophthalm.*, 33, 1325.
- (1951a). *Ibid.*, 34, 945.
- (1951b). *Amer. J. Syph.*, 35, 517.
- (1952). *Brit. J. Ophthalm.*, 36, 401.

## 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.

Mr. A. J. KING said he had been interested in what Dr. Ashworth said about ophthalmic conditions and the effect of cortisone, and also in the addendum by Dr. Lees. He was pleased to hear that it was just as effective to use the local application of cortisone as to give the drug by sub-conjunctival injection. The latter had advantages as regards economy and greater concentration of the drug, but seemed to be rather a painful form of treatment which was unpopular with patients. Dr. Ashworth and Dr. Lees were both impressed with the effects of cortisone in the treatment of interstitial keratitis. Clearly a good deal was achieved by the suppression of symptoms which made the patient so uncomfortable; but he wondered if it would be found that the results were so much better than the older methods in the matter of ultimate effective vision. It was early to assess results in so variable a condition. So many cases of even severe interstitial keratitis did in the long run have such excellent results that it was very hard to make a true assessment. It was inevitable that enthusiasm should enter into the judgment of a form of treatment which gave so satisfactory an immediate result from the patient's point of view. However it was clear that much was achieved by the relief given to the patient.

Most of his own experience of this type of remedy had been in the treatment with ACTH of arthritis due to gonococcal infection and arthritis associated with non-gonococcal urethritis, which were very different conditions. As one would expect, the immediate results had been strikingly good in some of the cases, but they were disappointing in the long run. The drug was so expensive and in such short supply that adequate dosage could not be continued for months and the treatment had to be stopped after a few weeks with the result that the condition usually relapsed. The patient had much comfort in the first place and was much disappointed at the outcome. Certainly it appeared that these patients did not get well any more quickly than with other methods of treatment. If properly treated, the joints made an excellent recovery with other methods, and it was an open question whether anything was gained by using cortisone or ACTH for arthritis of this type.

He added that there was a point on which he would be grateful if Dr. Ashworth would give his opinion. One speaker mentioned that in certain patients the first eye was treated by older methods and then the second eye was treated with cortisone and did much better. Was it not the usual experience that the second eye to be involved was less severely affected irrespective of the method of treatment.

Dr. F. J. G. JEFFERISS said that a number of patients had been treated at St. Mary's Hospital, Paddington, with similar results. In the twenty or thirty cases seen there, none had shown any permanent scarring, whereas in the old days there would certainly have been some left with such scarring. He had found that drops were the most satisfactory form of cortisone to give; the sub-conjunctival injections did not seem to have any advantage at all. One case had relapsed repeatedly for nearly a year after the original treatment, but it now

seemed finally to have settled down, so that one had to be prepared to persist with the treatment for a long time. He was sure that this treatment was so good that one should not hesitate to give it in any case of active interstitial keratitis.

Dr. J. B. BITTNER said that in making a contribution to the discussion from his experience in Leeds, he was speaking also on behalf of Dr. Horne, Director of the Department there, in collaboration with whom the contribution had been prepared. Dr. Horne had asked him to say that he regretted that he was unable to be present at the meeting, but that he had read a draft of Dr. Ashworth's paper, and had also had the opportunity on two occasions of attending Dr. Lees's and Dr. Ashworth's clinic at the Manchester Royal Eye Hospital and of seeing some of their cases. He was much impressed by the cooperation which existed there between the ophthalmologists and the venereologists, an important factor in the management of cases of ocular syphilis. Obviously, the greatest benefit to the patient could only result where active cooperation existed.

In contrast to this happy situation in Manchester, there was reason to believe that some ophthalmologists were still unaware of the value of cortisone in the treatment of syphilitic interstitial keratitis, or were sceptical of the reported results, and that the experience of others had not been so encouraging as that of Dr. Lees and Dr. Ashworth. Recent literature emphasized the poor reputation of cortisone in many quarters in the treatment of interstitial keratitis. There were several possible explanations for this; first, ophthalmologists might have been unduly influenced by Professor Woods' somewhat pessimistic views and his reiterated statement that harm might be done by preventing vascularization of the cornea. There was no evidence yet that the latter was the case, indeed, all the evidence was to the contrary.

Secondly, experience might have been based principally on the treatment of the long-standing cases in which fibrosis or necrosis had already occurred. Such experience was bound to be uninspiring because these cases could not be expected to yield good results.

Thirdly, the dosage employed in some cases had obviously been too small. This had been admitted as a probable cause of failure by two ophthalmologists who had recently been "converted" to cortisone in Leeds after a disappointing experience at another centre. Dr. Bittner and Dr. Horne felt that it was important that this obviously unfair judgment should be corrected as soon as possible, and it was hoped that the meeting that evening would help to do this.

Experience at Leeds was limited to some twenty cases of interstitial keratitis treated over the past 2 years with topical cortisone, in nearly every case in the form of drops. Not all the cases had been under their clinical control for the whole of the time, and there were not sufficient data from which to draw definite conclusions, although certain strong impressions had been gained. On the whole, their experience had been very similar to that of Dr. Lees and Dr. Ashworth.

They would like to stress the importance of starting

cortisone at the earliest possible moment. Though they had seen almost perfect end results when treatment had been delayed, it would seem justifiable in the light of what was known about the mode of action of cortisone and about the pathology of interstitial keratitis, to conclude that the sooner treatment was started the better were the results to be expected. In any case, the patient's distress should be alleviated as soon as possible. There should be no need to delay starting cortisone until a definite diagnosis of syphilis had been made, since there was no reason to believe that any harm would be done if cortisone was used before anti-syphilitic treatment was started. In one of the most severe and most dramatically successful cases, cortisone was used for 12 days before any anti-syphilitic treatment was given. In several other patients who had not received any anti-syphilitic treatment for a year or two before the attack treated with cortisone, no further anti-syphilitic treatment was given. In all these patients the end results were perfect, although the impression had been gained that the attacks were more prolonged. In other words, they believed with Dr. Lees, although they were not yet in a position to prove it, that concurrent anti-syphilitic treatment was important.

The fact that attacks could be controlled completely in this way, without concurrent anti-syphilitic treatment, incidentally provided confirmatory evidence that syphilitic interstitial keratitis was purely a hypersensitivity manifestation. About half the patients had been treated as in-patients from the beginning, and the results in such cases were better than in those treated as out-patients. It was believed that the difference was attributable at least in part to the more frequent and satisfactory application of the hormone. Experience was principally confined to drops, but for out-patient treatment ointment or even sub-conjunctival injections might be preferable, depending on the cooperation to be expected from the patient.

Like Dr. Ashworth, they were unable to give any contribution to the solution of the difficult problem of how long cortisone should be continued. In some cases the cortisone had been stopped within a few days of all evidence of activity having disappeared, and in none of these had there been any recurrence of the keratitis. In two, however, further cortisone had to be used to control a slight exudate into the anterior chamber of the eye. The range of days during which cortisone was used in in-patients was from 14 to 56, and in a few out-patients cortisone was continued in almost homoeopathic doses for periods up to several months. It was impossible, however, to discover what would have happened had cortisone been stopped earlier. This was the crux of the whole problem, since each episode was self-limiting, and since there was such an individual variation. It was doubtful whether such homoeopathic doses were likely to have any influence on the course of the attacks.

While it was obviously not justifiable to convince the sceptical of the value of cortisone by using it in one eye when both were involved at the same time and keeping the other as a control, the material at Leeds had incidentally provided a number of cases in

which this comparison could be made. In these cases one eye had been involved before cortisone was available and on every occasion some impairment of vision had resulted; when the second eye became involved cortisone was used and there had been no impairment of vision.

Evidence was still required regarding the types of long-standing cases which would benefit from cortisone therapy. It was apparently very difficult to determine from clinical examination when the cornea had reached its final stage of fibrosis and the process was irreversible. Long-standing cases should not always be dismissed as unsuitable until an adequate trial had been given.

Dr. Ashworth had stressed the value of atropine. Cortisone prevented the inflammatory reaction and atropine stopped the formation of posterior synechiae. If the cortisone stopped the inflammatory reaction which was the cause of posterior synechiae, why was the atropine needed?

DR. R. M. WARREN said that one case treated at his hospital was worthy of note. A girl aged 13 had had an attack of interstitial keratitis in the pre-cortisone era and the response to treatment had been slow. Her mother brought the girl to see him in a great state of distress because in 3 weeks' time she had to sit for a scholarship examination and would have no further chance of sitting it. The girl had a history of pain and photophobia. She was admitted to hospital immediately and given cortisone drops and penicillin treatment. In 3 days she had no pain and no photophobia and asked to be allowed to return home and continue to work for the examination. This she was allowed to do, and she continued studying while her own doctor supervised the daily penicillin and the cortisone drops night and morning for 2 weeks. The girl sat for the examination and it had been very gratifying to learn that she had got her scholarship.

DR. C. S. NICOL agreed with Mr. King that the uses of cortisone must not be over-emphasized. It was only fair to say that Dr. Ashworth had also made this plain. He gathered that the cases which Dr. Ashworth described had all had anti-syphilitic treatment in dosage which approached that described by Sorsby (1948). This type of penicillin therapy had quite recently been the treatment of choice for interstitial keratitis.

Another point of interest was the question of the involvement of the second eye once cortisone and anti-syphilitic treatment had been given for the first eye involved. He had seen only a few patients with interstitial keratitis himself, but one of these, a girl with Clutton's joints, developed keratitis after a large dosage of penicillin. She was given sub-conjunctival and intramuscular cortisone and then developed interstitial keratitis in the second eye within a few weeks. He would like to ask Dr. Ashworth how often the second eye had been involved in his cases. If this could happen, it had to be recognized that treatment with cortisone was not the complete answer, however much the disease had been modified.

Dr. Ashworth had said he had treated a number of

cases of iridocyclitis but none had been syphilitic in origin. He had also said that cortisone might be used in these cases, but in work carried out on rabbits (Turner and Hollander, 1950) it had been found that the administration of cortisone in early syphilis increased the number of spirochaetes in the lesions. Therefore one should be cautious in advocating the use of cortisone in early syphilis even combined with penicillin. Cortisone, while relieving the symptoms and signs of iridocyclitis, might at the same time interfere with effective antisyphilitic therapy.

DR. R. C. L. BATCHELOR said that Dr. Ashworth had given a very admirable presentation of a subject of general interest. The experience in Edinburgh had been of better results in boys and girls than in adults. There had been some definite failures among the adult patients, but these had been fairly advanced cases. He thought that possibly that was what one might expect because of the power of recovery in young people. In one adult, the drug was given by sub-conjunctival injection; perhaps the patient had too many, fourteen being given, and the end result was a staphyloma of the cornea. He did not think that cortisone would have any influence at all in preventing the involvement of the second eye. With regard to the idea that the second eye might be less severely involved than the first, one adult developed interstitial keratitis for the first time at the age of 50 and her second eye was very much worse than the first.

He was afraid he could not speak from a large experience of cortisone therapy; these were just personal impressions.

DR. C. P. HEYWOOD said that in two cases he had treated in Bradford the second eye had developed an acute interstitial keratitis while the patient was still under cortisone. The first was a girl of 18; she was treated for a month with a combination of penicillin, bismuth, and cortisone, but because of the short supply of cortisone this drug was discontinued and treatment was continued with penicillin. The initial eye relapsed at the end of a month and the second eye began to go a week later. The patient was told to put the drops into both eyes and the second eye settled down immediately. The cortisone was continued for 6 to 8 months and eventually the first eye recovered.

The second case was that of a man of 37 who developed interstitial keratitis in one eye. He was given intensive treatment with cortisone, penicillin, and bismuth and it was decided to carry on the treatment at home. After 3 months the second eye was affected and the patient was brought into hospital. He was put on to cortisone and recovered.

Another patient was a girl of 10 years who had had interstitial keratitis for 6 months. She came to the department when the acute inflammatory process had subsided and there was intense opacity. Since the condition was congenital and the child was so young, she was admitted to hospital, although normally such a case would be regarded as not likely to respond to

treatment. To his amazement the condition had cleared within 10 days.

LT.-COL. B. LEVY asked whether Dr. Ashworth had treated any cases with cortisone alone, without penicillin or other anti-syphilitic treatment.

Recently he had seen a soldier with interstitial keratitis, who had been treated a year previously for the same condition with cortisone and penicillin. On this occasion the patient was treated with cortisone only and responded well.

THE PRESIDENT (DR. D. J. CAMPBELL) said that he would like especially to ask a question relating to interstitial keratitis in the second eye of a patient recently treated with cortisone. The old bugbear of occurrence in the second eye, with which they were all familiar and about which it was still necessary to warn patients, was still present with them even when cortisone was the adjuvant in the first case. Many theories had been advanced for the formation of interstitial keratitis in conjunction with syphilis, one such theory being concerned with allergy. It was thought that cortisone acted as an anti-allergic agent, and yet in two cases which he had seen there had been marked allergy in the treated eye with oedema of the lids and down the cheek on the affected side. In each case the allergy was due to atropine. Once one got down to it, having pushed on the anti-syphilitic and cortisone therapy, it was found that the atropine was the cause of the inflammatory reaction. This was a point to remember; that there might be something behind the condition of congenital syphilis.

The two worst cases he had seen in the last year had been in patients who had not in the first instance been accepted by the ophthalmologist as congenital syphilitics, because they were serologically negative. Treatment was carried on for a considerable time with cortisone alone until in the end the ophthalmologist asked him if he thought that the old congenital syphilis which had not been treated for more than 10 years, might have left some mark in the other eye. Somewhat empirically, he agreed to carry out anti-specific treatment and there seemed no doubt that the effect of penicillin plus bismuth, in conjunction with cortisone, caused a reasonably rapid improvement. There again, getting it at a later stage, one saw the idiosyncrasies of the condition, with the eyes at the turning stage before one saw them. He wondered if Dr. Ashworth had any views as to the relation between age of patient and the efficacy of cortisone.

DR. ASHWORTH, replying to the discussion, thought that Mr. King was quite right to say that one should not be too enthusiastic about cortisone at such an early stage. It was a remarkable thing that a cornea could be so completely involved, and still produce such a remarkably good visual end result. He thought, however, that there was still the odd case which did give a bad visual result. It seemed difficult to say at first sight what the eventual result would be whether cortisone

was used or not. There might always be an odd case in which a bad visual result might have been prevented by the use of cortisone.

It was also remarkable that the patient was saved much discomfort by the use of cortisone; this was an important factor, and, after all, so far as one could say at present, no harm had been done by using cortisone in these cases.

As Dr. Bittiner had suggested, one had to be sure that the patients were in fact getting the treatment prescribed. One could judge whether the atropine had been used by the condition of the pupils, if they did not respond correctly one might assume that the atropine, and therefore the cortisone also, had not been used.

He had been asked whether atropine was necessary, and would say from his own experience, although he had never actually treated a case without atropine, that it was most decidedly important to give it. Cortisone suppressed the signs of inflammation. One could not tell what was happening in an eye simulating a cure, and he thought that, if atropine were left out in these cases, the number of relapses on withdrawal might be greater.

No cases had been treated without penicillin. In some about a week had elapsed between starting cortisone and giving penicillin, but he thought that since cortisone was really only an ancillary treatment, it was most important that concurrent therapy should also be given.

He was interested in the point about atropine causing irritation, whilst the case was still on cortisone. He had also had the experience that local cortisone would not always suppress atropine irritation.

They had tried one case with systemic cortisone and the irritation had been controlled, but he understood from the literature that cortisone would not always prevent atropine irritation. If irritation occurred, the answer was to change to some other mydriatic, such as hyoscine.

With regard to the second eye, he agreed with Mr. King that the degree of involvement was often not so severe in the second eye, but he did not think that cortisone would prevent an attack in the second eye.

In fact, in a few cases, interstitial keratitis had developed in the second eye within a month or two. So far as he was aware, cortisone acted only at the time it was being put in the eye.

The cortisone suppressed the inflammation and the exudation at the time it was used, and when it was stopped its effect was discontinued. He did not think it would play any part in preventing an attack in the second eye. Where cortisone was used topically, an eosinophil count was taken to see whether there was a drop in the figures, but this was not seen, and from the information obtained, it was assumed that the effect was purely a local one.

He was interested in Dr. Batchelor's mention of the young girl. Their series included several children about 4 years old, who seemed to respond better than the older patients, the results in those he had treated having been exceptionally good.

#### REFERENCES

- Sorsby, A., ed. (1948). "Modern Trends in Ophthalmology," vol. 2, p. 409. Butterworth, London.
- Turner, T. B., and Hollander, D. H. (1950). *Bull. Johns Hopk. Hosp.*, 87, 505.