AUREOMYCIN IN OPHTHALMOLOGY (A Preliminary Report)

BY

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AUREOMYCIN (Lederle), a new antibiotic which has been obtained from a mould belonging to the streptomyces group, has not been employed sufficiently in ophthalmology to allow an accurate assessment of its value. The fact, however, that it has been shown to inhibit the growth of a considerable number of organisms such as staphylococcus, pneumococcus and *H. influenzae*, as well as of rickettsiae and a number of viruses, indicates that it may perhaps occupy a valuable place in our therapeutic armamentarium. One important use, of course, is in the treatment of organisms which are insensitive to penicillin. It is extremely suggestive that it has been found to be effective against the group of large-sized viruses typified in those responsible for lymphogranuloma venereum and psittacosis.

The only reports of a large group of infections treated by aureomycin in the literature, are those of Braley and Saunders (1948-1949). These authors treated a number of various conditions, finding the drug to be effective against several gram-positive cocci and gram-negative bacilli; they also found it to be an effective therapeutic agent in inclusion conjunctivitis and in herpes simplex of the cornea. While being unable to reach a definite conclusion, they found it more effective against the virus of epidemic keratoconjunctivitis than any other antibiotics or drugs which have yet been tried. It is interesting that they treated with success one case of trachoma. A second report on the treatment of trachoma has come from Portugal (Moutinho, Grilo and Moura, 1949). These authors, using both drops and an ointment given two-hourly day and night for a period of from 2-6 days, reported extraordinarily encouraging results in 15 cases of trachoma at various stages of the disease, many of them showing well developed follicles, cicatrization or ulcerative pannus. They claimed that for the first time a remedy had been found which causes the disappearance of the lesions in a matter of days.

The supplies of aureomycin available to us were small, so that the number of cases reported here are insufficient to allow any firm conclusions. It is interesting that with regard to the various infections found commonly in Great Britain reported in the first part of this paper, the results have not been extremely dramatic; the

control of a virulent case of recurrent hypopyon uveitis, however, is of interest. A small quantity of the drug was sent to Uganda, in view of the fact that trachoma of a virulent type is exceedingly common in this country, and the dramatic results reported may be of great importance. To reason from 8 cases, of course, is extremely dangerous, and before any conclusion can be reached much larger numbers will require to be treated, preferably in different parts of the world; but if the promise of these early cases is maintained, a therapeutic agent will have been discovered which may bring great changes, socially and economically, to vast tracts of the world.

SOME CASES TREATED WITH AUREOMYCIN

BY

D. AINSLIE

ALTHOUGH the number of cases treated here with aureomycin is still too small to enable any definite conclusions to be drawn, I think it may be of value to record the results obtained so far. Reports of 33 cases are given and these consist of inflammatory diseases of uncertain aetiology, those due, or believed to be due to viruses and those due to organisms insensitive to penicillin. Many staphylococci, streptococci and pneumococci are highly sensitive to aureomycin, but simple infections with the organisms have not been treated as they also respond readily to penicillin.

Administration

For systemic use the drug was administered orally in the form of aureomycin hydrochloride in doses (for adults) from 500-750 mgms. six-hourly up to a total of approximately 20 gms.

The HCl salt is too irritating to be instilled into the conjunctival sac and consequently aureomycin borate must be used for local application. In every case the drops consisted of:

Aureomycin HCl	...	...	...	...	25 mgm.
Sodium borate	...	...	...	...	25 mgm.
Sodium chloride	...	...	...	...	625 mgm.
Distilled water	...	...	...	...	5 cc.

One or two drops of this solution were instilled hourly or two-hourly.

After the water has been added to the mixture, the aureomycin

rapidly loses its antibiotic activity and therefore fresh drops must be prepared at least every 48 hours.

Cases requiring local administration only were treated as out-patients except where there was reason to believe that the drops were not being properly instilled. With the exception of three cases, all who had the drug systemically were admitted to hospital.

Toxic Manifestations

No serious toxic effects were noticed. Of the eighteen cases receiving aureomycin orally twelve had mild diarrhoea and of these nine complained of nausea; vomiting occurring in three. The administration of Aludrox gm. 2 following the dose of aureomycin reduced the nausea in some cases only. One patient complained of no symptoms until, after receiving 18 gm., she had a syncopal attack. The drug was stopped and she improved rapidly. It is difficult to say whether or not the attack was caused by the aureomycin.

Cases Treated

Blepharitis (one case). This patient had had blepharo-conjunctivitis for six months. This was associated with recurrent styes, thirteen having occurred. The eyes were constantly red and sore. Previous treatment had consisted of three courses of intramuscular penicillin, the total dosage being about 7 million units. There had been several courses of penicillin drops. Intra-muscular colloidal manganese had also been given. When seen on October 13, 1949, she had marked blepharitis with minimal conjunctivitis. A culture had been taken and had shown a staphylococcus pyogenes which was insensitive to penicillin but sensitive *in vitro* to aureomycin.

Treatment with aureomycin was started, giving 750 mgms. six-hourly up to a total of 18 gms. In addition, drops were instilled hourly. At the end of a week the eyes felt comfortable and appeared much improved. When seen again on November 13, 1949, the left eye appeared normal, but there was slight conjunctivitis of the right. Further drops were given for four days. On November 27, 1949, both eyes appeared normal. It is impossible to say that the condition will not recur, but it certainly appears that aureomycin has been of great value.

Conjunctivitis due to H. influenzae (one case)

This patient was a child aged 2½ years who had had discharging eyes and nose for nine months. Penicillin drops, albucid and mercury oxycyanide lotion had failed to bring any improvement. On May 16, 1949, aureomycin drops were instilled into each eye and to each nostril every hour and continued for four days. At the end of this time the eyes and nose were dry for the first time in nine months. Treatment was stopped, but three days later the symptoms recurred. On May 25, 1949, treatment with further drops was started and also 250 mgm. of aureomycin was given six-hourly by mouth to a total of 5,500 mgm. The lacrimal sacs were syringed daily with aureomycin. On June 1, 1949, the eyes began to discharge slightly. The condition remained static until June 23, 1949. A further culture on this date revealed *H. influenzae* and culture from the eyes and noses of the parents also revealed the same organism, though the parents were symptom-free. It was thought desirable to treat all three subjects, as there was the possibility of re-infection. This was suggested but, unfortunately, the patients did not attend again and it has been impossible to get them to do so.

Although the child was certainly not cured aureomycin was the only drug that had affected his condition favourably.

Inclusion conjunctivitis (one case)

This patient had complained of pricking eyes for seven months. Penicillin and albucid drops had been ineffective. When seen on June 22, 1949, both upper tarsal conjunctivae were injected and covered with minute follicles so small as to give a velvety appearance. Scrapings from the tarsal conjunctivae showed numerous inclusion bodies; there was no growth on culture. Aureomycin drops were applied half-hourly to the everted lids and the lacrimal sacs were syringed with aureomycin daily. Improvement of symptoms and signs occurred. On July 21, 1949, the eyes were slightly red and a further scraping of the conjunctiva showed a few inclusion bodies. Further drops were given and also 12 gm. of aureomycin *per os*. On August 11, 1949, the eyes appeared normal and scrapings revealed no inclusion bodies. The patient has been seen from time to time since, and, though much better, still has a sensation of grittiness. Further scrapings have not revealed inclusion bodies. Although there are now no follicles of the tarsal conjunctivae these remain slightly injected and additional aureomycin has failed to improve this.

Dendritic ulcer (nine cases)

Seven cases of fresh dendritic ulcers were treated with aureomycin drops. In none was there any improvement. One longstanding case with deep corneal ulceration failed to respond to aureomycin drops and a systematic course was equally ineffective. One case which had been carbolyzed two days previously was treated. The ulcer no longer had a dendritic form, but there was a large, deep ulcer in the lower cornea. Aureomycin drops were given and the ulcer healed after five days. I feel that in this case aureomycin was useful only in so far as it prevented secondary infection.

Herpes ophthalmicus (one case)

This was a case of ophthalmic herpes with iridocyclitis. 15 gm. of aureomycin was given without noticeable effect.

Superficial punctate keratitis (five cases)

All cases were characterized by numerous small points of superficial keratitis, the majority of which involved the epithelial surface and led to staining with fluorescein. In every instance treatment with aureomycin drops was continued for at least seven days, but, apart from temporary subjective improvement in two cases, the conditions were unaffected.

Disciform keratitis (two cases)

The first case, which followed a corneal abrasion, had been receiving treatment with albucid and atropine drops for two weeks before aureomycin was started. The condition was remaining approximately static. Slight improvement occurred during this period.

The second case followed superficial punctate keratitis. On August 22, 1949, keratitis disciformis was diagnosed. Treatment with mydriatics, guttae penicillin and sulphathiazole ionization were tried, but by October 10, 1949, the condition was not improved. On this date there was a dense central corneal opacity, the cornea was thickened centrally and there was marked ciliary injection. Lacrimation was extreme. Aureomycin drops were given hourly for ten days and at the end of this time there was marked improvement, there being only slight ciliary injection and lacrimation. The corneal opacity appeared unchanged.

Iridocyclitis (twelve cases)

In eleven cases the iridocyclitis was chronic and characterized by numerous fine keratic precipitates and circulating cells in the anterior chamber. In every case

the condition was bilateral. In addition two cases showed periphlebitis retinae and in one there was a patch of acute choroiditis. No general disease was found in any of these cases. All patients were treated with aureomycin given orally, the total dosage ranging from 15 to 20 gm. In no case could any definite improvement be observed.

One case of recurrent hypopyon uveitis was treated. The history was of attacks of misty vision and redness of the eyes for nine years until, in 1948, the left vision "went altogether" and the right became permanently much worse than previously. When seen on August 17, 1948, the left eye was quiet with old k.p. and lens opacities, the visual acuity being bare perception of light. The right eye was injected and there was a 1.5 mm. hypopyon and numerous circulating cells in the anterior chamber. The pupil was dilated from previous atropine. Vision was reduced to counting fingers at one metre. Systemic aureomycin was given to a total of 20 gm. On August 24, 1949, the hypopyon had gone and the eye was white, but an aqueous flare remained. The patient continued to be well until October 20, 1949, when the hypopyon again recurred in the right eye. A further 23 gm. of aureomycin was given. On October 27, 1949, the eye was again white and the anterior chamber was clear, except for a few circulating cells. Vision was 3/60. The patient is convinced that the aureomycin has cut short his acute attack in each case. It is, however, uncertain as yet whether it has really influenced the disease favourably.

Sympathetic ophthalmitis (one case)

The case was one of sympathetic ophthalmitis occurring two months after cataract extraction. Systemic penicillin and N.A.B. had been given without success. Aureomycin was given orally, but only up to 7,500 mgms., as the patient, who was already mentally unstable, became unmanageable and the course had to be stopped. No improvement was noticed.

SUMMARY

1. Results obtained in 33 cases treated with aureomycin are given and the method of administration described.
2. Cases of chronic iridocyclitis did not appear to benefit with the possible exception of a case of recurrent hypopyon uveitis.
3. Dendritic ulcers and superficial punctate keratitis did not respond. One case of keratitis disciformis appeared to benefit.
4. A case of blepharitis due to non-penicillin-sensitive staphylococcus has benefited initially.
5. An infection with *H. influenzae* improved while under treatment.
6. An example of inclusion conjunctivitis was treated and showed marked improvement.
7. One case of herpes ophthalmicus and one case of sympathetic ophthalmia were treated without benefit.

I wish to thank the Surgeons of Moorfields, Westminster and Central Eye Hospital and St. George's Hospital for their kindness in referring cases for treatment.

AUREOMYCIN IN TRACHOMA

BY

A. J. BOASE

UGANDA

THROUGH the kindness of Sir Stewart Duke-Elder I have been able to put to a clinical trial the new antibiotic aureomycin (Lederle) in a few cases of trachoma. The number is very small, as was the quantity of aureomycin at my disposal. Nevertheless I feel that a description of the cases and the results obtained will be of interest to others working on the problem of trachoma.

CASE 1. Ganda woman, age 30 years. Profuse lachrimation and photophobia for over a month. There were numerous follicles scattered over the tarsi, and very many of MacCallan's "bleb-like excrescences" chiefly at the transition folds. An early papillary hypertrophy was present. Pannus was obvious to the unaided eye, the vessels reaching to the centre of the corneae. There was nothing to choose between the two eyes.

She was put on 3-hourly aureomycin drops for ten days, after which no treatment of any sort was given. On the 15th day a careful slit-lamp examination was made. I could detect no follicles. The tarsal surfaces which now appeared normal to the naked eye showed a slight roughness under the microscope. Indefinite "sago grains" still seemed to be present in the lower fornices. The most surprising finding was in regard to the pannus: the corneae were bright and had a normal window reflex, and with the slit-lamp all that I could see was the merest fringe of vessels at the upper limbus.

Through an oversight a conjunctival scraping was not taken until the third day of treatment: inclusion bodies were not found.

The patient refused to stay any longer in hospital, insisting that she was cured, and as she has not returned since discharge (August 8, 1949) it might be assumed that there has been no relapse.

CASE 2. An elderly Ganda woman was admitted with acute muco-purulent conjunctivitis superimposed on a trachoma which was otherwise similar to Case 1 though more advanced. She had drops of penicillin and sulphacetamide for three days before being put on aureomycin. The subjective symptoms of the conjunctivitis were considerably relieved by that treatment, but the objective signs of the trachoma were uninfluenced. As in the first case, aureomycin was used in 3-hourly drops. After a few days there was a remarkable improvement in her condition as seen with the unaided eye. Unfortunately she decamped from hospital before I could make a slit-lamp examination, having told the nurse that she saw no sense in staying as she was cured. (The absconding of interesting cases in the middle of a piece of research is something that those working in native hospitals have to contend with.)

CASE 3.—Ganda male, about 40 years old. Eyes bad for two months: profuse lachrimation, distressful photophobia, much mucoid discharge. Gross shaggy papillary hypertrophy interspersed with large blebs which in the fornices stood out in the classical manner of boiled sago or frog's eggs. Pannus vessels large and well below centre of corneae. The right tarsus showed a large splotch of melanin-like pigment from top to bottom and about one third its width. Altogether a typical "bad" trachoma as we see the disease in Uganda with a correspondingly bad prognosis. Conjunctival scraping was unsatisfactory because of haemorrhage from the papillae at the lightest touch: inclusion bodies were not identified.

Patient was put on one drop of aureomycin at 4-hourly intervals. Discomfort soon disappeared and the secretion stopped. On the 10th day I noted that his appearance was normal and that he would not be picked out as a likely trachoma in a parade. He himself said he was cured. The right tarsus still showed obvious

papillae and there was no change in the pigmented patch; in the left tarsus regression of the papillae was more evident. Pannus was now represented by a very narrow fringe of vessels across the limbus. Patient was persuaded that his relief might be only temporary and that an operation would ensure a permanent cure. He readily agreed and a bilateral tarsectomy was performed ten days after stopping aureomycin treatment. The excised tarsi were sent to Sir Stewart Duke-Elder, who has since kindly informed me that "there is no doubt whatever that the slide you sent us is trachoma."

CASE 4. Toro girl, age 15 years. Admitted because of a severe trachoma in her only seeing eye. This, the left, showed gross papillary hypertrophy and macro-pannus over the upper fifth or quarter of the cornea. Photophobia and mucoid secretion were pronounced. The right cornea was opaque and the bulb phthisical, the tarsus similar to the left. There was a marked improvement in the subjective symptoms after a week's treatment with aureomycin one drop at 4-hourly intervals but not as dramatic as in the foregoing cases. It was thought that vernal catarrh might be a complicating factor as the papillae showed a tendency towards cobbling, so the tarsi were excised. The histopathology of the section is that of trachoma and does not suggest vernal catarrh. Noteworthy is the fact that the cellular infiltration is nowhere as dense as one would expect to find in a case of trachoma with similar clinical signs: follicles are conspicuously absent. An unusually high proportion of the deeply-invading epithelial cells show gross distension of the goblet-cell type. I have not recognized any inclusions in the sections.

CASE 5. Ganda male, age about 40 years. Eyes bad for nearly two years. In February, 1949, he was in hospital for two weeks with a trachomatous ulcer in the left cornea. His record shows that there was then gross papillary hypertrophy and marked macro-pannus in each eye. On September 6, 1949, he was readmitted with a very inflamed right eye, the lids being swollen and lacrimation profuse. There was a large trachomatous ulcer just above the centre of the cornea. Each eye showed gross shaggy papillary hypertrophy, and pannus was obvious to below the corneal centre without optical aid. He was put on aureomycin one drop 4-hourly for ten days, during which period he had an acute attack of bacillary dysentery and was treated with a four days' course of sulphaguanidine. On September 19 he insisted on his discharge saying he was cured. A careful examination was made and the following notes recorded. The left tarsus is smooth, shiny and shows fine criss-cross scarring; the right is smooth with just a trace of roughness and shows rather pronounced band-form scarring. Pannus in the left eye is represented by very attenuated vessels in the upper quarter of fifth of the cornea; in the right there are more vessels leading to the healed ulcer but all are thin and regressing. Each cornea shows in the horizontal central area a brown pigmentary stippling in the epithelium (a common finding in trachoma as seen in Uganda).

CASE 6. Ganda male, age about 45 years. Three weeks' history of sore eyes. There was a very fine papillary hypertrophy and many follicles scattered over the upper tarsi with numerous blebs at the transition folds. Macro-pannus was obvious in the upper third of each cornea. The centre of the left cornea was occupied by a large leucoma which extended nearly to the lower limbus. The usual subjective symptoms of photophobia and lacrimation were marked. He was treated with aureomycin, one drop at 4-hourly intervals, for ten days when I recorded that although the fine papillary hypertrophy was still present his condition was vastly different from what it was on admission. He left hospital and was not seen again for six weeks. My notes then recorded that the tarsi appeared perfectly normal and that all that remained of the pannus were a few empty vessels across the limbus. Corrected vision in the right eye was 6/6.

CASE 7. An elderly European lady had had sore eyes for nearly a month, and had been bathing them with boric lotion. Lacrimation was marked in the right eye, less in the left. Numerous follicles were present on the upper tarsi, more so in the right. The slit-lamp showed profuse vascular "bouquets" rising towards the canthi into small papillae. There was no pannus but the upper limbal vessels were full and gave the impression that it would not be long before they started budding. My diagnosis was trachoma, stage 1, but pending pathological

confirmation she was given penicillin drops. The report on a conjunctival scraping was "a very adequate scraping. Purple-staining granules are present in many of the epithelial cells. I am not, however, prepared to say that this undoubtedly trachoma." (A. B. Raper.) Patient returned two days later and said that if anything she thought she was worse; there was certainly no objective amelioration. She was given a 5 mil. bottle of aureomycin and told to put a drop in each eye every three hours. Four days later she reported that she felt a different woman and was certain she was cured. But while the distressing lacrimation had entirely ceased, I was not satisfied that there was any real change in the appearance of the tarsi, so I instructed her to carry on with the drops for another week. When she returned at the end of this period the tarsi appeared normal to the naked eye, although with the slit-lamp a few small follicles and capillary trees could still be identified. She was told to return if the symptoms recurred, however slightly. This was over three months ago, and as she lives quite near me it may be taken that there has been no relapse.

CASE 8. A senior European official had had a sore left eye for over a week. There was no real pain but the discomfort and incessant watering were "getting him down," to use his own words. On the advice of his medical officer he had been using drops of albucid and of penicillin without any benefit, in fact he thought he was getting worse. Like many others who have spent years in the open in tropical countries he has a chronic catarrh of the conjunctiva. On examination I found the left tarsus red and velvety. With the slit-lamp very small follicles could be identified; there was a suspicion of neo-vascularization at the upper limbus. There was no secretion apart from the lacrimation. Conjunctival scraping was inconclusive. He was put on aureomycin 2 drops at 3-hourly intervals for eight days. By then all his symptoms had gone; as a matter of fact he had said he was cured after the third day. Treatment was finished off with an ionisation with zinc sulphate, since when (over three months) he has had no further trouble. In this case the diagnosis of trachoma, stage 1, was made on the slenderest of grounds, and I would not cavil with anyone who declines to accept it. Nevertheless the treatment was based on the diagnosis and the outcome is what was desired.

SUMMARY

Eight cases of trachoma are presented. All were treated with the conjunctival instillation of drops of aureomycin. The therapeutic results, even although the series is much too small to warrant a final conclusion, warrant the opinion that aureomycin will cure the disease in an incredibly short time. The optimum dosage and mode of administration is not yet settled, but in these cases highly satisfactory results followed the simple (and economical) routine of one drop at four-hourly intervals.

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