Felidae and other Carnivora now introduces an additional element of value—namely, stereoscopic vision, by which I mean that the images from both eyes are now beginning to be laid over one another alternately in the visual centres, first, in the external geniculate bodies, and thence via the optic radiations in the calcarine and neighbouring cortex. This factor doubtless increases the accuracy of fusion of images in depth.

Development of the Hand and Thumb in Co-ordination with Stereoscopic Vision

In the higher mammalian group of primates and man the importance of catching living food has disappeared, as apes and monkeys are mostly fruit eating, and man also is largely fruit eating and agricultural. There is now a more important reason for the development of stereoscopic vision of the highest type, in the increasing importance of the hand in seizing objects for inspection, and for important manual work of all descriptions requiring accurate vision. No one could watch the monkeys in the outdoor cages at the Zoo without noticing how they use the hand and vision in co-ordination for receiving and inspecting the morsels offered to them. Though improvement in vision for hunting animal food is no longer necessary, the human hand is an immense improvement on that of the monkey, chimpanzee, or gorilla—in the development of the thumb and thenar muscles in proportionate strength and the power of opposition of the thumb to the other fingers. By this improvement the value of the hand as a working tool acquires much greater delicacy of movement and co-ordination with vision in its manifold uses of building and of manufacturing tools, objects of vertu, and works of art of every description, as exemplified by a Michelangelo or a Raphael in sculpture and painting, or a Cellini in gem making. In these arts the closest co-ordination of eye and hand is essential, but with musical instruments vision plays little part in the marvellous execution of a Paganini or an Abbé Liszt. Here the ear and memory, and the intensity of practice, take the place of vision.

The monkeys and apes have concentrated on developing all four limbs with four hands, as *Quadrupana*, and the South American monkeys have added even a fifth "hand" in their prehensile tail, thus making an ideal machine for tree-climbing and swinging from branch to branch, and enabling them to travel long distances along the upper regions of the primeval forests without danger from carnivorous enemies on the ground. The offshoot, man, has concentrated on his fore-limb only, and by hand and vision combined—with increasing brain development, the acquisition of speech, and the discovery of fire, of agriculture, firearms, steam power, electricity, the telephone, the internal combustion motor, and, lastly, the means of flying, in ever-hastening speed of invention—has gradually developed from his doubtful position as a cave man to his present supremacy in the living world.

We have yet to see whether the most recent and most powerful invention, atomic fission, will be harnessed for peaceful production of power for all the nations, when all the coal and oil have been used up, or whether it will lead to the greatest means of destruction of civilization in history.

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AUREOMYCIN, CHLORAMPHENICOL, AND TERRAMYCIN IN OPHTHALMOLOGY

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The place of the sulphonamides and of penicillin in ocular infections mainly due to Gram-positive organisms, and of streptomycin in infections mainly due to Gram-negative organisms, is now well established. None of these agents has, however, proved of much use in virus infections, except that the sulphonamides are valuable in the treatment of trachoma and in inclusion blennorrhoea, with penicillin almost as effective in the latter infection. The newer antibiotics with their alleged efficacy over a wider range of viruses offer the possibility of therapeutic agents in ocular infections which are due to viruses and are not readily controlled. Outstanding among these are dendritic ulcer, disciform keratitis, epidemic keratoconjunctivitis, and herpes ophthalmicus. Dendritic ulcer of the cornea, a not uncommon condition, shows varying severity and a tendency to frequent relapses. Disciform keratitis, with its dense interstitial infiltration, generally leads to much loss of vision from the resultant interstitial fibrosis. Ocular complications of herpes ophthalmicus, which include a variety of corneal reactions, iridocyclitis, both active and quiescent, and episcleritis, as well as destructive corneal ulceration, are serious considerations. Epidemic keratoconjunctivitis is the least significant from the point of view of resultant damage, but its prolonged course, marked symptoms, and occasional sequels of dendritic ulceration and disciform keratitis, as also the frequency with which it occurs during epidemic periods, present problems of some magnitude. Evidence for the virus origin of these affections is best in herpes ophthalmicus, and almost as definite in dendritic ulceration and in disciform keratitis; the virus origin of epidemic keratoconjunctivitis is less definitely established. Whilst there is little doubt that the first three of these affections are due to a virus of the herpes group, such little as is known of the morphology of the virus of epidemic keratoconjunctivitis suggests that it has some affinity to the virus of trachoma. The assumption that viruses are responsible for a variety of other nondescript corneal and iris reactions has as yet little support.

In the present study an attempt has been made to assess, experimentally and clinically, the value of the different modes of administration of aureomycin, chloramphenicol, and terramycin. The difficulties in establishing experimental virus lesions in animals on which these agents could be tested have precluded any experimental assessment of these drugs. We have had to rely instead on clinical observations.

Aureomycin

Experimental Studies

Intraocular Levels on Systemic and on Subconjunctival Administration.—Preliminary findings in the rabbit gave the following tentative results. (1) Intramuscular injection (100 mg.): No aureomycin could be demonstrated in the aqueous, vitreous, and cornea after two and four hours, except for one reading of 0.8 $\mu\text{g./ml.}$ in the aqueous of one rabbit. (The blood level was adequate at two hours.) (2) Subconjunctival injection (10 mg.): At one and a half and two and a half hours there were tangible levels in the aqueous (2 and 1.25 $\mu\text{g./ml.}$ respectively) and in the cornea (10 and 20 $\mu\text{g./g.}$ respectively). The levels in the vitreous were lower (0 and 0.5 $\mu\text{g./ml.}$ respectively).

Using a plate diffusion method, with *B. subtilis* as the test organism, the results recorded in Table I were obtained. It will be seen that levels reached with aureomycin when

TABLE I.—Aureomycin Hydrochloride: Concentrations in the Aqueous, Vitreous, and Cornea of the Rabbit Reached by Different Dosages and Methods of Administration (Test Organism: *B. subtilis*)

Mode of Administration	Time in Hours	Aureomycin Levels ($\mu\text{g./g.}$ of Tissue)			
		Blood	Aqueous	Vitreous	Cornea
Intramuscular injection: 200 mg.	1	0.5	<0.2	<0.2	<0.3
	2	0.5	<0.2	<0.2	<0.3
	4	0.3	<0.2	<0.2	<0.3
Oral: 200 mg.	1	4.0	1.8	<0.1	1.4
	2	2.9	<0.1	Tr.	<0.3
	4	2.5	Tr.	Tr.	Tr.
	4	2.0	<0.3	<0.3	—
	6	Tr.	<0.3	<0.3	<0.3
	15†				
Subconjunctival injection: Crystalline 50 mg.	1	<0.1	<0.5	<0.5	11.8
	2	0.1	<0.5	<0.5	1.3
	4	<0.1	0.56	<0.3	>25.0
	6	Tr.	Tr.	<0.3	27.3
	15†	<0.1	Tr.	<0.3	33.7
Crystalline micronized: 20 mg.	1	0.8	3.8	<0.5	<1.0
	2	<0.1	1.1	0.5	3.3
	1	<0.1	0.8	<0.5	1.0
	2	2.1	<0.5	<0.5	20.7
	4	<0.1	<0.4	<0.3	5.0

given intramuscularly, or orally, were considerably higher in the blood than in the aqueous, vitreous, or cornea. It would therefore seem that the systemic use of aureomycin encounters the same difficulties as were observed with penicillin and streptomycin. The subconjunctival route, which proved so effective in the older antibiotics, has, however, distinct limitations with aureomycin, for the drug is highly insoluble—some 0.02 mg./ml., and this is not increased substantially even if the solution is buffered with sodium bicarbonate. As micronized crystalline aureomycin was available an attempt was made to inject larger quantities of the agent in fine suspension subconjunctivally, and a fairly easily injected suspension containing 20 or even 50 mg. per ml. can be prepared. But such suspensions brought difficulties of their own. In the first place, even when buffered these suspensions are inclined to be irritating, and in the experimental rabbit the more concentrated suspensions tended to produce transient corneal haze and other symptoms of irritation. Secondly, and more significantly, these suspensions were not apparently absorbed into the eye but tended to form a cheese-like deposit subconjunctivally with necrosis of the overlying conjunctiva, so that even after eight days most of the suspension could be scraped away mechanically. As can be seen from Table I, even these extreme measures led to disappointing levels of concentration in the aqueous and vitreous. In fact, there is some suggestion that the smaller, and presumably less irritating, doses give rather better intraocular levels.

The use of aureomycin is therefore beset by two considerable difficulties: systemic administration gives low intraocular levels, while subconjunctival injections are limited to small doses, with resultant low levels of intraocular concentration.

Clinical Studies

Aureomycin, given as subconjunctival injections of 10 mg., was used in 15 cases: in seven fresh cases of disciform keratitis and two cases of dendritic ulcer it was given twice at intervals of five days, in four cases of "superficial punctate keratitis" and two cases of epidemic keratoconjunctivitis it was given once. Ointment of 0.1%, generally at two-hourly intervals, was used in 10 cases—two being of dendritic ulcer, two of herpes ophthalmicus with corneal involvement, five of epidemic keratoconjunctivitis, and one of chronic blepharitis in a patient sensitive to nearly all treatment. The results were almost consistently poor. The promise of a good result obtained in the first case of disciform keratitis treated by subconjunctival injection was not fulfilled in further observations. The only positive results in this series were symptomatic relief within three to five days in cases of epidemic keratoconjunctivitis treated by ointment, though the corneal staining persisted; and a fairly good response to blepharitis in a patient who had proved intolerant to other forms of treatment.

We have no experience of the use of aureomycin in trachoma and inclusion blennorrhoea: the poor results obtained with the herpes group of ocular infections and the equivocal results with epidemic keratoconjunctivitis do not exclude the possibility of good results with the large-sized viruses responsible for trachoma and inclusion blennorrhoea, or in infections due to bacteria insensitive to sulphonamides and penicillin.

Chloramphenicol

Experimental Studies

With a plate diffusion method, using *Shigella sonnei* as the test organism for assay of the antibiotic concentration in the tissues, trials gave the following results in the rabbit. (1) Intramuscular injection of 250 mg./kg. body weight: the levels in both the blood and ocular tissues at two and four hours were nil or negligible. (2) Oral administration of 375 mg./kg. body weight: the blood levels at two hours in two animals were adequate (10 and 20 $\mu\text{g./ml.}$). The levels in the cornea were nil; in the aqueous 5 and 15 $\mu\text{g./ml.}$, in the two animals respectively; and 0 and 10 $\mu\text{g./ml.}$ in the vitreous. At four hours all levels were nil.

As intramuscular injection looked unpromising, fuller studies were confined to assessing the relative value of oral administration and subconjunctival injection. The results are shown in Table II. The first section of this table shows that the intraocular levels of concentration of chloramphenicol compare unfavourably with those reached in the blood when 500 mg. of the drug is administered orally to the rabbit. These results suggest that the oral use of chloramphenicol is not likely to give adequate concentrations in the eye. Subconjunctival injections of chloramphenicol met with the same initial difficulty as in the case of aureomycin. Chloramphenicol, too, is highly insoluble (2.5 mg./ml.), but it has the advantage over aureomycin that it did not prove irritating when 50 mg. was injected subconjunctivally as a suspension. There were not the same irritative reactions in the cornea, nor any necrosis at the conjunctiva. Particles of chloramphenicol were, however, too large for a suspension to be readily injected, and again micronized chloramphenicol proved better. Several types of micronized suspensions were obtained, and it was found that the 15% chloramphenicol suspension in 1:10,000 benzethonium chloride ("phemeride") could fairly readily be injected in quantities up to 1 ml. without irritation. The intraocular levels obtained in the rabbit with 1 ml. of such suspension injected subconjunctivally are shown in the second section of Table II. It will be seen that the aqueous levels in particular are much higher than those obtained from oral administration of 500 mg. The effect of adrenaline on these levels is seen in the third section of the table. The injection of the suspension in 0.1% adrenaline leads to

TABLE II.—Chloramphenicol: Concentrations in the Ocular Tissues of the Rabbit Reached by Different Dosages and Methods of Administration (Test Organism: *Shigella sonnei*)

Mode of Administration	Time in Hours	Chloramphenicol Levels ($\mu\text{g./g. of Tissue}$)						
		Blood	Aqueous	Vitreous	Cornea	Lens	Ant. Tissues	Post. Tissues
Oral, 500 mg.	1	56.5	2.0	15.7	10.0	<2.0	19.5	33.3
		21.7	6.85	5.64	2.56	—	10.5	12.6
	2	11.2	6.31	7.93	—	<2.0	5.0	6.78
		20.7	6.12	10.25	10.41	—	12.12	13.66
	4	0.86	2.45	2.40	<2.0	<2.0	<2.0	<2.0
		<1.0	<1.0	1.68	<3.0	—	<2.0	<2.0
Subconjunctival injection (one eye) of 1 ml. of 15% suspension of the micronized base	1	1.7	25.0	2.5	—	<2.0	9.9	ca. 25.0
		1.99	34.0	<2.0	54.3	<2.0	99.2	41.4
	2	3.35	9.54	18.4	—	6.0	56.0	<40.0
		Trace	4.26	4.75	—	<3.0	—	3.97
	4	<1.0	2.5	<2.0	6.52	<2.0	9.99	6.28
		<2.0	<2.0	<2.0	—	<2.0	<2.0	<2.0
Subconjunctival injection (one eye) of 1 ml. of 15% suspension of the micronized base in 0.1% adrenaline	1	5.34	28.8	22.0	163.0	<3.0	129.0	53.2
		<1.00	<5.0	<3.0	—	<3.0	17.25	<5.0
	2	<1.0	<3.0	<3.0	33.7	<3.0	13.8	32.4
		3.65	61.0	11.0	195.0	<3.0	179.0	127.0
	4	<1.0	<2.0	<3.0	12.2	<3.0	18.4	27.9
		ca. 1.0	<5.0	<3.0	30.25	<3.0	27.5	<5.0
	1	Trace	34.9	3.24	40.0	<3.0	48.4	77.8
		<1.0	<2.0	<3.0	24.1	<3.0	16.5	10.2
	2	0.77	41.2	<2.0	148.0	<3.0	58.4	3.0
		<3.0	11.2	<3.0	—	<3.0	6.46	10.5
	4							

higher and more consistent levels—a finding reminiscent of the observations with penicillin and streptomycin.

Apart from subconjunctival injections, chloramphenicol was also available in the form of drops 0.5% and ointment 1%, both of which were well tolerated by the experimental rabbit.

Clinical Studies

Chloramphenicol was used in 72 cases, distributed over the following groups: (1) 29 cases treated with ointment 1%, generally at two-hourly intervals—9 being disciform keratitis, 6 “superficial punctate keratitis,” 2 neuroparalytic keratitis with hypopyon, 3 “chronic follicular conjunctivitis” with acute subjective symptoms, and 9 epidemic keratoconjunctivitis; (2) 28 cases treated with drops 0.5%, generally at two-hourly intervals—2 being “superficial punctate keratitis,” 8 dendritic ulcer, 1 neuroparalytic keratitis with hypopyon, and 17 epidemic keratoconjunctivitis; (3) nine cases treated with subconjunctival injections of 15% suspension, generally 0.5 ml. with adrenaline—3 being disciform keratitis and 6 dendritic ulcer.

In addition four cases of herpes ophthalmicus and one case of dendritic ulcer were treated by oral administration combined with the use of ointment locally, and one case of post-operative infection was treated intensively by different methods as indicated below.

Apart from the striking exception of epidemic keratoconjunctivitis, the results with drops or ointment were almost consistently poor for disciform keratitis, dendritic ulcer, and the other presumed virus infections. The diagnosis of epidemic keratoconjunctivitis was not made unless the typical picture of hyperaemic conjunctiva, watery discharge, enlarged preauric nodes, and superficial punctate staining of the cornea were all present. All the 26 cases treated responded well to either ointment or drops; among these were eight cases that had previously been treated unsuccessfully by other methods. Cases of “superficial punctate keratitis” without the other components of epidemic keratoconjunctivitis did almost uniformly badly.

The disappointing results from drops and ointment in dendritic ulcer and disciform keratitis led to the use of subconjunctival injections in six cases of dendritic ulcer and three of disciform keratitis. The subconjunctival injections were generally 0.5 ml., or rather more, at daily intervals for three or four days. No improvement was obtained.

That subconjunctival injections of chloramphenicol may, however, have a definite, even if limited, place in ophthal-

mology is suggested by the isolated case of post-operative infection treated by this method.

A woman aged 81 was found to have an infected wound with the beginning of a hypopyon at the first dressing 48 hours after a cataract extraction. Subconjunctival injection of 500,000 units of penicillin and a similar dose intramuscularly were given, and a smear for bacteriological examination was taken. This treatment was continued for three days, the eye steadily becoming worse. The bacteriological report showed the presence of pneumococci which were resistant to sulphonamides, penicillin, and streptomycin but sensitive to aureomycin and chloramphenicol, and *Micrococcus tetragenus* which was sensitive to streptomycin and chloramphenicol. Chloramphenicol in ointment form was given three-hourly for three days without result. It was then supplemented by oral administration for two days more. At this stage the hypopyon had increased to almost three-quarters of the anterior chamber, and subconjunctival injection of chloramphenicol with the addition of 2 minims (0.12 ml.) of adrenaline was instituted. A marked improvement had occurred by the following day, and within another 24 hours the hypopyon was barely visible. In all, four injections were given at 24-hourly intervals, with chloramphenicol ointment 1% four-hourly. A fairly good red reflex could be obtained ophthalmoscopically on the third day, and the subsequent course was uneventful. Six months later vision with correction was 6/12.

Terramycin

Experimental Studies

Terramycin, like the other two agents, is largely insoluble in water, the maximum solubility of the terramycin base being 0.25 mg. per ml. Micronized terramycin is not readily taken up in suspension. Subconjunctival injections containing a suspension of more than 20 mg. are not tolerated, as there is marked injection of the eye and opacification of the cornea.

Administration by the subconjunctival route is therefore of limited value. As can be seen from Table III, the intraocular levels of concentration reached by various routes were disappointing.

(a) *Oral Administration*.—With doses of 100 mg., the serum and intraocular levels were poor at one and at three hours.

(b) *Intravenous Injection*.—With the same dose the serum level was high, but the intraocular levels, though better than on oral administration, were low.

(c) *Intramuscular Injection*.—Whether terramycin hydrochloride or micronized terramycin was used, doses of 100 mg. once more gave low intraocular levels.

TABLE III.—*Terramycin: Concentration in Ocular Tissues of the Rabbit reached by Different Dosages and Methods of Administration (Test Organism: B. subtilis)*

Mode of Administration	Time in Hours	Terramycin Levels ($\mu\text{g./g.}$ of Tissue)						
		Blood	Aqueous	Vitreous	Cornea	Lens	Ant. Tissues	Post. Tissues
Intramuscular: Terramycin HCl, 100 mg. in 1 ml.	1	2.1 0.89	3.2 2.3	<0.5 <0.5	<2.5 <2.5	<1.5 <1.5	<2.5 <2.5	<2.5 <2.5
Intramuscular: Micronized base, 100 mg. in 1 ml. suspension	1	0.964 0.47		2.07 0.95	13.0 13.4	2.70 <1.5	6.00 4.19	20.2 1.45
	2	1.44 1.12	<0.48 <0.48	<0.5 <0.5	6.00 <1.5	<1.5 <1.5	8.69 1.50	2.18 <1.5
Oral: Terramycin HCl solution aq., 100 mg. in 5 ml.	1	<0.5 <0.5	2.83 1.37	<0.5 <0.5	<1.5 <1.5	<1.5 <1.5	<1.5 <1.5	<1.5 <1.5
	3	<0.5 <0.5	<0.5 <0.5	<0.5 <0.5	<1.5 <1.5	<1.5 <1.5	<1.5 <1.5	<1.5 <1.5
Intravenous: Terramycin HCl buffered, 100 mg. in 1 ml. water	1	37.9 35.6	<2.5 <2.5	<2.5 <2.5	<2.5 2.50	<2.5 <2.5	5.68 9.76	10.0 5.01
	2	47.7 37.7	<2.5 <2.5	<2.5 <2.5	3.36 4.82	<2.5 <2.5	5.52 7.32	4.78 10.2
Subconjunctival: Terramycin micronized base, 100 mg. in 1 ml. suspension	1	<0.4 <0.4	3.14 1.04	1.5 <0.4	<2.0 <2.0	<1.2 <1.2	6.56 12.3	23.8 10.5
	2	<0.4 <0.4	4.4 1.39	<0.4 <0.4	<2.0 <2.0	<1.2 <1.2	7.4 <1.2	7.9 <2.0
	4	<0.4	<0.4	<0.4	<1.0	<1.2	2.0	3.5
		<0.4	<0.4	<0.4	<1.0	<1.2	1.3	1.11

(d) *Subconjunctival Injection*.—Suspensions of 100 mg. of the micronized base were both poorly tolerated and unproductive of any adequate intraocular levels. Most of the terramycin remained at the site of injection as an irritating mass that could be removed four days later.

These results suggest that with clinical doses administered systemically little penetration into the eye is to be expected, and the subconjunctival injection does not overcome this difficulty.

Clinical Studies

These were confined to the use of terramycin ointment (crystalline terramycin hydrochloride 0.5%) at two-hourly intervals. There was no result in five cases of dendritic ulcer nor in three cases of disciform keratitis. The results in five cases of epidemic keratoconjunctivitis were of the same order as those obtained with chloramphenicol.

Summary

Aureomycin, chloramphenicol, and terramycin administered systemically do not penetrate readily into the eye, so that adequate intraocular therapeutic levels are not obtained by such administration.

The poor solubility of these agents limits their use as subconjunctival injections. Even in the micronized form, both aureomycin and terramycin cannot be given in suspension, for any substantial concentration produces marked irritative reactions. Chloramphenicol, however, can be fairly readily administered as a 15% suspension; it is well tolerated, and gives adequate intraocular levels; these levels can be both increased and maintained for a longer time if the suspension contains 0.1% of adrenaline.

In the absence of suitable techniques for the experimental study of virus infection of the eye, clinical assessments were made of the value of these agents in several ocular infections assumed to be due to viruses.

(a) Aureomycin in the form of ointment 1% or subconjunctival injection of 10 mg. did not improve dendritic ulcer, disciform keratitis, herpes ophthalmicus with corneal involvement, and in a nondescript group of corneal lesions with superficial punctate staining. In five cases of epidemic keratoconjunctivitis there was symptomatic relief to ointment, but no effect on the superficial corneal staining.

(b) Terramycin ointment 0.5% did not improve dendritic ulcer and disciform keratitis. There was a gratifying response in five cases of epidemic keratoconjunctivitis, the condition clearing up within two to seven days.

(c) Chloramphenicol, in the form of 1% ointment or drops 0.5%, or subconjunctival injection of 0.5 ml. of 15% solution, did not improve dendritic ulcer and disciform keratitis. There was also no improvement with any of these methods, or with oral administration, in four cases of herpes ophthalmicus and in one case of sympathetic ophthalmia. The results were likewise negative in neuroparalytic keratitis, "chronic follicular conjunctivitis," and "superficial punctate keratitis." Gratifying results were obtained in 26 cases of epidemic keratoconjunctivitis treated either by 1% ointment or by drops of 0.5%. A good result was also obtained by repeated subconjunctival injection of the 15% suspension in a case of post-operative infection of the eye caused by a pneumococcus insensitive to penicillin and the sulphonamides.

It may be concluded that, of the newer antibiotics, aureomycin is of little value in ophthalmology; terramycin is useful in ointment form for epidemic keratoconjunctivitis; and chloramphenicol gives results as good as or better than terramycin in epidemic keratoconjunctivitis. Of these three antibiotics, chloramphenicol is the only one which can be given in a relatively high concentration subconjunctivally; it may be of value in the occasional cases of intraocular infection due to organisms sensitive to chloramphenicol but insensitive to the sulphonamides, to penicillin, or to streptomycin.

Apart from the control of epidemic keratoconjunctivitis—a presumed virus infection—by both terramycin and chloramphenicol, the virus diseases of the eye still remain a therapeutic problem.

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