Summary

A hitherto undescribed condition is described, in which secondary carcinoma is growing in the anterior chamber after the manner of a tissue culture.

Attention is drawn to the differences in manner of intra-ocular extension between neuro-epithelial retinal tumours and secondary carcinoma within the eye, and it is suggested that these are largely the result of the different sites in which the two types of growth originate.

Attention is also briefly drawn to the use made in experimental cancer research of the capacity of the aqueous fluid to act as a tissue culture medium.

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CHOICE OF SULPHONAMIDE IN THE TREATMENT OF OPHTHALMIA NEONATORUM*

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THE value of the oral administration of sulphapyridine in the treatment of ophthalmia neonatorum was established in an earlier communication (Sorsby, Hoffa and Smellie, 1942). In a series of 273 cases clinical cure of the affection was obtained within 8 days in 61.9 per cent, as against cure in 15.2 per cent. in a control series of 46 cases treated by the classical local methods. It was also pointed out that the results were actually better than these figures indicated, for this series contained many cases treated—during the earlier stages of the investigation—with an inadequate dosage. A subsequent communication (Sorsby and Hoffa, 1944) confirmed and extended these findings. In a series of 133 cases treated to a conclusion with sulphapyridine 88.7 per cent. showed clinical cure

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within 8 days, but to achieve these results a dosage cumulatively larger than suggested at first had to be employed. The initial dose of half a tablet (0.25 g.) was followed by a maintenance dose of 0.125 g. four-hourly day and night, and this was maintained for 2 days after apparent clinical cure. Under these conditions it was found that, whilst there were no serious toxic complications ensuing from the use of the drug in such dosage, the babies were not free from toxic symptoms. In fact twenty-three cases showed intolerance to sulphapyridine and another sulphonamide had to be exhibited. Comparative studies with sulphathiazole in 43 cases, sulphadiazine in 31 cases, and sulphamezathine in 28 cases showed that each of these drugs was better tolerated, and gave results of the same order as sulphapyridine. The percentage of cases giving clinical cure within 8 days for each of the four drugs was 88.7, 93.0, 83.9 and 92.9 respectively. Actually a considerable percentage of cases showed clinical cure within 3 days, the percentages being 30.8, 32.5, 32.3 and 39.8 respectively. (In the case of sulphapyridine the percentage of cures within 8 days was reduced to 82.7 per cent. if the cases in which intolerance was shown are included and to 27.0 per cent. of cures within 3 days.)

No further work with sulphapyridine has been undertaken. The material that has accumulated during the past year (January 1-December 31, 1944) consists of 120 cases. One baby suffering from gonococcal ophthalmia died from prematurity on the second day after admission and is excluded from this series. Of the

TABLE I
Comparative results in 75 cases of Ophthalmia Neonatorum treated with different sulphonamides

Clinical Cure	Sulphanilamide		Sulphamezathine		Sulphathiazole		Sulphadiazine	
	Gonococci positive	Gonococci negative	Gonococci positive	Gonococci negative	Gonococci positive	Gonococci negative	Gonococci positive	Gonococci negative
1-3 days... ..	1	6	3	19	—	1	—	1
4-8 days... ..	—	3	2	20	—	2	—	—
Relapses... ..	—	1	1	6	—	—	—	—
Poor response ...	—	1	2	3	—	1	—	—
Drug discontinued because of toxic effects	—	2	—	—	—	—	—	—
Totals	1	13	8	48	—	4	—	1

remaining 119 cases 75 were treated with sulphonamides and 44 with penicillin. The penicillin cases are the subject of a separate communication (Sorsby and Hoffa, 1945).

As can be seen from Table I, 56 of these 75 cases were treated with sulphamezathine, 14 with sulphanilamide, whilst 4 cases and 1 case were treated with sulphathiazole and sulphadiazine respectively.

Sulphanilamide was soon discarded. Though it proved satisfactory in its therapeutic effects, it was not well tolerated; in 2 cases it had to be discontinued because of cyanosis and dyspnoea and six more babies showed minor toxic symptoms. No such difficulties were met with sulphamezathine or with the 5 cases treated with sulphathiazole or sulphadiazine. The essential point that emerged from this study was that babies tolerate sulphamezathine in full doses in contrast to their intolerance of such doses of sulphapyridine and sulphanilamide.

Combining the present data with those previously published on treatment by full doses of sulphapyridine, sulphamezathine, sulphathiazole and sulphadiazine, comparative data on the efficacy of these five drugs are available. These are shown in Table II. (See also Fig. 1.)

COMPARITIVE EFFICACY OF VARIOUS SULPHONAMIDES IN
OPHTHALMIA NEONATORUM

FIG. 1.

The four columns in each block represent cases treated by sulphapyridine, sulphamezathine, sulphathiazole, and sulphadiazine respectively. Heavy shading = percentage showing clinical cure within 1-3 days. Light shading = percentage showing clinical cure within 4-8 days. Numbers over each column = the total number concerned.

TABLE II
Comparative Results with some Sulphonamides in Ophthalmia Neonatorum
333 Cases treated with full doses

(0.25 g. on admission and 0.125 g. 4-hourly day and night until 48 hours after clinical cure)

Clinical Cure	Sulphapyridine			Sulphanilamide			Sulphamezathine			Sulphathiazole			Sulphadiazine		
	Gonococci positive	Gonococci negative	Total	Gonococci positive	Gonococci negative	Total	Gonococci positive	Gonococci negative	Total	Gonococci positive	Gonococci negative	Total	Gonococci positive	Gonococci negative	Total
1-3 days ...	15 (45.7%)	26 (21.5%)	42 (27.0%)	1	6	7 (50.0%)	6 (46.2%)	27 (38.0%)	33 (39.3%)	7 (63.6%)	8 (22.2%)	15 (31.9%)	5	6	11 (34.4%)
4-8 days ...	13 (37.1%)	74 (61.9%)	87 (55.7%)	—	3	3 (21.4%)	4 (30.7%)	33 (46.5%)	37 (44.0%)	4 (36.3%)	24 (66.6%)	28 (59.6%)	4	12	16 (50.0%)
9-30 days; relapses, poor response and intolerance ...	6 (17.1%)	21 (17.4%)	27 (17.3%)	—	4	4 (28.6%)	3 (23.1%)	11 (15.5%)	14 (16.7%)	—	4 (11.1%)	4 (8.5%)	—	5	5 (15.6%)
Totals ...	35	121	156	1	13	14	13	71	84	11	36	47	9	23	32

Several points of interest emerge:—

(1) Accepting a clinical cure within 8 days as a satisfactory result, it is seen that sulphapyridine and sulphamezathine give almost identical percentages of successes, viz., 82.7 per cent. and 83.3 per cent. respectively.

(2) The smaller series treated with sulphathiazole and sulphadiazine give rather better results, whilst sulphanilamide shows a somewhat poorer response.

(3) Sulphamezathine gives a larger percentage of successful results within 3 days than sulphapyridine.

(4) With sulphapyridine, sulphamezathine and sulphathiazole cures within 3 days appear to be obtained more readily for cases of gonococcal ophthalmia than for cases of ophthalmia neonatorum due to other organisms.

For the present the choice of a sulphonamide in the treatment of ophthalmia neonatorum lies therefore between sulphamezathine, sulphathiazole and sulphadiazine. The last—an American product—is not readily obtainable.

Sulphonamide-resistant cases

Table II shows that whatever sulphonamide is used there is a residue of cases that do not do well. Taking the two larger series, the 156 cases of sulphapyridine and the 84 of sulphamezathine, it is seen that in each group about 17 per cent. of cases required either treatment for more than 8 days, or showed relapses, poor response, or (in the case of sulphapyridine) intolerance. What sulphamezathine gains in being more tolerated it appears to lose in having a larger proportion of cases showing poor response.

No clear relationship could be established between clinical type and failure to respond satisfactorily to the sulphonamides. The failures were seen in the non-gonococcal cases as well as in the gonococcal cases, and there was nothing in the clinical appearances to indicate in any particular instance that the case would not do well with sulphonamide treatment. Whether this resistance to sulphonamide treatment centres on sulphonamide-resistant strains of organisms, or is due to some constitutional factor, or perhaps to inadequate dosage cannot be indicated at the present. It is, however, worth stressing that an unsatisfactory response to sulphonamide does not generally mean a complete failure; it is only exceptionally that the condition is not improved to a considerable extent, and only in rare instances is the response so poor that anxiety for the state of the eye and the ultimate outcome is felt.

Actual data on the 15 failures in the present series of 75 cases treated with sulphonamide are:

(1) Seven cases showing poor response. Five of these were treated with sulphamezathine and the causal organisms were gonococcus in 2 cases, staphylococcus aureus in 2 more, and diphtheroids in one. The 2 remaining cases were a case of staphylococcus with Koch-Weeks bacilli treated with sulphanilamide, and a case with non-haemolytic streptococcus treated with sulphathiazole. In these last 2 cases the general condition was not good; the one case suffered from severe bronchitis, and the other developed broncho-pneumonia whilst under treatment. Ultimately these cases cleared up either by the administration of another sulphonamide, or by the local application of penicillin.

(2) Eight relapses. In all but one case sulphamezathine had been employed and the organisms present were: pneumococci and diphtheroids 2 cases each, gonococcus, no organisms, and inclusion bodies one case each. In one case, in which pneumococci were present, sulphanilamide had been used. In all these 8 cases there was nothing in the general condition to explain the relapse, and they all cleared up when a further course of the original sulphonamide was instituted.

Degree of severity

The present series contained 26 cases in which the condition was mild, 34 in which it was moderate, and 15 severe, the criteria used being the amount and nature of discharge and the swelling of the lids. As can be seen from the subjoined summary table there was no striking difference in the percentage of cases giving a rapid cure in each of these sub-divisions.

Clinical Cure	Mild	Moderate	Severe
1-3 days	13	11	7
4-8 days	9	14	4
9-30 days. Relapses, poor response and intolerance	4	9	4
	26	34	15

Whilst no fine conclusions can be drawn it would appear that severe cases respond as well as those showing milder degrees of the infection. The rapid response that some severe cases give to sulphonamide treatment is so striking that the clinical impression was formed that severe cases do better than those less heavily affected. This is not borne out by the actual analysis. It is, however, clear that severe affections do not necessarily mean prolonged treatment.

In this series 22 cases were unilateral, giving a percentage of 29.3 a close approximation to the 30.5 per cent. and 33.0 per cent.

reported in the two previous studies. No tangible difference was observed in the results of treatment of the unilateral cases as contrasted to those in which both eyes were affected.

Causal organisms

The subjoined table amplifies the data contained in Table I. in giving the details on the bacteriology of the 66 non-gonococcal cases in this series of 75.

No organism found in smear or culture ...	...	13
Staphylococcus		
Staphylococci ...	...	1
Staph. aureus ...	...	19
Staph. albus ...	...	9
Staph. aureus and diphtheroids...	...	4
Staph. albus and diphtheroids ..	...	3
Staphylococcus and Koch-Weeks bacilli ...	...	1
Staphylococcus and Morax-Axenfeld bacilli ...	...	1
Staphylococcus and diphtheroids	1—	39
Other coccal organisms		
Pneumococci ...	...	4
Micrococcus catarrhalis...	...	1
Streptoc. viridans ...	...	1
Streptoc. haemolyticus ...	...	1
Non-haemolytic streptococcus ...	1—	8
Bacilli		
Diphtheroids ...	...	5
Friedlander's ...	1—	6
Gonococcus ...	...	9
		75

As in the previous series staphylococcal infection is the commonest. Gonococcal infection was low in this particular series accounting for only 12.0 per cent. (though in the whole series of 120 cases seen during the year the incidence was higher: 24 out of 120 or 20.0 per cent.).

Cases showing inclusion bodies.—The present series contained 7 cases (9.3 per cent.) in which inclusion bodies were found in epithelial scrapings taken from the conjunctiva. In 6 of these cases no organisms could be recovered. In the 7th staphylococcus aureus was present. In 4 cases the mother did not accompany the baby on admission, so that scrapings from the cervix could not be taken. In the remaining 3 such scrapings were negative in two cases, and inclusion bodies were found in the third. The age

of onset of the ophthalmia in the one case in which inclusion bodies were found in both the conjunctiva and cervix was 3 days. In the two cases where the cervical scraping was negative the onset was at 11 days (in the case complicated by the presence of staphylococcus aureus) and 18 days. In the 4 remaining cases the onset was 8, 11, 13, and 23 days after birth. All babies made an uneventful recovery, 3 after 3 days, 2 after 4 days, 1 after 5 days, and 1 after 10 days treatment. These results bear out the observation previously made that cases of inclusion blenorrhoea do well under sulphonamide treatment—the sulphonamide used in these particular cases being sulphamezathine in all but the case complicated by the presence of staphylococcus aureus which was treated with sulphathiazole.

Though inclusion bodies were recovered in only 7 cases in the series of 75 it is likely that they are present in a higher percentage than these figures suggest. In three mothers inclusion bodies were found in epithelial scrapings taken from the cervix though no such bodies could be recovered from the babies' conjunctiva.

These results agree with those previously reported in 27 cases of ophthalmia neonatorum with inclusion bodies (Sorsby, Hoffa and Young, 1944). Of those 27 cases 6 showed clinical cure within 1-3 days, 18 within 4-8 days and the remaining 3 required a longer period.

Complications

In no case did any local complications arise during the course of treatment. Two babies admitted with slight unilateral corneal ulceration did well and were discharged with clinically clear corneae. As already indicated no general complications from intolerance to sulphamezathine were noted.

Routine procedure in treatment

On admission a swab of the pus is taken, both for a smear preparation and for culture. The eyes are then irrigated with a bland lotion, such as half normal saline solution at room temperature. Guttae atropinae sulphas 1 per cent. and drops of medicinal paraffin are instilled as a routine measure in all cases, and half a tablet of sulphamezathine (0.25 g.) crushed into powder is given by mouth in a teaspoonful of water or milk. Sulphamezathine administration is continued in doses of 0.125 g. every four hours, day and night, until forty-eight hours after a clinical cure is obtained. Local treatment consists of three-hourly irrigation with saline solution during the first day in cases with profuse discharge; as a rule there is no need for further irrigation on the subsequent

days. After irrigation medicinal paraffin is instilled as a precaution against the sticking together of the lids. Atropine is instilled three times daily in cases with corneal haze or ulceration.

With this treatment swelling of the lids generally subsides within twelve hours after admission; purulent discharge disappears within twenty-four hours, so that a threatening purulent ophthalmia becomes a simple conjunctivitis giving no anxiety. The eyes are either dry or very nearly so within seventy-two hours.

Summary

1. On the basis of 333 cases of ophthalmia neonatorum treated with a standard dosage of five different sulphonamides it is concluded that the least tolerated drug is sulphanilamide and that sulphapyridine is less well tolerated than sulphamezathine, sulphathiazole or sulphadiazine.

2. In their efficacy against the infection, as distinct from their tolerance by the babies, these five sulphonamides are not strikingly different.

3. With the standard dosage employed in this series some 30-40 per cent. of cases show clinical cure within 3 days. Well over 80 per cent. of the total are cured by the end of 8 days' treatment.

4. Gonococcal ophthalmia neonatorum responds more readily than other varieties of ophthalmia. Cases showing inclusion bodies respond satisfactorily.

5. Initial severity of the affection does not affect the course unfavourably. Many severe cases clear very rapidly.

6. Irrespective of the causal organism some 15 per cent. of cases show a sluggish or poor response.

7. The routine management of cases is described.

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