pneumococcal horse or rabbit sera. Complement fixation by atoxyl azo antigens and homologous antisera have already been described.[14]

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Excretion of Sulfathiazole in Tears.

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Seven cases of conjunctivitis occurring during the administration of sulfathiazole have been observed at the Beth Israel Hospital during the last 5 months. Quantitative determinations of the sulfathiazole concentration in the tears were made in 4 of these. Similar quantitative studies were carried out in 10 patients who were taking sulfathiazole but had no evidence of conjunctivitis (Table I). Blood sulfathiazole determinations were made in all cases at the time that the lachrymal secretion was collected.

Technic. The eyelids were first carefully cleansed with ether to rid them of sebaceous material. Tears were stimulated by the gentle application to the inner canthus of a cotton swab moistened with ether. The lachrymal secretion was then collected at the outer canthus by a fine capillary pipette. Controls had shown that this procedure did not cause any conjunctival irritation. Since sulfathiazole secretion in sweat had been demonstrated by the authors, care was exercised not to collect any tears which had overflowed on to the cheek.

The total amount of lachrymal secretion obtained from both eyes varied from 0.4 cc to 0.9 cc, and, in each case, 1.2 cc of 4 N HCl was added to the entire measured amount. This was then diluted with distilled water to a volume of 25 cc. Ten cc of this was used as a blank control. Another 10 cc was diazotized using N (1-naphthyl)

[14] Klopstock, A., and Selter, G. E., *Z. Immunitats. Forsch.*, 1928, **55**, 450; **57**, 174.

TABLE I.

No.	Case No.	Therapy: Total No. g given orally	Therapy: No. days administered	Conc. of drug, mg% Blood	Conc. of drug, mg% Tears	Comment
1	128647	8	1	2.6	.40	No conjunctivitis
2	128701	12	1	4	.57	" "
3	128448	6	1	3.4	.35	" "
		12	2	3.6	.30	" "
4	128843	4	1	2.8	.56	" "
		12	3	2.3	.64	" "
5	128277	8	1.5	4.8	.40	" "
		23	4	3.8	.40	" "
6	128767	8	2	4.4	.50	" "
		23	6	3.4	.98	" "
7	128864	4	1	2.8	.64	" "
		12	3	3.6	.66	" "
		22	6	3.4	.70	" "
8	128917	4	1	2.9	.30	" "
		16	4	2.8	.10	" "
		26	7	2.6	.75	" "
9	128473	28	9	9.8	.90	" "
10	128839	29	8	5.0	.50	" "
11	128136 1st course	4	1	3.6	.30	" "
		21	4	3	.80	Mild conjunctivitis, bilateral, palpebral and bulbar injection.
		24	5	3.4	.60	Severe conjunctivitis, bilateral.
12	128758 1st course	10	1.5	8.5	.75	Mild conjunctivitis, bilateral, palpebral and bulbar injection.
13	127632 2nd course	4	1	1.7	.21	No conjunctivitis.
		12	3	4.2	.75	Mild conjunctivitis, left eye. Moderate conjunctivitis, right eye. Triangular patch of bulbar injection.
14	125546 4th course	6	2	3.8	.66	Moderate conjunctivitis of right eye only.

ethylene-diamine dihydrochloride as a coupler.[1] Readings were then made on a photo-electric colorimeter.

Analysis of Results. Sulfathiazole was found in the tears of the 14 patients examined in concentrations varying from 0.1 mg % to 0.98 mg %. The concentration tended to rise with the continued administration of the drug. However, no relationship was established between the blood and the tear levels. For example, of 6 patients who showed a rise in tear concentration, only 2 (Cases 9 and 11) revealed a corresponding rise in the blood level. Three patients (Cases 4, 8 and 9) failed to show any consistent blood elevation and one (Case 6) showed a definite decline. A constant tear level was demonstrated in Case 5 despite a fall in the blood concentration. These findings indicate that the amount of drug secreted in the tears is not proportional to the blood concentration, but depends perhaps on other factors such as the secretory function of the lachrymal gland. The relationship between the blood and tear concentration also does not appear to be proportional to the water content of these 2 fluids and in this respect sulfathiazole differs from sulfanilamide.[2]

The sulfathiazole concentration in the tears reached 0.6 mg % or more in all cases of conjunctivitis. On the other hand, in 6 of the 10 cases without conjunctivitis, the concentration was 0.56 or more. Obviously, therefore, the conjunctival inflammation cannot be ascribed to an increased concentration of sulfathiazole in the tears. The eyes of 5 patients not receiving sulfathiazole were irrigated for 15 minutes of every hour for a period of 16 hours with solutions of 0.3 mg %, 0.8 mg %, 2 mg %, 5 mg %, and 10 mg % of sulfathiazole respectively. Conjunctivitis did not appear in any of these patients.

Discussion. The conjunctivitis occurring during the administration of sulfathiazole is, in all likelihood, a reaction peculiar to this drug. Although sulfanilamide has been found in tears in greater concentration than sulfathiazole,[3, 4] conjunctivitis following its administration has not been observed. In like manner, conjunctivitis due to sulfapyridine has not been seen. Of the 7 cases of sulfathiazole conjunctivitis observed by the authors, 4 had no eye manifestations during the first course of therapy. The conjunctivitis in these cases

1 Bratton, A. C., and Marshall, E. K., Jr., *J. Biol. Chem.*, 1939, **128**, 537.

2 Marshall, E. K., Jr., Emerson, K., Jr., and Cutting, W. C., *J. Pharm. and Exp. Therap.*, 1937, **61**, 196.

3 Bellows, J. G., and Chinn, H., *J. A. M. A.*, 1939, **112**, 2023.

4 Venco, L., *Ann. di Ottal. e Clin. Ocul.*, 1939, **67**, 30.

appeared during the second or during a subsequent course, suggesting that this reaction is due to drug sensitization in susceptible individuals.

The eye nearest the window and therefore more exposed to sunlight, was in one instance the only one involved (Case 12), and in another (Case 11) it was more severely inflamed.

Haviland and Long[5] reported 6 instances of conjunctivitis in 78 patients receiving sulfathiazole. In 31 consecutive patients treated by the authors on the Urological Surgical Service, 5 instances of conjunctivitis were observed. This greater incidence may be due to the fact that in many of our cases more than one course of therapy was given. No serious sequelae were seen, and the conjunctivitis disappeared in from 1 to 4 days, following cessation of therapy. It has been accepted[5] that this complication is an indication for the interruption of the sulfathiazole therapy. However, in one of our cases the administration of the drug was continued despite the conjunctivitis since no other signs of toxicity were present. The eyes were treated with drops of .25% zinc sulphate solution and after 4 days the conjunctivitis disappeared completely despite the uninterrupted administration of sulfathiazole. However, in view of the frequent relationship of conjunctivitis to other more severe toxic manifestations it is safer to discontinue the drug immediately if conjunctivitis appears.

Summary. The tears of 14 patients receiving sulfathiazole were quantitatively analyzed. Sulfathiazole was found in all the cases. The concentrations varied from 0.1 mg % to 0.98 mg %.

Four patients suffering from sulfathiazole conjunctivitis showed a tear concentration of 0.6 mg %, or more. On the other hand, 6 of 10 patients without conjunctivitis had a tear concentration of 0.56 mg %.

A single case of conjunctivitis was observed in which the eye inflammation disappeared without sequelae despite the uninterrupted administration of sulfathiazole.

Among 31 consecutive patients receiving sulfathiazole, 5 developed conjunctivitis. In 4 of these the conjunctivitis appeared during a second or a subsequent course of therapy.

Conclusions. 1. The amount of sulfathiazole secreted in the tears is not proportional to the blood sulfathiazole concentration.

2. The concentration of sulfathiazole in the tears does not of itself appear to be the cause of the conjunctivitis.

5 Haviland, W. J., and Long, P. H., *Bull. Johns Hopkins Hosp.*, 1940, **66**, 313.