

## THE INFLUENCE OF SULFONAMIDES UPON THE DYE-EXCRETING FUNCTION OF THE LIVER

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The literature concerning the influence of sulfonamides on the liver has been reviewed by Long and Bliss<sup>1)</sup> (1938). They are of the opinion that the use of a large amount of sulfonamides may cause fatal disturbances in the liver, but fortunately it is practically rare that such untoward reactions occur. Yet, the disturbances of the liver seem to play an important role in the ill-reactions of sulfonamides. Since such disturbances of the liver induced by different compounds of sulfonamide have rarely been reported, the author attempted to examine the influence of sulfonamides on the liver-function, chiefly based upon the dye-excretion test in rabbits.

### METHODS

#### (1) Examinations with a single-injection of sulfonamide.

Healthy adult rabbits were employed. A volume of 2.0 ml of 10 per cent sulfonamide solutions (0.2 gm of sulfonamide) per kg of body weight was injected into the ear-vein. After bilateral nephrectomy had been performed, a glass canule was inserted into the common bile duct, and the bile was collected at intervals of 15 minutes for two hours. (we<sup>2)3)</sup> know experientially that bilateral nephrectomy renders the results fairly uniform.)

Thirty minutes after the administration of sulfonamide, 1.0 ml of 0.6 per cent aqueous solution of phenolsulfonphthalein per kg of body weight was injected intravenously. The time between the injection and the first appearance of the dye-stuff into the bile was measured. The total amount of the dye-stuff excreted into the bile during the two hours after injection was determined with the Duboscq's colorimeter. Then the percentage amount of excreted dye-stuff to the total amount injected was calculated.

#### (2) Examinations with repeated injections of sulfonamide.

By daily intravenous injections of 2.0 ml of 10 per cent solution was given to rabbits weighing approximately 2 kg. After ten days, the dye-excretion test was carried out, and histological examination of the liver was made in sections stained with hematoxylin-eosin.

(3) As control experiment for (1) and (2), 2.0 ml of physiological salt solution per kg of body weight was injected instead of sulfonamide, and the rate of dye-excretion was examined.

## RESULTS

(a) The control percentage amounts of dye-stuff excreted in the bile in 2 hours varied from 16.4 to 23.8%, averaging 20.7%, and the time of the initial appearance of the dye-stuff was 2' 25" to 3' 10" after injection, averaging 2' 36".

(b) Acetsulfamine ("Neo-Gerison", "Region" and "Neo-Therapol") showed no influence upon the dye-excreting function and the histological picture of the liver, even when repeatedly injected for several days.

(c) Homosulfamine ("Paramenyl") had no effect on the rate of dye-excretion with a single injection. Repeated injections were followed by a marked loss of weight and a lowered excretion-rate, with negative histological findings.

(d) Sulfapyridine ("Trianon") caused a marked increase of the dye-excreting function with single injection; if given repeatedly, the function was slightly

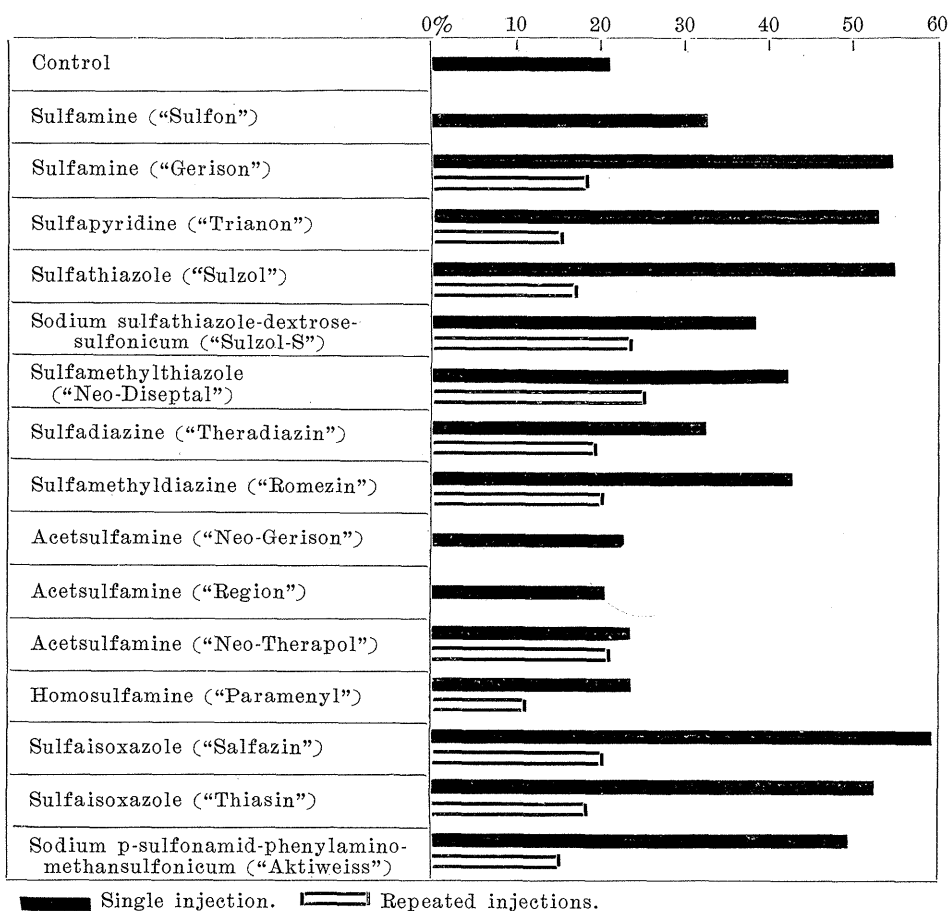


Fig.1. Percentage of the pigment-excretion in two hours.

disturbed with histological evidence and a marked loss of weight.

(e) Sulfamine ("Sulfon" and "Gerison"), Sulfathiazole ("Sulzol"), Sulfadiazine ("Theradiazine"), Sulfaisoxazole ("Sulfazin" and "Thiasin") and Sodium p-sulfonamid-phenylamino-methansulfonicum ("Aktiweiss") produced an increase in the rate of dye-excretion with single-injection, while repeated injections caused to a slight degree a decrease accompanied with a histological damage of the liver in some cases.

(f) Sulfamethylthiazol("Neo-Diseptal"), Sulfamethyldiazine("Romezin") and Sodium sulfathiazole-dextrose-sulfonicum ("Sulzol-S") caused an increase in the dye-excreting function of the liver after either single or repeated injections with a slight degree of liver damage in some cases.

The data are presented in Table I and in Fig. 1.

#### DISCUSSION AND CONCLUSION

A number of sulfonamide compounds were tested for their effects upon the dye-excreting function of the liver. After the single intravenous injection, almost all of the compounds studied produced a marked increase in the rate of dye-excretion from the liver, while others failed to do so. When injected repeatedly, several of the compounds studied induced either a marked or a slight disturbance of the liver-function. The results do not permit speculation as to the relationship between the chemical structure and the physiological effects upon the dye-excreting function. With regard to the clinical applications of sulfonamides, however, the present results suggest that the use of the sulfonamides which are not stimulant to the liver at all (Acetsulfamine) seem most reasonable. Other compounds which are stimulating the liver-function but not harmful even after repeated injections (Sulfamethylthiazole, Sulfamethyldiazine, Sulfaisoxazole and Sodium sulfathiazole-dextrose-sulfonicum) seem also applicable, so far as chronic hepatic diseases are concerned.

#### LITERATURE

- 1) LONG & BLISS : "The Clinical and Experimental Use of Sulfonamide, Sulfapyridine and Allied Compounds", 1939.
- 2) MATSUDA, T. : *Japanese Jour. Gastroenterology*, **3** : 281, 1931.
- 3) MIZUTA, M. : *Jour. Japanese Soc. Int. Med.* **40** : 124, 1951.

TABLE I

Amount of sulfonamides injected	No. of rabbit	Body weight (kg)	Amount of dye injected (ml)	Time of initial appearance after injection	Amount of bile excreted in 2 hrs. (ml)	Amount of dye excreted in 2 hrs. (%)	
Control	1	1.5	1.5	2/30"	14.2	23.6	
	2	1.8	1.8	3/10"	16.6	23.8	
	3	2.3	2.3	2/25"	20.4	19.2	
	4	2.0	2.0	2/30"	11.7	16.4	
		(1.9)	(1.9)	(2/36")	(15.7)	(20.7)*	
Sulfamine (5% Sulfon)							
2.0 ml per kg	5	2.2	2.2	2/25"	12.0	35.7	
	6	2.1	2.1	2/30"	17.4	26.8 (31.3)	
4.0 ml daily for 4 days	7	1.8	1.8	3/ 0"	16.0	23.2	
Sulfamine (5% Gerison)							
2.0 ml per kg	8	1.8	1.8	1/45"	13.0	55.0	
4.0 ml daily for 9 days	9	2.1-1.9	1.9	2/40"	10.7	16.5	
	10	2.2-2.1	2.1	1/55"	10.8	21.1 (18.8)	
Sulfapyridine (10% Trianon)							
2.0 ml per kg	11	2.1	2.1	1/10"	19.3	48.6	
	12	2.2	2.2	1/50"	14.3	52.1 (50.4)	
2.0 ml daily for 9 days	13	1.8-1.5	1.5	3/20"	8.7	15.7	
	14	1.9-1.5	Dying of shock during the operation.				
Sulfathiazole (20% Sulzol)							
1.0 ml per kg	15	2.2	2.2	1/30"	13.3	55.0	
	16	2.2	2.2	1/45"	11.7	53.3 (54.2)	
1.0 ml daily for 9 days	17	2.3-2.1	2.1	2/05"	14.1	11.9	
	18	2.3-2.1	2.1	2/10"	11.9	21.5 (16.7)	
Sodium sulfathiazole-dextrose-sulfonicum (10% Sulzol-S)							
2.0 ml per kg	37	1.6	1.6	1/45"	13.5	34.9	
	38	2.6	2.6	1/50"	14.8	42.6 (38.8)	
2.0 ml daily for 9 days	39	2.4-2.4	2.4	2/10"	12.8	22.0	
	40	2.4-2.1	2.1	2/10"	16.5	25.7 (23.9)	
Sulfamethylthiazole (5% Neo-Diseptal)							
4.0 ml per kg	25	1.8	1.8	2/30"	13.5	51.1	
	26	2.1	2.1	1/30"	15.8	35.2 (43.2)	
4.0 ml daily for 9 days	27	2.2-1.7	1.7	1/30"	10.8	30.6	
	28	2.0-1.5	1.5	2/05"	9.8	19.8 (25.2)	
Acetsulfamine (30% Neo-Gerison)							
1.0 ml per kg	19	2.0	2.0	1/45"	14.4	22.2	
Acetsulfamine (30% Region)							
1.0 ml per kg	20	1.8	1.8	2/50"	10.9	20.1	
Acetsulfamine (30% Neo-Therapol)							
1.0 ml per kg	21	2.0	2.0	1/40"	10.6	23.3	
0.7 ml daily for 9 days	22	1.7-1.5	1.5	2/20"	14.1	22.9	
	23	1.7-1.5	1.5	3/ 0"	9.4	18.3 (20.6)	
5.0 ml daily for 4 days	24	1.7-1.6	1.6	2/15"	9.2	32.8	
		(The test was carried out 3 hrs. after the last injection.)					
Sulfadiazine (10% Theradiazin)							
2.0 ml per kg	29	1.5	1.5	2/30"	9.8	32.9	
	30	1.8	1.8	2/15"	12.2	32.5 (32.7)	
2.0 ml daily for 9 days	31	2.5-2.5	2.4	3/10"	18.0	17.3	
	32	2.4-2.4	2.4	1/50"	25.4	24.5	
	50	1.8-1.7	1.7	2/20"	14.5	17.6 (19.8)	
Sulfamethyldiazine (10% Romezin)							
2.0 ml per kg	33	2.3	2.3	2/30"	8.1	38.8	
	34	1.8	1.8	1/45"	11.9	48.5 (43.7)	

Continued on page 35

TABLE I Continued

Amount of sulfonamides injected	No. of rabbit	Body weight (kg)	Amount of dye injected (ml)	Time of initial appearance after injection	Amount of bile excreted in 2 hrs. (%)	Amount of dye excreted in 2 hrs. (%)
2.0 ml daily for 9 days	35	1.7-1.4	1.5	1/50"	18.0	17.9
	36	1.6-1.4	1.4	1/30"	19.8	22.9 (20.4)
Homosulfamine (10% Paramenyl)						
2.0 ml per kg	41	1.7	1.7	2/45"	13.3	23.9
	42	2.2	2.2	2/20"	10.0	22.3 (23.1)
2.0 ml daily for 9 days	43	2.1-1.8	1.8	3/10"	5.1	9.2
	44	2.1-1.8	1.8	2/50"	5.8	11.3
	45	2.1-1.9	1.9	3/10"	8.9	12.4 (11.0)
Sulfaisoxazole (20% Sulfazin)**						
1.0 ml per kg	51	1.8	1.8	2/30"	12.1	53.7
	52	2.0	2.0	1/50"	22.1	65.0 (59.4)
1.0 ml daily for 9 days	53	2.1-2.0	2.0	2/50"	14.0	18.0
	54	2.1-2.0	2.0	2/40"	11.0	22.0 (20.0)
Sulfaisoxazole (10% Thiasin)***						
2.0 ml per kg	55	1.9	1.9	1/10"	15.7	62.6
	56	2.1	2.1	2/30"	18.3	42.4 (52.5)
2.0 ml daily for 9 days	57	1.8-1.8	1.8	1/50"	12.3	23.8
	58	1.7-1.5	1.5	2/50"	10.7	14.0 (18.9)
Sodium p-sulfonamid-phenylamino-methansulfonicum (8.5% Aktiweiss)						
2.0 ml per kg	46	2.0	2.0	2/10"	13.2	51.0
	47	2.1	2.1	1/20"	22.7	48.2 (49.6)
1.0 ml daily for 6 days	48	2.2-2.1	2.1	2/10"	12.9	22.0
2.0 ml daily for 9 days	49	1.75-1.65	1.65	2/25"	11.0	15.8

\* The parenthesized figures indicate the average in each experiment.

\*\* 20% aqueous solution of ethanolamin salt of 3,4-dimethyl-5-sulfanilamido-isoxazole.

\*\*\* 10% aqueous solution of lithium salt of 3,4,-dimethyl-5-sulfanilamido-isoxazole.

#### Histological findings of the liver

- No.13 : Slightly congested. The central areas of the lobules are very slightly infiltrated with fat. The Kupffer cells appear somewhat swollen.
- No.14 : Slightly congested.
- No.17 : Slightly congested. The Kupffer cells are slightly swollen.
- No.18 : Fairly congested.
- No.39 : Partially congested.
- No.40 : Partially congested with partial infiltration of fat of slight degree.
- No.27 : Partially congested. The Kupffer cells are slightly swollen.
- No.28 : Slightly congested.
- No.22 : Formation of a few vacuoles in the peripheral region.
- No.23 : Formation of a few vacuoles in the central and peripheral regions.
- No.31 : Moderately congested. Considerably infiltrated with fat in the peripheral region, and infestation of some coccidia.
- No.32 : Moderately congested. Moderately infiltrated with fat in the central region. The Kupffer cells are swollen.
- No.50 : Normal figure.
- No.43 : A slight degree of degeneration in the liver cells. The Kupffer cells are slightly

swollen.

No.44 : Normal figure.

No.45 : Very slightly congested. The Kupffer cells are slightly swollen.

No.53 : Parenchymal cells enlarged, partially unequal in size, and the granules in protoplasm coarse, though the changes are not remarkable.

(Histological findings of the kidney : Remarkable cloudy swelling of the contorted tubules, with partial slight necrosis. Some of the glomerules are congested without cellular infiltration.)

No.54 : The same as No.53.

No.57 : Congested, though the change is not remarkable.

(Histological findings of the kidney is the same as No.53.)

No.58 : Liver and kidney are normal.

No.48 : Very slightly congested.

No.49 : Very slightly congested.