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Mechanism of Liver and Kidney Damage Caused by Sodium Sulfamethylthiazole.*

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In a previous investigation the occurrence of severe degenerative lesions in liver and kidney following the administration of sodium sulfamethylthiazole was observed. It was noted that histologically, the liver showed fatty degeneration and was almost devoid of glycogen, while the livers of rats receiving equimolar amounts of sulfapyridine and sulfathiazole were strikingly rich in glycogen. Increase in liver glycogen after the administration of sulfanilamide and sulfapyridine has been reported in the literature.[1, 2]

In order to analyze the different response to the administration of these 3 sulfanilamide derivatives the content of glycogen and drugs in the liver and the concentrations of the drugs in the blood were determined in experiments with rats. Urinalysis and determination of blood urea were used to indicate the functional state of the kidneys.

Results. Table I gives the results of a representative experiment.

The presence of high normal or increased amounts of glycogen in the liver after administration of sulfapyridine and sulfathiazole, as seen in histological sections, was confirmed by chemical analysis, as was also the glycogen depletion after sulfamethylthiazole.

The data seem to indicate that damage to the excretory function of the kidneys plays an important part in the production of the lesions after sulfamethylthiazole administration. In Table II the renal lesions caused by a single injection of sodium sulfamethylthiazole are clearly reflected in the urinary findings. Further proof of pronounced impairment of kidney function can be deduced from the high blood urea levels and retention of sulfamethylthiazole in the body.

The diminution or complete disappearance of acetylation in animals having toxic drug concentrations (Table I) can be regarded

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1 Greisheimer, E. M., Hafkesbring, R., and Magalhaes, H., *Proc. Am. Physiol. Soc.*, 52d Annual Meeting, 1940, p. 75.

2 Antopol, W., and Robinson, H., *Arch. Path.*, 1940, **29**, 67.

TABLE I.

Groups of 5 rats received 3 intraperitoneal injections each, on 3 successive days, of 0.5 g/kg sodium sulfapyridine and equimolar amounts of the sodium salts of sulfathiazole (0.486 g/kg) and sulfamethylthiazole (0.515 g/kg), respectively. The controls were injected with equimolar amounts of sodium acetate (0.225 g/kg) in equal amounts of fluid. The animals were sacrificed 24 hours after the last drug injection; food was withdrawn for the last 12 hours.

		Liver		Blood			
				Drug mg%			
Compound	Rat No.	Glycogen mg%	Free drug mg%	Free	Total	Urea N mg%	
Sodium sulfapyridine	183	1330	st. tr.	tr.		18	[1]
	184	594	tr.	st. tr.		14	
	185	120	"	tr.		16	
	186	910	"	"		16	
	187	244	0	0		14	
Sodium sulfathiazole	195	823	0	0		14	[1]
	196	1535	0	tr.		24	
	197	726	0	0		18	
	198	1800	0	tr.		18	
	199	458	0	0		18	
Sodium sulfamethylthiazole	180						[2]
	182	0	126				[3]
	192	96	19.5	5.7	8	*50*	[4]
	193	295	tr.	1.4	1.6	14	[5]
	194	0	44	23	23	*92*	[6]
Controls: Sodium acetate	200	790				20	
	201	151				16	
	202	185				16	
	203	262				20	
	204	70				20	

tr.—Trace.

st. tr.—Strong trace.

[1] No precipitation in the urinary tract.

[2] Died after 1st injection, kidneys congested.

[3] Sacrificed in dying state 6 hours after 2nd drug injection. Precipitation in renal papillæ, concrements in ureters, liver damage.

[4] Precipitation in renal papillæ, concrements in bladder, bloody urine, liver damage.

[5] Liver and kidneys of normal appearance, no concrement formation.

[6] Precipitation in renal papillæ, concrements in bladder, bloody urine, liver damage.

as evidence of damage to the detoxifying activity of the liver. It seems very probable that the accumulation of high amounts of sulfamethylthiazole is responsible for the degeneration of parenchymatous organs. This possibility is strengthened by the fact that those few animals which showed no lesions in the kidneys after sulfamethylthiazole, and therefore had no retention of the compound in the body (as *e.g.* rat 193 in Table I), failed to develop any signs of liver damage.

TABLE II.
Urinary Findings After a Single Intraperitoneal Injection of 0.5 g/kg Sodium Sulfamethylthiazole in Rats.
(Pronounced hematuria, albuminuria, polyuria and hypostenuria.)

Days after injection	No. of rats	Urine ml per rat	Sp.Gr.	Alb.	Sediment	Drug excretion	
						mg per rat	% acetyl.
0*	5	6	1045	neg.	Amorph. precip.		
1†	5	18	1014	++++	r.b.c. 100§	22	28
2	4	35	1012	+	r.b.c. 50-100	6.5	32
3	4	16	1028	trace	r.b.c. 20-30	1.5	30
4‡	3	10	1038	neg.	single r.b.c.	0.3	

*Control—day before injection.
†1 died: precipitation in renal papillæ, kidney and liver damage.
‡1 died: precipitation in renal papillæ, kidney and liver damage.
§r.b.c.—red blood cells per high power field.

In all other experiments, which will be reported elsewhere in detail, the findings were essentially the same.

Conclusions. Degenerative lesions of liver and kidneys following administration of sulfamethylthiazole are explained as a consequence of the damaging effect of high concentrations of the compound in the body. The accumulation of these toxic concentrations is believed to be due to severe impairment of the renal excretory function caused by precipitation of the acetyl sulfamethylthiazole in the collecting tubules of the kidneys.

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Nasogenital Relationship: III, Some Aspects of Sexual Function in Female Rats Deprived of Sphenopalatine Ganglia.

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The study of the nasogenital relationship has revealed the production of pseudopregnancy in the female rat following silver nitrate applications to the nasal mucosa[1] and following local anesthetization of the nasal mucosa.[2] The bilateral removal of the sphenopalatine ganglia in adult female rats is followed by pseudopregnancy. This condition is characterized by the persistence of leucocyte cell smears

1 Rosen, S., and Shelesnyak, M. C., PROC. SOC. EXP. BIOL. AND MED., 1937, **38**, 832.

2 Shelesnyak, M. C., and Rosen, S., *Endocrinology*, 1938, **23**, 58.