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Interstitial Myocarditis in Mice and Rats Produced by Neoprontosil, Sulfanilamide, Sodium Sulfapyridine and Sodium Sulfathiazole.

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In the routine examination of autopsy material at the University Hospital, examples of interstitial myocarditis, in which the cellular infiltrations included eosinophile cells in varying numbers, have been encountered with increasing frequency in recent years. After excluding all cases with trichinosis, rheumatic heart disease, demonstrable septicopyemia and other recognized causes of interstitial myocarditis, there was left a group in which the only factor possessed in common was that each patient had received medication with a drug of the sulfonamide group.

Dozzi,[1] and Scheinberg and Ingle[2] have independently described electrocardiographic changes suggestive of myocardial damage following the use of sulfonamide drugs. No other reference to myocarditis resulting from such medication has been found in a careful search of the literature, save for the observation by Nelson[3] of myocarditis, with infiltrating polymorphonuclear and monocytic cells, in a hen to which sulfanilamide had been administered.

1 Dozzi, L., *Am. J. Med. Sci.*, 1938, **195**, 771.

2 Scheinberg, D., and Ingle, C. W., *Memphis Med. J.*, 1939, **14**, 87.

3 Nelson, A. A., *Pub. Health Rep.*, 1939, **54**, 106.

As a preliminary procedure, groups of rats (Wistar strain), Swiss mice and domestic rabbits were given neoprontosil by the daily intraperitoneal injection of an amount computed to be comparable to the usual clinical dosage (4 g per 24 hours for a man weighing 75 k). The following volumes of a 5.0% solution of neoprontosil were used: Mouse, 0.015 cc; rat, 0.15 cc; rabbit, 1.5 cc. Interstitial cellular infiltrations were found in many of these animals. Accordingly larger groups of animals were employed and sulfanilamide, sodium sulfapyridine and sodium sulfathiazole were employed as well as neoprontosil. The daily dosage is shown in Table I.

The mice and rats were killed at intervals of 10, 20 and 30 days. The rabbits were treated for but 10 days since sodium sulfathiazole and sodium sulfapyridine were not available in sufficient quantities for protracted use, and it seemed desirable to use the sodium salts because of their greater solubility. To smaller groups of mice and rats doses 10 times the computed clinical amount were given. The combined results follow: 68 mice treated, 38 showed myocarditis; 56 rats treated, 42 showed myocarditis; 20 rabbits treated, 17 showed myocarditis. Myocardial infiltrations followed the use of each of the 4 drugs administered. No significant differences among the 4 as to the danger of producing myocarditis were revealed. In general, the frequency of myocarditis increased with the duration of treatment and with increased dosage.

As controls, 29 mice, 26 rats and 26 rabbits from the same stocks of animals, all bred, housed and fed in the same manner as those treated, were killed and their hearts examined microscopically. "Spontaneous" myocarditis[4] was found in several of the control rabbits. The results in the treated rabbits were therefore excluded from further consideration. No cellular infiltrations were found in the hearts of either the control rats or mice.

Summary. In the mouse and rat an interstitial myocarditis, of which the cellular infiltration is in part eosinophilic, results from the

TABLE I.

	% Sol.	Mouse, cc	Rat, cc	Rabbit, cc
Neoprontosil	5.0	.015	.15	1.5
Sulfanilamide	0.5	.15	1.5	15.0
Sodium sulfapyridine	5.0	.015	.15	1.5
Sodium sulfathiazole	5.0	.015	.15	1.5

[4] Miller, C. P., *J. Exp. Med.*, 1924, **40**, 543.

intraperitoneal injection of neoprontosil and certain other drugs of the sulfonamide group. This myocarditis is histologically similar to that observed in the hearts of humans dying after the administration of these drugs.

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Biotin and Scaly Dermatosis of the Chick.

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In a recent communication,[1] chicks raised on a heated diet[2] were reported to show symptoms of a severe dermatosis similar to the one described by Hegsted, *et al.*[3] As shown in Tables I and II, the deficiency syndrome was readily obtained with chicks reared on diet X-5, which is ration K-11[4] modified by the addition of 2 mg of 2-methyl-1,4-naphthoquinone per 10 kg of diet. The symptoms most frequently developed on the toes and feet, often in the cor-

TABLE I.
Effect of Biotin Concentrates on Growth and Scaly Dermatosis in Chicks.*

Depletion period Wt and symptoms†						Test period Wt and symptoms†		
26th day, g	55th day, g	68th day, g	Daily doses, γ	Route‡	No. of chicks	8th day, g	17th day, g	25th day, g
130 N	230 D	290 M	0	O	20	340 S	——	350 S
160 N	270 M	350 S	2.5	O	5	440 DH	530 C	550 C
130 N	220 M	260 S	1.25	O	5	330 DH	410 C	440 C
140 N	210 M	230 S	24	SC	4	290 DH	340 C	350 C
150 N	250 M	290 S	18	SC	4	360 DH	440 C	480 C
140 N	250 M	280 S	12	SC	4	360 DH	460 C	500 C
130 N	270 M	310 S	6	SC	4	410 DH	530 C	600 C
130 N	210 M	250 S	2.5	SC	3	340 DH	440 C	490 C

[1] Ansbacher, S., *Science*, 1941, **93**, 164.

[2] Ansbacher, S., PROC. SOC. EXP. BIOL. AND MED., 1940, **44**, 248.

[3] Hegsted, D. M., Oleson, J. J., Mills, R. C., Elvehjem, C. A., and Hart, E. B., *J. Nutrition*, 1940, **20**, 599.

[4] Ansbacher, S., PROC. SOC. EXP. BIOL. AND MED., 1941, **46**, 421.