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Mechanism of Bradycardia in Rats with Thiamine Deficiency.

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Bradycardia is a well-known phenomenon in thiamine-deficient rats. The following experiment was carried out to determine whether bradycardia could be demonstrated in the isolated auricles of such animals. The effect of addition of thiamine to the isolated preparations was also studied.

Healthy albino rats, adult males, were used. Half were fed the Sherman and Sandels diet,[1] the remainder received the routine laboratory diet. Litter mates were scattered in the two groups.

The thiamine-deficient rats remained on the diet 31 to 40 days. All animals were accustomed to being handled by almost daily weighing. Satisfactory electrocardiograms were obtained by smearing contact jelly on both sides of the animal's body just behind the forelegs; large aluminum electrodes were held in position by the operator who wore rubber gloves. The importance of training in obtaining basal heart rate tracings was evident. Keeping in mind the difficulties encountered by Robertson and Doyle,[2] counts were made at different places in the tracings. The greatest variation in any tracing was 10 beats per min. In most cases the variation was 2 or 3 beats per min. Three to 7 tracings were made on the thiamine-deficient rats and 2 to 6 on the normals.

After the last tracing the animal was killed by a blow on the head, the heart was removed and the auricles were dissected free under iced Ringer's solution. The auricles were then strung up in a Dale bath in oxygenated Ringer's at 35°C. Auricles from a normal and a vitamin-deficient rat were set up in the same bath, and the beats were recorded simultaneously by means of heart levers on a smoked drum.

After allowing the auricles to establish a regular rhythm (15 to 20 min), a control tracing was made. Thiamine chloride in Ringer's was then added. Two concentrations, 1/1,000,000 and 1/100,000 were used, and the preparation was washed twice between each addition. Records were made 5 min after each addition and a final control record was made with Ringer's alone. The pH remained unchanged throughout and was not altered by the additions of thiamine.

A summary of the results is recorded in Table I.

Results. The final mean heart rate of de-

TABLE I.

No. of animals used		Intact animal Heart rate per min		Isolated auricles—beats per min					
		Initial	Last	Control	B_1 1/1,000,000	% Change	B_1 1/100,000	% Change	Control
Normal	13	466	445	234	254	+8	250	+7	233
Deficient	10	505	344	216	236	+9	202	—6	214
Difference			—101 (±31.1)	—18 (±28.5)	—18 (±39.8)		—48 (±27.2)		—19 (±29.6)
T =			3.23	1.23	0.45		1.84		0.74
P =			0.05	0.24	0.65		0.10		0.44

[1] Sherman, H. C., and Sandels, M. R., *J. Nutr.*, 1931, **3**, 395.

[2] Robertson, E. C., and Doyle, M. E., PROC. SOC. EXP. BIOL. AND MED., 1937, **37**, 139.

ficient animals was 344 per min, compared to 445 per min for controls. This degree of bradycardia was not reflected, however, in the beat of the isolated auricles, the mean rates for the two groups being 216 per min and 234 per min respectively. Addition of thiamine chloride to isolated auricles caused no greater increase of rate in those from deficient animals than in controls. MacDonald and McHenry[3] have shown that the bradycardia in intact animals is not relieved by administration of thiamine unless food is also given.

The bradycardia would not seem to be a function of metabolic changes in the heart muscle as, for example, the tachycardia of hyperthyroidism, which persists after the auricles are isolated from the intact animal.[4] It is possible that chemical factors responsible for bradycardia might diffuse out of the myocardium during the period of isolation but it is more likely that the bradycardia is of neurogenic origin.

Summary. The bradycardia of thiamine-deficient rats disappears when the auricles are isolated *in vitro*. It is probably of neurogenic origin.

[3] MacDonald, D. G. H., and McHenry, E. W., *Am. J. Physiol.*, 1940, **128**, 608.

[4] Lewis, J. K., and McEachern, D., *Bull. Johns Hopkins Hosp.*, 1931, **48**, 228.

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Protection of Mice Against Meningococcal Infection by Sulfadiazine, and Inhibition of Protection by Para-aminobenzoic Acid.

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During the course of an investigation into the immunological response of patients following meningococcal infection,[1] a number of mouse-protection tests were undertaken with serums obtained from patients during the early and convalescent stages of the disease. All of these patients with meningitis or meningococcemia had received treatment with sulfonamides, and most of them received sulfadiazine. It was noted that mice were protected against multiple lethal doses of meningococci by serum containing sulfadiazine, even in amounts less than 1 mg %, regardless of the stage of illness during which the serum was obtained from the patient. The addition of para-aminobenzoic acid to such serum, in a concentration of 5 mg %, had no inhibitory effect on this protection. Similar protective action was exerted by small amounts of sulfadiazine diluted in normal serum or in physiological saline, and again the addition of para-aminobenzoic acid was without effect. Because of these observations, further investigations were carried out in order to determine (1) the amount of sulfadiazine necessary to induce protection of mice against a virulent strain of Group I meningococcus and (2) under what circumstances this protection was inhibited by para-aminobenzoic acid.

Materials and Methods. Three solutions of sodium sulfadiazine in physiological saline were made, containing 1.0, 0.5 and 0.1 mg per 100 ml. Similar concentrations of the drug were prepared in normal human serum which had been diluted 1:5 in saline. These were injected intraperitoneally into 3 groups of mice, in 0.5 ml amounts, so that the doses for each group were 0.005, 0.0025 and 0.0005 mg, respectively. These injections were made 30 min before the injection of organisms.

The following methods were employed for

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[1] Thomas, L., Smith, H. W., and Dingle, J. H., submitted for publication.