

TABLE II.  
Apparent Volume of Distribution\* of Bacitracin in Male Mongrel Dogs.

| Dog No. | Wt kg | Total dose in units | No. hr after inj. | Plasma conc. units/cc | Total urinary output in units | Apparent volume of distribution in liters | % body wt |
|---------|-------|---------------------|-------------------|-----------------------|-------------------------------|-------------------------------------------|-----------|
| 156     | 6.4   | 19,200†             | 3                 | 7.5                   | 2,200                         | 2.3                                       | 36        |
| 156     | 6.4   | 19,200†             | 5                 | 6.7                   | 4,300                         | 2.2                                       | 35        |
| 151     | 7.3   | 7,300†              | 3                 | 1.3                   | 2,000                         | 4.1                                       | 56        |
| 229     | 9.2   | 27,600‡             | 7                 | 0.44                  | 26,200                        | 3.2                                       | 34        |

\* The total dose, minus the fraction excreted, divided by the plasma concentration gives the number of liters of body water in which the bacitracin appears to be distributed. The apparent volume of distribution is expressed in terms of body weight.

† Dose administered intravenously.

‡ " " intramuscularly.

weight were administered. The recovery of the drug in the urine appeared, in general, to increase in direct ratio to the dose administered, but the recoveries were widely variable. Significant concentrations of bacitracin

persisted in the urine for more than 7 hours after administration of a single dose of the antibiotic. Bacitracin is not freely diffusible. It did not penetrate the red blood cell, nor did it enter the spinal fluid freely.

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### Effect of Muscular Activity on Curarization in Rabbits.

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In studying the curariform action of a group of quaternary quinine derivatives by the rabbit head-drop method, one of us<sup>1</sup> observed that if rabbits struggled following a single intravenous injection of these paralyzing substances, head-drop seemed to occur more rapidly than usual. More recently, in the course of studies with *d*-tubocurarine, it was observed that shortly after recovery from, or even during, convulsions induced in rabbits by the injection of cocaine or veratrine, the amount of *d*-tubocurarine required to produce "head-drop" was markedly reduced. Torda and Wolff<sup>2</sup> have demonstrated the presence of a curare-like agent in the serum of blood obtained from the hind limbs of anesthetized cats following tetanic stimulation of the sciatic nerve or following passive

exercise of the extremities. In view of these findings, quantitative studies have been made of the synergistic effect of exercise on curarization, using the rabbit "head-drop" assay method.

*Method.* Several types of muscular exertion were investigated.

(1) *Running.* Rabbits were exercised in a long corridor for 5 minutes, in response to gentle stimuli from the experimenter, who followed the animal at a rate no faster than a normal walk. Animals, thus exercised, showed signs of exertion such as increased respiration, but, of course, were by no means exhausted. This method proved more satisfactory than were attempts to exercise rabbits in a treadmill.

(2) *Violent exertion.* When the hind legs of rabbits were grasped and held off the floor, the animals made violently active attempts to escape; these repetitive efforts were punctuated by brief intervals of rest. One-half-

<sup>1</sup> Chase, H. F., Lehman, A. J., and Rickards, E. E., *J. Pharm. and Exp. Therap.*, 1944, **82**, 266.

<sup>2</sup> Torda, C., and Wolff, H., *Proc. Soc. Exp. Biol. and Med.*, 1945, **58**, 242.

TABLE I.  
Rabbit Head-Drop Doses (mg per kg) of *d*-Tubocurarine Before and After Exercise.

|                 | Type of exercise |                  |                  |                     |
|-----------------|------------------|------------------|------------------|---------------------|
|                 | 5 min<br>running | ½ min<br>violent | 2 min<br>violent | 10 min<br>hind legs |
| Before exercise | (30)*<br>0.245   | (8)<br>0.252     | (10)<br>0.268    | (10)<br>0.258       |
| After     "     | 0.112            | 0.16             | 0.119            | 0.151               |
| Critical ratio  | 16.3             | 5.4              | 10.0             | 5.4                 |
| % reduction     | 54%              | 36%              | 55%              | 41%                 |

\* No. of rabbits.

and 2-minute periods of this extreme type of muscular exertion were investigated.

(3) *Moderate exercise of hind limbs only.* Rabbits were placed in their usual sitting posture and gently restrained manually. The hind legs were pulled alternately from under the animal at a rate of 100 to 120 times per minute for a period of 10 minutes. During the latter part of the period passive exercise was often necessary, though even then some voluntary resistance was noticeable. If the animal moved forelimbs or body it was momentarily released and such efforts promptly ceased.

Within one minute after exercise the "head-drop" assay was started. Increments of 0.05 cc of a solution of *d*-tubocurarine containing 0.65 mg (4.0 "Intocostin" units) per cc were administered intravenously every 15 seconds until head-drop occurred. Control and test values were obtained on the same animals by the cross-over technic.

*Results.* The data in the accompanying table demonstrate that in the production of head-drop in rabbits there is a definite synergism between *d*-tubocurarine and muscular activity. The physiological significance of these results is indicated by the fact that they are demonstrable after only one-half minute of intermittent, but strenuous exercise; further, a prolongation of the period of exertion to 2 minutes measurably augmented the synergism. These findings would tend to substantiate the findings of Torda and Wolff and of others.

*Comment.* The mechanism of this apparent synergism is being investigated further. Possibly a central synaptic fatigue of postural reflexes is involved, exhaustion of neuro-humoral mechanisms at the nerve endings might occur, or an accumulation of products of muscle metabolism may be involved.

The demonstration of this susceptibility of overactivated muscles to the action of curarizing agents may serve to explain the clinical observation that the hyperinnervated muscle groups of spastic paralytics respond to doses of curare which have no demonstrable influence on normally innervated muscles. In anesthesia these findings suggest greater exercise of caution in the use of curare following a stormy induction, in which the patient is hyperactive, than following a quiet induction.

This phenomenon may help in explaining the beneficial action of sodium amytal which, by preventing convulsions, protected rats against ordinarily fatal doses of *d*-tubocurarine.<sup>3</sup>

*Summary.* Muscular exercise has been demonstrated to be synergistic with *d*-tubocurarine in producing head-drop in rabbits. Synergistic effects are apparent following short bouts of exercising and the degree of additive effect increases with the duration and intensity of the exercise.

<sup>3</sup> Cohnberg, R. E., *J. Lab. and Clin. Med.*, 1946, **31**, 866.