

children and adults, to insure a degree of spectral purity, and because the rods, of primary interest in vitamin *A* estimations, are maximally sensitive to this part of the spectrum.

With children and adults it is possible to obtain an approximate measure of the speed of dark adaptation by exposing the eyes to a bright light for 2 or 3 minutes, following which observations of the rapidly descending threshold are made at frequent intervals until dark adaptation is relatively complete.

Measurements we have made of the visual thresholds of infants, children, and adults using this apparatus and procedure will be described elsewhere.

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Prolonged Administration of Cobra Venom in Relation to Kidney and Liver Function.

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The increasing therapeutic use of cobra venom as an analgesic in advanced malignant disease¹ and the extension of such clinical usage to other chronic painful conditions,^{2, 3} prompted the senior author to further pharmacological study of the effect of repeated administration of the drug for prolonged periods on certain vital physiological functions. The present communication describes the effect of repeated injection of large doses of cobra venom for long periods of time on the kidney and liver function of rabbits. A standard solution of the drug, prepared in these laboratories and assayed biologically to ensure a content of 5 mouse units of cobra venom per cc, was administered to a series of rabbits in doses of 5 or 10 mouse units daily 5 and sometimes 6 times a week. The results obtained in 10 such animals are exhibited in Table I. The weight of each rabbit, its kidney function, liver function and general condition were recorded at the beginning of the investigation. All the rabbits were kept on a liberal diet of rabbit food (Purina Chow) supplemented with fresh greens. In some rabbits the venom solution was injected intra-

¹ Macht, D. I., *Proc. Nat. Acad. Sc.*, 1936, **22**, 61.

² Macht, D. I., *Ann. Int. Med.*, 1938, **11**, 1824.

³ Rottmann, A., *Klin. Wechschr.*, 1937, **16**, 1051.

TABLE I.
Effect on Kidney and Liver Function of Rabbits of Prolonged, Repeated Injection of Cobra Venom.

Rabbit	Time of Test		Weight in kilo		Kidney function		Liver function		Total amount of cobra venom injected	
	Began	Ended	Initial	Final	Initial	Final	Initial	Final	cc	Mouse units
I	9-21-38	11-2-38	2.4	2.5	95	90	5	5	33	165
II	9-21-38	11-2-38	2.4	2.5	90	90	5	5	30	150
III	12-3-38	2-7-39	2.4	3.7	80	85	10	7	54	270
IV	12-3-38	2-7-39	1.5	2.7	80	80	7	7	—	—
V	12-3-38	2-7-39	3.6	3.4	50	65	10	10	90	450
VI	1-17-39	5-8-39	3.8	3.2	80	80	6	6	100	500
VII	2-6-39	5-8-39	3.2	3.0	80	85	7	5	209	1045
VIII	2-6-39	5-8-39	3.4	3.0	65	77	10	0	125	625
IX	2-6-39	5-8-39	3.5	3.4	60	70	6+	4	56	280
X	2-6-39	5-9-39	2.6	2.8	70	75	5	4	60	300

venously and in others intramuscularly, but the results obtained were the same regardless of method of administration. The dosage generally employed was 5 mouse units but some of the animals were injected with 10 mouse units. Inasmuch as 5 mouse units is the ordinary and 10 mouse units the exceptional therapeutic dose which the senior author recommends for human patients, such doses must be regarded as massive when considered in relation to rabbits weighing from 1.5 to 3 kg. Kidney function of the animals was measured by the phenolsulphonphthalein method with the Dunning colorimeter, and the urine was expressed exactly one and 2 hours, respectively, after injection of 6 mg of the dye in the ear vein. Liver function was determined by a modification of the Rosenthal⁴ method as follows: 5 mg of bromsulphalein per kilo weight of rabbit are injected intravenously, and a sample of blood is withdrawn from the heart precisely 15 minutes thereafter. In normal healthy rabbits the bromsulphalein content of the serum 15 minutes after its injection is usually not more than 5% and sometimes is too small to measure at all.

Results. Examination of the tabulated data shows that such injections were made in all the animals for a number of weeks and in some instances for several months. As a matter of fact, some of the animals are yet alive at this writing and still in good condition. Additional experiments on another series of rabbits are in progress. Nevertheless the data reveal that such administration of cobra venom impaired neither kidney nor liver function. Microscopic examination of the kidneys and liver of some of the animals, which were killed with ether, also revealed no pathological change. In fact, although the kidney and liver function of Rabbit V was definitely impaired at the outset, no damage was produced by the venom injections. Rabbit IV became impregnated in the course of the investigation, had a normal gestation and reared 2 of her 3 normal offspring, the third being accidentally killed after birth. This animal received nine intravenous and 81 intramuscular injections of cobra venom, a total of 90 cc or 450 mouse units of the drug. Rabbit VI received 40 intravenous injections of 10-mouse-unit doses, then 61 intramuscular injections of 10-mouse-unit doses, and finally 7 other injections of the ordinary dosage, or 5 mouse units of cobra venom. Rabbit VII received 17 intravenous and then 38 intramuscular injections of 5-mouse-unit doses of cobra venom. Rabbit IX received the same dosage in 18 intravenous and 38 intramuscular injections. The rest of the animals received only intramuscular injections. The

⁴ Rosenthal, S. M., and White, E. C., *J. Pharm. and Exp. Therap.*, 1924, **24**, 265.

histological findings as well as the results obtained in the author's studies on a new series of rabbits will be described in detail in another paper. In conclusion it may be stated that although thousands of doses of cobra venom have been injected by numerous physicians in different parts of the country, the authors have never received a single report describing any impairment of kidney function by this medication.

Summary. Large doses of cobra venom solution, 5 to 10 mouse units, equivalent to the ordinary and the exceptional dosage employed for adult humans, were administered to rabbits 5 or 6 days a week for periods ranging from 7 to 22 weeks. Functional tests made at the beginning and end of the investigation revealed that neither kidney nor liver function of any of the rabbits had been impaired during the whole course of experimentation.

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Relation of Suprarenal Hemorrhage to Loss of Vitamin C in Experimental Diphtherial Intoxication.

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The most characteristic lesion of acute experimental diphtherial intoxication in the guinea pig, other than the local disturbances at the site of injection, is the enlargement of the suprarenal glands with the accompanying congestion and hemorrhage, an extensive study of which was reported by Abramow.¹ Harde² found that the vitamin-C content of these organs was greatly diminished when death followed the injection of diphtherial toxin. Torrance³ confirmed this finding and reported that the injection of other toxic bacterial products, such as filtrates of the meningococcus, which give rise to congestion and hemorrhage of the suprarenal glands, cause the vitamin-C concentration to fall to similar low levels.

Since the essential tissue-changes in acute scurvy are associated with alterations in the capillary walls which result in generalized hemorrhage, it seemed not unlikely that the extravasation of blood

¹ Abramow, S., *Z. f. Immunitäts.*, 1912, I, 15, 12.

² Harde, E., *C. r. Acad. de Science*, 1934, 199, 618.

³ Torrance, C. C., *J. Bact.*, 1937, 38, 645.