Cocarboxylase (pyrophosphoric acid ester of thiamin) has a specific protective action upon the enzyme carboxylase.

I am greatly indebted to Professor Lohmann for a sample of natural cocarboxylase, and to J. Ruppert Brewery, through the kindness of Mr. E. Muhlhausen, for furnishing the yeast.

10054 P

Pathologic Changes Produced by Subcutaneous Injection of Rattlesnake (Crotalus) Venom into *Macaca mulatta* Monkeys.*

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Reports of the gross and microscopic lesions in fatal cases of rattlesnake poisoning are rare. Knowledge of the pathologic changes is based mainly upon findings in experimental animals.[1] These changes have been described in detail in dogs.[2,3] Taube and Essex[3] administered large doses of venom (crotalin) intravenously and produced widespread hemorrhagic lesions throughout the body. In nature, however, the venom is usually injected subcutaneously. It is our purpose to report the lesions produced by the subcutaneous injection of a lethal dose of crotalin into the *Macaca mulatta*[4] monkey.

Nine young *Macaca mulatta* monkeys were given rattlesnake *(Crotalus atrox)* venom into the subcutaneous tissues of the lumbar region. The dose, given as a 1% solution in saline, corresponded to 7 to 10 mg of the dried venom per kilo of body weight.

For several hours after injection the animals behaved about as usual, but later became weak, lethargic, and refused to eat. The lethargy and weakness increased in severity until death occurred at an average of 36.5 hr after injection.

* Aided by a grant from the American Association for the Advancement of Science.

1 Noguchi, H., *Snake Venoms*, Carnegie Institution of Washington, 1909.

2 Jackson D., *Southern Med. J.*, 1929, **22**, 605.

3 Taube, H. N., and Essex, H. E., *Arch. Path.*, 1937, **24**, 43.

4 Zuckerman, S., and Fulton, J. F., *The Nomenclature of Primates Commonly Used in Laboratory Work*, Tuttle, Morehouse & Taylor Co., New Haven, 1934.

Postmortem examination revealed in the subcutaneous tissues an intense hemorrhagic edema which involved about 50% of the body area. It extended from the mid-thoracic region to the buttocks and groin, and, in several cases, down as far as the knees. At the advancing edges of the lesion there was marked edema but no hemorrhage. The regional lymph nodes in the groin, and to a less extent the iliac, pre-aortic, mediastinal and axillary nodes, were swollen and red. In the heart there were small subendocardial hemorrhages in the left ventricle in the region of the interventricular septum near the aortic ring. This occurred in 6 of the 9 animals. Other lesions were not constant and consisted in one animal of small sub-pleural hemorrhages, and small sub-capsular hemorrhages of the liver, and in 2 others of petechial hemorrhages into the mucosa of the cecum. The lungs and abdominal viscera were pale and dry.

Microscopically, in the region of subcutaneous hemorrhagic edema, necrotic changes were found in the walls of small blood vessels and capillaries. Actual ruptures of the walls were seen in places. Many of the vessels contained thrombi which partially or completely filled the lumens. The surrounding tissues were infiltrated with erythrocytes, fluid, and scattered collections of polymorphonuclears. At the advancing edge of this lesion the blood vessels showed only dilatation and some swelling of the endothelium, while the exudate consisted mainly of fluid, with very few erythrocytes. The regional lymph nodes revealed marked dilatation of the medullary sinuses, but little change in the cortex. The medullary sinuses contained erythrocytes and large phagocytic reticuloendothelial cells, some of which were distended with as many as 15 to 30 erythrocytes. No necrotic or thrombotic lesions were found in the blood vessels or lymphatics of the lymph nodes. Some polymorphonuclear infiltration and fatty degeneration of muscle were observed in the region of the subendocardial hemorrhages of the heart. The hepatic cells showed slight granular degeneration, and the convoluted and collecting tubules of the kidney showed granular and fatty degeneration. No definite glomerular lesions were present. The lungs, gastrointestinal tract, spleen, pancreas, adrenals, gonads and urinary bladder showed no significant changes.

It is evident from these observations that crotalin acts as a powerful tissue irritant, causing necrosis and actual dissolution of blood vessels. At the edge of the subcutaneous lesion the venom is more dilute, the vascular lesions less severe, and it is from here that maximum absorption of venom probably takes place. The regional lymph nodes show the most intense reaction, but as the venom-containing

edematous fluid passes by way of the abdominal and thoracic chains of nodes into the thoracic duct and subclavian vein, lymphadenitis is seen in these other nodes, varying in severity in direct proportion to their proximity to the primary lesion.

Clinical observations and the autopsy findings of widespread vascular dilatation, hemorrhage, and edema led Taube and Essex to conclude that their animals died in shock. Whereas shock seems the most probable major factor in the death of animals subjected to venom intravenously, the evidence is not so clear for this assumption following the subcutaneous administration. Our animals showed none of the generalized vascular lesions which Moon[5] has suggested as the pathologic basis of shock. There was only a subcutaneous loss of blood and fluid, which was so extensive, however, that it might be considered capable of causing shock.

10055 P

Cerebral Blood Flow Changes During Insulin and Metrazol (Pentamethylenetetrazol) Shock.

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The use of insulin and metrazol in shock therapy for schizophrenia is now well known.

Using a greatly modified, flexible thermoströmuhr simultaneous records of blood flows in carotid artery and meningeal branch of the jugular vein were made in rabbits throughout the course of 128 shock experiments.

Normal venous and arterial blood flows were recorded for one hour. Blood was taken for initial glucose determination.* Insulin was injected subcutaneously (2 units per kilo). Blood sugars were estimated at half-hour intervals for 1½ hours, after which 15-

[5] Moon, V. H., *Arch. Path.*, 1937, **24**, 642, 794.

* True glucose was determined on 0.3 cc blood precipitated by the method of Herbert and Bourne[1] and glucose determined by a modified Shafer-Hartman reagent (Harding and Downs[2]).

[1] Herbert, F. K., and Bourne, M. C., *Biochem. J.*, 1930, **24**, 299.

[2] Harding, V. J., and Downs, C. E., *Can. Chem. Met.*, 1932, **16**, 12.