13892

Occurrence of Brain Hemorrhages in Choline-Deficient Rats.*

GEORGE A. JERVIS. (Introduced by Warren M. Sperry.)
From the Research Department of Letchworth Village, Thiells, N.Y.

The importance of choline in animal nutrition has been the object of much recent interest. In young rats reared on diets adequate in dietary essentials other than choline, hemorrhagic degeneration of the kidney, and, at times, intraocular hemorrhages are characteristic pathologic findings.[1,2] Symptoms of involvement of the nervous system, apparently caused by choline deficiency, have been observed by Sure[3] and by György and Goldblatt.[2] In young rats of mothers reared on choline-deficient diets, these authors described a paralysis which develops at about the thirteenth day and is followed by death in 3-5 days if choline is not added to the diet. The pathology underlying this type of paralysis has not yet been investigated. It is the purpose of this note to put on record the changes in the nervous system occurring in young rats of mothers reared on a diet low in choline and high in cystine.

Experimental. Five female rats were given the following diet from about the eighth day of pregnancy on:

Purified Casein Smaco	25
Cystine	0.5
Dextrine	58.5
Agar	2
Crisco	10
Salt mixture	4

In addition, daily doses of 100 γ of thiamine, riboflavine, pyridoxine and calcium pantothenate and 6 mg of nicotinic acid were given. Two drops of haliver oil were added weekly to the diet. As controls two female rats were reared on the same diet without cystine and with the addition of 100 mg of choline per 100 g of food.

No significant differences were noted between the young born from deficient and normal rats until the 10th-12th day when cessation of growth was noted in the deficient group. About 50% of the rats died at this stage without showing symptoms of involvement of the nervous system; the others developed paralysis of the limbs. This was often accompanied by tremors of the head and the whole body and occasionally by violent paroxysms of jerking movements similar to generalized convulsions. Death followed in 3-5 days.

The nervous systems of 5 rats which had shown conspicuous neurological symptoms were examined histologically by the common methods of neuropathologic technic. The most striking alteration consisted of extensive hemorrhagic lesions of the cerebellum. From one-third to half of the cerebellar lamellæ appeared involved (Fig. 1). Hemorrhage was most extensive in the central part of the lamella, often occupying the entire white matter. Myelin sheaths and axis-cylinders were destroyed. In the granular layer only scattered foci of hemorrhage were present which appeared roundish in configuration. The layer of Purkinje cells was relatively well preserved whereas in the molecular layer extensive hemorrhages were present involving particularly its external portion. Blood was present also in the subpial spaces. The central medullary substance and the nucleus dentatus were intact.

By the Pickworth stain for blood vessels, no hemorrhages were demonstrable in the mesencephalon and diencephalon. In the cerebral cortex small foci of hemorrhages scattered throughout the gray matter and the subcortical white matter were found in 2 cases.

In every instance the hemorrhages appeared to be recent in character. No reaction of glia or connective tissue was observed.

* Aided by a grant from the Penrose Fund.

1 Griffith, W. H., and Wade, M. J., *J. Biol. Chem.*, 1940, **131**, 567.

2 György, P., and Goldblatt, H., *J. Exp. Med.*, 1940, **72**, 1.

3 Sure, B., *J. Nutrition*, 1940, **19**, 71.

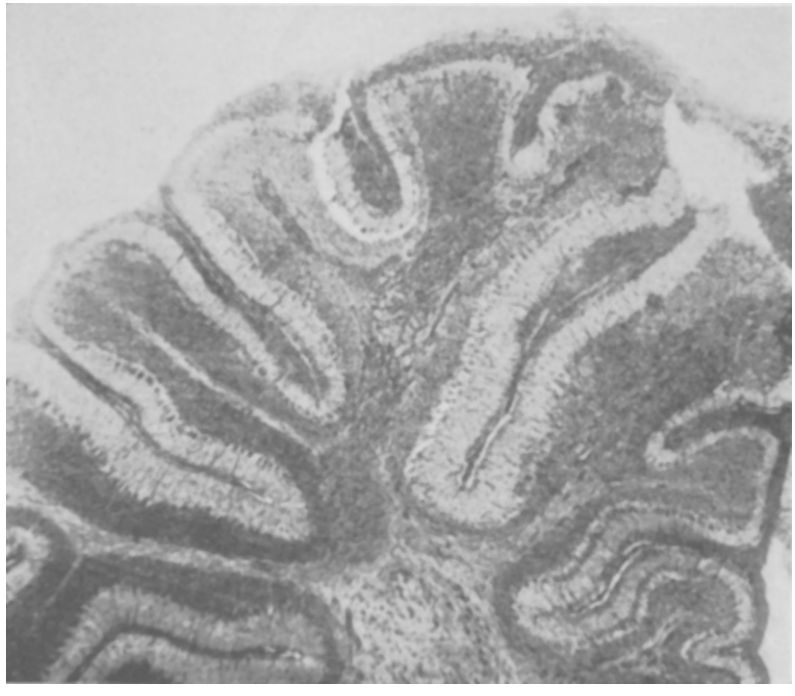

FIG. 1.
Showing extensive hemorrhagic lesions of the cerebellum. Nissl stain. Low power.

Alterations other than hemorrhagic appeared of little significance. Frequently there were acute degenerative lesions of the neuron cells diffusely distributed. The peripheral nerves showed no pathology.

Comment. Hemorrhagic lesions within the nervous system have been previously described in thiamine deficient rats[4,5] and pigeons.[6,7] However, these hemorrhages are apparently different from those found in choline deficiency. In thiamine deficiency the hemorrhagic lesions are localized in the vestibular nuclei, the thalamus, hypothalamus, periventricular region of the third ventricle, oculomotor nucleus, culliculi and, only occasionally, the cerebellum, whereas in choline deficiency the cerebellum and, occasionally, the cerebral cortex are involved, the other regions being intact. Moreover, in thiamine deficiency the hemorrhages are circumscribed and small, while in choline deficiency they are diffuse and massive. Finally, in thiamine deficiency the hemorrhages are preceded by, and apparently secondary to, degenerative changes in neighboring nervous parenchyma[5,7] while these primary parenchymatous changes have not been observed in choline deficiency.

Hemorrhagic lesions of the cerebellum have been previously recorded in Vitamin E-deficient chicks,[8] but they appear to be preceded or accompanied by degeneration and necrosis of the nervous tissue and thrombosis of the blood vessels, features which were not observed in the present experiments.

Although the causes of hemorrhage in the brain of choline-deficient rats are unknown, the lesions of the blood vessels appear primary in character and similar in nature to those encountered in the kidneys of rats reared on similarly deficient diets.

Summary. Hemorrhagic lesions of the

4 Prickett, C. O., *Am. J. Physiol.*, 1934, **107**, 459.

5 Church, C. F., *Am. J. Physiol.*, 1935, **111**, 660.

6 Alexander, L., *Am. J. Path.*, 1940, **16**, 61.

7 Prados, M., and Swank, R. L., *Arch. Neur. and Psychiat.*, 1942, **47**, 626.

8 Wolf, A., and Pappenheimer, A. M., *J. Exp. Med.*, 1931, **54**, 399.

cerebellum, occurring in young rats of mothers reared on a diet containing a high percentage of cystine and deficient in choline, are described and briefly compared to the brain hemorrhages observed in other vitamin deficiencies.

13893

Quinones as Blood Pressure Reducing Agents in Hypertensive Rats.*

BEN FRIEDMAN, SAUL SOLOWAY, JOSEPH MARRUS AND B. S. OPPENHEIMER.
From the Laboratories of The Mount Sinai Hospital, New York City, and the Chemical Laboratories of the Carnegie Institute of Technology, Pittsburgh, Pa.

Introduction. Following the work of Holtz,[1] Bing and his co-workers[2,3] have demonstrated that experimental renal hypertension can be produced by the injection of amino acids into the ischemic kidney of cats. This work has provided a basis for the hypothesis that the hypertension resulting from an interference with the blood supply to the kidney may be due to faulty deamination of certain amino acids. This process is catalyzed by amine oxidase and requires the presence of oxygen. Under anaerobic conditions, however, such as may exist in renal ischemia, decarboxylation without subsequent deamination would occur, thus leading to the formation of pressor amines. An accumulation of these substances would tend to elevate the blood pressure.

It has been shown that certain pressor amines can be inactivated by quinone precursors.[4,5] The present study deals with the effect of certain quinones on the blood pressure of rats with experimental renal hypertension.†

Method. Young male rats weighing 150-200 g were used. Hypertension was produced by wrapping one or both kidneys in cellophane.[6] Blood pressures were recorded in the tail using the method of Williams, Harrison and Grollman.[7] The systolic blood pressures of over 600 normal rats tested by this method in our laboratory ranged between 100 and 140 mm of mercury. The blood pressure of hypertensive rats was generally 40 to 80 mm of mercury above the preoperative level. Rats were considered suitable for testing when the blood pressure level had been elevated and stable for a period of at least one month. Daily readings were made for one week prior to, during and immediately following administration of the agent to be tested. Nine compounds were tested by the subcutaneous and 5 by the oral route. When used orally a weighed sample of the compound was mixed daily with a submaximal quantity of the food which the animal had been accustomed to consume. Thus the daily dosage in feeding experiments was approximate and not exact. Quinones which proved effective in reducing the blood pressure in hypertensive animals were tested also on rats with normal blood pressure.

Results. Four of the 10 compounds tested were effective in lowering the blood pressure of hypertensive rats. As will be seen in

* Several of the compounds used in this work were secured through the courtesy of the Wallerstein Laboratories, to whom we are deeply indebted.

1 Holtz, P., Heise, R., and Luedtke, K., *Arch. Exp. Path. u. Pharm.*, 1938, **191**, 87.

2 Bing, R. J., *Am. J. Physiol.*, 1941, **132**, 497.

3 Bing, R. J., and Zucker, M. B., *J. Exp. Med.*, 1941, **74**, 235.

4 Soloway, S., and Oster, K. A., PROC. SOC. EXP. BIOL. AND MED., 1942, **50**, 108.

5 Oster, K. A., *Nature*, 1942, **150**, 289.

† Similar experiments on hypertensive dogs are being conducted.

6 Friedman, B., Jarman, J., and Klemperer, P., *Am. J. Med. Sc.*, 1941, **202**, 20; Page, I. H., *Science*, 1939, **89**, 273.

7 Williams, J. R., Jr., Harrison, T. R., and Grollman, A. J., *J. Clin. Invest.*, 1939, **18**, 373.