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Effects of Cyanide Anoxia on Adrenal Gland of the Rat.

JOHN NICHOLS AND A. T. MILLER, JR.

From the Department of Anatomy and Laboratory of Applied Physiology, University of North Carolina, Chapel Hill.

Armstrong and Heim[1] reported that anoxic anoxia induces hypertrophy of the adrenal gland in rabbits. Since that time many papers have appeared on this subject (for references see Tepperman[2] and Nichols[3]). The most characteristic findings are hypertrophy of the gland and depletion of lipids from the cortex. To our knowledge the effects on the adrenal gland of other types of anoxia have not been studied, with the single exception of the work of Messerle[4] who made incidental observations during chronic exposure of pigeons to hydrogen cyanide gas. He reported gross hypertrophy of the gland but on histological observation found no cytological changes. It was thought that additional information on the mechanism of anoxic stimulation of the adrenal gland might be derived from experiments in which the oxygen tension of the arterial blood is normal.

Materials and methods. Twenty male rats of the Long-Evans strain, each weighing 150 g, were used in this study. Preliminary experiments indicated that 2 mg of sodium cyanide would kill a 150 g rat in about 30 minutes; accordingly, a maximum dose of 1 mg of cyanide was adopted for use in the remainder of the experiments. This was sufficient to give a severe but safe level of anoxia. Seven rats were injected subcutaneously with 1 mg of sodium cyanide contained in 1 ml of saline, followed by ½ mg of sodium cyanide every hour for the next 20 hours. Seven animals were injected with 1 mg of sodium cyanide followed by ½ mg of cyanide every half hour for the next 28 hours. The remaining 6 animals were treated as controls, being injected with 1 ml of saline every hour for 20 hours. All animals were killed by a blow on the head and the adrenals removed and placed in 10% formaldehyde for 24 hours. The surrounding fat was then carefully dissected away and the glands weighed. They were cut in half, embedded in gelatin and sectioned on the freezing microtome at 14 microns, stained and mounted as previously described.[3]

Results. The average weights of the adrenal glands were: controls 40 mg, treated 20 hours 45 mg, and treated 28 hours 54 mg. Histologically, the adrenals of the control animals were entirely normal as compared with other normal glands studied in this laboratory (Fig. 1). The glands of the animals treated for 20 hours showed marked depletion of lipids in the inner cortical zones (fasciculata and reticularis), while the zona glomerulosa remained relatively unchanged. The animals treated for 28 hours showed the same adrenal changes except to a more striking degree (Fig. 2); in certain of these animals the lipids were depleted in the zona glomerulosa to almost the same extent as in the inner zones. These histological changes are the same as those that occur in anoxic anoxia.

Discussion. As previously mentioned Messerle[4] reported gross hypertrophy of the adrenal, but no cytological changes, on chronic exposure of pigeons to hydrogen cyanide; however, he used standard hematoxylin and eosin preparations which had been dehydrated in alcohols that would dissolve out the fats.

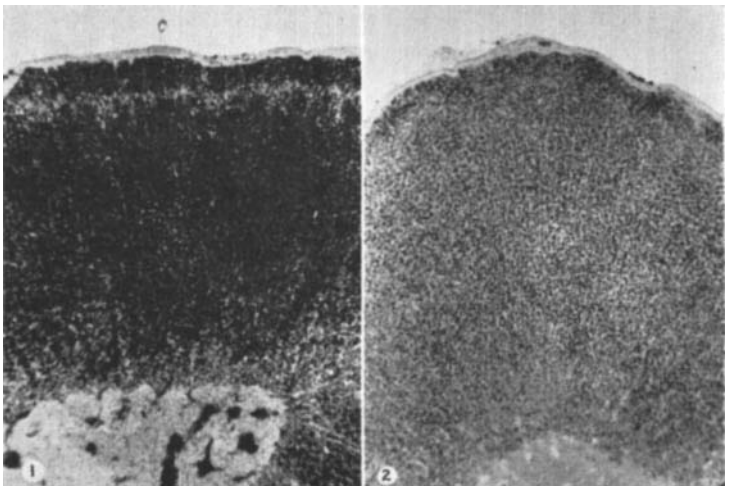
Adrenal cortical lipid depletion in anoxia is believed to be mediated by way of the pituitary gland since the zones first involved (*i.e., fasciculata* and *reticularis*) are known to be under control of the pituitary; these zones elaborate the fraction of the cortical hormone which influences carbohydrate meta-

1 Armstrong, H. G., and Heim, J. W., *J. Aviation Med.*, 1938, **85**, 162.

2 Tepperman, J., Tepperman, H. M., Patton, B. W., and Nims, L. F., *Endocrinology*, 1947, **41**, 356.

3 Nichols, J., *J. Aviation Med.*, 1948, **19**, 171.

4 Messerle, N., *Virchow's Arch.*, 1926, **262**, 305.



Frozen sections stained with Sudan III. Photographed with a green Wratten filter No. 29 at 135 diameters magnification and reduced to 68 by the engraver.

FIG. 1. Cortex of the adrenal gland of a normal animal.

FIG. 2. Cortex of the adrenal gland of an animal injected with 1 mg of sodium cyanide followed by ½ mg every half hour for 28 hours. Note depletion of lipids especially in the inner zones while the outer zona glomerulosa is relatively resistant.

bolism. Alterations of carbohydrate metabolism may be prevented by ablation of either the pituitary or adrenal (Evans[5]). The zona glomerulosa, which reacts last to anoxia, is not under control of the pituitary and, at least in the rat, regulates electrolyte balance (Nichols[6]; Deane *et al.*[7]).

The factor(s) responsible for pituitary stimulation in anoxia are uncertain. In anoxic anoxia, the most likely factors are the reduced oxygen tension of the arterial blood and the hypocapnia incident to hyperventilation. That hypocapnia may be a significant factor is indicated by the observation of Hailman[8] and that of Langley *et al.*[9] that the addition of sufficient carbon dioxide to give a partial pressure of 30 to 48 mm Hg prevents the usual anoxic changes in the adrenal gland and also prevents the increased deposition of liver glycogen. The changes in the adrenal are probably the result of the lowered blood carbon dioxide tension *per se,* rather than the resultant disturbance in acid base equilibrium. In unpublished experiments in this laboratory it was found that alkalosis and acidosis induced by oral administration of sodium bicarbonate and ammonium chloride respectively had no effect on adrenal changes in anoxic anoxia.

In this study we have not eliminated the hyperventilation possibility, since the animals did hyperventilate after each injection. In order to avoid this it would be necessary to denervate the carotid body. However, our findings indicate that histotoxic anoxia induced by sodium cyanide produces the same changes in the adrenal as does anoxic anoxia and that these changes can occur while the arterial blood is saturated with oxygen.

Summary. Sodium cyanide was administered in small repeated sublethal doses to rats. The resulting changes in the adrenal gland were hypertrophy and marked depletion of lipids in the inner zones of the cortex. This effect is identical with that of anoxic anoxia and occurs while the arterial oxygen tension is normal.

5 Evans, G., *Am. J. Physiol.*, 1935, **114**, 297.

6 Nichols, J., *Arch. Path.*, 1948, **45**, 717.

7 Deane, H. W., Shaw, J. H., and Greep, R. O., *Endocrinology,* 1948, **43**, 133.

8 Hailman, H. F., *Endocrinology,* 1944, **34**, 187.

9 Langley, L. L., Nims, L. F., Harvey, T. S., and Clarke, R. W., *N.R.C. Committee on Aviation* Medicine Report No. 108, 1943.