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# Experimental Hypothalamico-Hypophyseal Obesity in the Rat.*

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Smith[1] produced obesity in rats by injecting chromic acid into the hypophysis via a subtemporal approach. Because hypophysectomy did not bring about the same result, Smith reasoned that hypophyseal deficiency could not be responsible for the adiposity—and that hypothalamic damage incurred during the chromic acid operation must have been the cause. Ranson, Fisher, and Ingram[2] have reported the effect of hypothalamic lesions on fat deposition in a large number of cats and monkeys observed in our laboratory, and lately the guinea pig has been added to this list. In all 3 species the results have been negative.

In an effort to discover the reason for this divergence of findings we have repeated, with modifications, Smith's chromic acid injections on rats. About 0.01 cc of 5% chromic acid was injected through a needle with a curved tip into the hypophyses of albino rats via a parapharyngeal approach. Using this method we hoped to minimize the danger of simultaneous hypothalamic damage. We have also placed lesions in the hypothalami of rats with the Horsley-Clarke instrument. Two electrolytic lesions were placed on each side in the lateral hypothalamic areas between the levels of the optic chiasma rostrally and the infundibulum caudally.

All rats were operated at about the time of sexual maturity. They had litter mate controls, and were allowed to survive well over the maximum time elapsing before any obese rat showed definite signs of its disorder. They were weighed at weekly intervals. At autopsy the brains were fixed in formalin, and the hypophyses in either Zenker-formol or Champy fluid. Serial sections of the hypothalami and neighboring areas were cut and stained with cresyl violet; the hypophyses were stained by either the Haterius modification of the Masson stain, or by the Severinghaus technic.

The chromic acid injections were performed on over 50 rats, but only 3 showed any sign of obesity—2 to a marked, and one to a mild degree. All 3 were stunted in length compared to their con-

* Aided by a grant from the Rockefeller Foundation.

1 Smith, P. E., *Am. J. Anat.*, 1930, **45**, 205.

2 Ranson, S. W., Fisher, C., and Ingram, W. R., *Endocrinol.*, 1938, **23**, 175.

trols; even so, the 2 heavier animals outweighed the normal litter mates, in one case by 7%, in the other by 40%. Histological examination of the base of the brains of these 3 rats showed damage extensively distributed from the tuberculum olfactorium rostrally to the mammillary bodies caudally. All destruction was fairly superficial with respect to the base of the diencephalon, and seemed to point either to damage done directly to the hypothalamus by the chromic acid, or injury to the vascular supply. The hypophysis of the mildly obese rat showed almost complete replacement by connective tissue, with only a few deeply basophilic nests of cells scattered along the edge of the scar. Each of the 2 markedly obese rats retained about 25% of its anterior lobe. The one surviving the shorter interval displayed a lack of normal well granulated basophils and an excessive number of what appeared to be large lightly staining basophils. The other (and fattest) rat showed a large portion of its hypophyseal remnant to be filled with a branching network of deeply staining basophilic cells. These last 2 animals also exhibited a scarcity of acidophils; those present were small and stained lightly.

Of the other rats which received chromic acid injections it may be said that only 4 or 5 had any hypothalamic damage worth mentioning, and this was minor compared to the obese cases. The hypophyses of the negative cases underwent all degrees of destruction from complete to negligible. In those cases where appreciable amounts of the anterior lobe remained the cell picture seemed fairly normal.

The results of the electrolytic hypothalamic lesions are quite different. Twelve rats have been operated to date, and practically every one has exhibited a pronounced and rapidly appearing obesity. Some rats have become almost twice as heavy as their controls. Dwarfing is only sometimes evident. Only 2 of this group have been sacrificed, and no histological studies have as yet been made; but the autopsy findings give a clue to the condition to be expected in the others. There was extensive damage to the ventral surface of the hypothalamus, involving particularly the anterior half, and being laterally disposed. Simple inspection revealed no abnormality of the hypophysis.

Injury to the hypothalamus in the rat would appear to be capable of causing marked adiposity but changes in the hypophysis may be revealed on microscopic examination.