Extra-hypothalamic Lesions Associated with Gold-Thioglucose Induced Obesity.* (26236)

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The specificity of goldthioglucose for the ventromedial nuclei and adjacent parts of the hypothalamus has been emphasized by several investigators(1,2,3). This specificity has been regarded as providing support for a theory that the ventromedial hypothalamus contains neurones that comprise the satiety portion of a "feeding center" and that these neurones are glucoreceptors. It has been postulated that gold is "dragged" into the ventromedial hypothalamic cells which are then destroyed because of their peculiar affinity for glucose. The present report deals with induction of lesions outside the ventromedial nuclear region of the hypothalamus by goldthioglucose. The amount of goldthioglucose used has already been determined to induce a massive obesity associated with lesions in the ventromedial nuclear region of the hypothalamus, and in the case of CBA mice, lesions in the region of the fornix as well(4).

Methods. The inbred C57 Black and CBA mice used in these experiments were fed Purina lab chow *ad libitum*. The C57 Black mice received an intraperitoneal injection (27 ga. needle) of 1.0-1.2 mg, or of 0.35-0.4 mg goldthioglucose† in 0.9% saline per gram body weight when they were 100 ± 10 days old. The CBA's were given 0.35-0.4 mg/g body weight, but otherwise were treated like the C57 Black mice. Autopsy was carried out 24-48 hours after injection, the brain fixed in 10% formalin or Heidenhain's Susa, and paraffin sections prepared using myelin, toluidin blue, hematoxylin and eosin, and chrome alum hematoxylin phloxine procedures. Fifteen C57 Black and 25 CBA brains were prepared as outlined and serial sections of all of these brains studied microscopically. Five additional brains from C57 Black mice that had been given 0.35 mg goldthioglucose per gram body weight were also studied.

Results. The results of these experiments confirmed previous observations(4) regarding distribution of the ventromedial lesions in the hypothalamus. Parts of the premammillary, arcuate, and anterior hypothalamic nuclei were damaged. Almost all of the neurones of the ventromedial nucleus were destroyed if the dose of goldthioglucose was 1 or 1.2 mg/g body weight in the C57 Black, or 0.35 or 0.4 mg/g in the CBA mice. When the smaller dose was administered to C57 Black mice, the lesion failed to involve the premammillary nucleus, and damage to the arcuate, ventromedial, and anterior hypothalamic nuclei was small (Fig. 1). These lesions were not associated with weight gain.

Destruction of neurones in the visceral sensory nuclei of the vagus or nucleus solitarius, especially its commissural part, has been observed in both strains at all dose levels. Commonly some neurones of the dorsal motor nucleus of the vagus, and hypoglossal nucleus were also destroyed (Fig. 2). Less frequently the lesion involved the gracile and cuneate nuclei. All these neurone cell bodies are contiguous to the area postrema.

Near the supraoptic crest, damage from goldthioglucose occurred in the preoptic nuclei (Fig. 3).

In the sector between the subcommissural organ caudally, and the subfornical organ rostrally, goldthioglucose administration was associated with damage to neurones of the dorsal hippocampal formation (Ammon's horn and dentate gyrus), psalterium, triangular septal, and occasionally the lateral septal nuclei and epithalamus (Fig. 4, 5).

With the notable exception of lesions in the vicinity of the area postrema, neurone destruction outside the hypothalamus did not occur when 0.35 mg goldthioglucose was given to C57 Black mice. It was also to be noted that neurone damage in the preoptic

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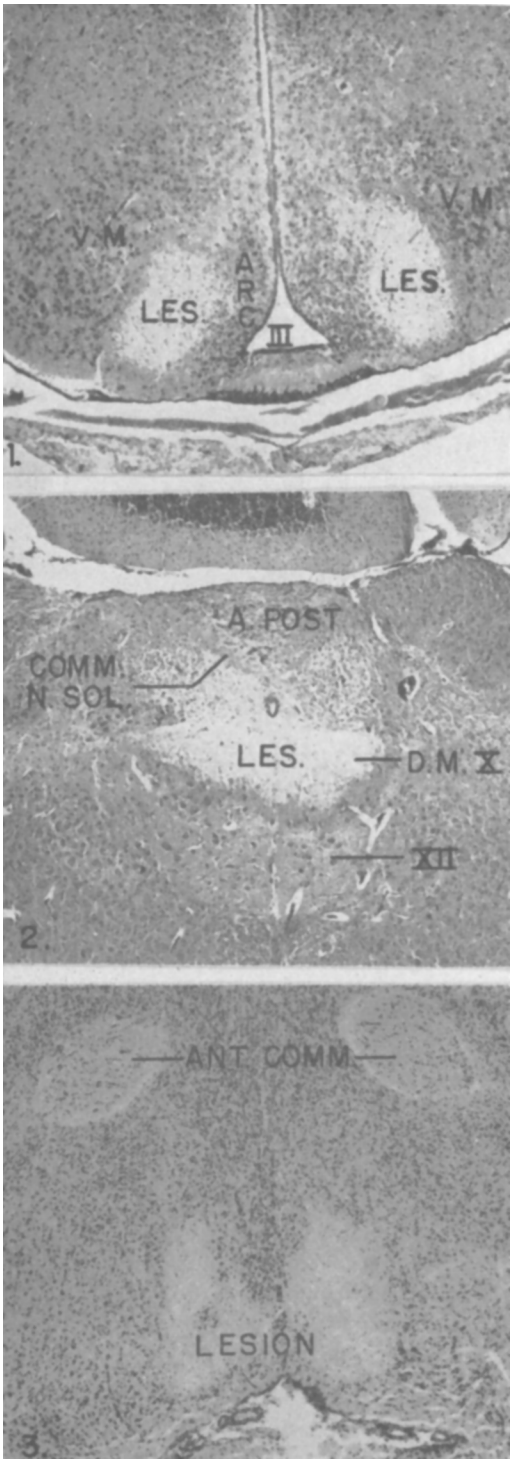

FIG. 1. Non-obese producing lesions between ventromedial (V.M.) and arcuate (ARC) nuclei of C57 BL mouse. 0.35 mg goldthioglucose/g body wt. Post inj. interval: 1 day. Stain: Chrome alum hematoxylin phloxine.

FIG. 2. Lesion of dorsal motor nucleus of vagus (D.M.X.), commissural part of nucleus solitarius (Comm. N. Sol.) and some cells of hypoglossal nucleus (XII) of CBA mouse. 0.35 mg goldthioglucose/g body wt. Post inj. interval: 1 day. Stain: Chrome alum hematoxylin phloxine.

FIG. 3. Lesion in preoptic region of C57 BL mouse. 1.2 mg goldthioglucose/g body wt. Post-inj. interval: 2 days. Stain: Toluidin blue.

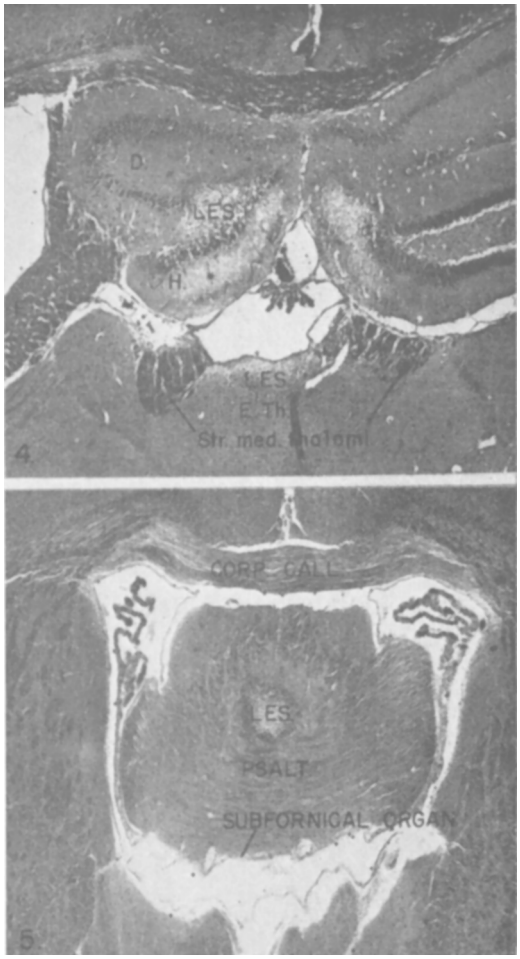

FIG. 4. Lesion in epithalamus (E.Th.) and dorsal hippocampus (D.H.) of CBA mouse. 0.35 mg goldthioglucose/g body wt. Post inj. interval: 1 day. Stain: Chrome alum hematoxylin phloxine.

FIG. 5. Lesion in septum of C57 BL mouse dorsal to transverse fibers of psalterium. 1.2 mg goldthioglucose/g body wt. Post inj. interval: 2 days. Stain: Weil's myelin.

nuclei was most often associated with 0.4 mg doses in CBA, and 1.2 mg of goldthioglucose per gram body weight in C57 Black mice. Preoptic damage, however, was consistently

noted in C57 Black mice receiving pretreatment with glucose 20 minutes before 1.0 mg goldthioglucose per gram body weight was administered.

Discussion. The results of these experiments show that administration of goldthioglucose, in amounts that have been shown to induce obesity(4), causes destruction in widely scattered areas of the brain. They are not limited to the ventromedial nucleus nor even the ventromedial region of the hypothalamus. The functions of many of the damaged nuclei, as classically defined, are rather remote from the function of regulating food intake. Damage to nuclei in the vicinity of the area postrema may occur at levels of goldthioglucose administration far below that requisite for hyperphagia and ensuing weight gain. Finally, it appears noteworthy that sites in the brain damaged by parenterally administered goldthioglucose have in common proximity to loci where the blood-brain barrier has been demonstrated to be deficient to trypan blue, to silver nitrate administered in drinking water(5), and to radioactive isotopes(6). Recent work using labeled goldthioglucose(7) demonstrated radioactivity in the hind brain as well as in the hypothalamus.

Conclusion. Goldthioglucose administration to inbred C57 Black and CBA mice, in amounts sufficient to induce hyperphagia and massive weight gain, results in lesions of nuclei adjacent to the area postrema of the medulla oblongata, to the median eminence of the hypothalamus, to the supraoptic crest between the hypothalamus and the basal telencephalon, and between the subcommissural and subfornical organs associated with the midbrain-epithalamic transition and the hippocampal formation. The hypothesis is advanced that the observed distribution of the lesions is related to deficiency of the blood-brain barrier at these sites.

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Effect of Synthetic Steroid or Phenanthrene Compounds upon Weight Gain and Feed Efficiency of Rats.* (26237)

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Previous work has shown that estrogens tend to increase rate of gain and efficiency of feed utilization in ruminant animals(1,2), but generally depress these responses in non-ruminant animals(3-5). Evidence has appeared in the literature(6,7) to indicate that modification of estrogenic compounds by oxidation reactions yields substances which are non-estrogenic and therefore have reduced inhibitory effect on non-ruminant growth, but nevertheless retain the properties of their parent substances in inducing pituitary release of trophic factors.

Randall and Selitto(8) indicated that the compound Ro - 2 - 7239 (2 - acetyl - 7 - oxo - 1,2,4,4a,4b,5,6,7,9,10,10a - dodecahydrophenanthrene) administered subcutaneously for 7 days at a rate of .5 mg/rat/day exhibited a tendency to increase the gain of female rats. It was of interest to investigate the effect of feeding this compound at somewhat lower levels upon body weight gain and feed efficiency in female rats and in nor-

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