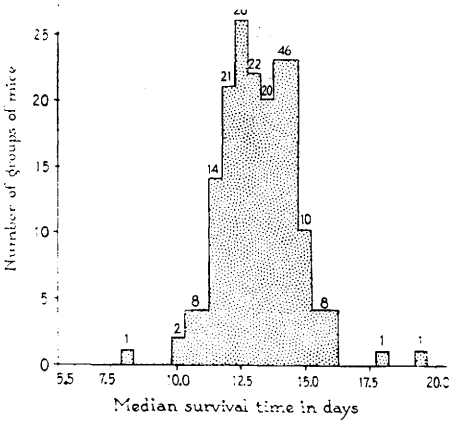

FIG. 2. Distribution of median survival times of groups of mice injected with 1.0 mg of H37Rv strain of *M. tuberculosis* var. *hominis*.

on the other, the virulence of strains of Mycobacteria.

The data also offer no support for the occurrence of any yearly or seasonal variation in the resistance of this strain of mice to tuberculous infection. This might in part be a reflection of the fact that these mice were housed in an air conditioned animal room and were therefore not subjected to extreme variations in temperature. However, this room faces south and during the summer temperatures in this room ranging between 90° and 5°F have been recorded. The observed extreme temperatures in this room have been approximately 65°F in the winter and approximately 95°F in the summer.

Summary. 1. Over a 5-year period, 1950 through 1954, one to 6 groups per month of 10 to 30 mice each were infected intravenously with a 1 mg inoculum of the H37Rv strain of *Mycobacterium tuberculosis* var. *hominis*. 2. The median survival times of 177 (98.3%) of the 180 groups infected during this period fell between the 10th and 16th day inclusive. Statistical analyses revealed that there was no significant difference between the yearly means of the median survival times nor was there significant difference between the monthly means of the median survival times.

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Received September 2, 1955. P.S.E.B.M., 1955, v90.

Hypothalamic Lesions in Goldthioglucose Injected Mice.* (21995)

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(Introduced by F. J. Stare.)

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Recent investigations have demonstrated the essential similarity of goldthioglucose obesity and hypothalamic obesity in mice(1-3). This in turn led to the re-examination of the possibility that hypothalamic lesions may be involved in the mechanism of action of goldthioglucose despite the fact that other investigators(4,5) did not succeed in demonstrating such lesions. Since the possibility existed that through a process of reabsorption and repair, any damage to the central nervous system may be at least in part obscured in the obese animal during the period required for the obesity to develop. it was decided to examine injected animals shortly after goldthioglucose administration. Goldthiomalate, though similar to goldthioglucose in gold content, molecular weight and toxicity does not produce obesity(6), consequently it was de-

* Supported in part by Grant No. A-49, National Institute of Arthritis and Metabolism, National Institutes of Health, Bethesda, Md.; Sugar Research Foundation, N. Y.; Kellogg Co., Battle Creek, Mich.; and Nutrition Foundation, N. Y.

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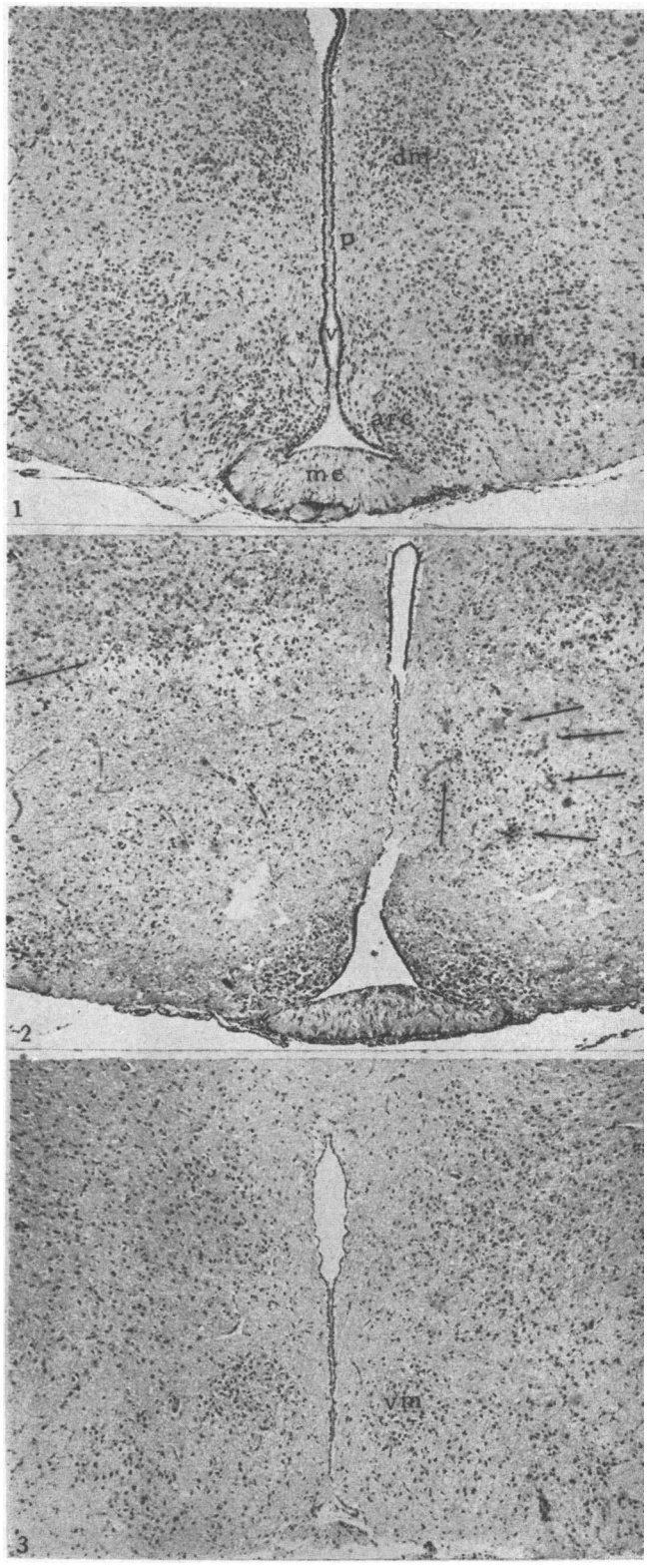

PLATE I: Photomicrographs (×65) taken of hematoxylin and eosin stained sections through tuberal or infundibular region of the hypothalamus showing the same area in 3 different animals.

FIG. 1. Section through hypothalamus of a goldthiomalate treated mouse, indicating a normal hypothalamic nuclear configuration and containing a normal number of neurons. Photomicrograph is labeled to indicate normal landmarks and nuclei seen in this region of the hypothalamus: dm, dorsomedial nucleus; f, fornix; p, periventricular region; v, third ventricle; vm, ventromedian nucleus; lat, lateral hypothalamic area; arc, arcuate nucleus; me, median eminence.

FIG. 2. Same area as in Fig. 1 of hypothalamus of mouse three days after the administration of goldthioglucose. Note marked loss of neurons and presence of pyknotic cells in ventral part of hypothalamus. Normal hypothalamic nuclear pattern has been lost. Arrows on right side of photomicrograph point to punctate hemorrhages. Arrow on left points to line of demarkation between area of edema (ventral) and normal tissue (dorsal).

FIG. 3. Section of hypothalamus of obese mouse three months after the administration of goldthioglucose. Compare with Fig. 1 and 2. This section is slightly posterior to Fig. 1 (more ventral position of fornix (f)). Although there is no evidence of edema as in Fig. 2, there is an obvious decrease in the number of cells. The ventromedial nucleus (vm) can barely be made out as a discrete nuclear mass. The tissue forming the median eminence (bottom) has been destroyed.

cided to use goldthiomalate injected animals as controls.

Materials and methods. All the animals used were female Swiss mice averaging in age from 4 to 6 months. Out of 100 or more animals of each type, the following representative animals were examined: 6 uninjected control mice, 7 mice injected with goldthioglucose 24 to 72 hours prior to autopsy, 5 mice which had become obese as a result of goldthioglucose treatment, 4 mice which failed to become obese after being injected with goldthioglucose at least 3 months prior to autopsy, and finally 5 mice injected with goldthiomalate 24 to 72 hours prior to autopsy. The non-obese mice weighed 25 to 35 g; the obese mice weighed 45 to 65 g. Each of the treated mice was injected with 1 mg/g of body weight of the appropriate gold compound. This dosage represents a 50% lethal dose(6). Each brain was carefully dissected free of its bony enclosures and fixed for 24 hours in 10% neutral formalin. The overlying thalamus, subthalamus, and cerebral cortex were not trimmed and were used for control neural tissue in each specimen. The blocks of brain were dehydrated in a routine manner, embedded in paraffin and serial sectioned at 10 mu throughout the entire block. The sections were stained with hematoxylin and eosin and examined.

Results. Hypothalami of the goldthioglucose injected animals showed remarkable lesions within one to 3 days generally consisting of diffuse and punctate hemorrhages, widespread and marked edema involving more neural tissue than the hemorrhagic areas and pyknosis and degeneration of nerve cells throughout areas of edema and hemorrhage (Fig. 2, 4, 5, 7). The ventral portion of the third ventricle, especially the infundibular recess, also showed changes in that it was frequently engorged with blood and the lining ependymal cells were sometimes pyknotic and disrupted (Fig. 2, 4, 7). Although the anatomical extent and severity of the hypothalamic damage varied from animal to animal, it was clear in all cases that at least the ventral portion of the hypothalamus was involved. In the most severe instances, there was marked destruction of tissue at the base of the brain between the optic chiasm and the mamillary bodies, so that the neural tissue lying ventral and lateral to the third ventricle was fragmented and necrosed. In these specimens the usual landmarks in the ventral hypothalamus such as the supra-optic nucleus, ventromedial nucleus, median eminence, arcuate nucleus, and the lateral hypothalamic area were completely destroyed. In the less severe cases, the hypothalamic tissue at the base of the brain was intact, and the hypothalamic nuclei recognizable as clumps of cells, but the neurones in this area showed the signs of damage, and the parenchyma was edematous and hemorrhagic (Fig. 2, 4).

The limits of this edemous hypothalamic tissue were in all cases sharply demarkated (Fig. 2, 4, 5, 7). Dorsal to the edematous area, the neurones appeared normal. There was an abrupt transition from the normal tissue to the less eosinophilic edematous tissue that contained damaged neurones. The punctate and diffuse hemorrhagic areas were nearly always found within the edematous regions. They were most frequently found in the neural tissue adjacent to the ventral portion of the third ventricle and in the lateral hypothalamic area (Fig. 2, 4, 7).

Anteriorly, at the level of the optic chiasm, the damage appeared restricted to the most ventral nuclei adjacent to the chiasm. A bit posteriorly, the damage was more extensive, reaching more dorsally, so that in several specimens the paraventricular nucleus was involved, but at the same level, the laterally placed fornix was unaffected in all specimens. The supra-optic nucleus, the suprachiasmatic nucleus, and the ventral parts of the anterior and lateral hypothalamic areas were damaged in all specimens.

In the middle hypothalamic region (infundibular), the most extensive and severe damage was found. The ventromedial nucleus, the ventral part of the lateral hypothalamic area, the arcuate nucleus, and the median eminence were always destroyed (Fig. 2, 4, 5, 7). In 3 animals the dorsomedial nucleus and the perfornical area were also involved (Fig. 3, 5), but in no cases were regions lateral or dorsal to these damaged. In the posterior hypothalamus, only the mammillary bodies and

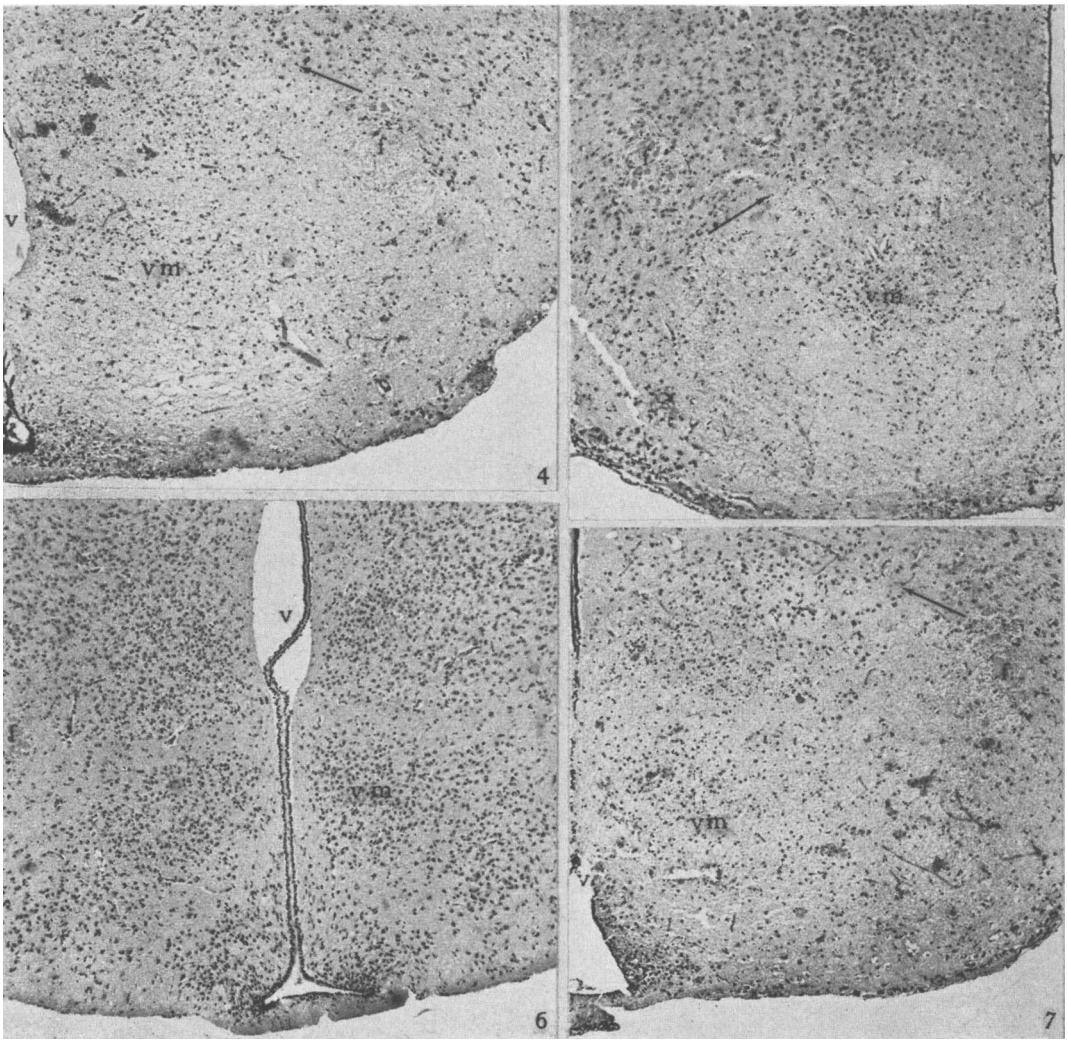

PLATE II: Photomicrographs (×65) taken of hematoxylin and eosin stained sections through tuberal or infundibular region of hypothalamus showing the same area in 4 different mice. Fig. 4, 5, and 7 were goldthioglucose treated. Fig. 6 was goldthiomalate treated. In Fig. 4, 5, and 7 note paucity of neurons in ventral hypothalamus, the pyknotic cell in edematous regions, and in Fig. 4 and 7, the widespread hemorrhages. In each figure position of the ventricle (v), ventromedial nucleus (vm), and fornix (f) is labeled. Arrows point to line of demarkation between destroyed (ventral) and normal (dorsal) regions.

the lateral area showed damage; the Fields of Forel and the cerebral peduncle outside the hypothalamus appeared normal.

Some inflammatory cells (polymorphonuclear leukocytes and lymphocytes) were present in the damaged areas, but their number was not great. Neurophagia and glial proliferations were observed, but these were scanty. In fact the large loss of neurons could not be accounted for in the 3 days after goldthioglucose administration by the amount of neurophagia observed. Presumably some of the neurons were lost by disruption and dissolution. There were no other areas of hemorrhage, cellular degeneration, and edema in the remaining parts of the brain overlying the hypothalamus.

The only lesion found in the brains of obese mice successfully injected with goldthioglucose at least 3 months prior to investigation was a paucity of neurons in the hypothalamus especially the ventral portion. This finding is

clearly demonstrable by a comparison of Fig. 1 and 3. The extent of the loss of neurons and replacement of glia was variable in the specimens examined. In one case this resulted in loss of discrete hypothalamic nuclear pattern which can be seen in the normal mice. In other specimens the nuclei could be recognized as clumps of cells, but they contained fewer neurons (Fig. 3).

Sections of the brain of animals given goldthiomalate showed nothing of the characteristic damage found in Swiss mice given goldthioglucose. In fact, as concerns the hypothalamus in particular, there were no differences from those of uninjected control mice. However, 2 of these animals had hemorrhages in the lateral ventricles, especially the frontal poles.

Examination of sections of brain of mice injected with goldthioglucose at least 3 months prior to autopsy and which failed to become obese revealed no distinct abnormality. The hypothalamic nuclei appeared distinct, and the number of neurons appeared within normal limits, though in some there seemed to be fewer neurons in a strip of hypothalamus lying ventral to the third ventricle.

The evidence presented here seems to support the conclusion that goldthioglucose produces obesity through causing hypothalamic lesions, always involving the ventromedial nuclei. Damage to the ventromedial nuclei has been shown to be essential to the production of obesity in rats(7) and mice(2). It is remarkable that, even though the hypothalamic area involved is often very large, only hyperphagia appears to result. The inactivity shown by hypothalamic mice(2) is not present in goldthioglucose obesity(6). Goldthioglucose obese mice do not show gonadal atrophy by weight(8).

Discussion. It would appear that the presence of the glucose component in the molecule makes this limited hypothalamic portion of the brain barrier much more permeable to this compound than to compounds not containing glucose. The hypothalamic area containing the feeding centers has been previously postulated to contain "glucoreceptors"(7). Larsson has since shown that this feeding center area effectively concentrates radioglucose with the receptivity apparently characteristic of the area rather than of discrete units(9). The results here would support the idea that the ventromedial feeding center area is a "glucoreceptive" area, in the sense postulated in the glucostatic theory of the regulation of food intake.

Summary. Goldthioglucose injections, in the dose which produces obesity in mice, cause in these animals extensive hypothalamic damage involving the ventromedial nuclei. Such lesions are permanent in animals which in fact become obese, but are not apparent in animals unsuccessfully injected. Goldthiomalate, though as toxic as goldthioglucose, does not cause obesity; its injection does not lead to hypothalamic lesions. Implications of these findings as regards the mechanism of the regulation of food intake are discussed.

The authors gratefully acknowledge the assistance of Dr. Charles DeWan. The goldthioglucose used in these studies as well as in previous studies was obtained through the courtesy of Dr. Edward Henderson and the Schering Corp., Bloomfield, N. J.

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