1978

Hypothalamic hypoactivity prevented but not reversed by subdiaphragmatic vagotomy.

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HYPOTHALAMIC HYPOACTIVITY PREVENTED BUT NOT REVERSED BY SUBDIAPHRAGMATIC VAGOTOMY

A Thesis Presented

By

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Submitted to the Graduate School of the
University of Massachusetts in partial fulfillment
of the requirements for the degree of

MASTER OF SCIENCE

August 1978

Psychology Department

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Acknowledgements

I wish to thank the members of my committee for their guidance and helpful suggestions. I thank Sue Rice for her encouragement and moral support during the conduct of the research. Thanks are also due to Paul Sawchenko and Earl Simson for their stimulating discussions of the data, and to Jay Alexander for technical assistance.

Abstract

Parasagittal hypothalamic knife cuts produce a syndrome which includes obesity and hypoactivity. When the subdiaphragmatic vagi were cut at the same time as the brain cuts were made, both the obesity and the hypoactivity were prevented. This suggested that both the obesity and the hypoactivity are mediated by vagal hyperactivity. In contrast, however, when the subdiaphragmatic vagotomy was done 40-70 days subsequent to the brain cuts, the obesity was reversed, but the hypoactivity persisted. Thus, some aspect of the interoperative period irreversibly prevents the ability of vagotomy to reinstate normal activity levels in the rat.

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Introduction

In the rat, lesions in the medial hypothalamus (MH) produce a complex syndrome whose components include: hyperphagia and obesity (Hetherington and Ranson, 1940), hyperdipsia (Sclafani and Grossman, 1971), decreased linear growth and growth hormone secretion (Bernardis and Frohman, 1970), gonadal dysfunction (Greer, 1953), hyperinsulinemia (Hales and Kennedy, 1964; Han and Frohman, 1970; Hustvedt and Løvø, 1972), gastric hyperacidity (Ridley and Brooks, 1965), slowed gastric clearance (Ralph and Sawchenko, 1978), hyperreactivity (Grossman, 1966, 1972; Sclafani et al., 1970), and dietary finickiness (Graff and Stellar, 1962). In addition, the syndrome includes decrements in spontaneous activity in running wheels (Brooks, 1946; Gladfelter and Brobeck, 1962; Hetherington and Ranson, 1942; Kennedy and Mitra, 1963; Kennedy, 1964), as well as in stabilimeters (Teitelbaum, 1957).

Parasagittal hypothalamic knife cuts also produce hyperphagia and obesity, but some of the other features of the syndrome are avoided, and therefore are presumed to be due to the non-selective nature of electrolytic lesions as opposed to the more discrete damage that can be inflicted with knife cuts. For example, by using knife cuts, the

hyperdipsia (Gold et al., 1977), decreased growth and growth hormone levels (Gold and Kapatos, 1975), gonadal dysfunction (Paxinos, 1974; Sclafani, 1971), hyperreactivity (Paxinos, 1974), and finickiness (Gale and Sclafani, 1977; Sclafani et al., 1976) are avoided, or attenuated, whereas the presumably vagally mediated functions: hyperinsulinemia (Tannenbaum et al., 1974), gastric hyperacidity (Sawchenko and Gold, in preparation), and slowed gastric clearance (Sawchenko, unpublished) persist. Hypoactivity also has been shown to persist after obesifying knife cuts (Sclafani, 1971; Eng, unpublished), despite the absence of any clear link between activity and vagal function.

Subdiaphragmatic vagotomy abolishes both hypothalamic lesion obesity (Inoue and Bray, 1977; Porte et al., 1973) and hypothalamic knife cut obesity (Sawchenko et al., 1977a). Subdiaphragmatic vagotomy also normalizes the lesion-induced hyperinsulinemia and gastric hyperacidity (Inoue and Bray, 1977; Powley and Opsahl, 1974; Sawchenko etal., 1977a). If the knife cut induced hypoactivity shares a common metabolic etiology with hyperphagia and obesity, then vagotomy simultaneous with knife cuts should prevent both hypoactivity and obesity, and vagotomy sub-

sequent to knife cuts should reinstate normal weight and activity levels.

Vagally-induced (neurogenic) hyperinsulinemia is most prominently mentioned as a possible cause of the obesity (Powley and Opsahl, 1974), especially since exogenous insulin can produce overeating and obesity (May and Beaton, 1968; Panksepp et al., 1975) and, most interestingly, hypoactivity in running wheels (Campbell and Fibiger, 1970). Furthermore, vagal stimulation has been shown to elicit insulin release, presumably through direct pancreatic beta cell innervation (Porte et al., 1973). We propose that hypothalamic obesity and hypothalamic hypoactivity are both due to disinhibition of a vagal mechanism which disrupts energy balance by increasing anabolic processes which diminish the availability of metabolic fuels for voluntary exercise.

Methods

Adult female Charles River CD albino rats were housed in Wahmann activity wheels, in an air conditioned (22° C.) room under a 12:12 light cycle. Purina chow pellets and tap water were available ad libitum.

The preceding day's activity (wheel revolutions) was

recorded during the last hour of the light period. Body weight was recorded twice a week, and daily food and water intakes were measured periodically. Daily vaginal smears were taken to provide an index of the contribution of gonadal dysfunction to activity changes. A one month period of adaptation to the activity wheels preceded any surgery. All surgery was performed under Nembutal anesthesia (40 mg/kg, i.p.).

Retracting wire knife cuts were made as previously described (Gold et al., 1977). Bilateral parasagittal cuts were placed 0.9 mm from the midline at the coronal level of the paraventricular nucleus. These cuts extended 3 mm rostro-caudally and 3 mm dorsally from the base of the brain. The correctness of the placements of the knife cuts was verified by two independent blind raters. Brain sections from the rats in the present study were examined along with selected sections from control rats that only received knife cuts and were not exposed to wheels. Some of these control cuts had produced hyperphagia and obesity, and some had not. The raters agreed with each other on all judgments and correctly rated all the sections. All of the data reported in the present study were from rats whose cuts were judged by

both raters to be sufficient to produce hyperphagia and obesity.

Subdiaphragmatic vagotomies were performed as previously described (Sawchenko et al., 1977b), using a 20X Zeiss operating microscope. The esophagus was exposed via an abdominal incision, and the branches of the vagus were visualized and cut as they run along the esophagus. This technique ensured the cutting of the hepatic, coeliac, and both gastric branches. Vagotomies were verified by an acute gastric acid secretion method (Powley and Opsahl, 1974) in which the failure to observe an increase in gastric acid secretion in response to electrical stimulation of the cervical vagi was taken as evidence that vagotomy was complete.

Data were statistically analyzed using the two sample Student's *t*-test, with alpha=.05 and df=4 (Spence et al., 1968).

Results

When vagotomy was performed at the same time as the obesifying hypothalamic knife cuts, the hyperphagia and hypoactivity predicted by the hypothalamic knife cuts alone were not seen (Figure 1, n=4). Activity levels

dipped significantly for a 20 day postoperative period ($p < .05$, one-tailed) and then returned to normal levels ($p < .10$). The transient decrease in activity was associated with a temporary (1-3 week) disruption of estrous cycling, after which normal cycling resumed.

The normal activity levels were not simply due to the absence of hyperphagia and obesity, because when rats with knife cuts and intact vagi were restricted to preoperative food intakes, they still were hypoactive (Figure 2, $n=4$, $p < .05$). Subsequently, these rats were free fed for 20 days, which behaviorally confirmed that these knife cuts would produce hyperphagia and obesity ($p < .05$). Finally, vagotomy on these obese hypoactive rats 70 days after the brain knife cuts reversed the weight gains ($p < .05$), but, surprisingly, the hypoactivity persisted ($p < .05$) even as the body weights fell below control levels ($p < .05$), and despite normal estrous cycling.

Similarly, when rats were not food restricted at all after knife cuts (2 on a high fat diet, 3 on pellets), subsequent vagotomy reversed the obesity ($p < .05$) but not the hypoactivity ($p < .05$, Figure 3). Individual data are presented in Figure 3. Two animals died at times indicated by the crosses.

Discussion

It is concluded that hypoactivity in running wheels is an unavoidable consequence of the neurological damage required for hyperphagia and obesity (Gold et al., 1977; Sclafani, 1971; Storlien and Albert, 1972). The hypoactivity and the obesity may share a common etiology since vagotomy can prevent both of these knife cut effects. The data presented suggest that the common etiology of knife cut obesity and hypoactivity is a vagal mechanism, such as hyperinsulinemia. In support of this, exogenous insulin has been shown to both elicit eating (May and Beaton, 1968; Panksepp et al., 1975) and depress running wheel activity (Campbell and Fibiger, 1970). The hyperinsulinemia seen in the MH damaged rat has been correlated with the degree of hyperphagia (Hustvedt and Lövø, 1972). It is proposed that hyperinsulinemia favors energy storage, and the resulting lack of available metabolic fuels causes hypoactivity. Similarly, a lack of available fuels to receptors may trigger appetite (Friedman and Stricker, 1976). Fuel availability would presumably affect physical endurance (Bergstrom et al., 1967). Unpublished data from this laboratory indicate that rats' swimming endurance (forced exercise) is also decreased by

obesifying knife cuts but is reinstated by vagotomy.

Gastric distention may have an inhibitory effect on activity via vagal afferents. In the intact brain rat, vagotomy abolishes the suppressive effect of non-nutritive bulk on deprivation induced running (Messing and Campbell, 1971), and changes the pattern of activity such that the normal periods of quiescence following a meal no longer occur (Bash, 1939). Could hypothalamic hypoactivity be due to the gastric distention brought about by excessive food intake (Gold, 1970; Gold et al., 1977; Hetherington and Ranson, 1942) and decreased gastric motility (Ralph and Sawchenko, 1978)? This possibility is unlikely, since prevention of gastric distention by food restriction did not abolish the hypoactivity in knife cut rats.

The role of the ovaries in running wheel activity and body weight is well known (Wade, 1976). High levels of running wheel activity are associated with estrus (Wang, 1923). Removal of the ovaries results in obesity (Kakolewski et al., 1968) and hypoactivity (Calvin and Sawyer, 1969). In MH lesioned rats, cyclic wheel running and other sex hormone mediated behaviors such as lordosis are abolished, even though normal vaginal cycling resumes (Kennedy and Mitra, 1963). Could hypothalamic obesity

and hypoactivity be due to ovarian dysfunction? Probably not. It has been demonstrated that ovarian obesity is separate from hypothalamic knife cut obesity since the obesifying effects of ovariectomy and hypothalamic knife cuts are additive (Gale and Sclafani, 1977). Although hypothalamic damage may cause obesity due in part to disruption of sex hormones (Hennessy and Grossman, 1976), the present knife cut obesity and hypoactivity were probably not caused by gonadal dysfunction, since normal cycling resumed.

The failure of delayed vagotomies to reverse running wheel hypoactivity is perplexing. Some aspect of the 40-70 day interoperative period, such as obesity itself or some related hormonal dysfunction, may cause permanent damage, such as pancreatic beta cell hypertrophy (Kennedy and Parker, 1963), that precludes renewed running wheel activity. Vagotomy appears to prevent but not to reverse this damage. Simultaneously operated rats never experience these presumably vagally mediated disorders, whereas rats that get knife cuts 40-70 days before vagotomy do.

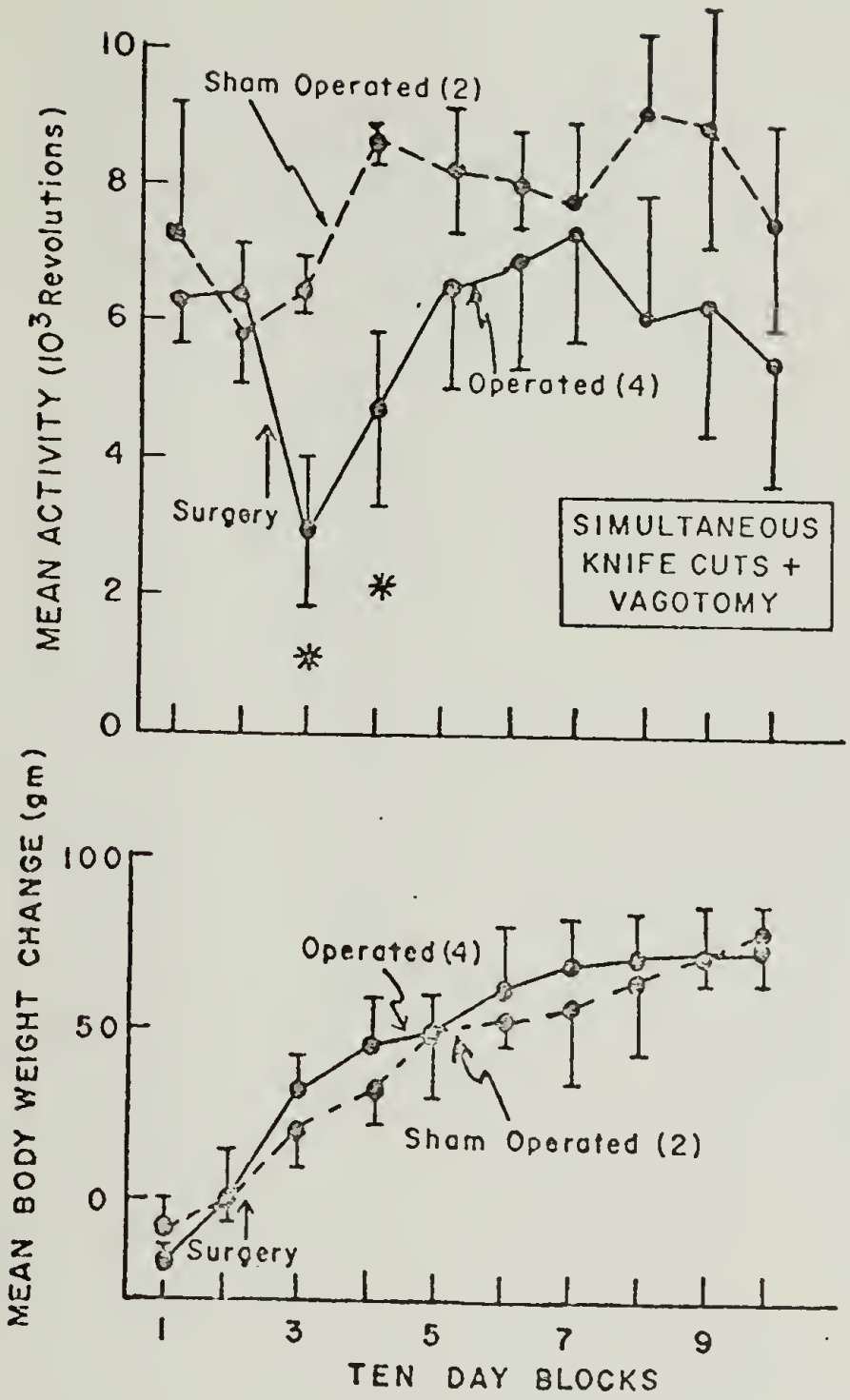

Figure 1. The mean activity (± SEM) and mean body weight change (± SEM) in rats with simultaneous knife cuts and vagotomy. *Indicates $p < 0.05$.

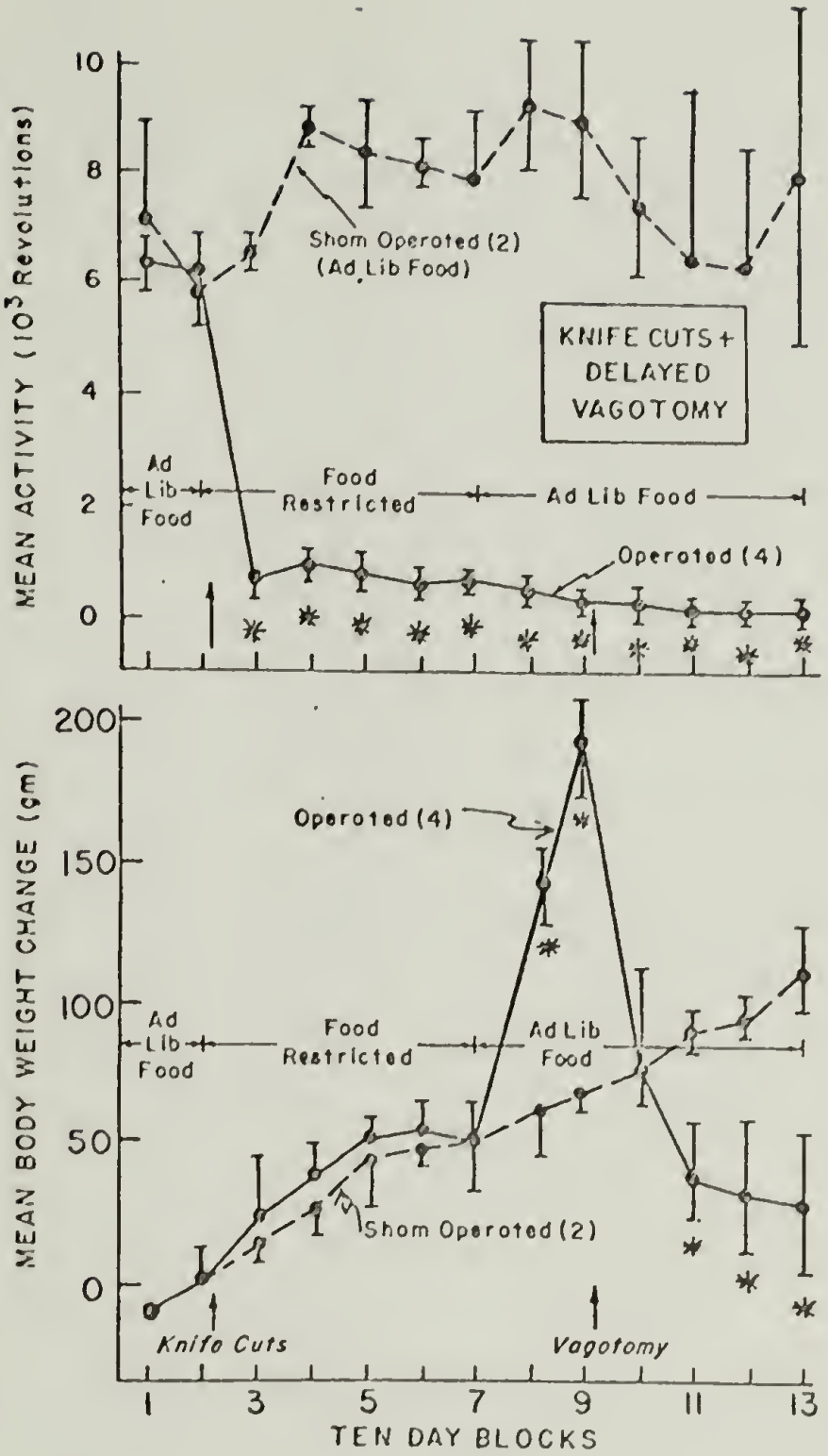

Figure 2. The mean activity (± SEM) and mean body weight change (± SEM) in knife cut rats subjected to 50 days food restriction, then ad lib food, followed by vagotomy at 70 days post knife cuts. *Indicates $p < 0.05$.

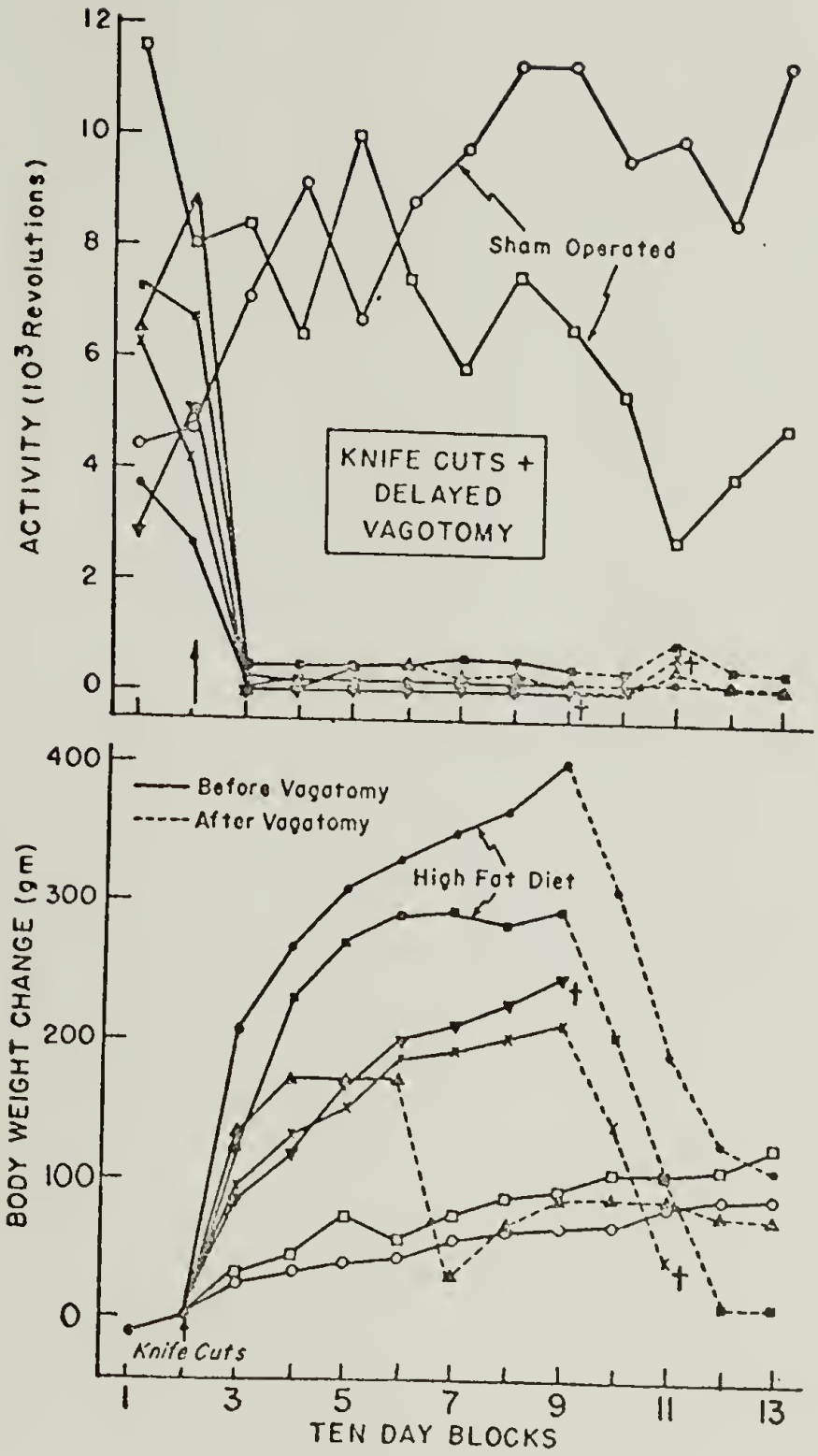

Figure 3. The activity and body weight data from individual animals with knife cuts followed by vagotomy at intervals of 40 or 70 days subsequent to the knife cuts. Dotted line indicates post vagotomy data. Two rats were on a high fat diet and three rats were on a pellet diet. Crosses indicate fatalities.

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