these 2 groups are compared by Fisher's method,[2] they are found to be significantly different ($t = 4.94$).

Summary. 1. Following hypophysectomy the eruption of the incisor of the rat becomes progressively slower and finally ceases.

2. If not administered too late after operation, growth-promoting hormone increases the eruption-rate of the incisor. An increase in body-weight, following the administration of hormone to the hypophysectomized animal, is always associated with an increase in the rate of the eruption of the incisor.

3. In the normal animal, the administration of growth-promoting hormone under the experimental conditions described, although definitely increasing body-weight, does not appreciably alter the eruption-rate of the incisor.

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Production of Ulcers in the Prostomach of Rats by Protein Restriction.

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(Introduced by A. J. Carlson.)

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Büchner, Siebert and Molloy[1] found that marked ulceration could be produced in the prostomach of rats by stimulating the gastric secretion with histamine on starvation days. Some ulceration also occurred in rats starved every other day during a period of 17 days, without histamine. Bürkle-de la Camp[2] confirmed these results with histamine but did not observe ulcers in the prostomach of rats after short periods of simple starvation. The question of ulceration following starvation was of particular interest because irritation of the parapyloric region by the gastric secretion was believed to explain a peculiar and intense hunger sensation that repeatedly developed with starvation or protein restriction in the senior author of the present report (Hoelzel and Kleitman[3]). Moreover, the observation that protein restriction led to an increase

[2] Fisher, R. A., *Statistical Methods for Research Workers*, 1930, 107.

[1] Büchner, Siebert and Molloy, *Beiträge z. path. Anat. u. allg. Path.*, 1928, **81**, 391.

[2] Bürkle-de la Camp, *Deut. Z. f. Chir.*, 1929, **220**, 31.

[3] Hoelzel and Kleitman, *Arch. Int. Med.*, 1927, **39**, 710.

in the fasting gastric acidity (Hoelzel[4]) made it appear that, if ulcers would develop in the prostomach of rats with starvation, ulceration might also occur as a result of protein restriction alone.

We first starved 35 rats every other day or during alternate 2-day periods and gave diets differing in their protein content to the various rats on feeding days. As a result, some rats seemed to develop ulcers in the prostomach regardless of the type of diet, but practically all rats that were intermittently starved and were fed diets low in protein for more than 2 weeks developed ulcers. No ulcers were found in the prostomach of any of 175 control rats.

The experimentation was therefore extended to determine the effect of more prolonged starvation, of protein restriction without starvation, and of adding salt, spices, alcohol, HCl or ant-acid salts to various diets. The effect of the major vitamin deficiencies, of high and low carbohydrate, or fat, or protein diets, and of various amounts and kinds of roughage in the diets was also investigated. In nearly all cases, 8 or more rats were used in determining the effect of each specific experimental procedure. Altogether over 1000 rats were used, besides the 175 controls referred to above.

The results primarily confirmed the belief that ulceration could be produced in the prostomach of rats by simple protein restriction. The most direct way of producing ulcers proved to be prolonged starvation and the most striking ulceration occurred when starvation or protein restriction was complicated by pregnancy. Some starvation or undernutrition was practically always involved when ulcers developed. Nevertheless, it could be shown that inanition or undernutrition *per se* was not responsible for the ulcers. For instance, when an exclusive diet of bran was given, no ulcers developed in the prostomach although the rats then practically starved to death in spite of eating enormous amounts. In fact, ulcers produced by starvation or protein restriction would heal on diets of practically nothing but bran. Incidentally, this indicates that mechanical irritation neither gave rise to the ulcers nor seriously interfered with their healing. Presumably, the effect of bran, in this connection, is explained partly by its acid-binding power and partly by the diluting effect of the bulk. The saliva swallowed in ingesting bran may also be a factor.

The ulcers produced in the prostomach of rats by protein restriction were similar to those described by Pappenheimer and Larimore[5]

[4] Hoelzel, *Am. J. Physiol.*, 1926, **77**, 166.

[5] Pappenheimer and Larimore, *J. Exp. Med.*, 1924, **40**, 719.

and attributed, by them, to the ingestion of hair. They found ulcers in about 61% of rats kept on diets like the Sherman-Pappenheimer rickets-producing diet, which contains 95% patent flour. Among 27 rats kept on a diet of white bread only, in our study, about two-thirds developed ulcers. The protein inadequacy involved in such diets is evidently responsible for the lesions. Our observations also indicate that the ingestion of hair leads to ulceration only when this interferes with a normal food intake. On the other hand, ulcers do not develop, even when the diet is somewhat poor in its protein content, provided that large amounts are eaten. Also, when from 5% to 10% of an ant-acid salt was added to bread, the food intake decreased and ulceration increased above what occurred on a diet of bread only, but, when from 15% to 30% of calcium carbonate was added to bread, the incidence of ulceration again decreased in spite of a low food intake, apparently because of the great excess of ant-acid salt. Rats on diets high in fat but low in protein developed ulcers, but not as readily as rats kept on high carbohydrate diets with a similar protein content. Rats on diets with as much as 90% protein did not develop ulcers, even when some HCl was added.

These observations indicate that a protein deficiency or the lack of sufficient acid-binding protein in the diet may be a factor in the etiology or in the chronicity of some cases of gastric or duodenal ulcer in man. The trial of a diet rich in protein in ulcer cases was suggested 5 years ago (Hoelzel[4]) and the recent advocacy of the use of mucin by Fogelson[6] seems to be a step in this direction. However, clinical experience and some experimental observations on man (Hoelzel and Kleitman[3]) and on rats in this study seem to indicate that an excessive protein intake immediately after more or less prolonged restriction may lead to a temporary aggravation of the symptoms or conditions due to protein restriction. Moderation in the protein intake in the early stages of ulcer healing is therefore suggested and this conforms with standard clinical practice. Prolonged protein restriction, however, is definitely contraindicated.

[6] Fogelson, *J. Am. Med. Assn.*, 1931, **96**, 673.