Some effects of hypophysectomy on gastrointestinal function and structure

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EDITORIAL SYNOPSIS  These investigations demonstrate the dependence of gastrointestinal function on pituitary gland secretions. Hypophysectomy decreased all indices of gastric secretion in the dog but these could be restored either by cortisone or growth hormone. No histological changes were found.

The dependence of gastric mucosal structure and function on hormonal activity has been the subject of many investigations (Welbourn and Ward, 1962; Zollinger and Craig, 1960; Grossman, 1950). The conflicting nature of experimental findings and interpretations, particularly as related to the effect of adrenal cortical hormones on gastric secretion, is reflected in many articles reviewing this subject (Bachrach, 1963; Sulman and Kirsner, 1963; Smith, Delamore and Williams, 1961; Clarke, Neill, and Welbourn, 1960; Wiederanders, Classen, Gobbel, and Doyle, 1960; Gray, 1957; Kirsner, 1957). Similarly, there is contradiction among reports dealing with the relationship between hormonal activity and small intestinal absorption (Adlersberg, Colcher, and Drachman, 1951), although the literature contains fewer papers on this subject. At best it can be stated that there are more articles presenting evidence that adrenal cortical hormones increase gastric secretion and accelerate intestinal absorption than there are denying this contention.

Hypophysectomy has been reported to decrease gastric secretion (Abrams and Baker, 1954; Enriquez de Salamanca, Garcia-Morato Castaño, López-Porrúa, and Castro-Rial Canosa, 1953; Crafts and Walker, 1947; Cutting, Dodds, Noble, and Williams, 1937). Intestinal absorption of carbohydrate and fat has also been reported to decline following hypophysectomy or adrenalectomy (Russell, 1938; Verzár and McDougall, 1936). Among the mechanisms implicated in these gastrointestinal responses to endocrine ablation are mucosal atrophy (Haeger, Jacobsohn, and Kahlson, 1953), cellular involution (Abrams and Baker, 1954), and the loss of various direct or indirect influences of adrenal cortical hormones (Clarke et al., 1960; Verzár and McDougall, 1936; Baker, 1957; Baker and Clark, 1961; Stempien and Dagradi, 1954) or other hormones (Welbourn and Ward, 1962; Clarke et al., 1960; Abrams and Baker, 1954; Baker and Clark, 1961).

The experiments in this paper were designed to assess further some of the mechanisms involved in gastrointestinal responses to hypophysectomy. A series of chronic studies of hypophysectomized dogs are reported.

MATERIALS AND METHODS

Six mongrel bitches weighing 9 to 15 kg. each were subjects of these studies. The animals were caged individually for one month before hypophysectomy and for the duration of the study thereafter. They were fed a fixed diet (4% fat) which maintained body weight constant in the pre-operative period.

Hypophysectomy was performed via a subtemporal intracranial approach (Keller, Lawrence, and Blair, 1945). The pars anterior was removed in all cases and in half the animals all visible stalk tissue was either coagulated or excised. The hypothalamic-hypophyseal region was examined histologically in two of these animals (nos. 1013 and 1128) and the findings conformed to the surgical impression.

Hypophysectomy was well tolerated by these animals. On a diet which had maintained a stable body weight pre-operatively, three of the six dogs gained more than 1 kg. and the other three remained within 1 kg. of starting weight. Weekly haematocrits exhibited no marked abnormalities. Blood glucose levels tended to be lower post-operatively. One animal (1268) manifested a three-fold increase in urinary output after operation, which was further increased during cortisone treatment.

Evidence that these animals had functional as well as anatomical hypophysectomy included the following.
There was a 10 to 40-fold increase in the sensitivity of the hypoglycaemic response to insulin (pre-operatively 1 unit of regular insulin per kilogram body weight reduced blood sugar 50%, whereas only 0·1 to 0·025 units per kilogram exerted the same effect by six weeks after hypophysectomy). The fur took on a soft, luxuriant appearance, fat was deposited around the hips, and the animals were less lively when walked. Sexual activity ceased.

Gastric and intestinal functions were investigated in these animals before surgery, at 6, 10 and 14 weeks after surgery, during prolonged cortisone acetate replacement treatment, and after cessation of the steroid regimen (up to five months after hypophysectomy). In addition, two of the dogs (nos. 1013 and 1128) were also observed during subsequent periods of adrenocorticotropic hormone (A.C.T.H.) and somatotropic hormone (S.T.H.) replacement (up to 10 months after hypophysectomy). The dosage schedule for the hormones used was: cortisone acetate (Upjohn Company, Kalamazoo), 50 mg. per day intramuscularly for two weeks; A.C.T.H. (Armour Pharmaceutical Co., Kankakee), 40 units per day subcutaneously for two weeks; and S.T.H. (Armour) 15 mg. per day subcutaneously for one week. This batch of S.T.H. contained only trace amounts of T.S.H., A.C.T.H., or F.S.H. It was used for only one week because it induced a doubling of fasting blood sugar in this time, confirming the reported severe diabetogenic effects of growth hormone in either normal or hypophysectomized dogs (Smith, Gaebler, and Long, 1955; Campbell, Hausler, Munroe, and Davidson, 1953) and lending assurance that this batch of S.T.H. was biologically active.

Gastric secretary function tests were conducted during basal conditions and following histamine stimulation (360 μg. base subcutaneously). These included measurement of the volume, pH (Beckman Instruments, Inc., Fullerton), and the total acid and pepsin hourly output and concentration. Total acid was determined in each sample by titration against 0·1 N NaOH in the presence of phenolphthalein indicator. The pepsin content of each sample was obtained by the method of West, Ellis, and Scott (1952) applied to gastric juice. With this method basal pepsin concentration was 15 ± 3 (S.E.) units per ml. and hourly pepsin output was 424 ± 97 units; histamine-stimulated pepsin concentration was 10 ± 2 units per ml. and output was 910 ± 147 units per hour in 23 determinations made on 15 dogs not used in this investigation.

Gastric juice was aspirated by continuous suction employing a double-lumen weighted tube which was passed through the mouth (Coy, McClaskey, and Thull, 1952). This procedure is well tolerated by dogs for hours and requires no physical or pharmacological restraint. During the aspiration each dog lay on the left side. The few samples grossly contaminated with bile were discarded.

Basal gastric secretory activity was not negligible in these animals before hypophysectomy. Aspirations were performed in the morning at a time when food would ordinarily have been given. The timing and the presence of a large-bore tube irritating the back of the throat may have provided vagally mediated stimulation to the "basal" secretory rate.

Intestinal absorption tests included serum d-xylose concentration and d-xylose output in the urine two hours after administering a loading dose of 5 g. via a stomach tube. In half the animals 24-hour urinary d-xylose outputs were also determined. This carbohydrate was measured by the method of Roe and Rice (1948). In 13 determinations performed in eight normal dogs not used in this study the two-hour urinary output of d-xylose was 1,401 ± 134 mg.

Other intestinal absorptive parameters followed included serum lipid concentrations obtained two hours post-prandially and 24-hour stool fat measurements. Total serum lipid was determined by the method of Kunkel and Ahrens (1948). In 21 determinations on six normal dogs not used in this study the mean two-hour post-prandial value was 2,086 ± 175 mg. per 100 ml. serum. Stool fat was measured employing the method of van de Kamer, ten Bokkel Huinink, and Weyers (1949). In 20 determinations on 11 dogs not used in this study fat in the stool comprised 2·4 ± 0·4% of stool weight.

Finally, mucosal tissue was biopsied from the stomach and jejunum using a biopsy capsule (Crosby and Kugler, 1957). Pre-operatively these biopsies were easy to obtain. However, after hypophysectomy gastric emptying was delayed and the capsule would remain in the stomach for many hours longer than notated (fluoroscopically) before operation. In addition, the character of gastric secretions was altered after hypophysectomy, and it became impossible to biopsy anything more substantial than rather thick mucus despite repeated attempts. Two of the dogs were sacrificed after the study and full-thickness specimens of stomach and gut were excised. All tissue was fixed in formalin and stained with haematoxylin and eosin. Statistical analysis of the results was performed using the t test of differences between means of two correlated samples (Tate, 1955).

**RESULTS**

**GASTRIC SECRETIONS Hypophysectomy** induced a decrease in basal or histamine-stimulated gastric secretory responses by all parameters assayed. The depression of gastric function became more marked with time after operation. Thus, the basal volume, acid and pepsin mean values were considerably reduced from control after hypophysectomy. An even more significant reduction was observed in the histamine-stimulated gastric secretory indices which were about half control values or less at 10 weeks after operation. Table I summarizes these findings.

The prolonged administration of cortisone acetate reversed most of the inhibition of gastric secretion induced by hypophysectomy. The degree of this reversal depended on the particular measure of gastric function being assayed. Thus, the hourly basal volume was not significantly increased from the post-hypophysectomy state, whereas the mean...
hourly histamine-stimulated volume during cortisone replacement was increased beyond values obtained after hypophysectomy or during the control period. Cortisone treatment appeared more effective in restoring the histamine-stimulated indices to control values than in increasing gastric secretion during basal conditions. There appeared to be some residual effects of cortisone treatment when gastric secretion was measured 10 days after cessation of the steroid hormone. These results also appear in Table I.

Two dogs were observed for approximately 10 months after hypophysectomy. During this time they were administered cortisone (for two weeks), A.C.T.H. (for two weeks), and S.T.H. (for one week). Hypophysectomy reduced all histamine-stimulated measurements of gastric secretion. The effects of hypophysectomy were reversed during either cortisone or S.T.H. treatment. A.C.T.H. appeared ineffectual in the dose used (40 units/day). The results from both of the dogs appear in Table II.

### Table I

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Weeks after Hypophysectomy</th>
<th>Cortisone</th>
<th>Ten Days after Cortisone</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>6</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Acid output (µEq/hr.)</td>
<td>18 ± 8</td>
<td>6 ± 3</td>
<td>4 ± 2</td>
<td>5 ± 5</td>
</tr>
<tr>
<td>Acid concentration (µEq/1.)</td>
<td>851 ± 408</td>
<td>321 ± 214</td>
<td>78 ± 55</td>
<td>52 ± 32</td>
</tr>
<tr>
<td>Pepsin output (units/hr.)</td>
<td>36 ± 17</td>
<td>23 ± 12</td>
<td>6 ± 4</td>
<td>2 ± 2</td>
</tr>
<tr>
<td>Pepsin concentration (units/l.)</td>
<td>224 ± 130</td>
<td>31 ± 22</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>Histamine-stimulated</td>
<td>14 ± 8</td>
<td>2 ± 1</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
</tr>
</tbody>
</table>

All values represent the mean ± standard error of the mean for the series of dogs.

### Table II

<table>
<thead>
<tr>
<th>Dog 1013 (Histamine-stimulated)</th>
<th>Control</th>
<th>Hypophysectomy</th>
<th>Cortisone</th>
<th>Hypophysectomy</th>
<th>A.C.T.H.</th>
<th>Hypophysectomy</th>
<th>S.T.H.</th>
<th>Hypophysectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (ml/hr.)</td>
<td>51</td>
<td>26</td>
<td>90</td>
<td>47</td>
<td>32</td>
<td>7</td>
<td>75</td>
<td>16</td>
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<tr>
<td>Acid output (µEq/hr.)</td>
<td>5,100</td>
<td>1,274</td>
<td>9,810</td>
<td>5,522</td>
<td>3,360</td>
<td>476</td>
<td>8,175</td>
<td>1,232</td>
</tr>
<tr>
<td>Acid concentration (µEq/1.)</td>
<td>100</td>
<td>49</td>
<td>109</td>
<td>126</td>
<td>105</td>
<td>68</td>
<td>109</td>
<td>77</td>
</tr>
<tr>
<td>Pepsin output (units/hr.)</td>
<td>690</td>
<td>33</td>
<td>1,242</td>
<td>285</td>
<td>19</td>
<td>40</td>
<td>1,238</td>
<td>55</td>
</tr>
<tr>
<td>Pepsin concentration (units/l)</td>
<td>14</td>
<td>1</td>
<td>14</td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>pH</td>
<td>1.8</td>
<td>1.8</td>
<td>2.0</td>
<td>1.0</td>
<td>0.8</td>
<td>1.5</td>
<td>1.0</td>
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</tr>
</tbody>
</table>

### Table II

<table>
<thead>
<tr>
<th>Dog 1123 (Histamine-stimulated)</th>
<th>Control</th>
<th>Hypophysectomy</th>
<th>Cortisone</th>
<th>Hypophysectomy</th>
<th>A.C.T.H.</th>
<th>Hypophysectomy</th>
<th>S.T.H.</th>
<th>Hypophysectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (ml/hr.)</td>
<td>84</td>
<td>4</td>
<td>51</td>
<td>38</td>
<td>33</td>
<td>20</td>
<td>72</td>
<td>42</td>
</tr>
<tr>
<td>Acid output (µEq/hr.)</td>
<td>10,500</td>
<td>232</td>
<td>7,599</td>
<td>3,344</td>
<td>1,485</td>
<td>1,500</td>
<td>7,632</td>
<td>3,276</td>
</tr>
<tr>
<td>Acid concentration (µEq/1.)</td>
<td>126</td>
<td>58</td>
<td>149</td>
<td>88</td>
<td>45</td>
<td>78</td>
<td>106</td>
<td>78</td>
</tr>
<tr>
<td>Pepsin output (units/hr.)</td>
<td>572</td>
<td>132</td>
<td>341</td>
<td>38</td>
<td>20</td>
<td>19</td>
<td>2,970</td>
<td>79</td>
</tr>
<tr>
<td>Pepsin concentration (units/l)</td>
<td>6</td>
<td>33</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>pH</td>
<td>1.5</td>
<td>2.0</td>
<td>1.0</td>
<td>1.8</td>
<td>2.0</td>
<td>1.1</td>
<td>1.2</td>
<td>1.1</td>
</tr>
</tbody>
</table>
E. D. Jacobson and T. J. Magnani with the technical assistance of E. B. McClaskey and T. J. Kallal

TABLE III

EFFECTS OF HYPOPHYSECTOMY AND CORTISONE REPLACEMENT ON INTESTINAL ABSORPTION

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Weeks after Hypophysectomy</th>
<th>Cortisone</th>
<th>Ten Days after Cortisone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>2-hour urine d-xylose (mg.)</td>
<td>1,912 ± 184</td>
<td>842 ± 133 ×</td>
<td>797 ± 195 ×</td>
<td>915 ± 196 ×</td>
</tr>
<tr>
<td>Serum d-xylose (mg./100 ml.)</td>
<td>38 ± 5</td>
<td>57 ± 4</td>
<td>54 ± 2 ×</td>
<td>50 ± 7</td>
</tr>
<tr>
<td>2-hour total lipid (mg./100 ml.)</td>
<td>1,906 ± 279</td>
<td>1,130 ± 222 ×</td>
<td>873 ± 164 ×</td>
<td>463 ± 154 ×</td>
</tr>
<tr>
<td>Stool fat (% stool weight)</td>
<td>4 ± 1</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
<td>2 ± 1</td>
</tr>
</tbody>
</table>

*Indicates a probability of no difference compared with control values of less than 0.05.

Indicates that the probability is less than 0.01.

serum d-xylose concentrations two hours after the pentose load were somewhat increased following hypophysectomy and this was reversed by cortisone. These results appear in Table III.

In the two animals followed for 10 months hypophysectomy lowered serum total lipid and urine d-xylose values. Cortisone, A.C.T.H., and S.T.H. elevated lipid values to pre-operative levels, while xylose values were increased somewhat by cortisone and not by the other two hormones.

GASTROINTESTINAL BIOPSIES  As noted in the methods section, biopsy of the stomach and intestine became technically extremely difficult after hypophysectomy. Frequently the tissue obtained was not entirely satisfactory for pathological study. However, the two long-term subjects (nos. 1013 and 1128) were sacrificed and ample specimens were obtained from the fundus, pyloric gland area, and jejunum.

With the standard fixation and staining employed no abnormalities of the gastric mucosa could be found. There was no reduction in either the parietal or chief cell population and no obvious reduction in size of these cells. The intestinal mucosa was

Fig. 1. Stomach tissue before and after hypophysectomy (dog no. 1128).
- a  Biopsy obtained before surgery (magnification × 92).
- b  Necropsy section obtained 10 months after hypophysectomy (× 92). No obvious differences were seen.
- c  High-power magnification (× 720) of necropsy section showing normally appearing parietal and peptic cells.

Fig. 2. Jejunal tissue before and after hypophysectomy (dog no. 1013).
- a  Biopsy obtained before surgery (magnification × 62).
- b  Necropsy section obtained 10 months after hypophysectomy (× 62). No obvious differences were observed.
Similarly not changed following hypophysectomy. The villi, epithelium, lamina propria, and submucosa were normal. These findings are shown in Figures 1 and 2.

DISCUSSION

The results of these investigations confirm the dependency of gastrointestinal function on pituitary gland secretions. Hypophysectomy decreased all indices of gastric secretion in the dog, and either cortisone or growth hormone in pharmacological doses restored gastric secretory activity to the preoperative level. Hypophysectomy also decreased the rate of intestinal absorption as measured by the amount of d-xylose excreted in the urine and the total lipid concentration in the serum two hours after a load. Studies of carbohydrate and fat excretion involving longer time periods, however, indicated no absolute malabsorption following hypophysectomy.

These findings allow only very limited references about mode of action of steroid hormones on gastric secretion under physiological conditions. However, if cortisone in the dose used acted solely as a direct stimulant of gastric secretion (additive effect), one would anticipate that the enhanced output of juice, acid, or pepsin would be the same whether the stomach were in a basal or histamine-stimulated condition. Analysis of Table I shows that this was decidedly not the case. The absolute effect of cortisone on the hourly output of water, acid, or pepsin was many times greater in the histamine-driven stomach than under basal conditions. Similarly, the absolute decrease in hourly output induced by hypophysectomy was also far larger in the stimulated state than in the basal. These results suggest that corticoids allow the gastric mucosa to respond to other stimuli (permissive effect).

The results obtained from the two dogs observed for nearly one year are of considerable interest. The failure of A.C.T.H. to restore gastric secretory function in these animals could have been due to use of an inadequate dose or to adrenal insensitivity. The dose used was quite large and was administered for two weeks. With hypophysectomy of the type performed, varying degrees of adrenal atrophy result (Keller et al., 1945), and adrenal output of corticosteroids in response to A.C.T.H. declines (Melby, Egdahl, and Spink, 1960). The potency of growth hormone was also surprising. In the doses used it was fully as effective as cortisone in restoring gastric secretory function after hypophysectomy. This gastric stimulatory action of S.T.H. helps to explain why destruction of the pituitary exerts a more profound inhibitory effect on gastric secretory function than is observed with loss of the adrenals (Friedman, Magee, Telfer, and Sandweiss, 1955; Escamilla and Lisser, 1942; Kyle and Welbourn, 1956). The stimulatory effect of S.T.H. on the stomach and the reported effects of thyroid (Nassett and Goldsmith, 1961) and sex hormones (McCarthy, Evans, and Dragstedt, 1954) suggest that the pituitary-adrenal axis is only one of several hypothalobal hormonal pathways involved in the control of gastric secretion.

If the rate of absorption from the small bowel in a brief time period is used as the only measure of intestinal absorptive capacity and if the material to be measured is instilled into the stomach or eaten, an erroneous picture of malabsorption due to hypophysectomy will result. Thus, in this investigation a decrease in d-xylose excretion or total lipid concentration was observed two hours after the load. Similarly, other investigators have found a decline in absorption of carbohydrate (Russell, 1938; Verzar and McDougall, 1936; Althausen, Anderson, and Stockholm, 1939) and fat (Verzar and McDougall, 1936; Bavetta, Hallman, Deuel, and Greeley, 1941) in hypophysectomized or adrenalectomized animals within a few hours after instilling the material into the stomach. By contrast, when the time factor is obviated by a lengthy study (as in the stool fat or 24-hour xylose recoveries) or in gut loop experiments (Marrazi, 1940), or other long-term balance studies (Samuels, Reinecke, and Bauman, 1943; Barnes, Wick, Miller, and MacKay, 1939), there is little or no decrease in the absolute amount of nutrient absorbed. This suggests that hypomotility, particularly trapping of the load in the stomach, may be responsible for the delay in the gut taking up the test substance. Hypophysectomy has been found to delay gastric emptying (Enriquez de Salamanca et al., 1953) and we observed similar hypomotility after hypophysectomy while following the movement of the biopsy capsule under fluoroscopy. However, since our results do not include measurements of transit time through the stomach or gut, a definite statement about the effects of hypophysectomy on motility cannot be made.

Hypophysectomy induced some elevation of serum d-xylose levels two hours after a load, indicating a decreased renal clearance of xylose which could also contribute to the decline in the two-hour urinary output after hypophysectomy.

We are at a loss to explain why the gastric tissue we examined exhibited no obvious changes after hypophysectomy when the literature is replete with descriptions of various sorts of gastric cellular atrophy following endocrine ablation (Baker, 1957). Thus, generalized gastric mucosal atrophy has been reported to follow hypophysectomy in cats (Haeger
et al., 1953) or rats (Friedman, 1953), although this has not been confirmed by others (Baker and Clark, 1961; Baker and Abrams, 1954; Baker and Bridgman 1954) who found instead involution of peptic cells and a decrease in the mean size of parietal cells in rats. In normal dogs corticosteroids have been reported to increase the number of parietal cells and reduce the chief cell population (Clarke et al., 1960). In humans, however, gastric atrophy or other abnormalities have been found in only a minority of cases of hypopituitarism (Smith et al., 1961). The gastric and intestinal mucosal tissue from our study was not obviously abnormal by ordinary microscopic criteria, but in the absence of actual measurements our finding is only a subjective evaluation. Furthermore, comparisons with the reports mentioned above are difficult because of differences in species, histological stain or design of the study.

A somewhat paradoxical conclusion of this study is that despite the profound effect of hypophysectomy on several functions of the stomach and intestine, there is no obviously adverse effect on the major activity of the gastrointestinal system, the nutrition of the animal. Thus, hypophysectomy markedly inhibits the ability of the stomach to secrete adequate amounts of pepsin in an acid juice and may also decrease gastric motility. These deficiencies are probably compensated, as it were, by other effects of hypophysectomy, namely, intestinal hypomotility, which allows a longer time for absorption and a decline in somatic energy requirements. The net result, as we observed, is that if the hypophysectomized bitch is well cared for, she does not lose weight nor exhibit an overt deficiency pattern.

The authors are grateful to Dr. A. D. Keller who performed the hypophysectomies in these dogs, to Dr. G. P. Smith who reviewed the manuscript, and to Mr. Thomas McBroom for computational support.

REFERENCES


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