2 The relationship of the gastric secretory response to hypoglycaemia and to changes in the level of plasma cortisol

The ability of hypoglycaemia to activate the pituitary-adrenal system (Porter et al., 1953), although denied by some authors (Thorn and Laidlaw, 1953) appears to have been demonstrated by others (Vogt, 1951; Bliss, Migeon, Eik-nes, Sandberg, and Samuels 1954; Marks, Weiss, Leftin, and Rossmeisl, 1958). The increase in the urinary excretion of 17-hydroxy steroid and in the plasma concentration of 17-hydroxy corticosteroids appears, however, to be confined to the period during which hypoglycaemia persists, after which the levels return to normal (Bliss et al., 1954).

It has been confirmed that corticotrophin and hydrocortisone are capable of promoting secretion from gastric pouches in fasting dogs and that hydrocortisone is particularly and consistently effective in augmenting secretion initiated by another stimulus (Sircus, Huston, and Preshaw, 1962).

The next logical step in the elucidation of the mechanism of the second phase of the gastric response to insulin was to examine in pouch dogs the effect of insulin-induced hypoglycaemia upon the blood level of endogenous cortisol and to study the chronological relationship of any observed changes to the effects upon plasma glucose levels and gastric secretion.

In view of the almost immediate effect of hydrocortisone upon histamine-stimulated gastric secretion, previously demonstrated, it could be expected that any rise of gastric secretion which was the result of an increase in the output of endogenous cortisol would closely coincide in time with a measurable increase of cortisol in the plasma.

METHODS

Four dogs were used, two with cannulation of the whole stomach with wide-bore stainless steel, capped, cannulae, one with a cannulated innervated Pavlov-type pouch, and one with a denervated Heidenhain pouch. Before experiments the dogs were fasted for 18 hours. Gastric secretion was collected continuously by gravity drainage throughout the experiments which lasted from six to nine hours.

In two control experiments, once the fasting gastric secretion remained steady, an intravenous injection of 1 ml saline was given. Venous blood, for the estimation of plasma glucose and cortisol, was removed before the injection of saline, and at approximately 30, 90, 180, 330, and 390 minutes afterwards.

In eight experiments, soluble insulin, 1 unit per kilogram body weight, was injected intravenously and blood was withdrawn at similar time intervals as stated above.
maximum in the specimen of blood removed at one and a half hours, and thereafter fell (Fig. 1a). Throughout the remainder of the experiment the levels showed no significant fluctuation although remaining at a higher level than the basal in three experiments and returning to basal levels in another three. The peak of the rise in cortisol occurred about half an hour before the peak of the initial rise in gastric secretion, and corresponded approximately with the lowest point of blood glucose. It is only in that group of cortisol estimations obtained at the peak of hypoglycaemia that the mean shows a highly significant ($P \approx 0.01$) difference from that of the basal levels.

**FIG. 1.** The effect of insulin-induced hypoglycaemia upon the level of cortisol in the plasma.

- **FIG. 1a.** Blood withdrawn at intervals throughout the experiment after injection of insulin.
- **FIG. 1b.** Blood withdrawn at intervals throughout the experiment after control injection of saline.
- **FIG. 1c.** Blood withdrawn after three hours after injection of insulin only.

When A.C.T.H. is infused intravenously the maximum output of 17-hydroxycorticosteroids occurs within four hours (Marks et al., 1958). With insulin-induced hypoglycaemia the maximum stimulation of the pituitary is likely to occur at the point of maximum lowering of the blood sugar. If the delayed phase of gastric secretion was due to the release of corticosteroids as a result of this stimulation of the pituitary, there should appear a second peak in the level of plasma cortisol somewhere between three and five hours after the injection of insulin. This was observed in only one of eight experiments and, furthermore, wholly basal levels were present from three to six hours after insulin in those experiments in which blood was not withdrawn before this period.

The failure to show any appreciable rise in plasma cortisol between three and seven hours after injecting insulin in those control experiments in which only three specimens of blood were withdrawn suggests that the probable explanation of the sustained moderate rise in three of the experiments in which blood was withdrawn throughout is the additional stress of repeated venepuncture and loss of blood and is not a factor of insulin-induced hypoglycaemia.

The 'permissive' role of corticosteroids in gastric secretion has been fully established by studies on human subjects with Addison's disease before and after treatment with corticosteroids (Gray, Ramsay, and Thorn, 1956; Delamore et al., 1961) but an increase in plasma levels of 17-hydroxycorticosteroids has not been demonstrated in human subjects with peptic ulcer (Gray, 1958; Freeman, Wheeler, and Hoegemeier, 1956). The ability of corticosteroid to augment exocrine secretion from another alimentary gland has been reported in the case of the pancreas (Sircus, 1961), so that the capacity of corticosteroid to 'permit' and to augment exocrine secretions is not unique to the stomach. However, there does not exist any evidence to show that a high output of gastric secretion under normal conditions is a product of excessive endogenous production of corticosteroids or that the adrenal cortex plays a specific augmenting or initiating role as opposed to a basal 'permissive' role in gastric secretory responses to stimuli. The fact that the initial gastric secretory response to insulin hypoglycaemia coincides with an outpouring of endogenous cortisol does not indicate that the gastric secretion has been promoted by it as the phenomenon does not appear when the gastric mucosa has been denervated. This suggests that this initial response is mainly a product of direct vagal stimu-
lation of the parietal cell-bearing mucosa. The outpouring of cortisol in the response to the hypoglycaemia presumably plays some part in determining the size of the secretory response of the parietal cells to the activated vagus in the first post-insulin phase. In the absence of repeated blood letting, however, the cortisol level in the plasma is basal during the period of time in which the second phase of the post-insulin gastric secretory response appears. The second phase therefore is unlikely to be due to the stimulation of the adrenals by the action on the pituitary of hypoglycaemia.

3 The effect of bilateral adrenalectomy

It has been claimed that in monkeys (French et al., 1953) and man (Shay and Sun, 1954) the second or delayed phase of the gastric secretory response to insulin-induced hypoglycaemia is abolished by bilateral adrenalectomy.

In our studies in parts 1 and 2 on the biphasic nature of the gastric secretory response to hypoglycaemia in dogs we failed to demonstrate any relation between the delayed phase of gastric secretion and the level of endogenous cortisol in the plasma. It was therefore considered necessary to examine in dogs the effect of removal of the adrenal glands upon the biphasic phenomenon.

METHODS

Two dogs were equipped with Pavlov-type innervated gastric pouches and the gastric secretory response to insulin hypoglycaemia was determined in the manner reported in part I. After suitable control experiments had been carried out bilateral adrenalectomy was performed in one stage, using the technique described by Freud, Uyldert, and Waterman (1938). The dogs were subsequently maintained in good health by a daily intramuscular injection of 25 mg. cortisone acetate (Glaxo), and when they were fully recovered from the operation the effect of insulin hypoglycaemia upon the gastric secretion was again studied. In both dogs following the removal of the adrenals a much smaller dose of insulin was required to induce a satisfactory level of hypoglycaemia. After the conclusion of the experiments the animals were sacrificed and a careful search of the abdominal cavity failed to reveal any residual adrenal tissue in either.

RESULTS AND DISCUSSION

No change appeared in the phasic character of the gastric secretory responses to hypoglycaemia in either dog following the adrenalectomy (Fig. 1a and b). In both dogs there appeared an increase in the volume and acid content of the gastric juice secreted,

![Graph](https://example.com/graph.png)

**FIG. 1a.** The effect of bilateral adrenalectomy on the secretory response to insulin hypoglycaemia of an innervated gastric pouch in dog A. (Data are for the means of five experiments before and two after adrenalectomy for each half-hour period.)

Continuous line = total acid  
Broken line = volume