Gastric Secretion During Anaesthesia and its Inhibition by Metiamide and Other Drugs

The stimulation of a brisk gastric secretion by various anaesthetics, particularly by a mixture of chloralose and urethane, was first demonstrated in 1949[1]. It had previously been assumed that anaesthesia inhibited gastric secretion[2]. The surprizing secretion of acid gastric juice elicited by various anaesthetics could be demonstrated easily if dogs carrying metal gastric cannulae chronically were anaesthetized without the surgical trauma of inserting the cannula acutely. Although this secretion was arrested by atropine or by acute vagal nerve section, the similarity of the secretion to that elicited by histamine suggested that 'the fact that the chloralose-urethane secretion is largely dependent on the integrity of the vagi indirectly supports the possibility of the mediation of histamine in this (vagal) phase of gastric secretion'[1]. The recent discovery of histamine H_2-receptors in the gastric mucosa and of the drug burimamide[3], and the more effective metiamide[4], which antagonize the gastric secretory effect of histamine[3], suggested to us that we test whether metiamide blocks the histamine-like acid gastric secretion produced by chloralose-urethane anaesthesia. We found that metiamide was an effective inhibitor of this secretion; also, metiamide blocked the 'spontaneous' gastric secretion in conscious dogs.

Methods. Anaesthesia was induced in dogs carrying metal gastric cannulae inserted at least 2 weeks earlier. A mixture of chloralose and urethane containing 25 mg chloralose and 250 mg urethane ml^{-1} was used. A moderate depth of anaesthesia was attempted, and the approximate dose of mixture required was 2.0 ml kg^{-1} i.v. Animals were never fed in the experimental room, nor by the experimenter, in order to reduce or eliminate psychic or 'spontaneous' gastric secretion. The animal was suspended in a cloth hammock after anaesthesia and secretion was collected from the cannula. Experiments on conscious dogs were performed in a Pavlov frame.

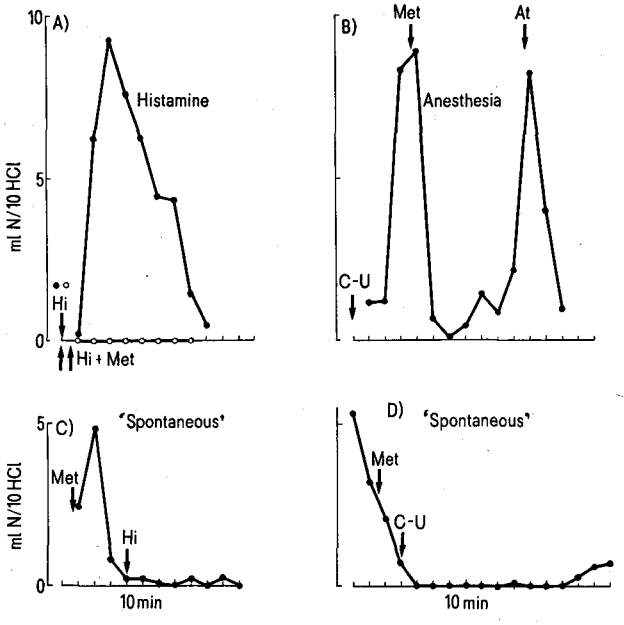
Metiamide was dissolved in HCl and the stock solution (100 m*M*) was adjusted to pH 6.0 with NaOH and kept at 4 °C for a maximum period of 1 month. Atropine was used as sulphate, mepyramine as maleate, and hexamethonium as bromide. Histamine was the diphosphate but its weight is expressed as the base.

Results. Effect of metiamide on histamine-induced and on 'spontaneous' secretion in conscious dogs: Metiamide (3.0 mg kg^{-1} i.v.) was given before or shortly after histamine (15–25 μg kg^{-1} s.c.) in 3 experiments on 2 dogs. The acid gastric secretion produced by this dose of histamine was always either abolished or reduced to near zero values by metiamide (Figure A and C). These results agree with recent similar experiments[4,5]. In 3 experiments on 2 dogs in which the animals were 'spontaneously' secreting despite an empty stomach, the administration of metiamide (3 mg kg^{-1} i.v.) also arrested this 'spontaneous' secretion, presumably of vagal origin, since it was also abolished by atropine (75 μg kg^{-1} i.v.).

Effect of metiamide on gastric secretion induced by chloralose-urethane anaesthesia: Metiamide (3.0 mg kg^{-1} i.v.) was administered either just before or during anaesthesia with chloralose-urethane mixture in 7 experiments on 5 dogs. The inhibition was similar to that observed with histamine-induced secretion in conscious dogs. The inhibitory effect was even more effective if metiamide was given just prior to induction of anaesthesia rather than if it was given during anaesthesia when secretion had begun (Figure B and D).

Effect of atropine and hexamethonium on acid gastric secretion induced by chloralose-urethane anaesthesia: Atropine (75 or 100 μg kg^{-1} i.v.) was administered to 2 dogs during anaesthesia. In each instance the secretion of acid was sharply reduced and then completely arrested for the observation periods of 30 and 40 min respectively, timed from the first measurement of the sharp reduction. In 2 other experiments, hexamethonium (3 mg kg^{-1} i.v.), like atropine, arrested secretion for observation periods of 30 and 60 min respectively. This effect of hexamethonium has also been reported by PUIL[6].

Discussion. The discovery of metiamide and of histamine H_2-receptors for gastric secretion has revived the old suggestion[7–10] that histamine is the final mediator of all stimuli for acid gastric secretion. The fact that metiamide effectively blocks diverse nervous and chemical ways of



The Figure shows the effects of various drugs on acid gastric secretion in 4 separate experiments (A, B, C, D) on a dog with a chronic gastric cannula. Secretion was produced by chloralose-urethane anaesthesia or by s.c. injection of histamine in the conscious animal (see text for details). Hi, histamine; Met, metiamide; C–U, chloralose-urethane anaesthesia; At, atropine. A) Acid gastric secretion after histamine ●—●, and after histamine plus metiamide ○—○. Metiamide abolished the response to histamine. B) Acid secretion due to chloralose-urethane, its inhibition by metiamide, and after recovery, by atropine. Gastric reaction was alkaline just prior to anaesthesia. C) Metiamide blocks 'spontaneous' and histamine-induced secretion. D) Metiamide blocks 'spontaneous' secretion in the conscious animal and also prevents secretion if given before chloralose-urethane anaesthesia.

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stimulating secretion in mammals[4,5,11,12] and that histamine is released from isolated gastric mucosa of the frog by both acetylcholine and pentagastrin[13] strengthens this theory. Our experiments which demonstrate that metiamide is a powerful inhibitor of the acid gastric secretion which accompanies chloralose-urethane anaesthesia appears to offer further support for this view, as is our observation that 'spontaneous' gastric secretion in conscious dogs is blocked by metiamide. Despite the above facts, there are observations which indicate that the question of whether histamine is the final common mediator must be left open as yet. For example, there are reports that the acid secretion evoked by cholinergic agents in the rat[3] or dog[3,14] appears to be more resistant to blockade by H_2-receptor antagonists than is the secretion produced by histamine or pentagastrin. The possibility, therefore, that several mediators act on distinct but overlapping receptor sites in the gastric mucosa cannot as yet be excluded. Perhaps there are other quite different explanations of these facts. What is clear, however, is that H_2-receptor antagonists, perhaps in combination with anti-cholinergic agents, offer a new and effective means for the suppression of acid gastric secretion of physiological or pathological origin.

Summary. The histamine H_2-receptor antagonist, metiamide, inhibits the acid gastric secretion produced by chloralose-urethane anaesthesia in dogs carrying gastric cannulae chronically. This secretion is also prevented by atropine and hexamethonium. 'Spontaneous' gastric secretion of vagal origin in conscious dogs is also blocked by metiamide.

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[15] Metiamide was kindly provided by Professor Jim Black, University College London, and by Dr. Hugh Sheppard, Smith, Kline and French Labs. Ltd. (Montreal).
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A New Glandular Organ in some Toxic Caterpillars

Previously undescribed exocrine glands associated with the tracheal system and producing a micellar lipoidal secretion are present in caterpillars of some families of Lepidoptera. The glands comprise a small number of large specialized cells lying midventrally in the third to sixth abdominal segments, slightly below and behind the ganglia of the ventral nerve cord. They are associated with and apparently derived from the nodes of the ventral transverse trachea. Tracheal nodes which are located segmentally on longitudinal trunks or medially on transverse commissures mark the anastomosis of adjacent tracheal rudiments. They have been recognized in larvae of both Diptera[1-3] and Lepidoptera[4] not only as points of anastomosis, but also as points of dehiscence that facilitate breakage and withdrawal of the tracheal lining at each ecdysis. In the larvae of most Lepidoptera the nodes occur as distinct dilations in which the tracheal intima is modified into a thin cuticle bearing inwardly directed spines. Usually the epithelium of the nodes is composed of cells that, although considerably larger than those of the adjacent unmodified tracheal epithelium, are not glandular. In larvae of some species however, the epithelium on nodes of 4 of the ventral transverse trachea is clearly modified into glandular organs. We have found such organs in caterpillars of 7 of the 20 families surveyed (Table). They are best developed in arctiids in which they occur as spheroidal clusters of very large cells.

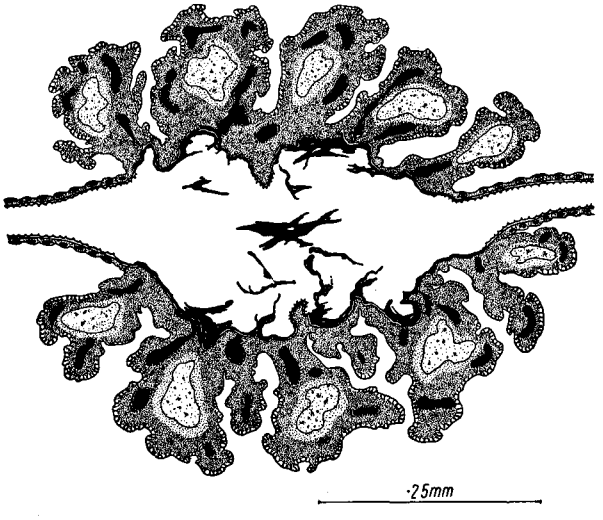

Fig. 1. Mid-ventral glandular tracheal node in 5th abdominal segment of *Pyrrharctia isabella* as it appears in section.

Histological and fine structural investigations of these glands in the banded woollybear caterpillar, *Pyrrharctia isabella* show the cells to be both highly specialized and unusual in structure (Figure 1). The prominent nuclei are large, irregularly shaped, and with sparse, evenly distributed chromatin. However, the most conspicuous feature of the cells are large, densely staining, cylindroid accumulations of secretory product. Ultrastructurally the secretion has a micellar structure with a lamellar periodicity of about 55 Å (Figure 3). It lies within an interconnected branching lacunar system that is lined with microvilli (Figure 2). The lacunar system opens at the apical end of the cell onto the tracheal lining of the gland. Although we have not found unequivocal evidence of channels or pores traversing the lining, the presence of material histochemically similar within the tracheal lumen indicates that it passes through the cuticular lining. The cytoplasm of the cells contains numerous mitochondria with dense

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