in the acid output to insulin. In these four experiments the reduction averaged 66\% (Fig. 7).

**COMMENT**

A gastric fistula provides a collecting system free of the uncertainties inherent in all pouch preparations whether partially innervated or not. The particular procedure employed here is closely related to that used in human studies and allows a very complete recovery of gastric juice. In this particular model SC 15396 has been shown to be a potent inhibitor of gastric juice stimulated by pentagastrin and insulin.

**SUMMARY**

SC 15396 in a single intravenous injection depresses the acid response to pentagastrin infusion but has a less marked effect on the response to histamine infusion.

Given orally it significantly inhibits the response to a subcutaneous injection of pentagastrin but not of histamine. It also significantly depresses the acid response to insulin.

Intragastric SC 15396 also depresses the acid secretion previously established by the infusion of pentagastrin.

**Part II  Inhibitory effect of SC 15396 on stimulated canine gastric secretion after surgical procedures**

I. B. MACLEOD AND R. A. HILL

**METHODS AND MATERIALS**

Eight dogs were used in the study, two of each of the following preparations being made: (a) gastric fistula, using a stainless steel cannula; (b) complete antrectomy with gastroduodenal anastomosis, a fistula being made from the residual stomach using a similar cannula to (a); (c) Heidenhain pouch (vagally denervated); and (d) Pavlov pouch (vagally innervated).

Gastric secretion was stimulated in the conscious animal by intravenous infusion of gastrin II, 0.5 μg/kg/hr; intravenous injection of soluble insulin, 0.15 U/kg, under cover of a constant infusion of KCl (0.5 m-equiv/kg/hr); and by intravenous infusion of histamine acid phosphate 2.0 mg/hr (= 90 to 115 μg/kg/hr).

SC 15396 was administered either intravenously or orally. For intravenous injection SC 15396 was dissolved in 1 ml of dimethylsulphoxide (DMSO) and 1 ml of saline. For oral administration SC 15396 was mixed in a pellet of bread, which the animal swallowed.

Pilot experiments indicated that 0.5 mg SC 15396 intravenously had no effect on gastrin-stimulated secretion, and that 5 mg had a variable effect. Therefore 50 mg was selected as the standard intravenous dose of SC 15396 to be employed in the main body of experiments. As dogs of different weights were used, this gave a dose range of 2.2 to 4.2 mg/kg body weight. For oral administration a higher dose range was used: standard doses of either 100 mg or 200 mg SC 15396 were given (4.4 to 12 mg/kg body weight). These higher doses were used for oral administration when it became apparent that 50 mg intravenously had little effect on histamine-stimulated secretion.

Acid output was determined on serial 15-minute samples by titration against N/10 NaOH. For the majority of estimations an endpoint of pH 7 was deter-
convey SC 15396 in the oral experiments) did not alter basal or stimulated secretion in the test animals.

**Effect on Gastrin-Stimulated Secretion** Intravenous injection of 50 mg SC 15396 produced prompt and highly significant inhibition of established secretion in gastric fistula dogs (p < 0.001 for 30-minute periods 15 to 45 minutes and 45 to 90 minutes after SC 15396) (Fig. 8). The effect of this dose (4 mg/kg) was maximal 30 to 45 minutes following injection, after which a gradual return towards control secretion occurred. Intravenous injection also inhibited established secretion from Heidenhain and Pavlov pouches. Figure 9 illustrates the effect of 2-2 mg/kg SC 15396 on secretion from a Heidenhain pouch.

When SC 15396 was administered intravenously 15 minutes before commencing an infusion of gastrin II, the appearance of secretion was markedly delayed (Fig. 8).

Orally administered SC 15396 also caused marked inhibition of gastrin-stimulated secretion in pouch dogs (Fig. 9). In both Heidenhain pouch and Pavlov pouch dogs 100 mg SC 15396 produced inhibition for two to three hours, with a return towards normal secretion after this time. Increasing the oral dose to 200 mg (9 to 12 mg/kg) prolonged the inhibitory period to at least three hours. In two experiments using the higher dose 90% inhibition continued for four hours but further study of the recovery period was not possible because of short supplies of gastrin II. The inhibition following oral administration appeared after a delay of 30 minutes, this time being presumably required for absorption, since the prompt appearance of inhibition following intravenous injection suggested that the drug was not significantly metabolized in the blood stream before exerting its effect.

Because of the difficulties inherent in studying the effect of oral administration of drugs in gastric fistula dogs during established secretion, pouch dogs only were used in this part of the experiment.

**Effect on Insulin-Stimulated Secretion** Insulin studies were conducted on two gastric fistula dogs. Three tests were carried out in each dog in which the total acid secretion (m-equiv/HCl) was collected for 150 minutes following intravenous injection of 0.15 U/kg soluble insulin. After these control experiments had been carried out, the tests were repeated, with 50 mg SC 15396 being injected intravenously at the same time as the insulin, but into a separate vein. In one dog, almost 90% inhibition of secretion in the two hours following insulin injection was achieved (range over three tests 77 to 93%) (Fig. 10). Individual variation between
animals occurred, as in the second dog (of similar weight) the inhibition achieved was only 50% (range over four tests 45 to 54%).

It was theoretically possible that the insulin was being directly inactivated in the blood stream by the SC 15396, and therefore the insulin tests were repeated with the SC 15396 being administered either 15 minutes before or 10 minutes after the insulin injection. The degree of inhibition achieved was of the same order as that produced when the two injections were given at the same time. Blood sugar levels were monitored during control tests and during tests in which SC 15396 was administered, and the degree of hypoglycaemia was the same in each situation (Table I).

Two dogs were subjected to antrectomy, with gastroduodenal anastomosis. The completeness of the antrectomy was confirmed by histological examination of the resected specimens. In both dogs, a small secretion could be produced by insulin stimulation. Intravenous SC 15396 produced marked inhibition of this secretion in one dog (Fig. 11), and complete abolition of secretion in the other.

EFFECT ON HISTAMINE-STIMULATED SECRETION Histamine-stimulated secretion proved more resistant

FIG. 10. Ninety per cent inhibition of insulin-stimulated secretion is achieved when 50 mg SC 15396 is given simultaneously with the insulin.

FIG. 11. After complete antrectomy, residual insulin-stimulated secretion is markedly inhibited by intravenous SC 15396.

Gastric Fistula Dog with Antrectomy.
Wt. 12.7Kg.
Effects of SC 15396 on gastric secretion

Heidenhain Pouch Dog
Wt. 22.7 Kg.

Gastrin II Infusion 0.5 μg/m/kg/hr

Mean of 3 Expts.
Nos. 23, 82, 91.

Histamine Infusion 90 μg/m/kg/hr

Mean of 5 Expts.
Nos. 19, 31, 39, 43, 46.

FIG. 12

FIG. 12. SC 15396, 50 mg, intravenously has little effect on maximal histamine-stimulated secretion, yet markedly inhibits gastrin-stimulated secretion in the same dog.

FIG. 13. When the dose of SC 15396 is increased to 200 mg, and given orally, histamine-stimulated secretion is markedly inhibited.

FIG. 14. Oral SC 15396 produces greater inhibition of histamine-stimulated secretion in the denervated pouch (p < 0.01).

Pavlov Pouch Dog
Wt. 19.8 Kg.

Histamine Infusion 2.0 mg/hr

Mean of 3 Expts.
Nos. 121, 125, 127.

FIG. 14

FIG. 13

Effects of SC 15396 on gastric secretion

Heidenhain Pouch Dog
Wt. 22.7 Kg.

Gastrin II Infusion 0.5 μg/m/kg/hr

Mean of 3 Expts.
Nos. 23, 82, 91.

Histamine Infusion 90 μg/m/kg/hr

Mean of 5 Expts.
Nos. 19, 31, 39, 43, 46.

FIG. 12

FIG. 12. SC 15396, 50 mg, intravenously has little effect on maximal histamine-stimulated secretion, yet markedly inhibits gastrin-stimulated secretion in the same dog.

FIG. 13. When the dose of SC 15396 is increased to 200 mg, and given orally, histamine-stimulated secretion is markedly inhibited.

FIG. 14. Oral SC 15396 produces greater inhibition of histamine-stimulated secretion in the denervated pouch (p < 0.01).
to inhibition by SC 15396 than secretion induced by either gastrin or insulin. Marked inhibition of gastrin-stimulated secretion was produced by intravenous injection of 2.2 mg/kg SC 15396, yet the same dose exerted no significant effect on maximal histamine-stimulated secretion (Fig. 12).

Inhibition of established secretion in pouch dogs could be achieved with large doses of SC 15396 (Figs. 13 and 14). These large doses were administered orally, as the risks of an acute toxic reaction were felt to be less by this route than if a similar dose were given by rapid intravenous injection. No toxic symptoms were observed in the four dogs (two with Heidenhain pouch and two with Pavlov pouch) used in this experiment. Because of the short delay in appearance of inhibition, the period from 0 to 30 minutes following administration of SC 15396 was omitted from consideration when calculating the degree of inhibition, and the secretion rate (m-equiv./HCl/15 min) in the two periods, (1) 30 to 90 minutes and (2) 90 to 150 minutes, following SC 15396 was compared with the secretion in the one-hour period before administering SC 15396. In both Heidenhain and Pavlov pouch dogs, the inhibition achieved in each of these two periods was highly significant (all $P$ values $< 0.001$).

The degree of inhibition achieved was greater in the Heidenhain pouch dogs than in the Pavlov pouch dogs (Fig. 14). The Pavlov pouches showed 45% inhibition in period 1 and 48% inhibition in period 2, while the Heidenhain pouches showed 70% inhibition in period 1 and 72% inhibition in period 2. The difference in degree of inhibition between the two types of preparation is significant ($P < 0.01$).

The duration of inhibition of histamine-stimulated secretion by these large oral doses of SC 15396 was very prolonged. In one experiment profound depression of secretion was still evident six hours after administration of SC 15396. Practical considerations prevented adequate follow-up of the recovery period, as by this time the dog had already been in the stand for eight hours. Tachyphylaxis to histamine did not account for the prolonged inhibition, as each dog had been shown to maintain secretion to histamine infusion for many hours. One experiment demonstrating prolonged secretion to histamine infusion is illustrated in Figure 15. In four experiments, 12.5 µg carbachol was given intravenously two hours after SC 15396. In three animals there was a prompt reversal of inhibition, with a return to normal (preinhibition) secretion levels.

Study of the effect of orally administered SC 15396 on gastric fistula dogs undergoing histamine stimulation had necessarily to be approached in a different manner. In five experiments 200 mg SC 15396 was

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**TABLE I**

<table>
<thead>
<tr>
<th>Blood Sugar Levels During Six Insulin Tests in Gastrointestinal Fistula Dog Illustrated in Figure 11</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time</strong></td>
</tr>
<tr>
<td>Before insulin</td>
</tr>
<tr>
<td>Half hr after insulin</td>
</tr>
<tr>
<td>One hr after insulin</td>
</tr>
<tr>
<td>One &amp; half hr after insulin</td>
</tr>
</tbody>
</table>

1The use of SC 15396 does not significantly affect the hypoglycaemia produced by insulin.

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**FIG. 15.** Prolonged plateau levels of gastric secretion were maintained by continuous histamine infusion. This chart shows a control experiment on the Heidenhain pouch dog illustrating the lower part of Figure 14.
Effect of SC 15396 on gastric secretion

Part III  The action in the rat

C. G. THOMSON AND W. SIRCUS

MATERIALS AND METHODS

A modification of the anaesthetized rat preparation described by Lai (1964) was used as the assay animal in this study. In this the animal (male, Wistar strain) is anaesthetized with urethane (1·25 g/kg intramuscularly) and is maintained at 34°C throughout the assay. After the oesophagus has been intubated, the stomach is exposed by a midline incision and the duodenum is cannulated. The stomach is washed free of debris with 0·9% NaCl and is then perfused at 1 ml/min with buffered saline, prewarmed to 34°C. The perfusate from the stomach is passed through a microflow pH electrode (EIL GMF 23) and the pH readings are recorded on a chart recorder linked to the meter. The perfusing buffer is phosphatecitrate-saline \( \left( 1.54 \times 10^{-3} \text{M} \right. \) NaHPO\(_4\) \( \left. 2.3 \times 10^{-4} \text{M} \right) \) citric acid: \( 1.54 \times 10^{-1} \text{M} \) NaCl, \( I = 0.160, \text{pH 6·6} \) which permits an approximately linear pH response to unit additions of acid over the pH range 6·5 to 3·5, so circumventing the problem of the logarithmic aspect of pH recordings inherent in techniques using pH monitoring of isotonic saline perfusions (see Ghosh and Schild, 1958; Amure and Ginsburg, 1964).

Solutions to be assayed are infused into the external jugular vein, which is maintained patent throughout the day's experiment with a constant slow infusion of 0·9% NaCl. Figure 17 shows a tracing typical of the response obtained to the infusion of gastrin II (Gregory and Tracy, 1964); pH begins to fall from the baseline during the infusion of the test material, and does not return to the original value until some time after the test infusion has been replaced with saline. Since the change in pH is related linearly to the concentration of acid secreted, it is valid to accept the area under the curve (shown in

![Histamine Infusion Graph](https://via.placeholder.com/150)

**FIG. 16.** SC 15396, 200 mg, given intravenously causes marked inhibition of histamine-stimulated secretion in a gastric fistula dog. A similar dose administered orally did not significantly affect secretion (see text).

SC 15396 has been shown to exert an inhibitory effect on canine gastric secretion stimulated by gastrin, insulin, and histamine.

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The authors wish to express their gratitude to Mr M. G. B. Walker for his skilled technical assistance.