An analysis of the autonomic control of gastrointestinal motility in the cat

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EDITORIAL COMMENT These observations in the cat show that the stomach has a high level of extrinsic, and a low level of intrinsic, cholinergic control, but this is reversed in the small intestine. Similar studies are clearly needed in man to provide us with logical tests for the management of motility disorders.

Ileus, or loss of gastrointestinal activity, may still be a mortal complication of abdominal surgery. In this condition the inherent myogenic contractility of the gut has often been demonstrated to be unimpaired and it retains its responsiveness to electrical stimulation (Wangensteen, 1955). The basic disturbance of motility in ileus remains to be identified, but there is a large body of evidence suggesting that it is, at least in part, the result of a reflex phenomenon mediated through the sympathetic nervous system. Goltz, working with frogs in 1872, noticed that when the spinal cord was destroyed or the nerves of the digestive tract were cut, the digestive tract became unusually active, as if inhibition had been removed. Bayliss and Starling in their classical work in 1899 demonstrated that ileus in dogs could be relieved by division of the splanchic nerves and Cannon and Murphy in 1906 showed that the duration of ileus depended to some extent on the amount of handling the gut underwent. At about the same time, Meltzer and Auer (1907) found that following destruction of the spinal cord in the rabbit, laparotomy did not cause intestinal inhibition and in 1922 Wagner introduced spinal anaesthesia in the treatment of ileus in man. Numerous workers in this field have since confirmed that both spinal anaesthesia and division of the splanchnic nerves can each reduce or abolish ileus (Olivecrona, 1927; Ochsner, Gage, and Cutting, 1928; Finkelman, 1930; McSwiney, 1931; Sealy and Witcher, 1936; Burstein, 1939; Douglas and Mann, 1941).

The plain muscle of the alimentary tract of man and animals has inherent tone and exhibits spontaneous rhythmic activity independent of an intrinsic or extrinsic nerve supply (Evans and Schild, 1953). The intrinsic nervous plexuses are necessary for coordinated activity (Bülbbring, 1958) but peristalsis can occur in the absence of the extrinsic nerve supply. The extrinsic nerves seem to exert their influence on motility by modifying, by excitation or inhibition, the intestinal activity induced by the local mechanisms mentioned above (Kewenter, 1965).

The sympathetic and parasympathetic nervous systems, which comprise the extrinsic nerve supply to the alimentary tract, may be viewed as physiological antagonists (Koelle, 1965a). If one system inhibits a certain function, the other normally augments it. Most viscera are innervated by both divisions of the autonomic nervous system, and the level of activity at any one moment is the net result of the two component influences. The action of one system is brought into relief by pharmacological stimulation of its end-organs or by surgical removal or drug-induced paralysis of the opposing system. The parasympathetic nervous system has but one type of pharmacological receptor end-organ, but Ahlquist in 1948 showed that there were two types present in the sympathetic nervous system and these he termed α and β. Shortly afterwards he and Levy (Ahlquist and Levy, 1959) showed that these receptors were both present in the dog ileum and that they both subserved inhibition. Furchgott later confirmed this in rabbits (Furchgott, 1960). In general the cells of a sympathetically innervated organ have a preponderance of receptors of one type, although a small proportion of the other type may be present (Innes and Nickerson, 1965a).

With the concept of the physiological antagonism between the sympathetic and parasympathetic nervous systems in mind, an analysis of the autonomic control of alimentary motility in the intact cat has
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been attempted using drugs which are either believed to be the naturally occurring neurohumoral transmitting agents or have a known effect on the autonomic nervous system. The recent introduction of the specific β-adrenergic blocking agents, in addition to the already available α-adrenergic blocking drugs, has made it possible to determine which adrenergic receptor predominates in the various portions of the alimentary tract. The use of a preparation, to be described later, requiring surgical manipulation to set up, usually resulted in loss of gastrointestinal activity. However, the preparation was reactive to stimulatory and inhibitory drugs and permitted the effects of these to be observed on the various parts of the alimentary tract. The effects of α-adrenergic and β-adrenergic blocking drugs on the return of gastrointestinal activity could also be studied.

The effective distribution of the parasympathetic nervous system has also been investigated by drugs which interfere with the destruction of the natural transmitter and by nerve section experiments.

METHOD

All the experiments were acute and were performed on adult cats. Anaesthesia was induced with ether and, when a venous catheter had been inserted, was maintained by chloralose-urethane intravenously (Catchpole, 1962). The trachea was then cannulated and the animal placed on a warmed table; additional heat was supplied as necessary by radiant lamp.

The anterior abdominal wall was excised and replaced by a transparent nylon film held in place with a running suture. This provided an abdominal window through which the stomach and most of the small and large intestine could be observed (Smith, Jepson, and Catchpole, 1965). During the insertion of this window a latex balloon of 30-40 ml capacity was introduced into the stomach via the oesophagus and filled to a flaccid state with warm water. A polythene tube was inserted into the colon through the anus and another polythene tube was introduced under the window edge into a loop of ileum through a needle puncture in its anti-mesenteric border. These tubes had open ends with adjacent side holes and a very slow continuous flow of Ringer-lactate solution was passed through them. A further polythene tube was inserted into a femoral artery and filled with heparinized saline. These cannulae were then connected via strain-gauge pressure transducers to a multichannel recording machine. Body core temperature was recorded by a rectal thermometer and serum electrolytes were determined in random animals. The motility recordings were supplemented by visual observations as it was not uncommon, especially in the small bowel, for motility to be present in a loop of intestine other than that from which recordings were being taken. A schematic representation of the experimental arrangement is shown in Figure 1.

The drugs to be used were appropriately diluted with normal saline and infused intravenously by means of a variable speed pump. Drugs with a cumulative action were infused at a slow constant rate while those which are destroyed rapidly were infused at increasing rates (Younams, Aumann, and Haney, 1939) and were given until a definite change in activity had occurred in the stomach, small intestine, and colon. Care was taken that the phasic activity of the gut did not influence this observation. The point at which an increase or decrease in motility occurred was determined both by visual observation and by examination of the recordings for an increase in total activity, having regard to amplitude and duration of the activity. The end-point for stimulating drugs was taken as the initiation of activity in inactive gut or, when activity was already present, as the increase in total activity. For inhibitory drugs, the end-point was taken as the cessation of activity.

PROCEDURE

DRUGS In this study the following drugs were used:

Neostigmine methylsulphate Although this reversible anticholinesterase agent acts mainly at the post-ganglionic nerve effector cell junction, it also has a direct stimulating action on sympathetic ganglia (Long and Eckstein, 1961; Mason, 1962) which must be taken into account when interpreting the results. The drug was infused very slowly in a solution of 0·025 mg./ml of normal saline. The blood pressure was well maintained in the majority of animals with the dosages used and the results were disregarded in the few cats which became hypotensive.

Physostigmine sulphate This is also a reversible anticholinesterase agent and has been shown to be devoid of any direct action on sympathetic ganglia (Kostowski and Gumutka, 1966). It was infused slowly on a 0·1 mg./
ml. solution and there was very little effect on the blood pressure with the dosages used.

Noradrenaline (noradrenaline acid tartrate) Noradrenaline acts predominantly on α-adrenergic receptors and has little action on β-receptors except in the heart (Innes and Nickerson 1965a). A solution of 0·1 mg./ml. was infused intravenously in step-wise increments until all motility had been ablated. A moderate rise in both systolic and diastolic blood pressures usually occurred.

Isoprenaline sulphate Isoprenaline has a powerful action on β-adrenergic receptors and almost no action on α-receptors (Innes and Nickerson 1965a). A solution of 0·25 mg./ml. in normal saline was used in the same manner as described for noradrenaline. At high rates of injection, a fall in blood pressure occurred but motility had invariably been inhibited before this point was reached. Following cessation of injection of the drug, a period of hypermotility occurred lasting approximately three to five minutes.

Phenoxymenzamine (Dibenzyline) This drug produces a prolonged blockade of α-adrenergic receptors that is effective against very strong stimuli. Responses to circulating catecholamines are inhibited more effectively than those to mediator released locally at nerve endings. β-Receptor activity is unaffected (Nickerson, 1965). As the onset of blockade is slow, the drug was given as soon as the cat had been anaesthetized and the experiment commenced more than one hour later. A dose of 2 mg./kg. body weight was used and the experiment was not begun until miosis was present. A marked fall in blood pressure occurs with this drug and results obtained in animals with a systolic pressure of less than 100 mm. Hg have been disregarded.

Propranolol This specific β-adrenergic blocking agent was introduced by Black, Crowther, Shanks, Smith, and Dornhorst in 1964. It has since been shown to be a potent β-receptor antagonist devoid of intrinsic sympathomimetic activity. A dose of 0·5 mg./kg. should produce about an 80% β-receptor blockade (Ledsome, Linden, and Norman, 1965) and this dosage was used in these experiments. The drug was infused slowly intravenously and caused some slowing of the heart and a slight fall in blood pressure.

Guaniethidine The pharmacology of this drug is complex. The most important reactions to the drug are due to sympathetic nerve blockade. Responses mediated by α and β-adrenergic receptors are suppressed equally (Nickerson, 1965).

A dose of between 2·5 and 5·0 mg./kg. body weight was injected slowly intravenously; an initial release of catecholamines from tissue sources resulted in a transient rise in the animal’s blood pressure followed by a gradual fall. No data from severely hypotensive animals have been used.

Atropine sulphate Atropine causes a competitive blockade at the post-ganglionic parasympathetic junction and has a marked effect on motility of the gastrointestinal tract blocking both the extrinsic nerves and the terminal neurones of the intramural plexuses. However, atropine-resistant tone and movements of the gut have been observed (Innes and Nickerson, 1965b). A dose of between 0·2 mg. and 0·5 mg./kg. body weight was used intravenously, a dose of 0·01 mg./kg. body weight is recommended for a 50% reduction of response to reference drugs in the chloralosed cat.

The actions of these drugs are summarized in Table I.

<table>
<thead>
<tr>
<th>DRUGS USED IN THESE EXPERIMENTS AND AN INDICATION OF THEIR ACTIONS</th>
<th>Sympathetic</th>
<th>Parasympathetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neostigmine</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>+++</td>
<td>(+)</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Phenoxymenzamine</td>
<td>Block</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>Block</td>
<td></td>
</tr>
<tr>
<td>Guaniethidine</td>
<td>Block</td>
<td></td>
</tr>
<tr>
<td>Atropine</td>
<td>Block</td>
<td></td>
</tr>
</tbody>
</table>

After the preparation had been allowed to stabilize for 15 to 20 minutes there was usually no visible or recordable activity in the stomach or small intestine, but not infrequently there was some mild activity present in the left colon, usually in the form of short runs of retrograde peristalsis. In the first group of experiments, neostigmine was infused intravenously in the hope that the order of the return of gastrointestinal motility would give an indication of the distribution of cholinergic activity. Neostigmine was chosen as it has been used extensively in motility studies (Schnohr, 1951; Liljedahl, Mattsson, and Pernow, 1958; Kewenter and Kock, 1960, Chaudhary and Truelove, 1961; Deller and Wangel, 1965, Painter, Truelove, Ardran, and Tuckey, 1965) and in the management of ileus (Harger and Wilkey, 1938; Levis and Axelman, 1936; Carmichael, Fraser, McKelvey, and Wilkie, 1934). In fact Koelle (1965b) states that it is the most satisfactory anticholinesterase agent for the treatment of ileus.

Once activity had been established with neostigmine, it was then ablated by the infusion in turn of noradrenaline and isoprenaline at steady increasing rates. The total amount of drug required to ablate activity in the different sections of the alimentary tract was noted. In the second and third group of cats, the same procedure was employed following α-adrenergic blockade and β-adrenergic blockade respectively. Because of the results obtained with neostigmine, which will be discussed later, the effect of physostigmine was tried in the fourth group of cats.

In the fifth and sixth groups of cats, the effects of β-adrenergic blockade and total sympathetic blockade were studied respectively and in the seventh group, vagotomy was performed and the effects of this on the reactions of the preparation to physostigmine determined.

RESULTS

As there was considerable variation in the general condition and reactivity of the cats used in these experiments, an analysis of the results using drug dosage to body weight gave such a wide scatter as to be statistically unsatisfactory. As the stomach was,
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**FIG. 2.** Histogram of the quantities of neostigmine, isoprenaline, and noradrenaline expressed in 'stomach units' (see text), necessary to affect motility in the stomach (S), small intestine (S.I.), and colon (C). The differences between the neostigmine requirements of the stomach and small intestine and between stomach and colon are significant at the 0.1 level, that between the small intestine and colon is significant at the 0.05 level. The difference between the isoprenaline requirements of the small intestine and colon is significant at the 0.05 level. There is no significant difference in the values obtained with noradrenaline. Data from 12 experiments.

**FIG. 3.** Comparison of the quantities of neostigmine, expressed in 'stomach units', necessary to stimulate motility in the stomach, small intestine, and colon before and after α-adrenergic blockade. There is no statistically significant difference between the neostigmine requirements of the stomach, small intestine and colon after α-adrenergic blockade. Data from experiments on six cats.

**FIG. 4.** Comparison of the quantities of neostigmine, expressed in 'stomach units', necessary to stimulate motility in the stomach, small intestine, and colon before and after β-adrenergic blockade. There is no statistically significant difference between the neostigmine requirements of the various parts of the gut after β-adrenergic blockade. Data from experiments on four cats.
in general, the portion of the digestive tract most constant in its reactions, the amount of drug necessary to stimulate or inhibit activity in the stomach was used as a reference dose. The quantities of the drug required to affect the other two parts of the gastrointestinal tract are given as a proportion of the gastric dose, the value for the stomach is therefore always unity. These ratios were analysed statistically and plotted in histogram form.

An analysis of the results was also made using both the small intestine and colon drug requirements as denominators; although there was some variation in degree the general trend of the ratios remained the same.

**OBSERVATIONS** Experiments involving 108 animals are available for study.

**Group 1** In this group of 12 cats, neostigmine was infused to stimulate alimentary activity and this was then ablated, first by noradrenaline and then by isoprenaline. The colon was most sensitive to neostigmine, the stomach less so, and the small intestine least sensitive (Fig. 2). The differences between the drug requirements of the stomach and small intestine, and the stomach and colon are significant at the 0.1 level, while that between the small intestine and colon is significant at the 0.05 level.

Under neostigmine stimulation there was no significant difference in the inhibitory effects of noradrenaline on the stomach, small intestine, and colon. The colon, however, was most sensitive to isoprenaline in these circumstances, the stomach less sensitive, and the small intestine least sensitive. Only the difference between the quantities of isoprenaline required to inhibit activity in the colon and small intestine is significant at the 0.05 level.

**Group 2** In these six cats α-adrenergic blockade was initially effected with phenoxybenzamine. This drug did not cause any change in alimentary motility but did affect the results of injected neostigmine, rendering the small intestine more sensitive and the colon more resistant to the drug relative to the stomach (Fig. 3). The differences between the neostigmine requirements of the stomach, small intestine, and colon after phenoxybenzamine are not significant.

**Group 3** In four cats the infusion of neostigmine after β-adrenergic blockade had been established with propranolol gave very similar results to that obtained with neostigmine alone (Fig. 4).

**Group 4** Because of the preferential action of neostigmine on the colon, the action of physostigmine was studied in seven cats and the results are

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**TABLE II**

**SUMMARY OF THE EFFECTS OF β-ADRENERGIC BLOCKADE WITH PROPRANOLOL ON GASTROINTESTINAL MOTILITY**

<table>
<thead>
<tr>
<th>No. of Experiments</th>
<th>Stomach</th>
<th>Small Intestine</th>
<th>Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial preparation</td>
<td>5</td>
<td>No effect</td>
<td>Slight increase in 2</td>
</tr>
<tr>
<td>In the presence of neostigmine</td>
<td>6</td>
<td>Slight increase in 1</td>
<td>Moderate increase in 3</td>
</tr>
<tr>
<td>Following α-adrenergic blockade</td>
<td>10</td>
<td>No effect</td>
<td>Slight increase in 2</td>
</tr>
<tr>
<td>In the presence of physostigmine</td>
<td>2</td>
<td>Slight increase in 1</td>
<td>Slight increase in 2</td>
</tr>
<tr>
<td>Following atropine</td>
<td>4</td>
<td>No effect</td>
<td>No effect</td>
</tr>
</tbody>
</table>

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*Fig 5. Histogram of the quantities of physostigmine, expressed in 'stomach units', necessary to stimulate motility in the stomach, small intestine, and colon. The differences between the physostigmine requirements of the stomach and colon and between the small intestine and colon are significant at the 0.05 level, that between the stomach and small intestine is not significant. Data from experiments on seven cats.*
shown in Figure 5. The small intestine was most sensitive to physostigmine and the colon least sensitive. The differences in the physostigmine requirements between the stomach and colon and the small intestine and colon are statistically significant. But that between the stomach and small intestine is not significant.

**Group 5** The effects of \(\beta\)-adrenergic blockade on gastrointestinal motility under various conditions were studied in 27 cats and the results are summarized in Table II. It appears from these results that in the initial preparation and after various drugs, notably phenoxybenzamine and atropine, the infusion of propranolol produces an almost consistent increase in colonic activity, but has less effect on the small intestine and virtually no effect on the stomach (Fig. 6).

**Group 6** In 24 cats the effects of sympathetic blockade with guanethidine were studied and the results are summarized in Table III. The most con-

### Table III

**Summary of the Effects of Non-Specific Sympathetic Blockade with Guanethidine on Gastrointestinal Motility**

<table>
<thead>
<tr>
<th></th>
<th>Stomach</th>
<th>Small Intestine</th>
<th>Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Experiments</td>
<td>Slight increase in 3</td>
<td>Marked increase in 5</td>
<td>Marked increase in 1</td>
</tr>
<tr>
<td>Initial preparation</td>
<td>No effect in remainder</td>
<td>Slight increase in 3</td>
<td>Slight increase in 5</td>
</tr>
<tr>
<td>Following  (\beta)-adrenergic blockade</td>
<td>Slight increase in 5</td>
<td>Marked increase in 5</td>
<td>No effect in 5</td>
</tr>
<tr>
<td>Following  (\alpha)- &amp; (\beta)-adrenergic blockade</td>
<td>No effect in 1</td>
<td>Slight increase in 1</td>
<td>Slight increase in 4</td>
</tr>
<tr>
<td>In the presence of neostigmine</td>
<td>Slight increase in 2</td>
<td>Marked increase in 2</td>
<td>Marked increase in 2</td>
</tr>
<tr>
<td>In the presence of atropine</td>
<td>No increase in 1</td>
<td>Slight increase in 1</td>
<td>Slight increase in 2</td>
</tr>
</tbody>
</table>

**Fig. 6.** The effect of \(\beta\)-adrenergic blockade on gastrointestinal motility. A slow, continuous infusion of propranolol was begun at the marker. The main response is in the colon. Time signal in minutes.
FIG. 7. The effect of non-specific sympathetic blockade with guanethidine on gastrointestinal motility. A slow, continuous infusion of the drug was begun at the marker. The main response is in the small intestine. Time signal in minutes.

FIG. 8. The effect of non-specific sympathetic blockade on gastrointestinal motility in a cat with previously established β-adrenergic blockade. A slow continuous infusion of guanethidine was begun at the marker and there is an obvious effect on the small intestine. Time signal in minutes.
consistent and marked effect is an increase in small intestinal activity (Fig. 7), even in the presence of β-adrenergic blockade (Fig. 8). There was some concomitant increase in colonic activity, especially in the presence of neostigmine which has a preferential action on the colon.

Group 7 In order to investigate the vagal influence on gastrointestinal motility, bilateral cervical vagotomy was carried out acutely and the effects of the infusion of physostigmine following this were studied in seven cats. As vagotomy had a considerable effect on the reactivity of the stomach to physostigmine, the results are correlated with those of group 4 in absolute amounts of drug dosage (Fig. 9). The vagotomized stomach was resistant to the action of physostigmine, the resistances of the small intestine and colon were increased, but they still remained fairly sensitive to the drug. As there was no correlation between the position of the colonic recording tube and the extent of the vagal innervation of the colon, it is difficult to interpret the colonic effect of vagotomy.

**DISCUSSION**

The rational treatment of disorders of gastrointestinal motility depends upon an understanding of the physiological mechanisms involved. The study reported here has sought to clarify these mechanisms.

The control of gastrointestinal activity is mediated through the autonomic nervous system and analysis of this system by pharmacological methods is to be preferred to an anatomical approach. Autonomic receptor end-organs are a pharmacological concept and autonomic nerves which were formerly thought to be purely cholinergic or adrenergic are now believed to contain a mixture of these fibres, although one type predominates (Youmans, 1952; Eliasson, 1952; Hillarp, 1960; Day and Rand 1961; Martinson, 1965). Thus nerve-section and nerve-stimulating experiments, for this reason alone, are unsatisfactory, but the functionally different fibres can be separated pharmacologically. Specific autonomic receptor-stimulating and blocking drugs are now available and characterization of receptors by pharmacological methods is feasible and rational provided certain precautions are taken (Moran, 1966). Blocking drugs in these experiments were used in the recommended dose range for laboratory animals, and the fact that the experimental results after these drugs differed considerably from those obtained before them suggests that a significant degree of blockade had in fact been achieved.

As a method of investigating the action of nervous outflows to the gut, nerve section is infinitely to be preferred to nerve stimulation. Simple section interrupts impulses normal in quantity and quality, while stimulation initiates nerve impulses probably abnormal in quantity and quality (Garry, 1934). For these reasons the vagal influence on the gut was investigated by nerve section methods.

Many workers in this field have used isolated segments of intestine *in vitro* with which to study the pharmacology of the gut, but ignorance of the details of normal intestinal activity is so great that from the practical and clinical points of view, investigation of the effects of drugs on intestinal motility would seem likely to be most profitable if carried out in preparations involving whole animals (Vaughan Williams, 1954).

A transparent abdominal nylon window is a useful method of observing the behaviour of the alimentary tract over several hours (Smith *et al.*, 1965). The merits and demerits of the various methods of recording gut motility have been thoroughly discussed previously (Quigley and Brody, 1950). Lorber and Shay (1954) have pointed out the advantages of using fine open-ended tubes compared with balloons, and these have been confirmed by Ritchie, Ardran, and Truelove (1962). However, we were unable to obtain satisfactory recordings from the stomach.
with open-ended tubes even though visible motility was present; this was presumably because changes in intraluminal pressures were minimal. Adequate recordings were obtained with a latex balloon, but it is possible that it may have stimulated some gastric activity (Eliasson, 1952). We have tried to avoid quantitating activity as far as possible as it does not seem reasonable to assess the activity, for example, in the whole of the small intestine from the recordings of the activity in one segment of the intestine. In the majority of experiments, the parameters were the presence or absence of activity, but on occasion a rough assessment of the degree of activity was necessary and this was made from both visual observations and recorded activity.

According to current concepts, the motor drive of the alimentary tract is controlled through the parasympathetic nervous system (Koelle, 1965a). This system can be considered as being composed of extrinsic parasympathetic nerves and intrinsic intramural plexuses. The detrimental effects of vagotomy on gastric motility have been known for many years though the effects on the small intestine are slight (Cannon, 1906). The stomach may thus be considered to have a high degree of extrinsic control and a low degree of intrinsic activity; the opposite state of affairs exists in the small intestine which readily exhibits spontaneous activity. Little evidence exists on the parasympathetic control of the large bowel, but Garry (1933) states that the motor influence exerted by the sacral outflow is not strong and there does not appear to be any parasympathetic ganglion cells in either the colonic circular muscle or the taenia coli (Bucknell and Whitney, 1964; Fishlock and Parks 1966). Our studies with physostigmine support the above findings; the results in the initial preparation imply a high degree of cholinergic activity in the small intestine, less in the stomach, and less still in the colon (Fig. 5). Bacz and Goffart (1941) obtained similar results by studying the acetylcholine content of the tissues of the alimentary canal of dogs. The acetylcholine values were moderately low in the stomach, high in small intestine and low in the colon. We have obtained different results with neostigmine and this discrepancy can be explained by the recent work showing that neostigmine has a direct action on sympathetic ganglia (Mason, 1962; Levy and Ahlquist, 1962; Takeshige and Volle, 1963). Vagotomy greatly increased the physostigmine requirement of the stomach while that for the small intestine and colon was only slightly increased (Fig. 9). This suggests that the stomach is more dependent on extrinsic vagal drive than is the small intestine and colon, and agrees with the clinical findings in post-vagotomy patients (Ross, Watson, and Kay, 1963; Rothnie, Harper, and Catchpole, 1963) and confirms previous experimental work already mentioned.

That the sympathetic nervous system mediates the inhibitory control of gastrointestinal activity has been known for many years (Cannon, 1906). Ahlquist introduced the concept of α and β-adrenergic receptors in 1948, but it was not until the recent introduction of the specific β-adrenergic blocking agents that it has been possible to make a satisfactory analysis of the receptors involved in the various sections of the alimentary tract. Consequently little work has been published on this subject, but it has been suggested from studies in vitro on guinea-pig ileum that the inhibitory action of catecholamines on the peristaltic reflex of the small intestine is on adrenergic receptors of the α-type (McDougal and West, 1954; Kosterlitz and Lees, 1964; Kosterlitz and Watt, 1965; Türker, Kiran, and Kaymakcalan, 1965). Blockade of the α-adrenergic receptors with phenoxybenzamine did not cause any significant alteration in gastrointestinal activity; this was considered to be probably due to the specific relaxant action of this drug on smooth muscle. The effects of α-adrenergic blockade on motility were therefore deduced from the result of non-specific sympathetic blockade following β-adrenergic blockade. It is thus more convenient to discuss the effects of β-blockade first. This was instituted by means of propranolol and the effects of this drug on motility, which are summarized in Table II, indicate that even in the presence of atropine there is considerable augmentation of colonic activity, a lesser effect on the small intestine and virtually no effect on the stomach. It would, therefore, seem likely that the colon has more β-adrenergic receptors than the rest of the alimentary tract.

Fishlock and Parks (1963), studying human colonic muscle in vitro, found that the inhibition produced by intramural ganglionic stimulation with nicotine did not occur in the presence of dichloroisoprenaline, a β-adrenergic blocker, and also that the inhibition produced by noradrenaline was sometimes blocked by dichloroisoprenaline. Bucknell and Whitney (1964), working with isolated human taenia coli, found that the inhibitory response to nicotine was removed by pronethalol, a β-adrenergic blocking drug, and this latter drug also abolished the relaxant response of the tissue to adrenaline, which has both an α and β action.

The infusion of the β-receptor stimulating drug isoprorenaline into the preparation activated by neostigmine showed that the colon was very sensitive and the stomach moderately sensitive to isoprorenaline; the small intestine, however, was resistant to the drug (Fig. 2). McDougal and West (1952) obtained similar results with isolated preparations of rabbit
intestine, finding that strips of small intestine were much more resistant to the inhibitory actions of isoprenaline than strips of colon. Kosterlitz and Watt (1965), using guinea-pig ileum, and Türker et al. (1965), using cat ileum, found them both to be resistant to the inhibitory action of isoprenaline. There is thus evidence, both from in vivo and in vitro studies, that sympathetic inhibition of colonic activity is mediated largely through \( \beta \)-receptors, whereas inhibition of the small intestine is not.

Guanethidine was selected to produce non-specific sympathetic blockade because it has shown promise in the management of ileus (Smith et al., 1965). This drug blocks sympathetic impulses to both \( \alpha \) and \( \beta \) receptors and its effect on gastrointestinal motility is summarized in Table III. It is apparent that both in the initial preparation and following \( \beta \)-adrenergic blockade, the main effect of guanethidine in augmenting intestinal activity is on the small intestine; there is a lesser effect on the colon and least effect on the stomach. This suggests that \( \alpha \)-receptors may predominate in the small intestine.

Noradrenaline, which predominantly stimulates \( \alpha \)-receptors, did not show a significant difference in its inhibitory actions on the various sections of the alimentary tract. McDougal and West (1954) obtained similar results from their studies in vitro but also found that the small intestine was much more sensitive to noradrenaline than to isoprenaline. As mentioned previously, other studies in vitro have suggested that inhibition of the peristaltic reflex of the small intestine is mediated through \( \alpha \)-receptors (Kosterlitz and Lees, 1964; Kosterlitz and Watt 1965; Türker et al., 1965) and our work in the whole animal supports this view.

The autonomic control of the colon merits further discussion. The cholinergic drive of the colon is so slight that we found a considerable degree of colonic activity occurring in the presence of atropine when the sympathetic nervous system was partially or wholly blocked. Garry as long ago as 1934 suggested that the dominant influence of the central nervous system on the large bowel was inhibitory and there is no pharmacological evidence for the presence of parasympathetic ganglion cells in the colonic wall (Bucknell and Whitney, 1964; Fishlock and Parks 1966). Alvarez (1948). experimenting on isolated segments of bowel from the duodenum to the colon, found that segments from the caudal end of the colon were the most sensitive to adrenaline and recent histofluorometric studies have shown that of all the intestinal tissues, the taenia coli is the richest in catecholamines (Hollands and Vanov, 1965). It seems that the autonomic control of the colon is largely mediated through the sympathetic nervous system and that the parasympathetic nervous system plays a minor role.

The results of this investigation therefore show that the stomach has a high level of extrinsic cholinergic control and a low level of intrinsic cholinergic control. Pharmacological analysis of the sympathetic control of gastric motility has proved difficult. The stomach is extremely susceptible to the effects of laparotomy (McSwiney, 1931) and neither \( \alpha \) nor \( \beta \) adrenergic blockade seems to have much effect upon it. It has emerged, however, that both \( \alpha \) and \( \beta \)-adrenergic receptors are present in the stomach wall though it is not possible to state for one type predominates. The relative sluggishness of the stomach, even in the presence of complete sympathetic blockade, and its dependence upon extrinsic cholinergic drive, might suggest that, under the conditions of the experiments, the vagal drive had been lifted to some extent.

The small intestine has a high level of intrinsic and a low level of extrinsic cholinergic drive. The sympathetic inhibitory influences are mediated largely through \( \alpha \)-receptors.

The colon appears to have a low degree of cholinergic control and sympathetic inhibition is mediated mainly through \( \beta \)-adrenergic receptors. These conclusions are summarized in Table IV.

<table>
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<tr>
<td>SUMMARY OF RESULTS</td>
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<tr>
<td>Motor</td>
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Our findings in the cat support the hypothesis that post-operative motility disorders are in part due to sympathetic inhibition of gastrointestinal activity. They also indicate the distribution of cholinergic activity and sympathetic receptor end-organs in the alimentary tract of the cat. If the findings in man prove to be similar, a logical approach to the management of motility disorders may have been provided.

SUMMARY

An investigation of the autonomic control of gastrointestinal motility in the cat is described. Evidence is produced to show that the stomach has a high level of extrinsic, and a low level of intrinsic cholinergic control; both \( \alpha \) and \( \beta \)-adrenergic receptors are present. The small intestine has a low level of extrinsic, and a
high level of intrinsic, cholinergic control; sympathetic inhibition is mediated largely through α-receptors. The colon has a low degree of cholinergic control and a sympathetic inhibition is mediated mainly through β-receptors.

Should the findings in man prove to be similar, a logical approach to the management of motility disorders may have been provided.

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REFERENCES


— (1965b). Drugs inhibiting the action of acetylcholine on structures innervated by postganglionic parasympathetic nerves. Ibid., pp. 521-531.


Nickerson, M. (1965). Drugs inhibiting adrenergic nerves and structures innervated by them. In The Pharmacological Basis of
An analysis of the autonomic control of gastrointestinal motility in the cat


Munksgaard, Copenhagen.


Schnorr, E. (1951). Treatment on intestinal paralysis in rabbits observed through an experimental abdominal wall window.