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ACTA PHYSIOLOGICA SCANDINAVICA
SUPPLEMENTUM 335

Extrinsic Nervous Control of Colonic Motility
and Blood Flow

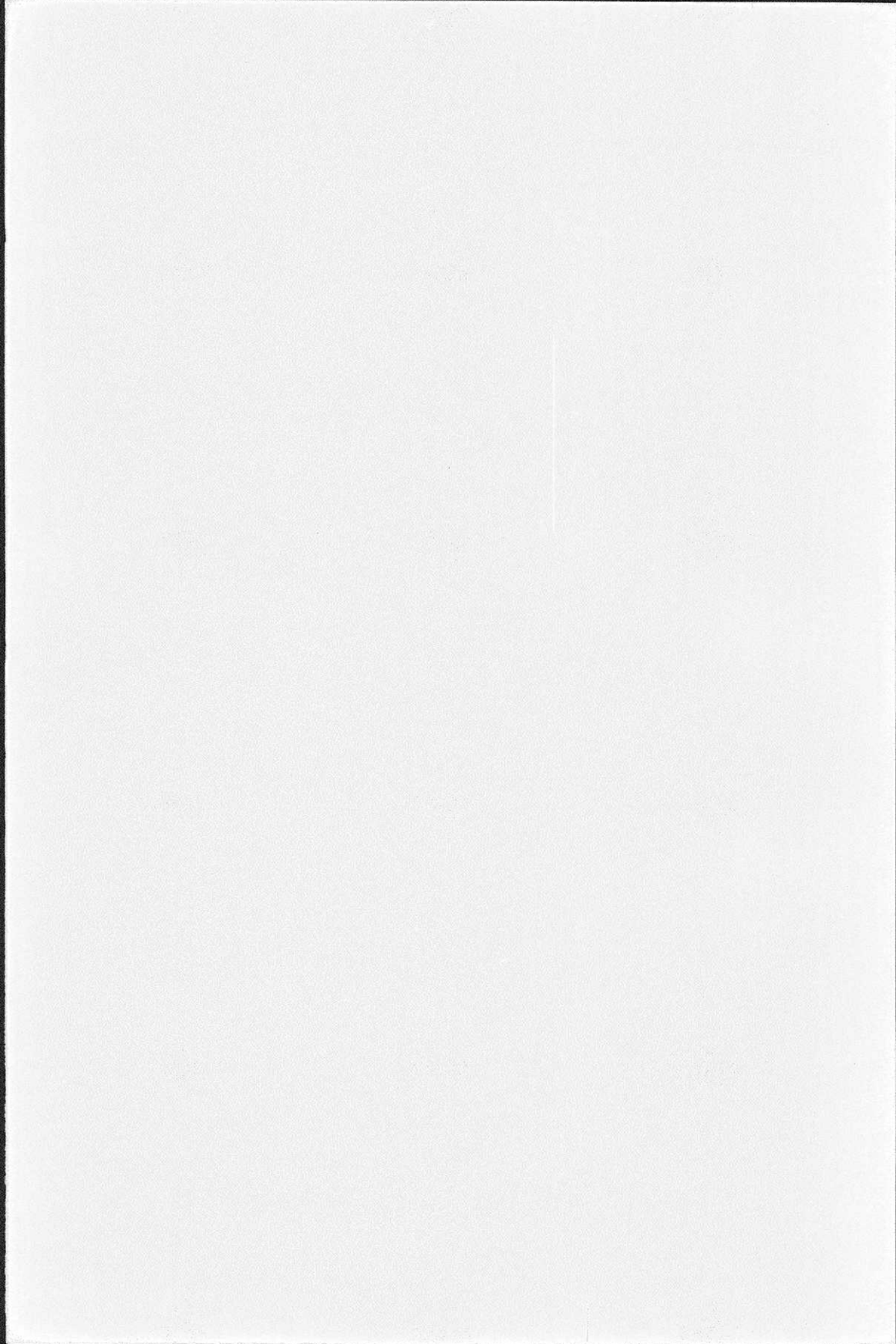
An experimental study in the cat

BY

LEIF HULTÉN

GÖTEBORG 1969

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Extrinsic Nervous Control of Colonic Motility and Blood Flow

An experimental study in the cat

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AND THE DEPARTMENT OF PHYSIOLOGY, UNIVERSITY OF GÖTEBORG,
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Extrinsic Nervous Control of Colonic Motility and Blood Flow

An experimental study in the cat

BY

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in collaboration with

M. Jodal and O. Lundgren

GÖTEBORG 1969

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GENERAL INTRODUCTION

In many respects the knowledge about the extrinsic nervous control of colonic motility and blood flow is incomplete. Around the turn of the century, gastrointestinal physiology attracted many investigators, and many studies were conducted not the least concerning the function of the large bowel and its nervous control. However, the apparent finality of the results obtained in animals seem to have discouraged further investigation, as relatively few experimental studies have been reported subsequently. In addition, the introduction of the opaque meal greatly stimulated clinical research in the field, and much of present knowledge concerning colonic function is therefore based on observations in man. However, the experimental conditions in such investigations are of necessity often too complex to allow any definite conclusions with respect to the detailed control of colonic function. Furthermore, only scant information is available, concerning the control of blood supply to the colon and its different wall compartments.

The aim of the present study therefore is to explore in cats the extrinsic nervous control of the colon, both with respect to motility and blood supply to the different wall compartments. As an introduction a survey will be given concerning present knowledge of the morphology and physiology of the colon, its blood supply and extrinsic nervous pathways.

I. MORPHOLOGICAL CONSIDERATIONS

A. Gross structure of the colon in different species

One may distinguish between two main types of large bowel, one being typical of carnivores and the other of herbivores with that of omnivorous animals falling in between (Garry 1934). In *herbivores* the proximal part, apparently designed for cellulose digestion, is large and sacculated and the longitudinal muscle coat is partially absent. The intermediate and distal parts are much narrower, have a uniform muscle coat and are devoid of sacculation. In *carnivores*, the large bowel is usually short with the outer longitudinal muscles constituting a more or less uniform coat with a vestigeal caecum so that the ileo-colic junction forms a nearly straight tube.

In the cat, used in this study, the colon approximates that of man in form and relative size. Thus, M'Fadden *et al.* (1935) described a fairly characteristic radiological picture of the resting colon of the cat, where two main flexures, one hepatic and one splenic, made it possible to distinguish a vestigial caecum, a short ascending colon, a transverse part and a descending part. The colon of the cat can, however, freely alter its position, often resulting in the disappearance of the mentioned flexures. Therefore, it is not fully justified to divide the colon of this animal into segments corresponding to those of human anatomy. Perhaps it is better to refer to a proximal and a distal segment and to regard the anal canal as that part encircled by the anal sphincters, a nomenclature which will be used throughout this study.

B. The organization of the colonic wall layers

As is the case with the small intestine, the wall of the colon consists of four layers; the mucosa, the submucosa, the muscular coat and the serosa.

The mucosa is covered by a single layer of tall, columnar, epithelial cells which include goblet cells, the source of mucus. In contrast to that of the small intestine, the colonic mucosa is devoid of villi, but its surface is punctuated by closely set epithelial crypts, forming the glands of Lieberkühn, which are also lined by abundant mucus-laden goblet cells. A thin muscularis mucosa separates the mucosa from the submucosa, which contains a rich network of blood and lymph vessels.

Whereas the mucosal organization is largely similar in different species, the muscular coat, comprising an outer longitudinal and an inner circular layer, differs somewhat. In the cat, the longitudinal muscle layer forms a continuous enveloping coat, while it is condensed into three separate taeniae in man.

As in other parts of the gastrointestinal tract, the intrinsic nervous system is built up by a submucous (Meissner) and an intermuscular (Auerbach) ganglion plexus. Variations in the general organization of the myenteric plexuses in different colonic parts have been described, with respect to the size of the meshes, the thickness of the fasciculi and the size, shape and cell content of the "ganglia" (for ref. see Schofield 1968). Auerbach's plexus is said to be better developed distally than proximally in the large bowel, and in man, where the longitudinal muscle coat is gathered mainly into the taeniae, neurons are more numerous adjacent to these. Concerning the submucous plexus, Müller (1921) found large numbers of neurons especially in distal colonic parts, whereas Bielschowsky and Schofield (1962), and Schofield (1962) reported that their number was reduced in these parts.

C. Vascular supply to the colon

The colonic vascular supply in the cat comes from two sources; proximally from the superior mesenteric artery and distally from the inferior mesenteric artery. These two arteries are interconnected by a long extramural arcade which extends distally along the dorsal wall and penetrates it tangentially. The intra-pelvic part of the colon, the

rectum and the anal canal are further supplied by small arterial branches from the internal iliac arteries. The veins generally follow the arteries but, except for minor collaterals at the anus, the colonic blood flow is finally drained via the superior mesenteric vein. There is no venous counterpart to the inferior mesenteric artery.

Thorough morphological investigations of the extra- and intramural colonic vessels have been performed by different techniques, both in animals and in humans. Brockis and Moffat (1958), using Neoprene latex in the human pelvic colon, described how the arteriae rectae after a subserous course pierce the muscle coat sequentially between the mesenteric and anti-mesenteric margins. These vessels give off small branches to the serosa and form an external plexus for the supply of the outer muscularis. More deeply, the arteriae rectae divide into submucosal branches which continue towards the anti-mesenteric border. Abundant anastomoses are formed with the arteriae rectae of the opposite colonic side. A primary and a secondary submucosal plexus is formed, the former one supplying inner muscularis parts and the latter one giving rise to numerous mucosal arteries, which take off at more or less right angles. After piercing the muscularis mucosae these arteries form a plexus from which the rich mucosal supply is derived. In general, the intramural veins accompany the arteries but the venous plexus in the submucosa is placed closer to the mucosa.

Thamm (1940) and Ross (1950) suggested the presence of specific arteriovenous anastomoses in the colonic submucosa. This was more recently investigated by Brockis and Moffat (1957). A few submucosal vessels were suggestive of true anastomoses, according to the latter investigators, but the majority of shunt-like vessels were undoubtedly distended capillaries. Boulter and Parks (1959), studying the submucosal vascular pattern in different gastrointestinal compartments of man, demonstrated arteriovenous communications with diameters around 30-35 microns in the stomach, while such shunt-like vessels were seldom seen in the small and large intestines. As an indication of their relative sparseness, 12/cm² were found in the gastric submucosa but only 2/cm² in the colon and rectum. Whether they are truly functional shunts, i.e. constituting a non-nutritional capillary bypass is not known so far (Wiedeman 1963).

D. Extrinsic nervous supply

The autonomic nervous pathways to the colon of cats and rabbits were studied in detail by Langley and Anderson (1895). Trumble (1933) emphasized the accuracy of this work, which was also fully confirmed in a similar study by M'Fadden *et al.* (1935). (For ref. see Alvarez, 1948.)

1. *The parasympathetic supply*

According to the mentioned investigators, parasympathetic fibres are conveyed mainly via *the sacral outflow*, forming *the pelvic nerves* (nn erigentes), which usually

arise from the second and third ventral sacral roots. The pelvic nerve ramifications to the colon have been traced in dogs and cats by Schmidt (1933). He demonstrated that after pelvic nerve section degeneration of nerve fibres throughout most of the colon occurred. Whether or not such fibres run to the most proximal colonic parts is not known for sure. In man, parasympathetic fibres have been traced from the pelvic plexus upwards along the hypogastric nerves as far as the origin of the inferior mesenteric artery; from here on the fibres may follow the branches of this artery (Telford and Stopford 1934). In similar studies, Mitchell (1935) and Lannon and Weller (1947) observed parasympathetic fibres passing upwards in the mesentery to the promontorial level, from where they obliquely crossed the branches of the inferior mesenteric artery. In dogs and cats, on the other hand, Wright *et al.* (1938), M'Fadden *et al.* (1935) and Mizeres (1955) presented strong evidence to indicate that the sacral parasympathetic fibres, rather than being distributed along the extramural vessels with the sympathetic nerves, enter the colonic wall in its pelvic part and from here on run intramurally in the proximal direction.

There are, however, reasons to believe that parasympathetic fibres to the colon are distributed in *the vagal nerves* as well, though few details are available. A junction in the parasympathetic innervation of the colon was actually first suggested by Cannon (1902). He observed in X-ray studies a ring of contraction dividing the cat colon into two portions, which according to Arendt (1945) was supposed to be caused by an overlap of a cranial and a sacral parasympathetic innervation in man. It would thus appear that the vagal influence in the human colon extends only to proximal parts of the transverse colon at most, a concept which is in agreement with the embryological development (Hunter 1928, Hollinshead 1962 and Schofield 1968). Thus, vagal fibres are supposed to reach proximal colonic parts intermingled with postganglionic sympathetic fibres along the arterial supply. However, convincing histological evidence concerning the extent of vagal fibre distribution to the large intestine seems to be lacking so far. For example, after subdiaphragmal vagal section in cats and dogs, Schmidt (1933) could trace degenerated nerve fibres in the ascending colon but not in its distal parts. Jayle and Cabanac (1932) and Wollard (1935), on the other hand, claim that vagal fibres also reach the distal parts of the colon. Mitchell (1935) and Lannon and Weller (1947) found it impossible to trace vagal fibres to more peripheral parts of the colon in dissections on man.

2. *The sympathetic supply*

Little is known whether splanchnic postganglionic fibres reach the colon along the superior vascular supply (Klee 1913). The main source of sympathetic fibres is therefore supposed to be derived from *the lumbar preganglionic outflow*, arising from the second, third, fourth and sometimes fifth ventral lumbar roots (Langley and Andersson 1895, Trumble 1933). All, or most of these preganglionic fibres pass without interruption through the sympathetic chains and run as four or five thin strands to

the inferior mesenteric ganglia, forming the "spinal rami of the inferior mesenteric ganglia". In addition, two or more bundles, arising from the coeliac or superior mesenteric ganglia, pass downwards, entering the inferior mesenteric ganglia as their "coeliac root".

The inferior mesenteric ganglia, usually four in number, lie close together, forming a ring around the inferior mesenteric artery not far from its aortic origin. From these ganglia the postganglionic *lumbar colonic nerves* arise, which accompany the inferior mesenteric artery to the colon. Furthermore, the paired hypogastric nerves, which are also derived from these ganglia run caudally to join the pelvic plexus and give off branches to the ureter, bladder, internal genital organs and to the sphincter muscles in the anal canal (Learmonth and Markowitz 1929, Trumble 1933).

The literature on the distribution of the extrinsic nervous supply to the large bowel is thus contradictory in several respects, especially concerning vagal and splanchnic nerve supply.

II. FUNCTIONAL CONSIDERATIONS

A. The motility pattern of the large bowel

According to earlier studies the acutely denervated colon in cats exhibits two types of "spontaneous" motility, rhythmic contractions travelling downwards, on which are superimposed, shortlasting contractions (Bayliss and Starling 1900). In unanaesthetized cats, Cannon (1902) found in X-ray examinations that antiperistalsis, occurring about every 15 minutes and lasting some 5 minutes, constituted a common type of motility in the proximal parts of the colon. The contents were then churned and mixed in a semi-closed sac as the ileocaecal valve prevented reflux. Similar observations were made on the proximal portion of the exteriorized colon in dogs by Barcroft and Steggerda (1932). The importance of colonic antiperistalsis was also emphasized by Elliot and Barclay-Smith (1904), and it was supposed to arise as a myogenic response to distension. These investigators also distinguished a coordinated peristaltic activity moving the contents downwards. This was found especially in middle colonic parts and was supposed to be due to intramural reflexes as a response to distension. The main activity of the distal colon, on the other hand, consisted of powerful contraction waves moving downwards and thus emptying the reservoir. This latter activity seemed to be largely dependent upon the central nervous system and conveyed by the pelvic nerves. It could be reflexly elicited by distension. According to Cannon (1902) and M'Fadden (1935) defaecation in cat was usually initiated by a powerful wave of constriction starting in middle colonic parts and pulling the shortened bowel towards the pelvis by the recto-coccygeal muscles. This motility pattern was associated with the characteristic defaecation posture, contraction of the diaphragm and abdominal muscles, and with relaxation of the anal sphincters.

Colonic motility is known to be affected by activity in more proximal gastrointestinal compartments, (Youmans 1949). Thus, food intake usually increases colonic activity within few minutes (Hertz and Newton 1913, Welch and Plant 1926, Barcroft *et al.* 1932) and initiates a mass peristaltic contraction that often leads to defaecation. The exact pathways of this gastro-colic "reflex" is unknown; Douglas and Mann (1939) observed that it was largely unaltered by vagotomy, suggesting that neither afferent nor efferent vagal fibres were needed. In fact, they suggested that the response might be mediated by a humoral mechanism. In experiments on dogs and humans, Logan (1967) and Connell and Logan (1967) presented evidence to show that gastrin may play a role in the mediation of the gastrocolic "reflex". (For ref. see Connell 1968.)

It has further been observed that topical stimulation of the lower brain stem, close to the vomiting centre, causes defaecation (Hatcher 1923, Koppányi 1930, Wang *et al.* 1940) and afferent vagal stimulation is claimed to elicit the same response (Lehman 1913), possibly by activating the bulbar defaecation centres. It is also well known that *stress and emotions* considerably affect colonic motility and presumably also colonic secretion and blood flow (e.g. Friedman and Snape 1946, Almy *et al.* 1949 and Grace *et al.* 1951). According to these studies, performed on humans, reduced colonic motility and mucosal pallor occurs in association with "overwhelming life situations provocative of abject fear and dejection", while situations "provocative of conflict with anger, resentment and anxiety" were associated with increased motor activity and mucosal flushing. The sight or smell of food brought about increased motor activity and reddening or engorgement of the mucosa.

B. Extrinsic nervous control of colonic motility

1. *The vagal supply*

It is still controversial as to what extent vagal fibres reach the colon and, certainly, as to what an extent they influence motility, blood flow and secretion. Thus, upon electrical stimulation of the vagal nerves in dogs and rabbits, Bayliss and Starling (1900), Elliot and Barclay-Smith (1904) and Klee (1912), were unable to detect any effects on colonic motility. Carlsson (1930) and Wells *et al.* (1942) came to the same conclusion in experiments on dogs, but the former investigator noted motor effects in proximal colonic parts in monkeys. Gray *et al.* (1955), recording motor responses from consecutive sections of the small and large intestines in dogs, observed that vagal stimulation regularly caused motor responses in the small intestine and usually delayed responses in proximal parts of the colon and sometimes even in the distal parts. However, in these studies the continuity of the intestinal tract appeared to have been left intact, implying that a vagally induced motility increase in the proximal intestinal parts might have been propagated to the colon along the intrinsic wall plexa.

The sympathetic neuro-hormonal influence appears not to have been taken into account in any of the above experiments. It is clear from studies by e.g. Celander (1959), Kock (1959) and Kewenter (1965) that sympathoadrenal influences may markedly affect intestinal motor responses induced by vagal stimulation, even to the extent that they can be completely suppressed. However, only in two recent studies of colonic motility (Fülgraff and Schmidt 1963 a, Stavney *et al.* 1963) one of these factors appears to have been considered, insofar as the splanchnic nerves had been cut. Vagal stimulation then produced excitatory responses in the proximal parts of the colon in dogs and cats and these responses were blocked by atropine.

2. *The pelvic nerve supply*

The distribution and functional significance of the sacral parasympathetic outflow to the colon (S II-S III; the pelvic nerves) is also to some extent debatable even though there is general agreement that these nerves constitute the main excitatory control of distal colonic parts. About two thirds of the medullated fibres in the pelvic nerves are efferent and fairly thin (M'Fadden *et al.* 1935), the remaining third being afferent and containing fibres up to 10 micron in diameter, also noted by Langley in his extensive study of the pelvic visceral innervation in cats, rabbits and dogs. These latter results, also based on experiments where weak tetanizing induction shocks were used and the motor responses were observed by naked eye, suggested that the pelvic nerves produce contraction of the descending colon and rectum. These responses were partly unaffected by atropine.

Bayliss and Starling (1900) reinvestigated the effect of pelvic nerve stimulation, recording colonic motility by means of balloons. They confirmed the results of Langley and Andersson (1895) and further claimed that all parts of the colon are simultaneously affected by pelvic nerve stimulation, although this effect appeared to be most pronounced in the distal parts. Preceding the contraction, they often noted transient inhibitory responses which were ascribed to a descending aboral inhibition analogous to the effects of vagal stimulation on the small intestine. Furthermore, they observed that upon continued stimulation the pelvic nerves appeared to be rapidly "fatigued".

Garry (1933), studying the nervous control of the caudal region of the large bowel in the cat, recorded a drastic fall in tone and some decrease in the rate of rhythmic activity after sectioning the pelvic nerves, indicating a considerable resting "tone" in these nerves. This finding could, however, not be confirmed by M'Fadden *et al.* (1935) in a radiological study on cats. With a balloon enterograph and electrical nerve stimulation, Wells *et al.* (1942) obtained results in dogs and monkeys suggesting that the pelvic nerve influence was limited to the distal colon only. Gray *et al.* (1955), on the other hand, concluded that the pelvic nerves affect the motility of the entire colon, confirming also Schmidt's dissection studies (1933). Their results thus suggest a considerable anatomical or functional overlap of the vagal and pelvic parasymp-

pathetics. Wells *et al.* (1942) concluded that the pelvic nerves to the colonic smooth muscles are cholinergic, although they were able to block the responses completely with atropine in only half of the experiments. They also noted that acetylcholine produced a greater circular but a lesser longitudinal response of the colon musculature than that produced by pelvic nerve stimulation and tried to explain this finding by "an unequal distribution of the pelvic nerve fibres to the two muscle layers". Garry and Gillespie (1955) showed in a study *in vitro* that the motility response to pelvic nerve stimulation could be abolished by atropine (see also Gillespie 1968), while Fülgraff and Schmidt (1964) concluded that the response was reduced in magnitude but not abolished by atropine. In another series of experiments, these investigators perfused the colonic vessels with Tyrode solution and under these circumstances the motor responses to pelvic nerve stimulation were easily abolished by atropine (Fülgraff and Schmidt 1963 b). After restoration of normal blood flow, the same atropine-resistant contractions were again observed. They assumed that the cause of the atropine-resistant contractions was a humoral factor dependent of the blood plasma, but they could not find any evidence for a bradykinin mechanism similar to that found in the salivary glands which here may explain the atropine-resistant vasodilatation (Hilton and Lewis 1955, 1956).

Motor responses in the colon, evoked reflexly by mechanical stimulation of the intestinal wall, have been studied in anaesthetized, decerebrated or decapitated cats by Garry (1933). This extensive investigation suggested that the lumbar sympathetic outflow to the colon is inhibitory in function, that both the afferent and efferent links in the colonic excitatory reflexes are contained in the pelvic nerves and that specific mechano-receptors are located in the mucosa or adjacent parts of the wall of the colon and rectum.

3. *The thoracic sympathetic supply*

The concept that splanchnic nerve fibres should be distributed to proximal parts of the colon seems to have little or no experimental support. The only functional studies dealing with this question were performed by Bayliss and Starling (1900), Klee (1913) and Arai (1922). However, they did not observe any effect on colonic motility when the splanchnic nerves were stimulated or cut.

The influence of these nerves on the motility of the small intestine is, however, well documented (see e.g. Kewenter 1965). In this study concerning the sympathetic and vagal control of the small intestine, it was concluded that distal parts of the small intestine are exposed to a more powerful inhibitory sympathetic control of a "tonic" nature than are the proximal parts. Furthermore, the sympathetic inhibitory fibres appear to exert their intramural effect mainly, or perhaps only, at the ganglionic level rather than directly on the intestinal smooth muscles. These functional results are in general agreement with the histochemical studies of Norberg (1964, 1965), which suggest that the great majority of adrenergic nerve terminals in the colonic

and gastric walls make contacts with the intramural ganglionic cells. However, no clearcut information is so far available concerning the effect of the splanchnic sympathetic outflow on colonic motility and blood supply.

4. *The lumbar sympathetic supply*

The lumbar sympathetic outflow, the postganglionic fibres of which are named the *lumbar colonic nerves*, are known to be mainly inhibitory in their action on colonic motility. This is indicated by the effects obtained when these nerves are blocked (Lehmann 1913, Learmonth and Markowitz 1930, Rankin and Learmonth 1930, Garry 1933) or when they are electrically stimulated (Langley *et al.* 1895, Bayliss and Starling 1900, Garry and Gillespie 1955, Wright *et al.* 1938, Fülgraff and Schmidt 1963 a).

Carlsson (1930) observed, on the other hand, that stimulation of these nerves could lead to powerful contractions if the colon was relatively atonic, while inhibition resulted if colonic tone was initially pronounced. Kuré *et al.* (1931) claimed that spinal parasympathetic motor fibres are conveyed to the intestinal tract in the dorsal roots, and these fibres should be cholinergic and run together with the sympathetic inhibitory fibres in the lumbar colonic nerves according to Semba (1956). In fact, in recent studies cholinergic fibres have been found to occur so frequently in sympathetic nerves that they may be considered as typical rather than exceptional. The detection of such fibres has been greatly facilitated by the use of reserpine or guanethidine, which effectively block adrenergic inhibitory fibres and hence unmask the presence of cholinergic fibres. Thus, Day and Rand (1961), Gillespie and Mackenna (1961) and Boyd *et al.* (1962), noted that stimulation of the sympathetic supply to the isolated colon in guanethidine- or reserpine-treated animals sometimes produced contraction instead of inhibition. The origin of these motor fibres could, however, not be determined, but the optimum frequency of stimulation was similar to that of the parasympathetic nerves. It has not been possible to differentiate between the two fibre sets by means of histological analyses. According to M'Fadden *et al.* (1935) the postganglionic lumbar colonic and hypogastric nerves contain a small proportion of medullated fibres with a diameter of 2-10 microns. However, these might as well represent "conventional" sympathetic preganglionic fibres which make their synaptic contacts more peripherally.

The hypogastric nerves take no obvious part in regulation of colonic motility, Learmonth (1931), Garry (1933), but seem to be mainly involved in the control of the anal sphincters, Bishop *et al.* (1956).

C. Extrinsic nervous control of colonic blood flow

1. *The vagal supply*

Besides their gastrointestinal motor control the vagus nerves were previously assumed to contain specific vasodilator fibres. However, Kewenter (1965) found no evidence of

such fibres to the vessels of the small intestine in the cat in accordance with earlier observations by Celander and Folkow (1951). Martinson (1965) observed that the high-threshold group of efferent vagal fibres produces mucosal vasodilatation concomitantly with gastric secretion and corpus-fundus relaxation. This mucosal vasodilatation could, however, as well be due to the increased production of metabolites in connection with the secretory response or of specific vasodilator agents, such as kinins or histamine. It is not known whether the colonic vessels are affected by the vagal nerves and, as mentioned above, considerable controversy still exists concerning the vagal influence on colonic motility.

2. *The pelvic nerve supply*

Langley *et al.* (1895) observed flushing of the mucosa in the distal colon upon stimulating the pelvic nerves. In an extensive investigation Wright *et al.* (1938) studied the effects of pelvic nerve stimulation on the mucosa of the distal colon exposed through a perspex window in decerebrated cats. Stimulation caused a longitudinal colonic contraction, a secretory response amounting to about 5 cc/hour and a mucosal vasodilatation. Afferent pelvic nerve stimulation produced reflex secretion, which remained after sectioning the spinal cord in the thoracolumbar region. Pilocarpine and acetylcholine after eserine produced similar effects which were blocked by atropine. Histological mucosal changes after pelvic nerve stimulation were characterized by increased vascularity around the crypts and a flattening of both goblet and chief cells with a widening of the crypts.

On the whole, knowledge concerning colonic blood flow and especially, its quantitative distribution to the different wall compartments is scant. The only studies which present quantitative figures of overall colonic blood flow are those of Geber (1960), Delaney and Custer (1965) and Bacaner (1966), while information concerning the capacity for autoregulation of colonic blood flow is presented by Hansson and Johnson (1967). Geber estimated the blood flow of the dog colon to be about $70 \text{ ml/min} \times 100 \text{ g}$ and Bacaner (1966) presented similar figures in man. Delaney and Custer, working on dogs, obtained a mean value of $82 \text{ ml/min} \times 100 \text{ g}$, employing the radio-rubidium distribution method. Nothing appears to be known of the normal range of colonic blood flow, from intense neurogenic vasoconstriction up to maximal functional hyperaemia.

3. *The sympathetic supply*

Langley and Andersson (1895) noted that stimulation of the lumbar colonic nerves produced blanching of the colon. This was later confirmed and extended by Drury *et al.* (1929), Barcroft and Florey (1929) and Wright *et al.* (1938). There appears to be no studies concerning the possible effects of stimulation of the splanchnic nerves on the colonic vessels. The vasoconstrictor fibre influence on the stomach and small intestine has, on the other hand, been studied (see e.g. Jansson *et al.* 1966, Wallentin

1966). It is well known that the vasoconstrictor fibres in the splanchnic nerves are tonically active, but the gastrointestinal vascular responses to vasoconstrictor fibre activity differ considerably from those in skeletal muscle or skin, insofar as e.g. the intestinal resistance vessels exhibit an "autoregulatory escape" from the vasoconstrictor fibre influence. At least partly, this "escape" phenomenon implies a redistribution of mucosal blood flow to submucosal layers (see Wallentin 1966).

III. SUMMARY OF EARLIER FINDINGS

Summarizing the results of earlier studies it may be concluded that—analogue to the situation in the small intestine—colonic motility is the result of myogenic activity as modulated and enhanced by the intrinsic ganglionic plexa which is, in turn, modulated in both directions by the different types of extrinsic autonomic fibres (Texter 1963 and Kewenter 1965). The considerable degree of autonomy possessed by the large bowel is evident from the fact that even complete decentralization causes only temporary disturbance in motility (Garry 1933). On the other hand, the most caudal parts of the large bowel, which are directly involved in defaecation, appears to be normally controlled by the central nervous system in a similar way as seems to be the case with the reservoir at the other end of the gastrointestinal tract, the stomach (e.g. Jansson 1969).

Opinions concerning the extrinsic nervous control vary considerably in several respects, e.g. concerning the extent and significance of the vagal control of proximal colonic parts, whereas most authors agree that the pelvic nerves affect almost the entire colon. It is therefore possible that proximal parts of the colon might have a double excitatory innervation. The significance of this seems obscure.

The lumbar sympathetic outflow exerts an inhibitory influence on colonic motility, mainly affecting the distal parts. However, this outflow also contains excitatory cholinergic fibres of unknown functional significance. There appears to be no experimental evidence of a thoracic sympathetic supply to the proximal colonic parts although this has sometimes been assumed.

Besides their excitatory influence on colonic motility, the pelvic nerves induce vasodilatation as well. The mechanism involved is however unknown, as is the extent of the response and its presence in the different wall layers. Whether the vagal colonic innervation also affects the colonic vessels is not known.

Vasoconstrictor fibres in the lumbar sympathetic outflow are, on the other hand, known to produce mucosal blanching, at least in distal colonic parts, but little is known about the vasoconstrictor fibre control in proximal parts or whether the splanchnic outflow is involved here.

IV. THE AIM OF THE PRESENT STUDY

The anatomical and functional arrangement of the extrinsic innervation of the large bowel and its influence on motility and especially on blood flow is thus in many re-

spects poorly understood, partly because earlier results are to a considerable extent controversial. The divergent opinions met in the literature may often be explained by different types of interferences between the various sets of parasympathetic and sympathetic nervous supplies. For example, a tonic activity in one of the fibre sets may suppress the impact of a nerve fibre blockade or of an electrical activation. This is especially true of certain nerve trunks which contain both excitatory and inhibitory fibres.

The aim of the present study is therefore to explore systematically and, when possible, with quantitative methods the functional organization of the reciprocal nervous control of colonic motility and blood flow, which may be unequally balanced in different parts of the colon. Therefore, the following aspects of this control were studied:

I. The extent to which the vagal and pelvic nerves influence motility and blood flow in various parts of the colon.

II. The arrangement of the sympathetic nerve supply and its influence on colonic motility and blood flow, as compared with that induced by the vagal and pelvic nerves.

III. The site of action of the nerve fibres producing colonic vasodilatation and vasoconstriction, both with respect to the different wall layers and the different consecutive vascular sections.

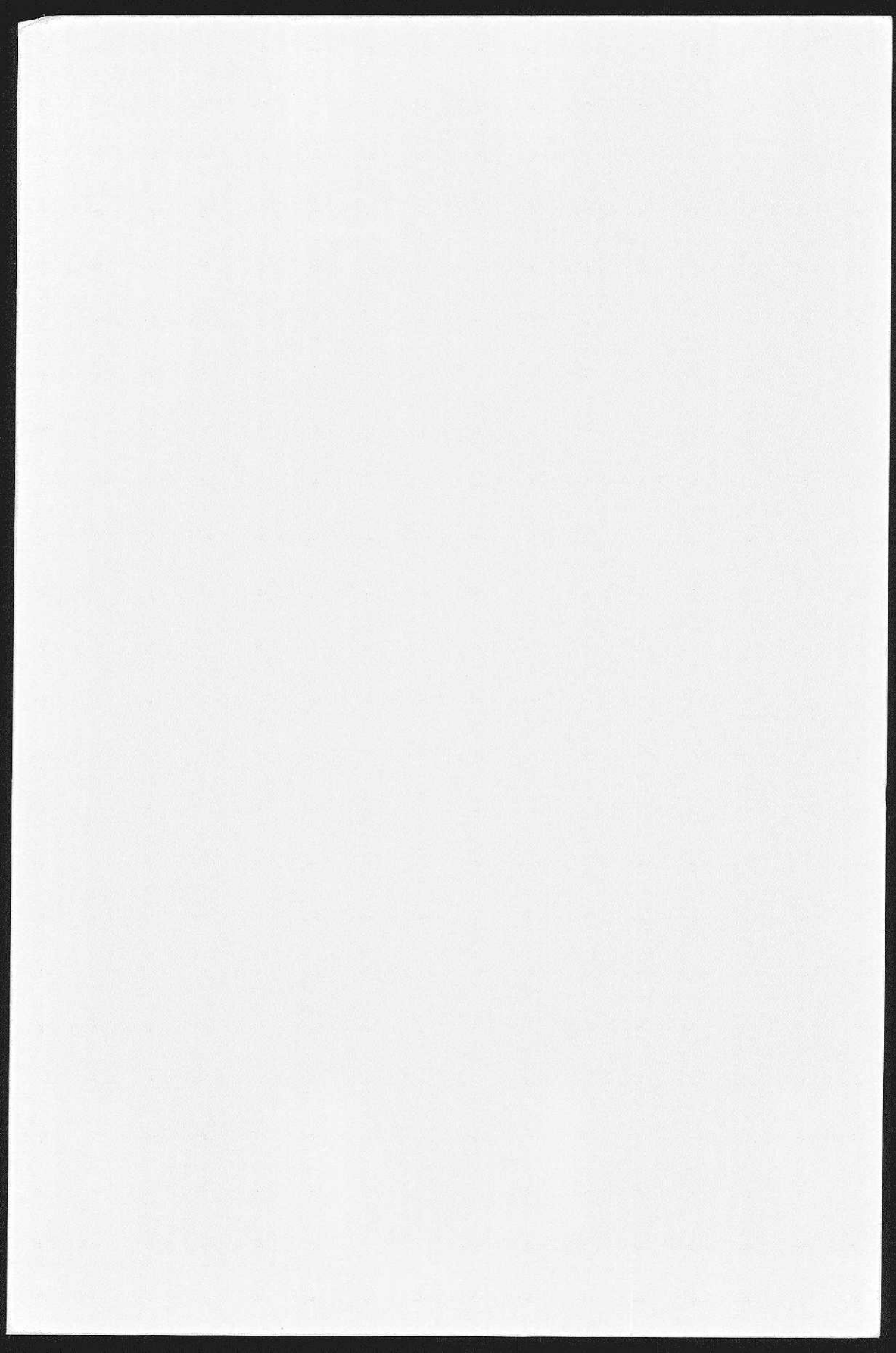
IV. The involvement of the various nerve fibre sets affecting colonic motility and vasodilatation in some of the main reflex patterns known to influence function of the large bowel.

It was thought possible that the results might shed further light on the classical concept that the large bowel—apart from its distal sphincteric section—is comprised by two main, functionally differentiated compartments. This opinion has so far been mainly based on theoretical and embryological grounds and on some observations of colonic behaviour in the intact organism. However, the organization of the involved control mechanisms that may establish such a differentiated function is still little understood in several important respects.

På grund av upphovsrättsliga skäl kan vissa ingående delarbeten ej publiceras här.
För en fullständig lista av ingående delarbeten, se avhandlingens början.

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GÖTEBORG
ELANDERS BOKTRYCKERI AKTIEBOLAG
1969