A STUDY OF INTESTINAL MOTILITY.

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(WITH COMMENTS ON POST-OPERATIVE PARALYTIC ILEUS).

Yves J. Guisan M.D.

Abstract of a thesis submitted to the Faculty of Graduate Studies and Research at McGill University in partial fulfillment of the requirements for the Degree of Master of Science.

The peristaltic reflex is regulated by complex nervous and hormonal mechanisms. It can be elicited in vitro by stimulation of the intestinal mucosa, but the functional relationships between the mucosa and the motor activity of the intestine are virtually unknown. Such a relationship is suggested by the frequent association of paralytic ileus with the stress ulcer syndrome. This problem was investigated in vivo in the awake dog. Elective stimulation of the mucosal periastaltic reflex was attempted by instillation of 0.1 N HCl into the intestine. Such a stimulation was followed by a reproducible motor response. This method was found more reliable than the simple recording of spontaneous intestinal motility since the stimulus can be standardized and the response quantitated. The response to 0.1 N HCl was inhibited by an intraluminal perfusion of xylocaine 10^{-2} or by the intravenous injection of Nembutal. In one experiment the integrity of the intestinal mucosa was disrupted by a period of acute arterial ischemia. It resulted in an hyperexcitable state followed by a period of irregular recovery. On the contrary "sham" operated control animals developed an intestinal adynamia for 12 to 24 hours. No specific role of the mucosa in the regulation of intestinal motility or in the pathogenesis of paralytic ileus could be identified in this study.

Department of Surgery
(Division of Surgical Research)

July 1971

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Department of Surgery
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McGill University
Montreal, P.Q.

July 1971

TO MY WIFE BARBARA AND MY FATHER GILBERT GUISAN

...Ex rebus materialibus ascendere
possumus in aliqualem cognitionem
immaterialium rerum; non tamen in
perfectam...

Sancti Thomae Aquinatis
Summa Theologica, I,
Quaest. LXXXVIII, Art.II

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CHAPTER I. REVIEW OF THE LITERATURE.

1. HISTORICAL SUMMARY.

The intestinal obstruction syndrome was well known to very early writers. At autopsy pathologic alterations such as volvulus and strangulation were described. Hippocrates described these findings as being the local manifestation of a more generalised inflammation, hence the term "Ileus Inflammatorius" introduced centuries later by Galenus. Although the mechanical variety of the syndrome was well recognized, no obvious obstruction of the intestinal passage could be found in certain cases. It was not until the early XIX th century that peritonitis received some credit as a pathogenetic factor in ileus, when the view was held that the intestine was paralysed owing to edema and inflammation of the bowel wall.

The entity of post-operative paralytic ileus as such was first described by Olshausen in 1888 [1]. As he could not find any signs of peritonitis he related ileus to the operative procedure itself and particularly to manipulation and exposure of bowel loops to air outside the abdominal cavity, and he qualified the post-operative intestinal dysfunction as "Pseudo-Ileus". This concept was not generally accepted by the contemporary authorities such as Reichel [2] or Kocher [3], who thought that fibri-

nous micro-adhesions were responsible for the condition.

In 1899 Bayliss and Starling [4] reported their classical studies of the peristaltic reflex and the observation that it was markedly inhibited by stimulation of the splanchnic nerves, thus ending a long lasting controversy on the subject. These studies initiated the start of enthusiastic experimental work which gave birth to the theory of sympathetic reflex inhibition of the bowel movements following laparotomy and manipulation of intra- or retroperitoneal organs. Cannon and Murphy [5] demonstrated in 1906 that operation was followed by delay in gastric emptying and sluggishness of the intestine. In a further paper these same authors showed that crushing the testicles could also inhibit intestinal motility [6]. According to their experience they indicated that manipulation and handling of the bowel caused "much greater effect in the direction of post-operative inactivity than any other of the factors under control during operation". Further work by Hotz [7], Arai [8], Olivecrona [9] and others demonstrated beyond any doubt the presence of a splanchnic mediated reflex in peritonitis and following operative procedures. However these investigations also cast some doubt on the paralytic nature of the intestinal dysfunction. In 1929 Alvarez [10] wrote that post-operative ileus "is not paralytic", because the muscle is active and apparently in good working order. Observing dogs living and digesting without apparent dis-

turbance after removal of all the muscle from long segments of bowel, he postulated that neither the intestinal smooth muscle nor inhibition were the main factors but rather a reversal of the physiological aboral gradient of rhythmic contractions in the development of what he called "Flat Gradient Ileus".

The frequent occurrence of massive abdominal distention in post-operative ileus has led many investigators to question the nature of intestinal gases and the factors involved in their production. McIver [11] demonstrated the predominant role of air swallowing in initiating distention and a vicious circle common to all types of obstructions in which the intestinal circulation is compromised [12], secretion increased and absorption decreased thus causing further distention [13]. Youmans [14] showed also that distention of a segment of intestine reflexly inhibited the rest of the bowel. In 1932 Wangensteen demonstrated that this sequence of events could be obviated by the use of continuous suction, a practice which has since become routine in most institutions and has been responsible for a drastic decrease in the incidence of serious complications and in mortality following major surgery [15, 16]. But in a small percentage of cases this measure fails to bring around recovery and other factors appeared to be of importance. In 1937 Mecray [17] drew attention to the importance of hypoproteinemia which resulted in edema of the bowel wall. Development of interest in body fluid and electrolytes re-

sulted in an understanding of their role in paralytic ileus. Streeten [18] was able to produce paralytic ileus in dogs by rendering them deficient in potassium. At a time when vitamins were fashionable, the idea of a relative deficiency in panthothenic alcohol was raised as an explanation for the decrease in total tissue acetylcholine which had been previously observed. The therapeutic implication of this hypothesis has been followed by rather unconclusive results in clinical practice, and neither the administration of panthothenic alcohol, nor parasympathetic stimulation by the means of acetylcholine analogues or anticholinesterases have proved to be undisputably helpful.

In the thirties spinal anesthesia was used to suppress the sympathetic inhibitory reflex. The obvious drawbacks of this technique do not deserve further comment. More recently, using a similar theoretical approach, Catchpole reported some success with adrenergic blocking agents [19]. Obviously further evaluation is needed.

Recent electrophysiological studies of the intestine have suggested that intestinal contractile activity may be driven by a pacemaker situated in the duodenum. However attempts to pace the bowel with an electrical stimulator during the immediate post-operative period or as treatment for paralytic ileus have been unsuccessful so far [225, 226].

The experimental work performed in the most recent years

as well as human clinical observation with refined techniques have suggested that the gastro-intestinal tract does not behave homogeneously following surgical operation or trauma. The small intestine appears to remain rather active while the most atonic parts are the stomach and the colon. This behavior consecutive to laparotomy is distinguished by Catchpole from "True Paralytic Ileus" which according to him is characterised by complete inactivity of the entire GI tract [19]. Of major interest is the recent observation that paralytic ileus is associated with about 50% of the cases of shock which develop stress ulcers [33, 229]. This is suggestive of another possible pathogenetic mechanism which is the purpose of the following investigation.

2. THE CLINICAL FEATURES OF POST-OPERATIVE PARALYTIC ILEUS: ATTEMPT OF A DEFINITION.

Distention is recognised widely as the characteristic hallmark of paralytic ileus following operation or trauma [13, 20, 21]. Simultaneously the bowel sounds are absent or only feebly audible and there is no passage of flatus, although diarrhea has been occasionnaly recorded [22]. Vomiting is also a common accompaniment [23]. Gas pains and abdominal tenderness are sometimes present, but are not a conspicuous feature. Depending on the degree of meteorism, there may be considerable breathing difficulty, the respiration being shallow and rapid. The pulse is also accelerated. Urinary output is scant and in severe cases there is progressive dehydration leading to hypovolemic shock in the absence of intravenous therapy [13].

Radiologically the classical picture consists of diffuse meteorism of the entire intestine and eventually the appearance of fluid levels with the progression of the derangement [13, 24]. However Stiess [25] suggested a number of years ago that gas and fluid levels could be absent. More recent appraisal using contrast studies have shown that gas is normally transported in the small bowel during the uncomplicated post-operative period, but it accumulates in the caecum and colon [26].

The clinical picture outlined above has been until recen-

tly the major basis for a concept of paralytic ileus and its diagnosis. It was widely accepted that operations were followed by a period of "Physiological Ileus" whose duration and severity were proportional to the extent of the abdominal procedure [27, 28]. Thereby a state of intestinal paralysis was present during the early post-operative course. This postulate found some support in human studies when direct measurements of intestinal pressures could be recorded [20]. This view which seemed still solidly established in the sixties [29] has been somewhat shaken by the development of more refined techniques such as the radio-telemetric capsule. One major advantage of the method was the capability of estimating the gastro-intestinal motility in very sick patients. This development was of particular importance because post-operative paralytic ileus could now be defined in terms of clinical facts and not only on the basis of clinical impression.

The present concept is as follows. During the first 2 - 3 days following an abdominal operation the stomach and the colon show a marked decrease in activity. In particular gastric emptying is markedly delayed causing the accumulation of air and fluid. Nausea and eventually vomiting result. If the swallowed air accumulating in the stomach eventually finds its way through the pylorus, it is rapidly moved down to the colon where it accumulates again. This has been demonstrated radiolo-

gically [26]. Similarly studies with the radio-telemetric capsule have shown that the small intestinal motility is diminished only transiently and returns rapidly to normal, even following vagotomy [28, 30, 31]. There is some evidence to suggest that the return of normal small bowel motility is hastened by narcotic analgesics [32]. Consequently the clinical picture includes only very moderate distention. The bowel sounds are absent or rare because of the absence of content in the small bowel rather than deficiency in propulsive motility [26]. This situation is rarely the source of any therapeutic difficulty and readily responds to the usual measures of gastric aspiration and fluid and electrolytes maintenance.

Sometimes the state of "True Paralytic Ileus" supervenes. It is characterized by distention of the whole GI tract from the stomach to the colon including the small bowel. The bowel sounds are virtually absent. Radiologically air and fluid levels are present. Constipation is complete and no flatus is passed [19]. Other complications such as stress ulcers are frequently present [33]. The situation is of concern and the prognosis can be serious. The usual therapeutic methods are often unsuccessful.

In summary, post-operative paralytic ileus can be subdivided according to the degree of severity into two conditions, one benign and readily reversible, the other more severe and

appearing as a development of the early transient post-operative motility disturbance or incident to other complications. This distinction is of some importance in order to avoid the existing confusion based upon published opinion related to clinical impression.

This study is related to the full-blown condition.

3. A CLASSIFICATION OF PARALYTIC ILEUS.

Most of the classifications proposed in the literature are in fact an enumeration of the conditions often associated with paralytic ileus, i. e. the generally accepted clinical pattern described in the preceding paragraph. However very few analysis of the precise behavior of the GI tract associated with these various disorders are available. Classifications of paralytic ileus very often appear to bring under the same heading diseases which have really very little in common. Though logical and of great practical help, they remain artificial.

Berning and Lindenschmidt (1961), in their very extensive review, outlined the following classification [29] :

1. Paralysis of central origin:
   a) Metabolic disturbances (diabetic acidosis, acetonemic vomiting, infections, inanition, hepatic coma, salt depletion syndrome in cirrhosis of the liver).
   b) Organic cerebral diseases (tumor, infarction, meningitis).
   c) Cranio-cerebral trauma.

2. Paralysis of the peripheral nerves:
   a) Operations on the oesophagus.

b) Cervical and ribs fractures.

c) Thoracic and abdominal contusions.

d) Bronchial carcinoma and mediastinal tumors.

e) Pharmacological neuroplegia.

3. Disturbances of the neuromuscular junction:

a) Potassium deficit.

4. Reflex disturbances, peritoneal inflammation and rare diseases:

a) Paralytic ileus in acute gastroduodenitis, gastric and duodenal ulcer, carcinoma of the stomach.

b) Cholelithiasis and choledocholithiasis with and without pancreatic involvement.

c) Acute appendicitis with and without peritonitis.

d) Diseases of the kidneys and urinary tract, retroperitoneal inflammation and tumors.

e) Paralytic ileus after extra- and intra-abdominal operations.

f) Paralytic ileus of myxedema, porphyrias, lead intoxication, dystrophias.

In the above classification, there is no mention of the vascular causes of paralytic ileus. Reference to Ochsner and

Gage (1933) is made concerning this matter [27]:

5. Vascular disturbances:

a) Strangulation:

1° Intramural: distention following mechanical ileus.

2° Extramural: compression of the mesenteric vessels.

b) Mesenteric thrombosis.

4. THE INCIDENCE OF PARALYTIC ILEUS.

Table I.

THE INCIDENCE OF PARALYTIC ILEUS IN REPORTED SERIES OF MECHANICAL OBSTRUCTIONS.

Reference	Total number of cases	Number of paralytic ileus	Number of post-operative paralytic ileus
Wangensteen 1955 (13)	630	353	195 (32%)
Gudladt 1939 (34)	190	41	6 (3%)
Wachsmuth 1964 (35)	996	116	-
Mlczoch 1961 (36)	1269	51	-

Table II.

THE INCIDENCE OF POST-OPERATIVE ILEUS.

Reference	Total number of operations	Total number of post-operative obstructions mechanical and paralytic	Total number of post-operative paralytic ileus
Wangensteen 1955 (13)	unknown	288	195
Zaccarini 1955 (37)	unknown	72	14
McIver 1926 (11)	107		36 (29%)
Berning 1961 (29)	450		27 (6%)

Table III.

THE MORTALITY OF POST-OPERATIVE PARALYTIC ILEUS.

Reference	Total number of cases	Total mortality	Mortality due to paralytic ileus
Wachsmuth 1964 (35)	996 obstructions	189	39 (4%)
Weisschedel 1955 (38)	14631 appendectomies	271	160 (0.1%)
Mlczoch 1961 (36)	1269 obstructions	317	20 (0.2%)
Devine 1946 (21)	1000 post-mortems	-	10 (0.1%)

Comment:

The reported incidence of post-operative paralytic ileus varies between 3% and 32% according to the above compilation of the literature. These figures are most difficult to interpret because of reference to different types of populations. The mortality figures appear strikingly low. It is worth mentioning that most authors do not quote their diagnostic criterias. Observations are recorded in pure descriptive terms. The shortcomings of pure clinical considerations have been mentioned previously. As a result what little data is available is difficult if not impossible to analyse.

5. ANATOMICAL CONSIDERATIONS ON THE INNERVATION OF THE SMALL INTESTINE.

Thanks to the electron microscope and the development of staining techniques, in particular fluorescent stains, the understanding of the innervation of the bowel wall has considerably progressed. New nervous connections and sometimes their chemical transmitter have been identified. The classical concepts of autonomic nerve supply of the gut have been revised as follows (G. C. Schofield 1968, Figure 1) [39].

1. Neural Plexuses.

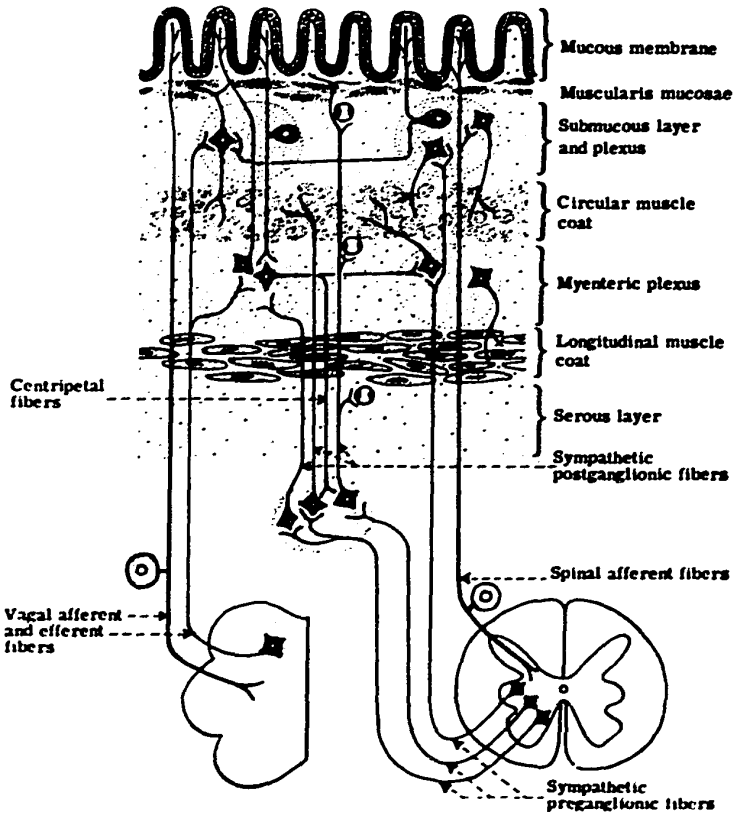
4 main plexuses have been identified:

a) The subserous plexus: the connections between the mesenteric nerve bundles and the myenteric plexus of Auerbach travel through this intermediary plexus. It consists of nerve fasciculi with a few neurones sometimes aggregated in ganglia. From there on to the myenteric plexus most nerve fasciculi follow the blood vessels as in the mesentery.

b) Auerbach's myenteric plexus: this plexus lies between the longitudinal and circular muscle coats. The plexiform meshwork of fibers can be divided into three components: a primary one which constitutes the main bulk of the plexus and contains nu-

Figure 1.

THE INNERVATION OF THE SMALL INTESTINE.



(After G. C. Schofield) [39].

merous neurones, particularly at the mesenteric border; fasciculi branch off from the primary plexus to form the secondary one; from there a tertiary plexus constituted by very fine unmyelinated fibers ramifies between the smooth muscle bundles of the longitudinal and circular coat. A portion of the myenteric plexus situated deep within the circular layer is called "deep myenteric plexus".

c) The submucous plexus of Meissner: it is constituted by a neural meshwork of unmyelinated fibers and neurones aggregated in ganglia. Ganglia are most numerous in the small intestine. The submucous plexus is connected to the myenteric plexus by indirect paravascular connections and also by direct connections. It sends minute twigs to the mucous plexus.

d) The mucous plexus: the fibers constituting this plexus are so fine that they are not identifiable with the light microscope. They are in direct contact with the epithelial cells [40].

The classical view that the sympathetic efferents are postganglionic past the celiac ganglia and the parasympathetic are preganglionnic and relay in the myenteric plexus is no longer tenable. There is a good deal of evidence that there are also preganglionic sympathetic fibers represented in the bowel wall. Consequently the enteric neurones belong to both the sympathetic and the parasympathetic pathways [39]. These neurones are of 2 types: afferent and motor neurones. They are involved

in both intrinsic and extrinsic pathways. The latter consequently represents a functional distinction and not an anatomical one.

2. The extrinsic system.

The extrinsic system comprises pre- and postganglionic sympathetic efferents, vagal afferents and efferents, and spinal afferents. Preganglionic sympathetic fibers have been referred to above. Classically they constitute the splanchnic nerves. These fibers synapse in the celiac, paravertebral or enteric ganglia and are distributed to the muscle coats and the blood vessels. There are cholinergic fibers travelling with the sympathetic [41]. Vagal fibers come from the dorsal vagal nucleus in the rhomboid fossa. The vagus has its own afferent system which relays in the ganglion nodosum. These afferent come generally from the mucosa and coils of varying complexity in the submucosa. Spinal afferents are linked with enteric neurones which project centripetally [39]. They are involved in a spinal reflex arc which receives probably also afferents from the celiac and other prevertebral ganglia. Their functional role is unclear.

3. The intrinsic system.

The intrinsic system is constituted by afferents and effe-

rents located exclusively in the intestinal wall. The peristaltic reflex is mediated by these pathways [4]. It involves a system of afferents from the mucosa and the different layers are connected to excitatory and inhibitory pathways acting probably in a reciprocal fashion. The exact lay-out is still conjectural. This is discussed further in paragraph 7.

6. MOTOR ACTION OF THE SMALL BOWEL.

Early authors have observed 3 types of movements:

1. Segmenting contractions.
2. Pendulum movements.
3. Peristaltic contractions.

A segmenting contraction is a localized circumferential contraction involving at the most 1 cm - 2 cm of bowel [42]. They occur in irregular patterns in a sequence of increased and decreased activity. Sometimes segmenting contractions appear at regular intervals at a maximum rate characteristic for a given segment of intestine. Cannon [43] called this type of segmenting activity "rhythmic contractions".

The frequency of the rhythmic contractions were studied by Alvarez [44, 45] who found that it decreased progressively according to a gradient from the duodenum to the ileo-caecal valve. In the dog this frequency is about 18 per min. in the duodenum and 12 per min. in the distal ileum under physiological conditions [46].

Reference to the term pendulum movement is a source of confusion. Pendulum movements and rhythmic contractions appear to be one and the same thing.

Peristaltic movements are characterised by a wave of contraction passing along the gut and were well described by Bay-

liss and Starling as the "Law of the Intestine": "...Since the whole act is evoked by the presence of the bolus in the gut, we must say that the stimulation of the mucous membrane and the streching of the walls of the gut at any point set up impulses which are transmitted both up and down the intestine and cause excitation above, inhibition below" 4. One can indeed state this conclusion more generally, namely that, if cerebrospinal reflexes be excluded, excitation at any point of the gut is followed by contraction above, inhibition and relaxation below. The presence of a wave of inhibition could not be confirmed by Alvarez [47]. Peristalsis appears to be propagated faster in the upper than in the lower small bowel [43]. Peristaltic rush is a strong contraction wave running down the entire length of the small intestine. It seems that the peristaltic rush is an abnormal motor action which for example appears in late agony [42].

Similarly antiperistalsis has been the subject of considerable controversy. There is little evidence that reverse peristalsis occurs in physiological conditions and there is no need to invoke antiperistalsis to explain retrograde transport [48].

The villi themselves have been described as exhibiting pumping and pendular movements together with tonic contractions. Villous motility is independant of the muscularis mucosae. It is activated by neural stimulation. A hormone, Villikinin, has

been postulated to stimulate these movements which probably facilitate absorption [49].

The motor action of the bowel has been studied with a variety of intraluminal pressure detection devices including water filled balloons, open tipped catheters and more recently radiotelemetric capsules.

Code et al. (1952) [50], using the open tipped catheter method, described motility in man in terms of 4 types of waves (Figure 2):

Type I waves are simple monophasic waves with an amplitude of 5 cm - 15 cm H_2O and last from 3 sec. to 7.5 sec.

Type II waves are of similar shape, but of greater amplitude and duration. They reach 50 cm H_2O.

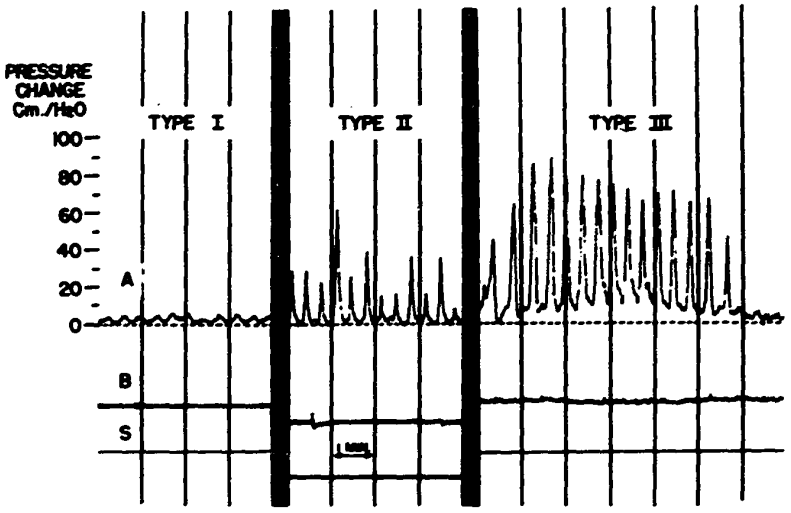
Type III waves are complex: there is an elevation in base line pressure due to a change in tonus. On this primary phenomenon, type I and II waves are superimposed. They last from 10 sec. to 2 min.

Type IV waves exist in the colon and the distal ileum. There is a long lasting moderate elevation of pressure (approximately 15 cm H_2O) with no superimposed waves.

In the small bowel only type I and III waves are detected [50]. Type I activity represents about 95% of the motor activity. Basic rhythm or rhythmic contractions represent a rare motility pattern corresponding to 1 - 2% [42].

Figure 2.

THE PATTERN OF INTRALUMINAL PRESSURE WAVES IN MAN.



(After Code et al.) [50].

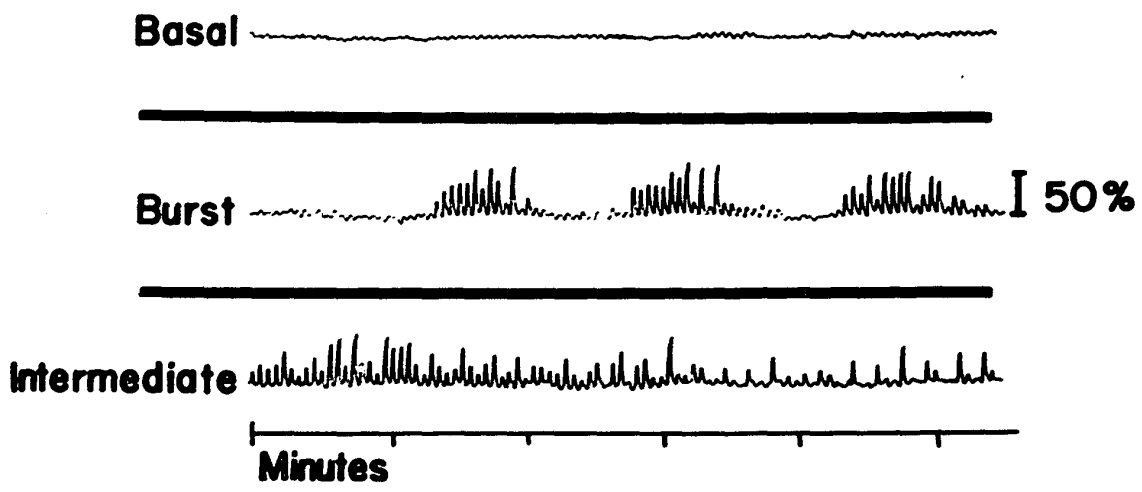
Correlation between the pressure waves and radiologic patterns is not a completely settled matter. Fluoroscopic studies show that type I waves correspond to segmenting contractions. Type III and IV are probably propulsive [51]. The type IV wave has been referred to as an "ileal pump" emptying the ileum.

There is evidence that segmenting contractions may represent either stationary or propagated waves. Consequently, peristalsis, in the sense of a propagated wave of contraction, is not necessarily correlated with the transport of chyme [52].

In the dog's small bowel, Reinke distinguishes 3 general patterns of activity: basal, bursts, and an intermediate type (Figure 3). The three types are found in the fasted dog when basal activity dominates and the remaining time is shared between bursts and the intermediate type. In the digestion state, the intermediate type predominates (80%), the other 20% consisting of basal activity. The three types can be also classified in terms of type I (basal activity), type II (intermediate), and type III waves (bursts). The intermediate activity is associated with a mixing and propulsive function, while the bursts represent more clearly propulsion. There are considerable variations in the contractile patterns among different dogs, each animal having rather an individual behavior [53].

Figure 3.

THE PATTERN OF INTRALUMINAL PRESSURE WAVES IN THE DOG.



(After Reinke) [53].

7. NERVOUS CONTROL OF MOTILITY.

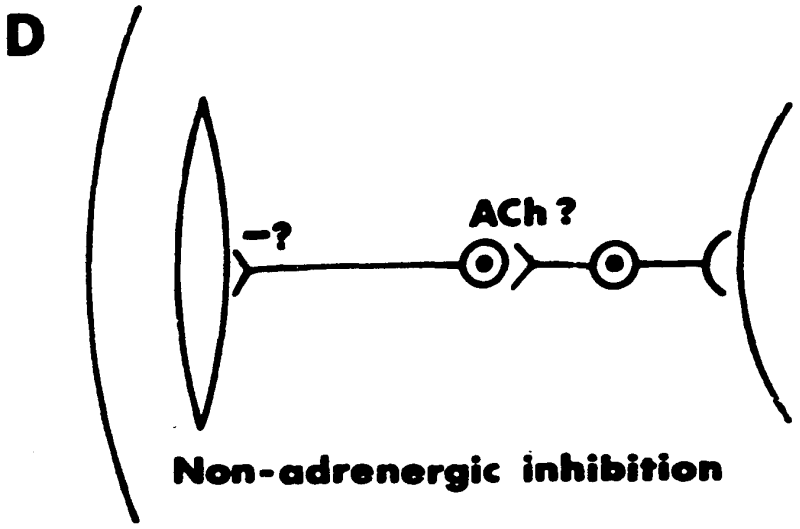
1. Extrinsic Regulation.

a) Inhibitory.

The inhibitory effect of discharges from the splanchnic nerve has been documented by inumerable studies since Bayliss and Starling's basic work [6, 7, 8, 9, 13, 19, 20, 23, 29, 54, 55, 55,56, 57, 58, 59, 60, 61, 62]. But the mechanism of inhibition is still subject to controversy. The intimate connection between the splanchnic nerves and the intrinsic elements is still debated. Histochemical studies have demonstrated connections with the myenteric plexus where even adrenergic neurones are present [63]. They may act by depressing the release of acetylcholine from the ganglion cells and the neuro-effector junction. This view finds support in the work of Szerb [64] who blocked the inhibitory response with atropine (Figure 4). Celander [65] is of the opinion that the inhibition is mainly secondary to vasoconstriction and to a direct effect on the smooth muscle due to "overflow" of the adrenergic transmittor. Mock [60] on the contrary claims that so-called "overflow" inhibition is an artefact due to high frequency "non physiologic" stimulation of the splanchnic nerves. At a physiologic range

Figure 4.

NON-ADRENERGIC INHIBITION.



(After Kosterlitz) [84].

of stimulation of the splanchnic nerves inhibition appears with considerable delay, unusual for a mechanism of neurogenic nature. The inhibitory response is not obtained in the absence of the adrenals and consequently he believes that the hormonal component of the sympathico-adrenal axis has precedence. Hiatt [66] casts some doubts on the role of circulating adrenalin as the cause of long standing inhibition: the response following intravenous injection of adrenalin in the experimental animal is only of short duration and does not parallel blood level variations. Further discussion on the mechanism of action of adrenergic inhibition can be found in paragraph 8.

The splanchnics contain a certain number of cholinergic fibers belonging to the vagus. They contain also spinal afferents. This fact explains the unreliability of direct electrical stimulation studies. Controversy exists over the possibility of generating antidromic impulses by this method and consequently artefacts [62, 67, 68, 69]. The results are influenced by the initial state of activity of the intestine. If inactive, splanchnic stimulation is followed by an increased motility, if active, then inhibition is observed [62].

An <u>intestino-intestinal inhibitora reflex</u> has been described by Youmans [14, 70] whereby distention of a segment of intestine causes inhibition of movements of the entire small intestine. The reflex is probably mediated by sympathetic afferents.

Section of both the splanchnic nerves and pelvic nerves is necessary to block it. It is a proprioceptive spinal reflex. A decentralized reflex through preaortic ganglia has been suggested but not confirmed. The intestino-intestinal reflex is under the inhibitory influence of supraspinal structures located in the rhomboid fossa [71].

A gastro-duodenal inhibitory reflex has been described by Daniel and Wiebe in 1966 [72]. Distention of the stomach inhibits the duodenum. The response is blocked by sympatholytic drugs and reestablished by norepinephrine. Reciprocally a duodeno-gastric reflex causes inhibition of the stomach when the duodenum is distended or contracts intensively. This response is abolished both by chemical sympathectomy and by bilateral vagotomy.

Vago-vagal reflexes control inhibition of the stomach initiated from gastric receptors sensitive to pH and stretch [73, 74, 75]. The vagus contains afferent fibers from intestinal mechanical sensors [75]. These are possibly involved in an entero-gastric reflex whereby distention and chemical irritation of the intestine causes paralysis of the stomach [48].

b) Stimulatory.

The vagus nerve is referred to in most text books as playing a major role in stimulating motility and maintaining an ade-

quate intestinal tone. If this holds true and is well documented for the stomach [48], the paucity of the data concerning its motor action at the level of the small intestine reflects how puzzling the question is. Stimulation studies revealed generally equivocal responses. Bayliss and Starling [4] observed first an inhibition followed by gradual increase in the number of contractions. This was most marked after withdrawal of the stimulus. More recent work showed that the basic activity of the intestine was of importance in the response obtained as in splanchnic nerves studies. A stimulation is obtained in the resting intestine and an inhibition in the active bowel [62]. Following vagotomy in the dog, Faik [76] could find only some slight delay and decrease in the feeding reaction. The peristaltic waves were less in number, of shorter duration and occurred at longer interval of time. Ross, using the radio-telemetric capsule, could only find slight changes in the motility of the small intestine in patients after vagotomy. These results point to the major role of the intrinsic nervous mechanism in promoting motility [30].

An "accelerative" <u>gastro-ileal reflex</u> has been described: an increase in gastric activity is followed by an increase in ileal motility. The reflex is not abolished by bilateral vagotomy [48].

Stimulation of multiple areas in the central nervous sys-

tem such as the cingulate gyrus and the insula are associated with an increase in gastric motility [48, 77]. The role of emotions on the motor functions of the gastro-intestinal tract are well known. However its pathways and mechanisms are not clear.

2. Intrinsic Regulation: The Peristaltic Reflex.

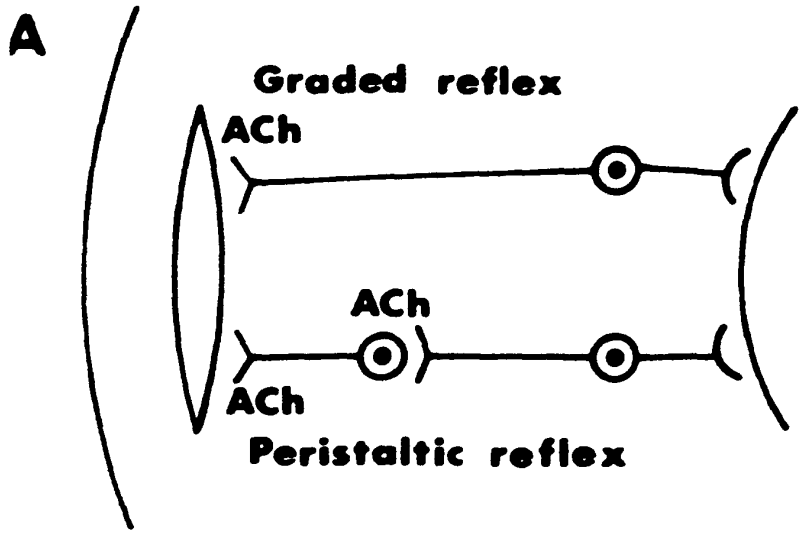
The peristaltic reflex is a mucosal reflex as it is a response to an irritation of the mucosa. It is independent of the extrinsic system as it can be elicited in an in vitro preparation where both the sympathetic and the vagus have been severed [4, 78]. It has been analysed pharmacologically using different autonomic and central nervous system transmitter blocking agents [40, 78, 79] or by transmural electric stimulation in conjunction with pharmacologic agents [80]. The peristaltic reflex can be obtained by radial stretch or the application of acid onto the mucosa [81]. The exact location of these receptors is not known, but the tiny nervous twigs related to the mucosa are probably concerned. Removal of the mucous membrane, local anaesthesia (administration of cocaïne intraluminally at a concentration of 10^{-4}) and asphyxia abolish the reflex in the guinea pig ileum [40]. But Zinzel [82] failed to obtain any disappearance of the reflex after intraluminal administration of 30% $AgNO_3$ des-

pite complete destruction of the mucosa and submucosa. Similarly, Diamant, Kosterlitz and McKenzie [83] described the progressive changes which unavoidably affect the mucosa after about 30 minutes in the in vitro bath. These changes consist of progressive shedding off of the mucosal cells and are similar to the observations made in this laboratory in tryptic enteritis of the dog after hemorrhagic shock (see paragraph 11). This process was not associated with any disturbance of the peristaltic reflex in vitro according to these authors.

Elicitation of the reflex causes contraction of the longitudinal muscle which is followed by contraction of the circular muscle. The contraction of the longitudinal muscle has 2 components: a graded response to subthreshold stimuli and a maximal response to above threshold stimulation (Figure 5) [84]. Kosterlitz estimated that the contraction of the longitudinal muscle does not trigger the one of the circular muscle as he was able to block the former with high concentrations of acetylcholine without affecting the latter. Contraction of the circular muscle could be blocked with hexamethonium and he assumed that a cholinoceptive mechanism was involved [84, 85]. Kottegoda did not confirm these findings. In his experiments, coaxial stimulation never causes simultaneous contraction of both muscle coats. While one layer contracts, the other relaxes or remains quiescent. The stimulation threshold was found to be higher for the circu-

Figure 5.

THE POSTULATED CONNECTIONS INVOLVED IN THE GRADED AND PERISTALTIC REFLEX.

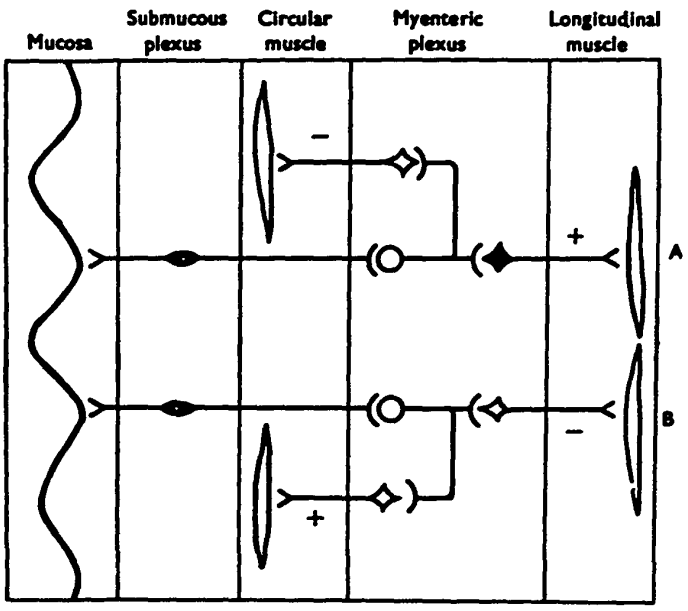


(After Kosterlitz) [84].

lar muscle than for the longitudinal one. Initiation of the longitudinal contraction raised sufficiently the intraluminal pressure to elicit a reflex contraction of the circular one. The latter was followed by reflex active relaxation of the longitudinal muscle (Figure 6). The circular contraction appeared also to have 2 components: first the reflex contraction just described; secondly, a delayed contraction could be observed after withdrawal of high frequency stimulation. The significance of the latter is quite mysterious. Kottegoda concluded from these observations that one coat modulates the activity of the other. He could not find evidence of cholinergic transmission to the circular muscle [80]. It is not within the scope of this presentation to go into the details of the pharmacological experimentations attempted to clarify the nature and role of the different neurotransmitters involved. Presently only the cholinergic nature of the excitatory pathways to the longitudinal muscle is clearly established [80]. The other transmitters are hypothetical. The neuroeffector junction itself is not of the synaptic type and is of conjectural nature [39].

Figure 6.

SUGGESTED INTRAMURAL NERVOUS CONNECTIONS EXPLAINING THE RECIPROCAL INHIBITION-STIMULATION OF ONE MUSCLE LAYER OVER THE OTHER.



(After Kottegoda) [80].

8. HORMONAL CONTROL OF MOTILITY.

1. Inhibition.

a) Epinephrine.

Epinephrine has been known for years to induce an immediate inhibition of intestinal activity when administered intravenously to vertebrate animals. It has no effect when administered intraluminally into the gut [86]. Adrenalin inhibition of the peristaltic reflex has been repeatedly demonstrated in the rabbit and the guinea pig, the most commonly used animals for in vitro experimentation in this field [78]. The action of epinephrine and other catecholamines is possibly three-fold:

1. Action on the intramural ganglionic apparatus: at this level adrenalin would influence acetylcholine release from the neurones and neuroeffector junction [64, 84]. This is discussed in paragraph 7.

2. Action on the smooth muscle itself: the mechanism would involve an hyperpolarisation of the cell membrane due to increased potassium conductance. The pacemaker potential is also suppressed [62, 87, 88]. The presence of calcium is necessary for these phenomena to take place. They are probably not related to the stimulation of phosphorylases and 3'-5' cyclic AMP conse-

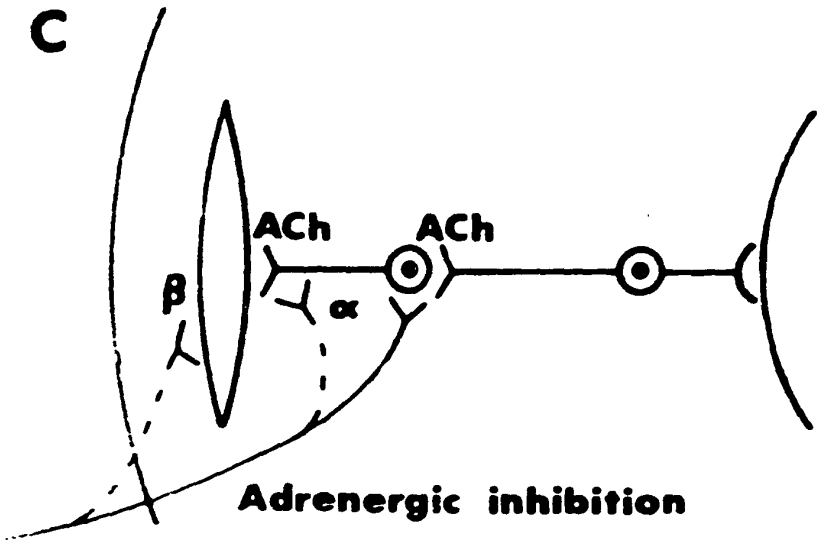
cutive to adrenalin [89, 90]. The precise mechanism of inhibition is presently not understood.

3. Action on the blood vessels: catecholamines cause a vasoconstriction. The relationships between motility and blood flow are presented in paragraph 9.

The nature of adrenergic intestinal receptors has been the subject of much controversy. The type and function of the receptors vary depending on the intestinal level and species. The stomach and ileum of the dog seem to contain exclusively inhibitory alpha and beta receptors while the duodenum is believed to possess alpha inhibitory and beta excitatory receptors [91, 92]. In man not only is the distribution and nature of the receptors unclear, but the clinical observations in this respect have been rather puzzling: patient with catecholamine secreting tumours do not have paralytic ileus as a rule and even diarrhea has been reported [93]. It is of interest that adrenolytic drugs have been used in the treatment of clinical paralytic ileus [19, 57]. Hosterlitz postulated the presence of alpha receptors in the intramural nervous structures while the muscle would possess exclusively the beta type [84] (Figure 7). Increase in potassium conductance has been ascribed by Bülbring to be an alpha effect. Abolition of the pacemaker potential would be a beta effect.[87] The relationships between both types of receptors are not known but would be of great interest as far as motility

Figure 7.

ADRENERGIC INHIBITION.



(After Kosterlitz) [84].

inhibition is concerned.

b) Antidiuretic Hormone.

Prior to the advent of naso-gastric suction pituitrin was frequently used in the treatment of paralytic ileus. It was thought to have excitatory influence similar to that seen with smooth muscle of uterine origin. Recent experimental studies by Hiatt, Goodman and Alavi however demonstrated an inhibitory effect [66]. These authors attributed also to ADH a role in "coordination" of intestinal motility. The precise mechanism of action is not understood but inference from some work by Wadlington points toward 3'-5' cyclic AMP [94].

c) Glucagon.

Experimental work by Mock (1967) has suggested an inhibitory effect upon intestinal activity following injection of glucagon. Once again recent studies on the mode of action of this polypeptide incriminate 3'-5' cyclic AMP [95, 96].

d) Prostaglandins.

Prostaglandins E_2 appear to have an inhibitory action upon

intestinal motility [97, 98]. They have been incriminated in the mechanism of excitation-contraction coupling of the smooth muscle and might be released following contraction of the smooth muscle itself or sympathetic discharge [98].

e) Secretin-Pancreozymin.

Pancreozymin and mainly secretin have an inhibitory action on the motility of the stomach. The mechanism is largely unknown but it is postulated to be related to the "enterogastrone" complex [99].

2. Excitation.

a) 5-Hydroxytryptamine.

5-HT applied on the mucosa of the intestine facilitates the elicitation of the peristaltic reflex in vitro. Applied on the serosa the facilitation effect is more transient and is followed by complete abolition [78, 100]. In vivo the effect is more marked after intraarterial than intravenous injection. The stimulation is usually followed by an inhibition of peristalsis. It was suggested that 5-HT was responsible for sensitization of the receptors involved in the peristaltic reflex. Other observa-

tions by Hukuhara (1960) indicated that 5-HT is probably not necessary for excitation of the mucosal receptors as the peristaltic reflex was maintained despite specific de-sensitization to 5-HT [101].

b) Histamine.

Histamine acts directly on the smooth muscle and produces a mass spasm when injected intraarterially and a variable motor response when given intravenously [86]. It probably acts on the movements of Ca^{++} at the level of the excitation-contraction mechanism [102].

c) Bradykinin.

Bradykinin has effects very similar to histamine [86]. Other workers observed a depression of peristalsis with bradykinin in vitro whether it was applied on the mucosa or serosa [103].

d) Substance P.

Substance P administered intravenously increases peristalsis. [104] Applied on the mucosa it has an effect similar to 5-HT and mucosal receptors have been postulated [105, 106]. Applied on

the serosa it inhibited the peristaltic reflex [107]. Substance P is involved also in stimulation of the villi [108].

e) Gastrin.

Gastrin I and II have a weak stimulating action on the motility of the small intestine as demonstrated experimentally in the cat [109] and man [110]. This is possibly a cholinergic effect. Multiple other polypeptides such as angiotensin also have a stimulating effect on the smooth muscle of the GI tract. Prostaglandins E_1 and F are also among recently studied excitatory substances [97].

f) Thyroid Hormone.

Myxedema is often associated with a decrease in motility and even sometimes with paralytic ileus. Reciprocally diarrhea is a frequent presentation of thyrotoxicosis. The intestinal mechanics of these disturbances have not been clearly analysed. Similarly the mode of action of the thyroid hormone on the neuro-muscular apparatus of the intestine is unknown [111].

g) Adrenal Cortical Hormones.

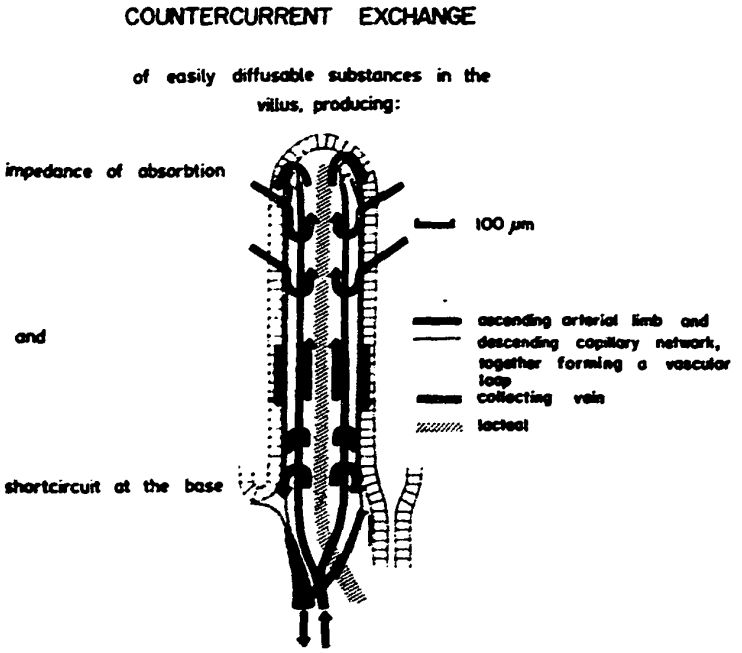
Adrenal cortical extracts enhance the peristaltic activity of the small intestine in the rabbit, dog and human at low concentrations. At higher concentrations an inhibition is observed. This might be due to the action of mineralo-corticoïds [112]. Obviously very little is known about the matter and further studies are needed.

9. INTESTINAL BLOOD FLOW REGULATION.

The mucosal blood supply of the intestine is considerable in order to satisfy the enormous metabolic requirements essential for normal absorptive and secreting functions. These "exchange vessels" exhibit in the intestinal villi a particular lay-out which has been postulated to present the properties of a countercurrent mechanism (Figure 8) [113, 114]. Rb^{86} fractionation techniques have shown that in the rat the duodenum has the highest functional perfusion rate per unit of tissue weight with a progressive decrease in functional flow from Treitz's ligament to the colon in accordance with Alvarez's metabolic gradient theory [115]. The flow through the mucosal, submucosal and muscularis beds is regulated by precapillary and postcapillary resistance sections exhibiting the properties of autoregulation (Figure 9). In the dog 2/3 of the blood supply is directed toward the mucosa and 1/3 to the rest of the bowel wall. The autoregulatory mechanism consists of a myogenic reflex and of a sympathetic axon reflex with receptors on the arterial side and effectors on the venous side. The mechanism is activated when blood flow decreases or when tissue anoxia supervenes irrespective of the cause [116, 117, 118, 119]. The sympathetic control of autoregulation has been extensively studied by Folkow [120]. Continued sympathetic discharge causes an initial increase in

Figure 8.

THE COUNTERCURRENT MECHANISM.



(After Folkow) [114].

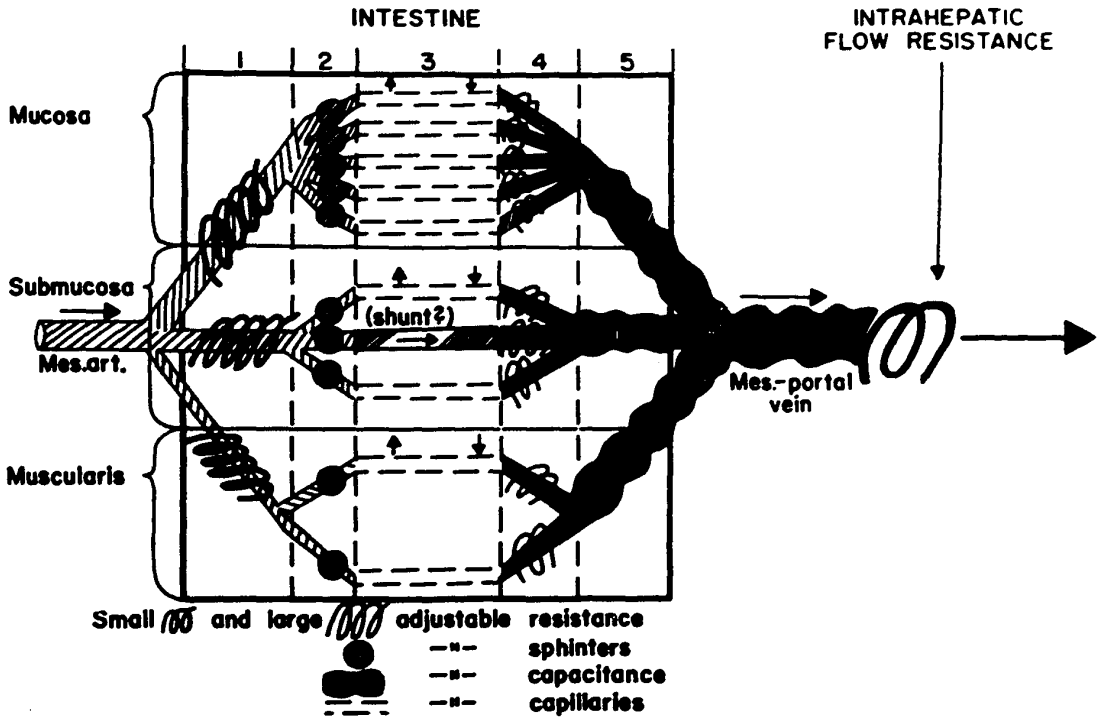
vascular resistance with a decreased mucosal flow. This is followed after a time by a decrease in vascular resistance owing to an "autoregulatory escape". The blood passes through low resistance submucosal channels and is shunted away from the mucosa due to persistent vasoconstriction of the mucosal vessels owing to a specific distribution of the alpha adrenergic receptors. The countercurrent mechanism implies a short-circuit at the base of the villi which decreases the blood flow at the tip of the villi, thus delaying absorption and offsetting the osmotic problems associated with this function. In ischemic conditions this mechanism appears to reinforce the detrimental influence of the "autoragulatory escape" action [114].

The segmenting contractions of intestinal activity are associated with a reduction in arterial flow and an increase in venous outflow. A positive pumping effect results [121]. Tonic contractions on the contrary can interfere with this pumping effect to such a degree as to eliminate it completely. But owing to valvular dispositives in the veins draining the submucous plexus, there is no reflux of blood.

The effect of gaseous distention upon blood flow of the intestine has been studied very extensively [12, 122, 123, 124, 125]. Even low levels of increased intraluminal pressure (20 cm H_2O - 40 cm H_2O), if maintained, are able to cause perfusion impairment of the intestine. Recent studies in dogs with Kr^{85}

Figure 9.

THE SITES OF AUTOREGULATION.



(After Folkow) [114].

and silicone rubber injections indicate that the flow is decreased by 30% at a pressure of 30 mm Hg or above, and provide evidence for a shift of blood away from the mucosa in these circumstances [126]. The caudad gradient in flow distribution and the anatomic disposal of the blood vessels along the bowel wall are responsible for an increase in ischemic susceptibility from duodenum to colon, the antimesenteric border being particularly sensitive [12].

The motor behavior of the small bowel, as well as being capable of influencing blood flow, is also reciprocally influenced by the blood flow. The consequences of hemorrhagic shock have been the subject of conflicting reports. Inhibition of gastric and small intestinal motility has been reported by some workers, whereas others have observed a stimulation [127, 128, 129]. Postmortem contractions have also been described, lasting a few minutes, and are related to acute ischemia such as aortic clamping [130]. More recent work by Schamaun (1966) and Zfass (1967) confirmed an increase in activity immediately after arterial clamping or during hemorrhagic shock in the dog [131, 132]. In the rat the relationships between the severity of ischemia and the propulsive motility are such that a moderate ischemia is associated with accelerated gastric emptying and increased intestinal propulsive motility, while a severe impairment in flow results in a marked delay [133]. Though the stimulatory effect of moderate or ini-

tial acute ischemia is well accepted, the relationships between blood flow and motility are often variable and inconsistent. A pharmacologic analysis by Shehadeh could not draw any parallel between the vasoconstrictor or vasodilator action of various drugs and their effect on motility. Thus acetylcholine, a dilator, and angiotensin, a constrictor, are both associated with a stimulation of motility. On the other hand, nor-epinephrine, a constrictor, and prostaglandin E_1, a dilator, were associated with an inhibition [97].

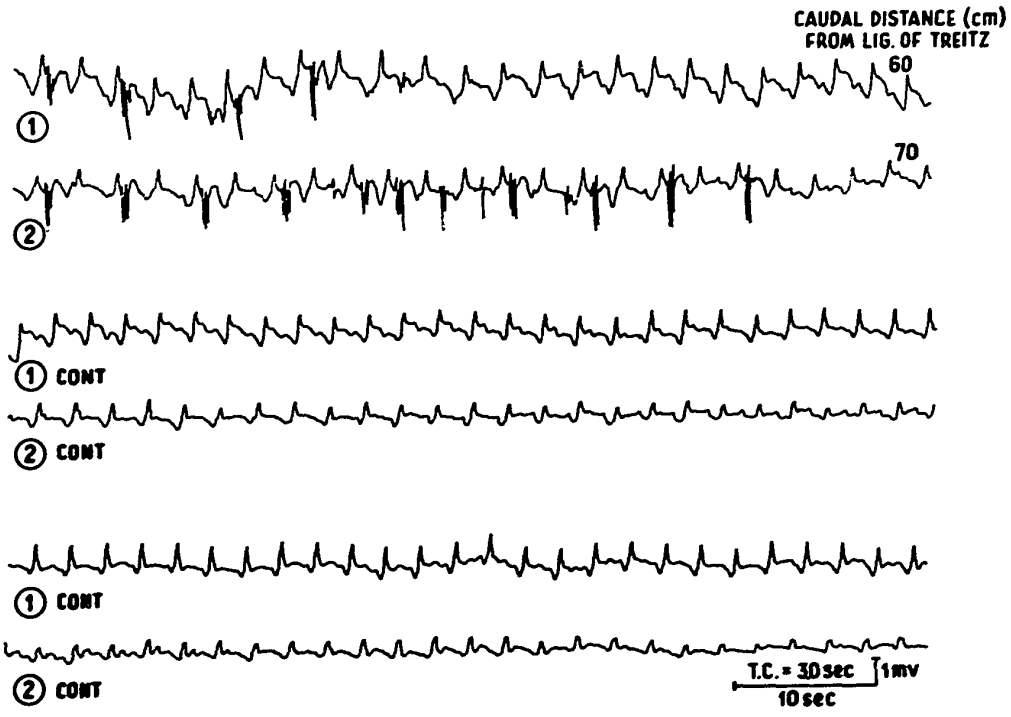
10. ELECTRICAL ACTIVITY OF THE SMALL INTESTINE.

The first recordings were obtained by Alvarez who demonstrated a correlation between electrical activity and rhythmic contractions of the small intestine [134]. But as his electronic equipment had a high intrinsic inertia, he was unable to record the fast components of electrical activity. The electroenterogram is composed of 2 types of potentials: one has a cyclic periodicity and has been called BER for basic electrical rhythm by Bass [135]. Other authors peak of "slow waves" as opposed to the fast potentials [136] or spike potentials [135].

The BER frequency is characteristic for the species, the level in the intestine and also the individual. It consists of repetitive depolarisation-repolarisation cycles. Its shape is somewhat variable depending on the recording technique. Spikes occur usually only during very intense activity. The depolarisation associated with an outburst of spikes is usually larger than the one which is not [137]. The BER originates in the longitudinal muscle and appears to be a basic characteristic of these cells. There is no slow waves activity in the circular layer. The BER is propagated distally at a progressively decreasing velocity from the duodenum to jejunum and ileum. Similarly there is an aboral frequency gradient [44, 138, 139]. Daniel demonstrated that spikes are always accompanied by mechanical activity,

Figure 10.

A PATTERN OF JEJUNAL ELECTRICAL ACTIVITY IN THE DOG.



(After Bass) [46].

but the reverse is not necessarily true [140]. Bass (1965) mentions that occasionally 1 - 3 spikes are generated without any change in intraluminal pressure [141]. In spite of this discrepancy he found an excellent correlation between the number of spike potentials, the duration of such an activity and intraluminal pressures. He believes that the occasional discrepancy is due to the fact that the electric recording technique is more sensitive than manometry. Spikes would reflect more closely the activity of the circular muscle than of the longitudinal one, but this belief which appears from time to time in the literature, has never been verified experimentally [46]. Daniel (1969) made the following hypothesis regarding the relationships between the slow waves and motility: "The general importance of slow waves to motility may be that they cause a propagated band of depolarisation (and possibly increased chemical excitability) to spread synchronously down the intestine. This travelling band would interact with local factors such as the release of acetylcholine or inhibitory transmitters to cause pikes and contractions or to inhibit them" [98]. It is of interest that the spikes are not propagated [46, 138].

As mentioned above each part of the intestine is characterized by its BER frequency. It is 17 - 19 cycles per min. in the duodenum and drops to about 12.5 - 14.5 cycles per min. in the distal ileum of the dog. Diamant (1969) found that the rhythmic

gradient was not a regular progressive decrease. The phenomenon occurs as a succession of different plateaus of frequency. The frequency of a single plateau is dependent on the frequency of the local pacemaker. The areas connecting the different plateaus form a zone of wave waxing and waning. The zones of waxing and waning and consequently the pacemakers are subject to shifting. The isolation of segments of intestine of different levels is followed by a drop of frequency in all the segments as if they were formerly driven by the higher frequency of the segment located immediately above [139]. Bortoff has compared the intestine to series of interconnected oscillators set at progressively decreasing frequencies. This model shows that the zones of waxing and waning correspond to the area of interference between two oscillators [142]. The practical consequence of this observation is that section and anastomosis of the small intestine are accompanied by a drop in frequency in the distal segment. This is permanent in the dog [141, 143, 144]. The drop at the duodeno-jejunal junction after section and anastomosis is from about 18 - 19 cycles per min. to 13 - 14 cycles per min. [145]. Electrical activity is metabolic dependent [146]. The BER frequency is consequently decreased by cooling and increased by heating [14].

a) Role of the intrinsic plexus on electrical activity.

Mukuhara (1961) described a procedure to destroy selectively the enteric neurones. He perfused loops of intestine with non-oxygenated Tyrode solution for 2 - 3 hours and observed histological degeneration of the neuronal cells. Apparently the BER is not affected by such a procedure and he concluded that the slow waves are essentially myogenic in origin [148]. Szurszewski repeated this type of experiments but was not able to confirm completely the findings of Mukuhara. He observed a 70% degeneration of ganglion cells after 4 hours of Tyrode perfusion. A drop in frequency ensued and he formulated the hypothesis that the intrinsic nervous pathways might have a role in the maintenance of the level of excitability of the smooth muscle cells by the constant production of acetylcholine. He observed also that destruction of the nervous plexuses led to an anarchic propagation. The intrinsic plexus seems consequently essential for aboral conduction [149].

b) Role of the extrinsic nerves on electrical activity.

Extrinsic nerves have no action on the BER. Stimulation of the sympathetic causes hyperpolarisation and cessation of spikes, while depolarisation and initiation of spikes follow vagal sti-

mulation. These effects are variable depending on the level of resting activity [62].

c) Action of drugs on electrical activity.

The BER is relatively resistant to ganglionic blocking agents and cholinergic drugs [150]. Intravenous epinephrine increases its rate and desorganizes the pattern of the recordings [151]. Serotonin and morphine cause an increase in amplitude and discharges of spikes [141, 150]. Pitressin decreases the rate and amplitude of the BER. In contrast to the BER spikes are very sensitive to pharmacological agents: cholinergic drugs initiate them while adrenergic and anticholinergic ones, including ganglion-blocking agents, eliminate them [150].

d) Role of the electrolytes.

It would appear that the slow waves are dependent on the oscillatory activity of the membrane sodium pumps [152]. Consequently subtances depressing the ion transport such as LiCl, NaF, ouabain, EDTA, obliterate the BER. This phenomenon is accompanied by depolarisation and consequently spiking and contraction. Despite these findings arterial perfusions with solutions low in electrolytes influence the BER very little [152]. High con-

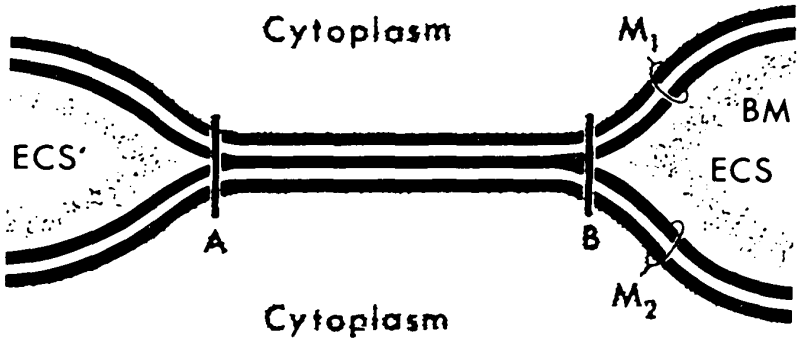
centrations of Na^+ and K^+ have a stimulatory action, probably through the liberation of acetylcholine. Other studies on the taenia coli strip have shown that the resting potential is mainly dependent on K^+ fluxes; spiking corresponds to entry of Ca^{++} while repolarisation is dependent on the extrusion of K^+ [153, 154]. Thouvenot and Dougereau have been interested in the effect of the intraluminal content on electrical activity in the rat. Glucose, other sugars, as well as ATP, cause an increase in tonus together with the appearance of a slowly propagated strip of hyperpolarisation, which they called "A" phenomenon [155, 156, 157, 158]. They could reproduce the "A" phenomenon by adding Ca^{++} in the bath of in vitro experiments or by perfusing with higher concentrations of Ca^{++} an in vivo preparation. They concluded that the mucosal activity can influence ion distribution in the submucosa and in the muscularis. Ca^{++} is an essential determinant of the contractile phenomenon itself [159].

e) Anatomic basis of electrical transmission.

Dewey and Barr demonstrated areas where the membranes of two adjacent cells are in intimate contact. These sites are called "nexus" by these authors and can be localised on the side or end of a smooth muscle cell. The nexuses are most probably related to electrical transmission. They are readily disrupted

Figure 11.

ELECTRON MICROSCOPIC VIEW OF A NEXUS.



(After Dewey, Handbook of Physiology, Sect. 6, Alimentary Tract, Vol. IV, American Physiological Society, Washington D. C., 1968).

by hyperosmolar solutions and as a result the electrical activity becomes desynchronized and anarchic [160, 161]. A nexus is represented in figure 11.

11. LESIONS OF THE SMALL INTESTINE ASSOCIATED WITH REDUCTION IN BLOOD FLOW.

The intestinal mucosa is very sensitive to ischemia irrespective of the cause. Undoubtedly the particular anatomical and physiological properties of the blood vessels of the villi, i.e. the countercurrent mechanism, are a major contributing element in pathogenesis. Such lesions possess a high degree of experimental reproducibility and the extent of the damage appears to be directly proportional to the duration and severity of the ischemia. They have been extensively studied in this laboratory where their microscopic appearance has been classified according to the degree and progression of the damage as follows (Figure 12) [162]:

Grade 0 : Normal mucosal villi.

Grade I : Edema and hyperemia. Eventually minimal subepithelial vesiculation at the tip of the villi.

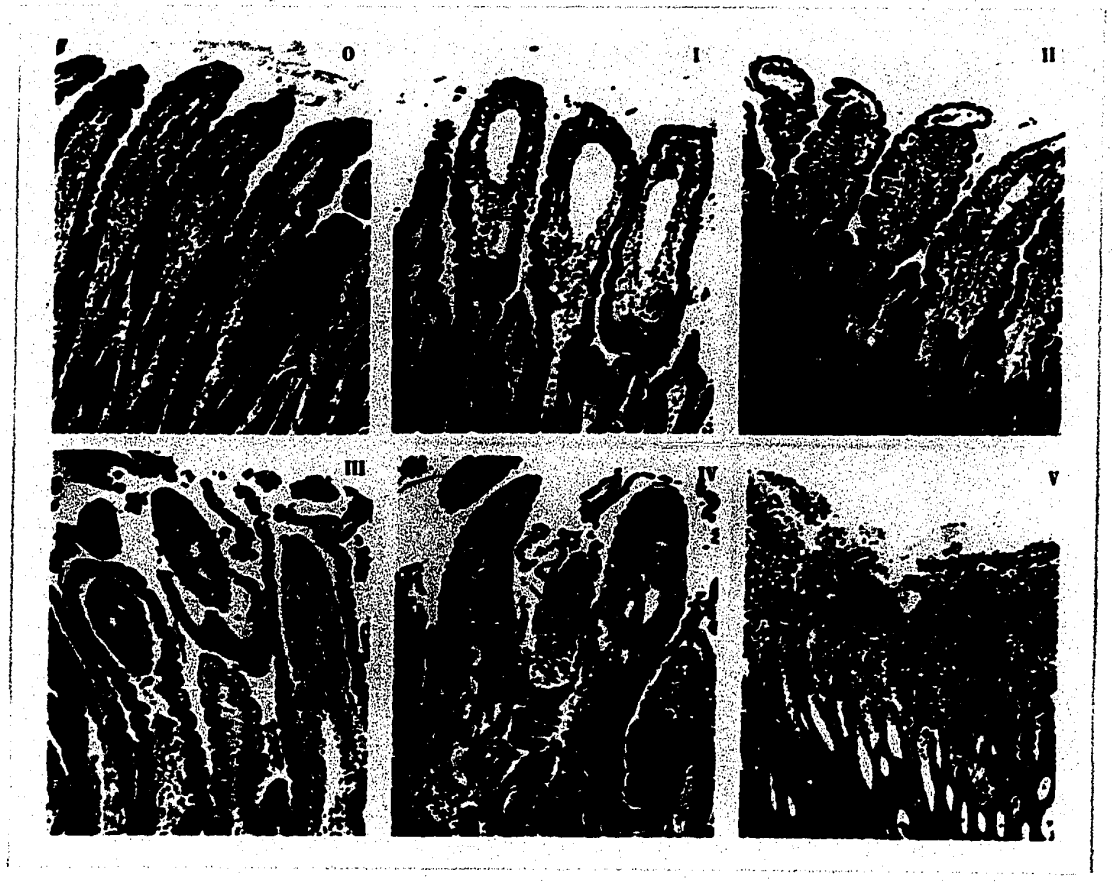
Grade II : Discrete lifting off of the epithelium from the lamina propria at the tip of the villi forming the so-called Grünhagen space. Capillary dilatation.

Grade III : Extensive shedding off of the epithelium from the tip down to the side of the villi.

Grade IV : Completely denuded villi with lamina propria

Figure 12.

THE MUCOSAL LESIONS CONSECUTIVE TO EXPERIMENTAL ARTERIAL CLAMPING.



(After C. J. Chiu) [162].

: and dilated capillaries exposed.

Grade V : Digestion and desintegration of the lamina propria with hemorrhage and ulceration.

This sequence of events can be followed in the dog during the course of experimental hemorrhagic shock or superior mesenteric artery clamping, proving that they are not a microtome or fixation artefact as was thought in the past [163, 164]. They have also been described in dysentery [165], following hypothermia [166], cardio-pulmonary by-pass [167], and in vitro preparations of the guinea pig ileum as an unavoidable concomitant of this type of experiment [83]. The mucosal changes have found their clinical counterpart in a wide range of conditions associated with impairment of blood flow or hypovolemia running the gamut from acute post-operative enterocolitis to congestive cardiac failure [168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178]. The fact that these conditions are often associated with "stress ulcer" and paralytic ileus is of particular interest. The suggestion by Folkow that sympathetic activation and nor-adrenalin are important factors in mucosal blood flow diversion provides a theoretically attractive pathogenetic link between the two conditions and is in this respect very appealing [114].

The intestinal chyme is of major importance in the pathogenesis of these lesions. The injury to the epithelial cells already metabolically depressed by the ischemic process is favored

by the intraluminal presence of powerful proteolytic enzymes such as trypsin and toxic products of digestion [179]. Thus they can be prevented by pancreatic duct ligation, trypsin inhibitors and by the administration of an elemental diet [180, 181].

The renewal of the mucosal epithelial cells of the small intestine is usually complete within 24 - 72 hours in the mouse or rat [182, 183, 184], about half the time needed for the same process in man [185]. It is possible that the renewal cycle is somewhat depressed in stress conditions. Very little data is available concerning the dog, but according to the experience of this laboratory, denuded mucosal villi are covered again by an atrophic cuboïd epithelium within 24 - 48 hours following shock or superior mesenteric artery occlusion [162].

12. THE PATHOPHYSIOLOGY OF POST-OPERATIVE PARALYTIC ILEUS.

The sequence of events leading to post-operative non mechanical obstruction can be divided under 2 headings:

1. The factors leading to distention.
2. The effects of intestinal distention and the vicious circle initiated thereby.

1. The factors leading to distention.

Experimental and clinical observations have led to 3 main theories of pathogenesis:

i) Actual paralysis or mechanical hinderance of motor activity.

ii) Neurogenic mechanism.

iii) Humoral mechanism.

i) Paralysis or mechanical hinderance of motor activity.

Early authors suggested that a pure paralysis was the cause of post-operative paralytic ileus [1]. The paralysis was believed to result from circulatory disturbances [3, 186] or due to inflammatory [187] and toxic factors [21, 188]. Paralysis as such, i.e. the inability of the intestinal muscle to contract, has not been

shown to play any role in paralytic ileus and is widely rejected as an etiologic factor [7, 8, 9, 10, 59, 189].

Mechanical factors such as micro-adhesions and fibrinous peritonitis were also suggested by Kocher [3]. Except in cases of frank adhesive mechanical obstruction, this explanation has but little credit nowadays. More interesting is the concept of gaseous dilatation as a cause of paralysis [190, 191]. The overstretched intestinal muscle is unable to cope with the greatly increased intraluminal pressure in accordance with the Laplace law. In this way a "paralysis" results. The clear understanding of the mechanism of distention has been complicated by the extreme difficulty in reproducing distention in the laboratory animal [192]. Intestinal gas has 3 sources of origin:

a) Fermentation inside the bowel:

Gas forming decomposition of the intestinal contents has been the subject of considerable study by early German writers. Diets rich in liquid carbohydrates are of particular importance in this respect. But the amount of gas formed in this way is highly variable and depends on the general condition of the subject, the amount of food ingested, and the state of secretory and absorptive activity of the intestine [192].

b) Diffusion of gas from the blood into the lumen:

Gas exchange takes place between the blood and the intestinal lumen on the basis of chemical diffusion gradients. Because

of the high partial pressure of nitrogen in the air and consequently in the serum, it is poorly absorbed from the lumen. Conversely it has a tendency to diffuse from the blood into the intestine depending on the gas composition of the intraluminal content. If hydrogen accumulates volumetrically significantly in the gut as a result of food fermentation, a diffusion of nitrogen from the blood will consequently take place until the equilibrium of the partial pressures is reached. This process is enhanced by the poor absorbability of hydrogen [192]. This same mechanism is responsible for the distention produced by the use of anesthetic mixtures rich in nitrous oxyde and ethylene. A significant degree of meteorism was obtained experimentally in dogs in this way by Cundy [193].

c) Swallowed air:

The fermentation process is responsible for no more than 30% of the accumulation of gas in the intestine. Dog experiments have demonstrated that the remaining 70% is due to swallowed air [13]. Belching further increases the amount of air swallowed as the amount retained in the stomach is bigger than the volume burped. The practice of mask anesthesia is another significant contributory factor [57]. Despite the experimental and clinical evidence in favour of gas retention as a causative factor in post-operative ileus, its importance is somewhat lessened by the recent demonstration that air is normally transported in the

small bowel in the post-operative state [26]. It is also readily obviated by the use of nasogastric suction, thus pointing toward the contribution of other factors.

ii) Neurogenic mechanism.

The presence of an inhibitory reflex mediated by the sympathetic nervous system following laparotomy, manipulation of the visceral organs and peritoneal inflammatory conditions has been supported by ample evidence in the past [6, 7, 13, 20, 23, 29, 54, 58, 59, 60, 61]. The different postulated mechanisms of such an inhibition have been amply discussed before and need not to be repeated here. But it is important to emphasize that, from an experimental point of view, both the purely neurogenic and the purely hormonal inhibition are of short duration [60, 86]. They are consequently not completely satisfactory explanations. Further, in normal circumstances the sympathetic system has been demonstrated to have little influence on intestinal motility [194].

iii) Humoral mechanisms.

This is believed by the German school to be a major determinant of the "ileus sickness". Of the various hormones adrenalin has received most of the attention and is claimed to be ele-

vated up to 3 times the normal in the full blown ileus [6, 35, 60, 65]. The role of the other amines and polypeptides is still unclear in the clinical situation. But recent experimentation suggests an action on the transport of electrolytes across the membrane of the smooth muscle cell which consequently affects excitation-contraction coupling (see paragraph 8).

The importance of electrolytes and fluid balance in post-operative paralytic ileus is well known to the clinician. Potassium deficiency was demonstrated to cause adynamic ileus in the dog by Streeten [18]. This observation was confirmed by clinical experience [195, 196, 197]. Following trauma and operation, potassium excretion is increased, presumably on the basis of aldosterone stimulation [198]. However the significance of potassium loss at the level of the smooth muscle cell is still poorly undertood. Daniel did not observe any marked alteration of the electrical activity of the intestine following arterial perfusion with potassium deficient solutions despite marked modifications of the cellular electrolyte content [152].

Magnesium deficiency has also been shown to cause paralytic ileus [200]. Magnesium excretion increases as a response to surgery in a pattern similar to potassium, but the amount lost is not significant from the point of view of the overall balance. On the other hand the deficit due to chronic gastro-intestinal fluid loss can lead to a significant deficiency if the intake

is reduced over a prolonged period of time [201]. Once established, magnesium deficiency can promote intracellular potassium deficiency [202]. Hypomagnesemia is also most often found in hypoparathyroïdism (where the hypocalcemia unmasks the symptoms of hypomagnesemia), multiple transfusions of citrated blood and in acute pancreatitis [201, 203]. Magnesium has been demonstrated in vitro to be required for the elicitation of smooth muscle contraction by ATP [204].

Potassium and magnesium deficiencies occur usually in the course of multiple electrolyte unbalance, but according to the presently available evidence the other ions are not as intimately involved in the genesis of paralytic ileus.

Another postulated humoral factor is a defect in acetylcholine synthesis following surgical trauma. A relative deficiency in panthothenic acid has been the most popular explanation [205, 206]. Panthothenic acid enters in the composition of CoA which is indispensable for the process of acetylation. Looking at the problem from another approach, Wekselman showed that strips of dilated stomach were less responsive to a given dose of acetylcholine.[207]

2. The effects of intestinal distention and the vicious circles initiated thereby.

Once distention is established by the conjoint action of gas accumulation, sympathetic reflex inhibition, liberation of catecholamines and other inhibitory hormones, the chain of events leads to a vicious circle which not only maintains and increases distention, but also results in a systemic deterioration. The pattern of derangements become essentially similar to mechanical obstruction.

Distention stimulates the intestino-intestinal and duodeno-gastric inhibitory reflexes; a complete standstill of the whole gastro-intestinal tract results.

The increased intraluminal pressure impairs the intestinal blood flow. At first venous congestion depresses the absorption of the accumulated gas and secretions. This is followed rapidly by increased secretions of water and electrolytes, particularly potassium [199]. The progressive ischemia of the mucosa is also responsible for an important loss of proteins because of increased permeability. With increasing pressure inside the lumen, the fluid is dispersed in a retrograde fashion until it meets a portion of bowel still capable of absorbing. The amount of secretions is enormous and far more than the mere addition of normal gastric, biliary, pancreatic and intestinal secretions.

The fluid secreted is isosmolar with the plasma and consequently systemic electrolytic disturbances appear late in the syndrome [199]. But the volume lost this way is so huge that severe hypovolemia can result. This calls for further systemic adjustments. Adrenalin output increases in order to compensate for the sloping blood pressure; but simultaneously the intestinal motility is further hindered. ADH and aldosterone are released and increase the secretion of potassium [208]. The body response sacrifices the intestinal function for the benefit of the maintenance of the circulatory volume; but by so doing it also promotes fluid and electrolyte loss, thus creating a dangerous vicious circle. With progressing toxemia and deepening shock, derangements in the serum electrolyte concentrations appear; potassium increases in parallel with the development of acidosis while the sodium slowly declines. These changes appear when the visceral organs start to be impaired in their function, in particular the kidneys, denoting a poor prognosis [35].

Wangensteen's mechanical concept of ileus shock which has been presented above with a few nuances, is based on the consequences of distention as a central event [13]. Other ideas have been suggested, mainly in the case of mechanical ileus. They are mentioned here for the sake of completeness. The concept of "primary ileus shock" has been developed by Reifferscheid in Germany. It is based on the observation of a decrease of both

the specific and non specific cholinesterases in the serum together with the development of histological lesions in the hypothalamus. These changes appear in the first hours following obstruction and eventually lead to the later phases of shock. Consequently, for Reifferscheid, intestinal decompression and maintenance of proper fluid and electrolyte balance is not a fully curative form of treatment [209]. Similarly Matsuruka postulated that ileus shock was basically an acetylcholine shock [210]. Much also has been written on the toxic effect of the intestinal content in mechanical obstruction. The ileus shock would be related to anaphylaxis or septic shock according to this hypothesis [211]. Whether these concepts are of any importance in paralytic ileus is totally unknown.

13. THE TREATMENT OF POST-OPERATIVE PARALYTIC ILEUS.

The prognosis of abdominal surgery has been radically improved since the introduction of internal intestinal decompression by Wangensteen and his group [15, 16, 212]. In the usual post-operative course simple naso-gastric suction is sufficient to prevent the effects of air swallowing and delayed gastric emptying. Together with parenteral fluid and electrolyte therapy this management is almost routine in most institutions. But this does not mean that it is absolutely devoid of any drawbacks. Gerber reported a significant increase in broncho-pulmonary infections in intubated patients, while non intubated patients kept fasting and with proper fluid and electrolyte management did just as well from the point of view of their ileus. Consequently he does not recommend naso-gastric suction as an integral part of routine post-operative care [213]. In addition prolonged suction can induce and maintain ileus by impeding the gastric acid from reaching the duodenum where it acts as a physiologic stimulant of motility. For this reason Dunphy suggests that aspiration should be arrested by the second day and the patient be fed at that time. 4 or 6 hours later the gastric residue if any is aspirated again, the tube being removed immediately afterwards. This is repeated a few times and this way the patient's condition should improve progressively [214]. In the established case long tube decompres-

sion should be performed, though it might be more difficult in paralytic ileus than in mechanical obstruction with a similar degree of distention as the progression of the tube is particularly slow [13].

Together with the measures previously described, a certain number of pharmacologic agents have been claimed to hasten recovery. The tenants of the "acetylcholine" theory have proposed various anticholinesterases. Prostigmine has been used by Miller [216], while long acting cholinesterase inhibitors such as Ubretid (Hexamethylene-bis-N-methyl-carbaminoyl-1-3-oxypyridium bromide) have been claimed to be of value [217]. Similarly D-panthothenyl alcohol is apparently of some benefit [205, 218].

Various sympatholytic procedures have been proposed by the proponants of the purely reflex theory. Spinal or splanchnic anesthesia was administered with some success in the 1930's [55, 219]. More recently this has been replaced by the use of adrenolytic drugs such as dihydroergotamine [57] or guanethidine [19].

In accordance with his neuro-hormonal concept of "ileus sickness" Heifferscheid proposes the addition of aldosterone antagonists to the sympatholytic agents in order to maintain an adequate potassium balance at the cellular level [220].

Since the suggestion by Milton of the presence of a "pacemaker" in the duodenum which would drive the motility of the small intestine, artificial pacing was attempted in the experi-

mental animal and man [221, 222]. Hasselbrack reported success in controlling the rhythmic contractions of the intestine in the dog [223]. Bilgutay and others claimed a beneficial effect in the treatment of post-oprative ileus in man [224]. More recent clinical trials have raised serious doubts regarding the efficacy of the method. Reifferscheid insists on the necessity of offsetting any sympathetic influence and of restoring electrolyte deficits before expecting any influence of the electrical stimulation [220]. Moran and Quast reported a failure of pacing [225, 226].

In the rare case resistant to all the usual therapeutic measures the question of operative exploration and decompression of the gastro-intestinal tract may be raised. The differential diagnosis between mechanical and paralytic ileus is extremely difficult during the post-operative period because the symptoms are masked by the absence of a previously adequate peristalsis and by the administration of analgesics. Many cases of protracted ileus are in fact due to mechanical obstruction and it is obvious that there will be no improvement unless the obstacle is removed. If none of the usual causes of paralytic ileus can be found, a mechanical cause should be suspected and laparotomy performed as soon as possible [227, 228].

CHAPTER II. EXPERIMENTAL STUDIES.

1. HYPOTHESIS.

Mucosal integrity is essential for normal physiological functions of absorption and secretion of the gastro-intestinal tract. Although intestinal motility is an integral part of these physiological functions, the relationship of the intestinal mucosa to motor activity of the digestive tract is virtually unknown. Little attention has been given to the mucosa in this respect. However there are both clinical and experimental observations which suggest that the integrity of the mucosa might be of importance in relation to motor function.

The mucosa contains afferent nerve endings related to the peristaltic reflex as mentioned previously [39]. Whether the mucosal cell itself is part of the afferent system is however unknown, but the demonstration of the existence of a mucosal reflex as such is highly suggestive [4, 40, 81]. It would appear reasonable to postulate that if the mucosa is affected by a pathologic process, intestinal motility in turn could be impaired.

Clinically such a concept is supported by the frequent association of paralytic ileus in relation to the development of stress ulcers. O'Neil found signs of distention and functional obstruction in 10 out of 22 patients with stress ulcers [33]. In

a recent clinical report from this institution, the presence of paralytic ileus was reported in 9 out of 21 stress ulcer patients [229]. Experimental studies have suggested that the lesions of the stress ulcer syndrome may be related to damage of the intestinal mucosa and alteration of the intestinal chyme. Guilbert demonstrated that reflux of the small intestinal content into the stomach is a significant pathogenetic factor [230]. The mucosal lesions incidental to experimental shock in the dog result in a considerable increase in proteolytic enzymes in the chyme liberated from cells which are shed and lysed in the lumen. The reflux of such an enzyme rich fluid into the stomach has been suggested by Bounous to cause digestion of the gastric mucus followed eventually by necrosis of the gastric mucosa [231].

It was shown by Sperling some years ago and more recently by Shields that the absorptive function of the intestinal epithelium was altered in mechanical bowel obstruction [125, 199]. Such changes could not be demonstrated following abdominal operations. Glucksman, using a perfusion technique in the human, failed to find any significant change between the pre-operative and the post-operative absorptive abilities of the intestine [232]. Cox observed only a minor transitory decrease in sugar absorption following vagotomy. These results provided the basis for the concept of early post-operative jejunal feeding [234, 235]. However reappraisal with a perfusion technique upon an

intestinal loop measuring only 30 cm in length revealed a decrease in absorptive capacity which persisted for as long as 48 hours. The duration of the functional defect appeared to be related to the magnitude of the operation. Thus it was most marked after abdomino-perineal resection [236]. Direct experimental studies of intestinal motility after mucosal damage in vitro have provided contradictory results so far. Bülbring reported abolition of the peristaltic reflex following scraping of the mucosa [40]. However her observations could not be reproduced by other investigators [82, 83].

The purpose of the present investigation is to study in an in vivo preparation the relationship between mucosal integrity and intestinal motility. An effort will be made to study the nature and characteristics of the intrinsic mucosal reflex by analyzing the wave patterns associated with the motor responses to various mucosal chemical stimuli. If mucosal injury does in fact adversely alter motility, the possibility of preventing such injury by means of an elemental diet as developed in our laboratory could hasten recovery of normal intestinal function and prevent subsequent secondary complications [181].

Epithelial shedding is one of the major consequences of experimental bowel autotransplantation. It is therefore of interest for the future development of this procedure to determine if possible the influence of such shedding upon the motility of

the intestine.

The experimental studies presented below are divided into two parts. The first part is mainly an evaluation of the physiologic processes inherent to chemical stimulation of the peristaltic reflex. In the second part the effect of mucosal shedding upon the motility of an intestinal segment is evaluated.

2. MATERIALS AND METHODS.

a) Animal preparation.

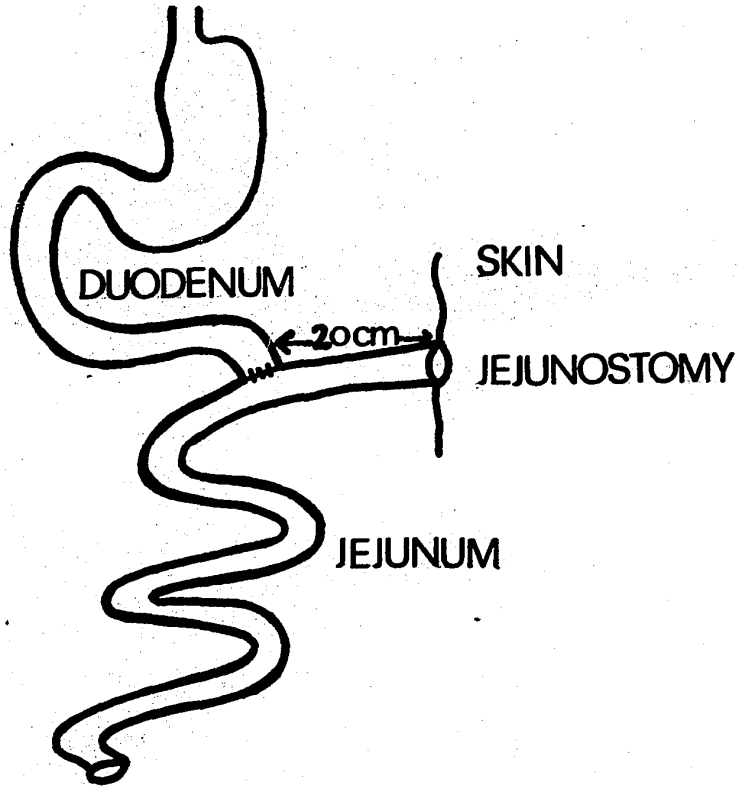
The experiments were performed on healthy mongrel dogs weighing between 16 and 28 kilos. A Roux-en-Y jejunostomy was created in the following way. The animals were anesthetized with intravenous Nembutal. With careful sterile technique, laparotomy was then performed and the continuity of the small bowel was interrupted 20 cm below the Treitz ligament. The proximal end was then reanastomosed to the upper jejunum 20 cm below the level of interruption in an end to side fashion. The free end of the distal jejunum was brought out through the skin to which it was anchored. The dogs were allowed from 2 to 4 weeks of recovery depending on the individual progress. Thus healthy dogs with easy access to the upper small intestine were made available (Figure 13).

b) Electroenterographic estimation of intestinal motility.

Ideally in an in vivo experiment the technique utilized to estimate intestinal motility should avoid laparotomy or anesthesia. In an effort to reproduce as closely as possible the sequence of events following operation in the human, initial experi-

Figure 13.

EXPERIMENTAL MODEL.



Access to the small intestine is provided by a Roux-en-Y preparation. The upper jejunum is severed 20 cm below the ligament of Treitz. The distal jejunum is brought out through the skin and a jejunostomy is constructed. The intestinal continuity is reestablished by anastomosing the proximal end in a termino-lateral fashion 20 cm below the stoma.

ments were designed to record the intestinal activity without interference by sedatives or analgesics. The recording of the electrical activity of the intestine with implanted electrodes according to the technique of McCoy seemed promising in this respect [237]. The method was tried on five dogs, and tracings similar to those reported in the literature were reproduced (Figure 14). However this technique was abandonned for the following reasons:

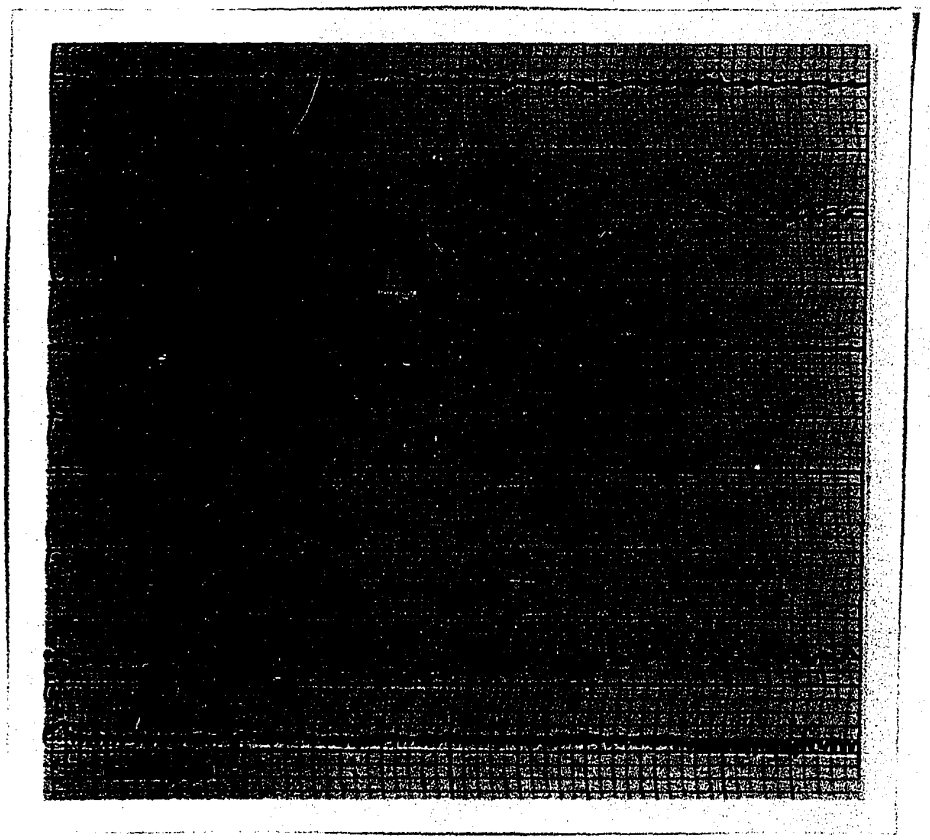
1) This experimental model involves the intraperitoneal presence of wires and electrodes and is associated with a high degree of infection. In addition these wires can cause mechanical interference with the movements of the intestine. Two cases of bowel obstruction were encountered in our experience using this technique.

2) As noted by McCoy himself the quality of the electrical tracing is quite variable and easily influenced by the movements of the dogs [237].

3) The amount of information provided by the electrical method is limited to an overall index of motility. It does not provide any information about the events taking place at the level of the smooth muscle cell membrane [46]. By contrast mechanical recordings of intraluminal pressures are not only a reflection of the overall motor activity of the intestine, but indicate in more quantitable terms the magnitude of the pressures

Figure 14.

ELECTRICAL ACTIVITY OF PROXIMAL JEJUNUM



Slow waves with or without spikes are clearly distinguished. There is no clear correlation between the episodes of spiking and the mechanical recording of intraluminal pressure because of the extreme difficulty of placing the open tipped catheter exactly under an electrical probe in our preparation.

developed and the pattern of the waves. However recording of intestinal electrical activity remains the technique of choice for the study of the basic rhythm and of propagation.

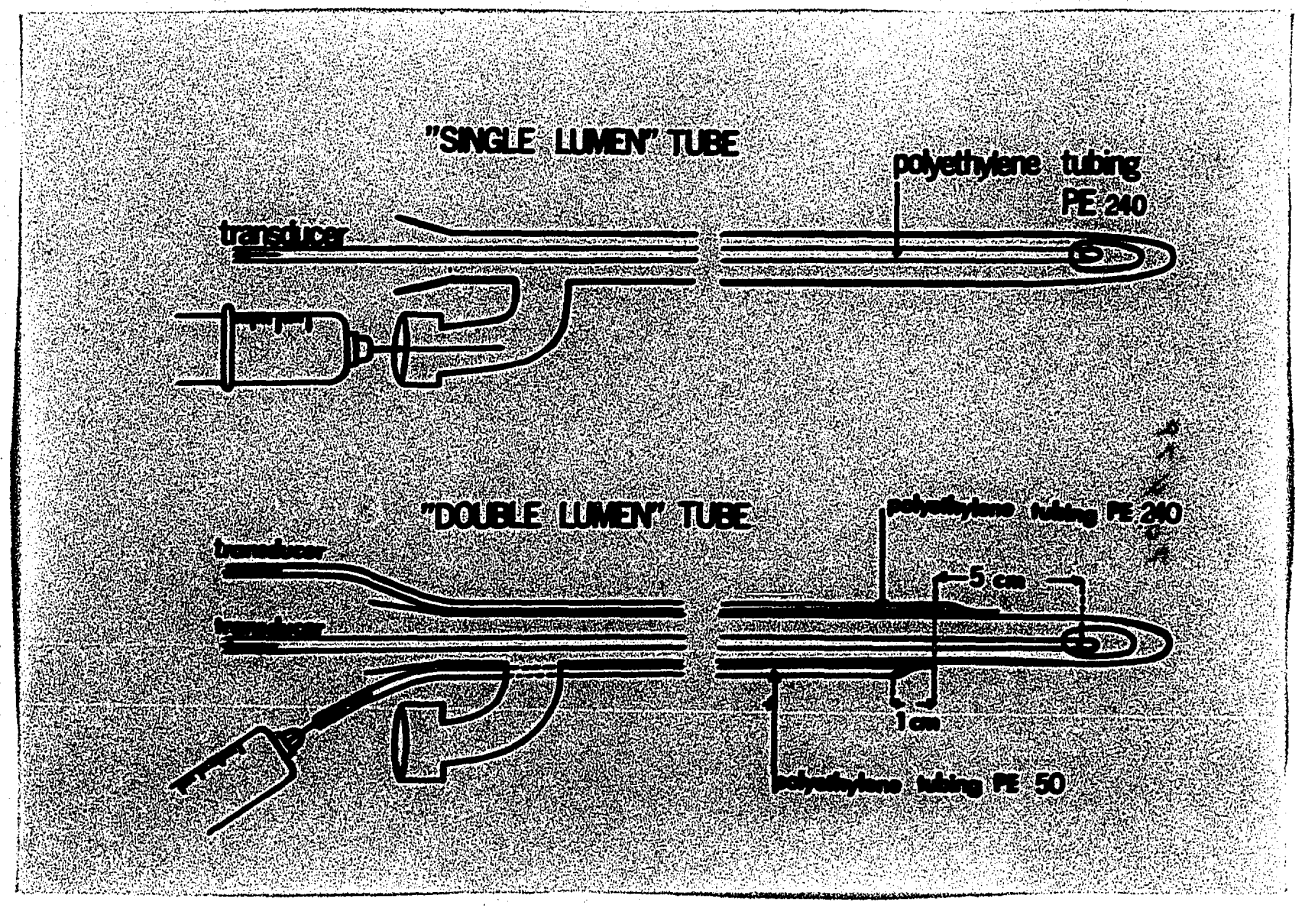
4) Finally it was felt that the technical difficulties inherent to the method were of such a magnitude as to preclude its use for the time available to carry out this study. The associated surgical complications were extremely high and the animals required a long time to recover post-operatively. This was a serious limiting factor in the number of experiments which could be performed, particularly in acute experiments ending with the death of the animal.

c) Estimation of intestinal motility by intraluminal pressure recordings.

Open tipped polyethylene catheters with an internal diameter of 0.066 inch (Intramedic PE 240) were used to construct two main types of tubes. The most simple "single lumen" type consisted of a polyethylene catheter introduced into the lumen of a number 16 Foley rubber catheter. This combination provided a tube of adequate rigidity to allow easy introduction without kinking. It was however sufficiently soft and supple to minimize any possible mucosal trauma. The balloon at the tip of the Foley catheter was perforated with multiple small holes at its distal

Figure 15.

THE TWO TYPES OF RECORDING TUBES USED FOR OUR EXPERIMENTS.

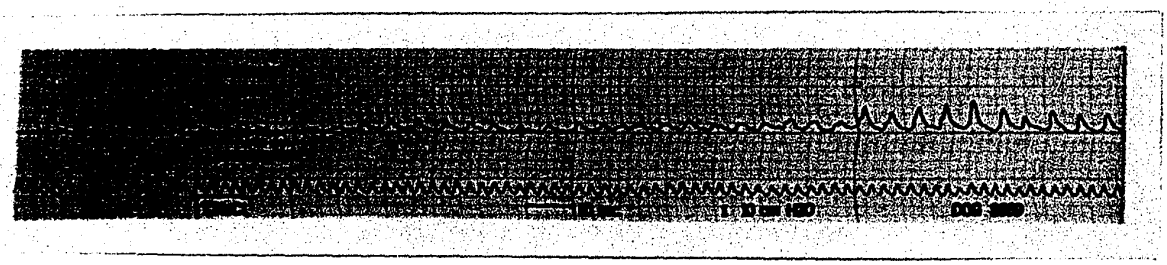


end in order to facilitate instillations into the intestinal lumen. In the second "double lumen" type two additional pieces of tubing were added. Another PE 240 catheter was attached to the side of the Foley, its opening being 5 cm proximal to the distal opening of the Foley. A third smaller polyethylene tube with an internal diameter of 0.023 inch (Intramedic PE 50) was attached to the side of the tube with its distal opening lying 1 cm proximal to the first polyethylene tube (Figure 15). Both main recording catheters were kept under constant irrigation by a microdrip of Ringer's lactate solution so that plugging of the catheter tips would be avoided. Ringer's lactate was used as irrigating fluid because of its similarity to plasma with regard to osmolarity, pH, and individual salt concentration; all these factors are known to cause some stimulation if their values deviate significantly from their plasma level. Single ion concentration is also of importance as physiologic saline was observed to be capable of stimulating intestinal motility (Figure 16).

As will be explained later, the estimation of the spontaneous intrinsic motility of the intestine alone as a measure of intestinal motor function can be misleading. Consequently it was elected to study the motor response to intraluminal mucosal stimulation. As shown previously by Mukuhara the peristaltic reflex can be elicited mechanically by rubbing the mucosa with a soft brush or chemically with the instillation of 0.1 N HCl [81]. It

Figure 16.

EFFECT OF AN INSTILLATION OF 5 cc OF PHYSIOLOGIC SALINE AT 20°C ON JEJUNAL MOTILITY.



was felt that mechanical stimulation would be difficult to control in an in vivo situation. The possibility of inadvertant distention of muscle using a mechanical stimulus thus causing a reflex contraction of myogenic origin would be a difficult problem to control. For this reason chemical stimulation was chosen. 0.1 N HCl was used. However in order to avoid any hypo-osmolar effect (the osmolarity of pure 0.1 N HCl is 200 Mosm/l.) the solution was made up from 1 N HCl diluted in 0.3% saline. Thus a solution having an osmolarity approaching roughly 280 Mosm/l. was obtained. For stimulation 5 cc of this solution were injected into the lumen of the intestine. Together with motility a pneumographic recording was always simultaneously obtained in order to rule out any artefact due to the respiration on the pressure tracing.

The studies were carried out in the following fashion. The dogs were fasted for a minimum of 18 hours prior to the experiment. The tested was placed upon a table where it would lie in a comfortable position. The recording catheter containing the open tipped polyethylene tube was lubricated with an appropriate jelly (Lubritine Abbott) and inserted into the small intestine through the jejunostomy. The catheter was inserted as far as possible, i.e. 37 cm - 38 cm, secured to the animal with tape, and attached to the terminals of a Grass Model 5 Polygraph. The dogs tolerated this procedure extremely well and reacted gene-

rally by complete indifference. After the introduction of the recording tube 5 minutes were allowed to elapse for adaptation to take place before the experiment was started. Then a 10 minute recording of spontaneous motility of the intestine was obtained as a base line before stimulation with 5 cc of 0.1 N NCl was performed. In the normal dog a dramatic response consisting of bursts of pressure waves appeared after a variable time lag. The response appeared somewhat fatigable so that it would become weak or even absent if stimulations were carried out repeatedly at too frequent intervals of time. Conversely the bursts of waves which constituted the response would sometime continue for a prolonged period of time in such a way that it would become impossible to differentiate between the stimulated response and the intrinsic spontaneous activity of the intestine. In addition some variability in the degree of intensity of the responses was also observed. The initial stimulation would be generally followed by a marked response. Following a second stimulation performed 5 minutes later the response was generally more pronounced than the first one though not always. The response to a third stimulation 5 minutes later would generally mimmick the first one. To overcome these problems, i.e. fatigability, responses indistinguishable from spontaneous motility, and variability of response, the following protocol was adopted in an attempt to standardize the interpretation of the responses.

The motor response was arbitrarily divided into three categories depending on whether the contractions would appear within or after 3 minutes after the stimulation, or not at all. Consequently 3 minutes were allowed to elapse after the stimulation and the motility recorded during this period of time was quantitated as described below. In this way the responses obtained during the first 3 minutes after stimulation could be compared in different experimental situations. After these 3 minutes the intestine was "rested" for 5 minutes before any other stimulation was performed. Thus there was an interval of 8 minutes between each stimulation. The above constituted the solution to the problem of determining the end point of the response and to the problem of fatigability. The problem of variability was solved by performing trains of three successive stimulations. The results reported below are the means of the measurements performed on each individual response. This method is comparable to biochemical tests where three determinations are made and their mean accepted as the most reliable value.

Although qualitative differences are easily recognized tracings are difficult to quantitate. Nevertheless they lend themselves to analysis by measurements of various parameters which describe their characteristics such as the time lag between the stimulation and the appearance of the response, the frequency, the maximum amplitude, the number of contractions and the mean

amplitude. The results presented below are reported in the following way:

1. Presence or absence of a response:

   i. presence of a response: a) within 3 minutes after the stimulation

      b) after 3 minutes after the stimulation, but before 8 minutes.

   ii. absence of a response.

The incidence of i, ii, a, b, is reported in absolute values and also as a percentage of the total number of experiments carried out.

2. When a response occurred within 3 minutes after stimulation, the motor activity during these 3 minutes only was considered for the estimation of the following parameters:

   i. time lag

   ii. frequency

   iii. maximum amplitude

   iv. number of contractions

   v. mean amplitude

3. If the response appeared after a delay of over 3 minutes, the following parameters are reported:

   i. time lag

   ii. maximum amplitude

iii. frequency

The number of contractions cannot come under consideration in the latter category because of the impossibility of determining whether the contractions observed are spontaneous or constitute a stimulated response such a long time after the stimulation.

The time lag and the maximum amplitude are measured on the tracing with a ruler. The frequency values are obtained by counting the waves and dividing the number found by the time elapsed. The mean amplitude is calculated by adding up the amplitude of each contraction and dividing the result by the number of contractions considered.

d) <u>The effect of a 5 cc bolus of 0.1 N HCl at 37°C</u>.

A total of 45 stimulations with a bolus of 5 cc 0.1 N HCl at 37°C were performed in 10 different healthy dogs. The motility was recorded with the second type of catheter with two recording lumens in order to detect peristaltic waves. Calculations were made from the tracing obtained from the most distal catheter.

The injection of HCl was invariably followed by a period of complete inhibition which constitutes the time lag period. This seemed to be a characteristic of intraluminal stimulation

as the same phenomenon was similarly observed after injection of physiological saline or local anesthetics. The time lag period is followed by a strong burst of waves presenting the properties of peristalsis as it appeared to be propagated. Initially 2 or 3 moderate contractions appear. They are followed by contractions of maximal intensity which last from 20 to 60 seconds and progressively taper off. A second burst of contractions, generally of lesser amplitude, frequently follows the first burst after a variable interval of 60 to 150 seconds. Rarely this cycle was repeated with the appearance of a third or fourth burst. As a rule a single burst appeared after each stimulation (Figure 17, 18, 19).

Results of the above experiment and analysis of data characterizing the normal response to a stimulus of 0.1 N HCl are outlined in the following tables.

Table IV.

THE INCIDENCE OF RESPONSES TO 0.1 N HCl IN THE NORMAL DOG.

number of experiments	number of responses within 3 minutes	number of responses after 3 minutes	no response
45	42 (93.3%)	1 (2.2%)	2 (4.4%)

Figure 17.

THE RESPONSE TO HCl IN AN ACTIVE INTESTINE.

As expected the time lag is shorter in the upper tracing than in the lower. Note the difference in the shape of the waves between the recording from the proximal and distal catheter.

Figure 18.

THE RESPONSE TO HCl IN A QUIESCENT INTESTINE.

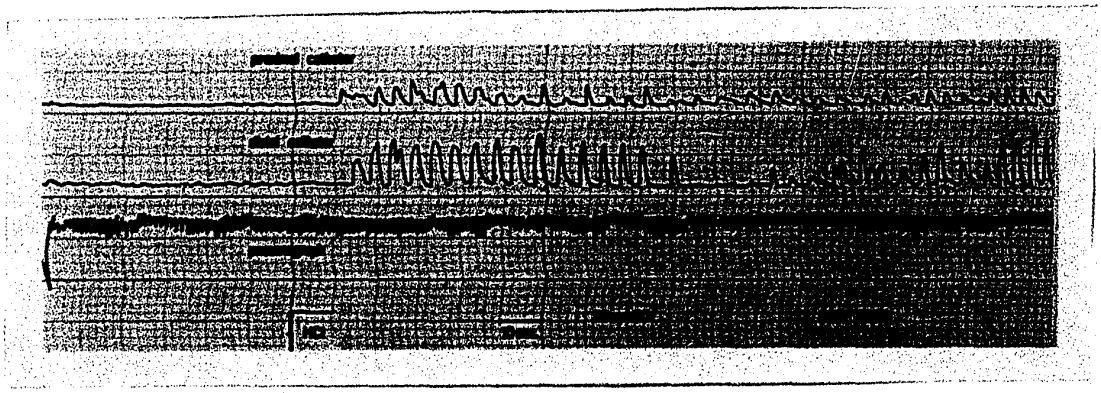
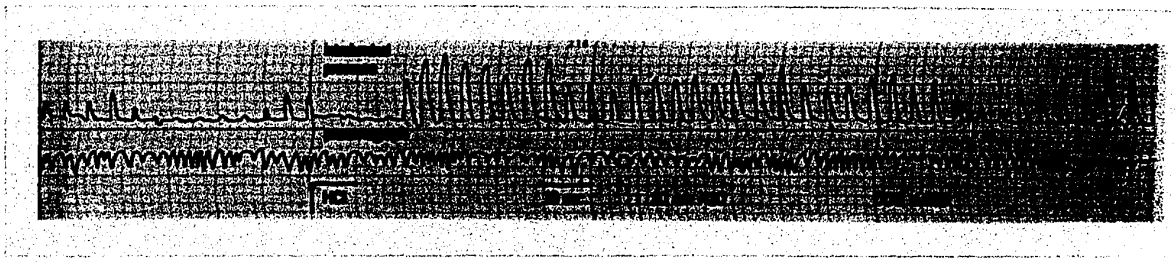


Figure 19.

THE HCl RESPONSE RECORDED WITH THE SINGLE LUMEN TUBE.



In the majority of the dogs a motor response was obtained within 3 minutes after the injection of HCl. This response is further analysed in Table V. Only one response appeared after 3 minutes after stimulation, characterized by a time lag of 220 seconds and a maximum amplitude of 56 cm of water.

Table V.

THE NORMAL RESPONSE TO THE INTRALUMINAL INJECTION OF 5 cc 0.1 N HCl at 37°C.

T.L.	Fr.	Mx.A.	N.Ctr.	Me.A.
41.0 ± 20.8 (42)	14.2 ± 1.0 (42)	88.4 ± 25.9 (42)	25.6 ± 7.1 (42)	39.5 ± 16.6 (42)

Data presented as mean ± SD.
(n): number of experiments.
T.L.: time lag, seconds.
Fr.: frequency, number of waves/minutes.
Mx.A.: maximum amplitude, pressure in cm of water.
N.CTr.: number of contractions.
Me.A.: mean amplitude, pressure in cm of water.

The maximum amplitude and the frequency of the response to HCl was compared with the same values measured in a 10 minutes strip of base line activity in 12 of these dogs. For reasons readily apparent the number of contractions or the mean amplitude of spontaneous contractions cannot be compared to those of a stimulated response.

Table VI.

COMPARISON BETWEEN THE MAXIMUM AMPLITUDE AND FREQUENCY OF SPONTANEOUSLY OCCURING CONTRACTIONS WITH THE RESPONSE TO HCl 0.1 N.

	maximum amplitude (cm of water)	(contractions/minute
spontaneous contractions	86.4 ± 27.1 SD (12)	14.0 ± 1.0 SD (12)
response to HCl	88.4 ± 25.9 SD (42)	14.2 ± 1.0 SD (42)

Data presented as mean ± SD.
(n): number of experiments.

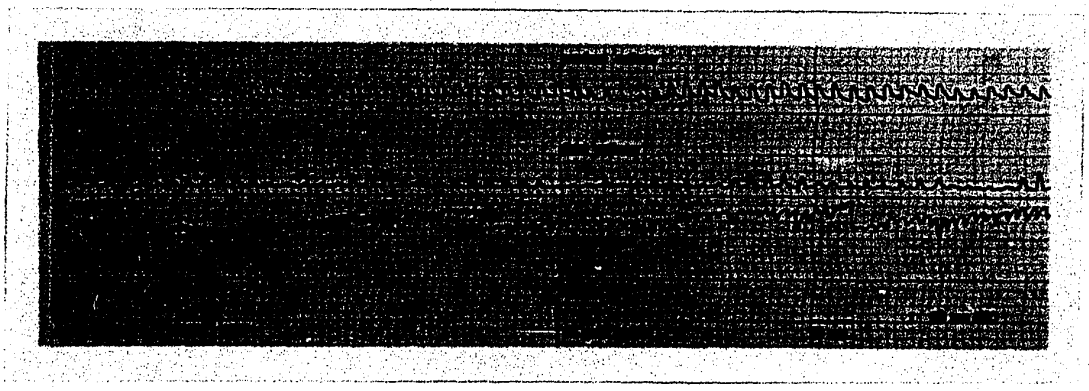
It is obvious that there is no difference between either the frequency or the maximum amplitude of spontaneous contractions and that of contractions following HCl stimulation. Thus the response to HCl is in the physiological range and does not represent "supercontractions". Also the frequency of the basic rhythm does not appear to be altered by HCl.

e) The effect of a 5 cc bolus of Ringer's lactate.

In order to verify the reproducibility of the response to HCl, a series of control experiments were performed with instillations of Ringer's lactate at 37°C. 21 such experiments were

Figure 20.

RECORDING PRESENTING THE FEATURES OF "NO RESPONSE" FOLLOWING RINGER'S LACTATE INJECTION.



performed in 4 of the same dogs. The characteristic pattern of the HCl response was seen to consist of a latent interval constituting the time lag period followed by a motor response. Such a response could not be consistently reproduced following the injection of Ringer's lactate. In 14 out of 21 experiments the spontaneous motility would continue uninterrupted without any sign of interference (Figure 20). This is in sharp contrast with the response to HCl which was invariably preceded by a period of inhibition. Although the motor activity was preceded by a time lag in 7 control experiments and could be labelled as a response to the injection (Figure 21), comparative analysis of the wave patterns revealed significant differences. Results of analysis of wave patterns of the control experiments are reported in tables VII and VIII. In table VII the motility during the first 3 minutes after the injection of Ringer's lactate is described whether a time lag was present or not. Both are compared with the HCl response. Even though the injection of Ringer's lactate might be capable of causing a "volume" response, the chemical action of HCl appears to influence significantly the maximum and the mean amplitude. In the so-called "response" to Ringer's lactate the maximum amplitude is only 46.4 $\pm$ 10.8 SD cm of water, but it reaches 88.4 $\pm$ 25.9 SD cm of water following HCl. The mean amplitude is only 20.8 $\pm$ 12.0 SD cm of water following Ringer's lactate versus 39.5 $\pm$ 16.6 SD cm of water fol-

lowing HCl. However the number and the frequency of the contractions do not appear to be influenced by HCl.

Table VII.

THE MOTILITY OF THE DOGS HAVING PRESENTED THE FEATURES OF A "RESPONSE" TO THE INJECTION OF 5 cc OF RINGER'S LACTATE AT 37°C.

T.L.	Fr.	Mx.A.	N.Ctr.	Me.A.
62.0 ± 44.9	14.6 ± 1.1	46.4 ± 10.8	28.2 ± 10.6	20.8 ± 12.0
(7)	(7)	(7)	(7)	(7)
		$p < 0.001$		$p < 0.05$

Data presented as mean ± SD.
p value obtained by Student's t test; comparison with the normal response to HCl (Table V).
(n): number of experiments.
T.L.: time lag, seconds.
Fr.: frequency, number of waves/minute.
Mx.A.: maximum amplitude, pressure in cm of water.
N.Ctr.: number of contractions.
Me.A.: mean amplitude, pressure in cm of water.

Table VIII.

THE MOTILITY OF THE INTESTINE FOLLOWING THE INJECTION OF 5 cc OF RINGER'S LACTATE AT 37°C. OVERALL RESULTS.

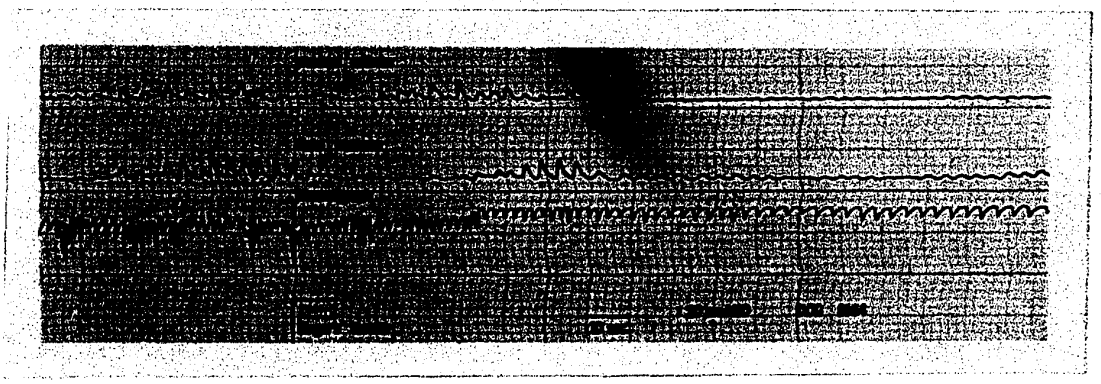
T.L.	Fr.	Mx.A.	N.Ctr.	Me.A.
	14.8 ± 0.9	51.5 ± 11.0	32.6 ± 9.3	22.7 ± 6.7
	(21)	(21)	(21)	(21)
		$p < 0.001$		$p < 0.01$

Data presented as mean ± SD.
p value obtained by Student's t test; comparison with the normal response to HCl (Table V).
(n): number of experiments.
T.L.: time lag, seconds.
Fr.: frequency, number of waves/minute.
Mx.A.: maximum amplitude, pressure in cm of water.
N.Ctr.: number of contractions.
Me.A.: mean amplitude, pressure in cm of water.

Remark: as the presence of a time lag was very unpredictable, even in the same dog, its mean was not calculated in Table VIII.

Figure 21.

RECORDING PRESENTING THE FEATURES OF A "RESPONSE" FOLLOWING RINGER'S LACTATE INJECTION.



f) The effect of a bolus of 5 cc 0.1 N HCl on the intraluminal pH.

In 2 dogs the pH of the intraluminal content was measured in the fluid aspirated from the intestinal lumen with the injection catheter of the double lumen tube. About 1 cc of fluid was aspirated 1 minute before the injection of HCl, and 1, 2, and 3 minutes after. Sequential measurements were obtained in two trains of stimulations, and the results are outlined in Table IX. Neutralisation takes place relatively rapidly during the first 3 minutes after the injection. Complete neutralisation is usually achieved before the next stimulation. No parallel could be drawn between the pattern of acid neutralisation and the magnitude of the response or the phenomenon of fatigability (Figure 22, 23). If a response was initiated, second and third bursts of contractions were frequently observed to occur in the face of progressive neutralization of intraluminal pH.

Table IX.

INTRALUMINAL pH CHANGES FOLLOWING INJECTION OF 0.1 N HCl.

dog number	1 min. before stimulation	1 min. after stimulation	2 min. after stimulation	3 min. after stimulation
	pH	pH	pH	pH
	7.3	1.0	1.7	3.5
8809	6.9	1.1	2.5	5.5
	8.0	1.0	2.0	3.9
	5.6	1.0	1.7	2.8
8872	6.4	1.0	1.7	6.5
	6.9	1.1	3.9	5.6

Figure 22.

THE pH VARIATIONS DURING THE RESPONSE TO THE INJECTION OF 5 cc 0.1 N HCl.

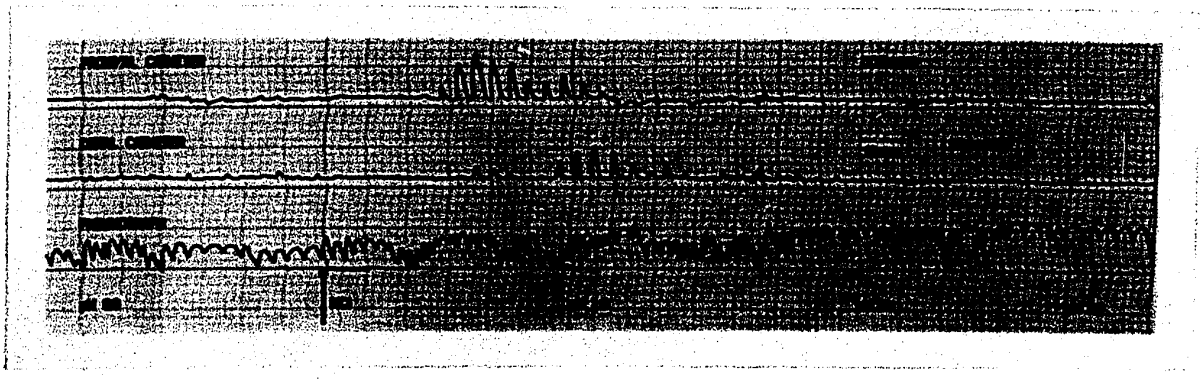
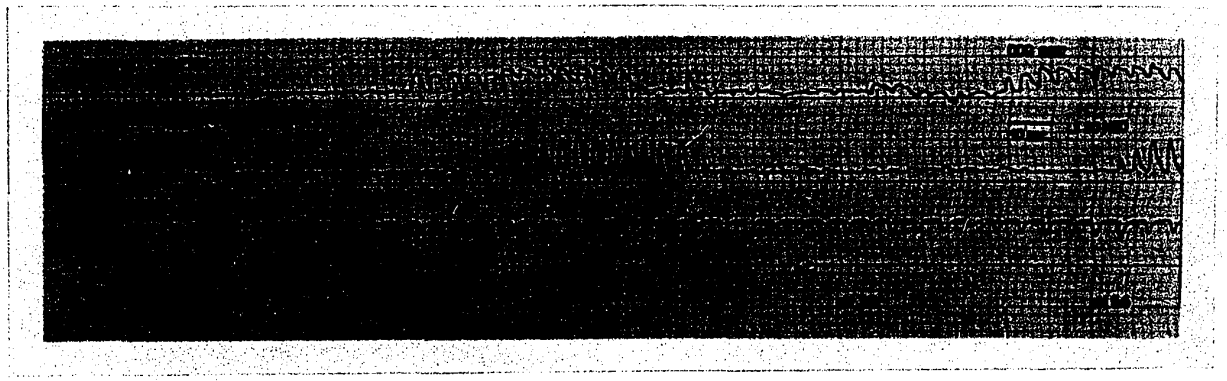


Figure 23.

THE pH VARIATIONS DURING THE RESPONSE TO THE INJECTION OF 5 cc 0.1 N HCl.



g) The role of temperature of the bolus of HCl.

The first stimulations attempted with 0.1 N HCl were performed at room temperature. Thus the question arose whether the observed response was due to the temperature of the bolus since sudden cooling of the mucosa following the injection could be conceivably an effective thermal stimulus. To clarify the matter 20 stimulations with HCl at 20°C were performed in 4 different dogs and the results compared with the measurements obtained at 37°C. The results are summarised in tables X and XI.

Table X.

INCIDENCE OF RESPONSES FOLLOWING HCl STIMULATION AT 20°C.

number of experiments	number of responses within 3 min.	number of responses after 3 min.	no response
20	16 (80%)	1 (5%)	3 (15%)

Table XI.

THE RESPONSES TO 0.1 N HCl AT 20°C OCCURING WITHIN 3 MINUTES.

T.L.	Fr.	Mx.A.	N.Ctr.	Me.A.
36.2 ± 19.9 (16)	14.8 ± 0.8 (16)	107.6 ± 29.2 (16)	24.9 ± 10.6 (16)	47.9 ± 15.7 (16)

Data presented as mean ± SD.
(n) number of experiments.
T.L. time lag, seconds
Fr. frequency, number of waves/minute.
Mx.A. maximum amplitude, pressure in cm of water.
N.Ctr. number of contractions.
Me.A. mean amplitude, pressure in cm of water.

The 3 totally unsuccessful stimulations all occured in the same dog.

Analysis of the responses occuring within 3 minutes sug-

gested an increase in maximal and mean amplitude following stimulation with cold HCl. However these apparent changes were not statistically significant. Thus in the experimental conditions described, stimulation with a cold bolus appeared to have little influence on the response. However all subsequent experiments reported in this study were carried out with HCl at 37°C to rule out any possible temperature influence.

3. PERFUSION STUDIES AND THE EFFECT OF LOCAL ANESTHETICS.

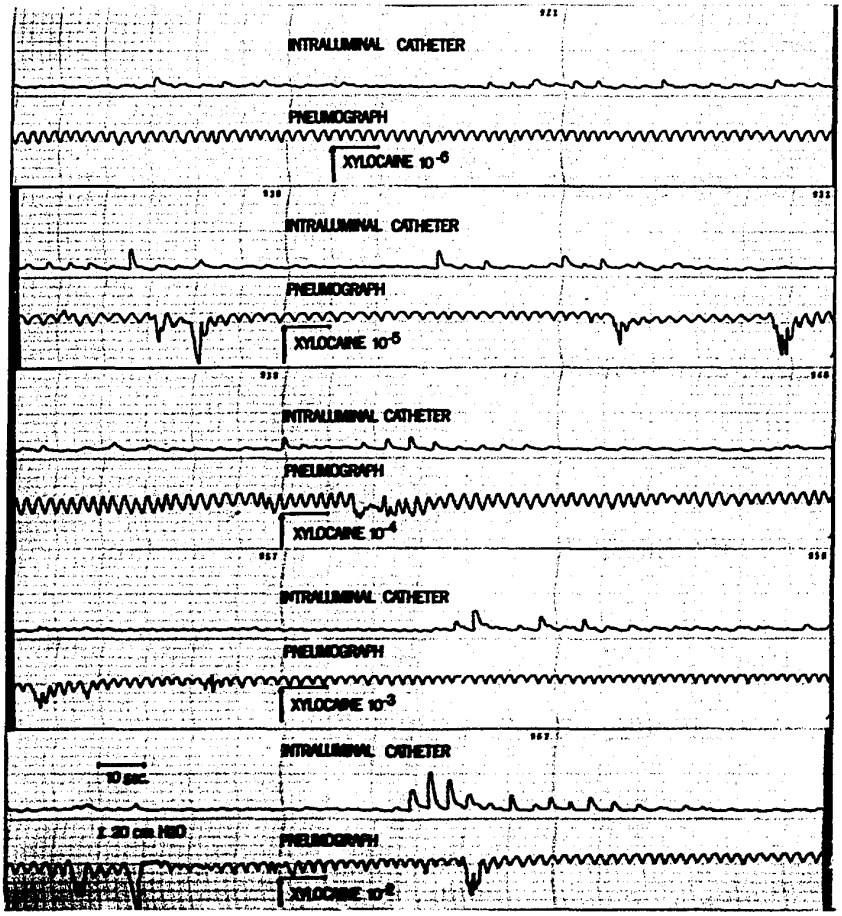
Gregory inhibited the stimulatory effect of acid on denervated loops of intestine with 5% procaine [238]. Similar studies by Bülbring et al. indicated that cocaine at a concentration of 10^{-4} abolished the peristaltic reflex by a selective effect on the mucosa. In accordance to the experimental hypothesis of this study it was important to determine whether the response to HCl could be blocked by a local anesthetic. Xylocaine was used as the anesthetic agent.

a) The effect of a 5 cc bolus of xylocaine.

Various concentrations of xylocaine ranging from 10^{-6} to 10^{-2} were prepared by dilution with Ringer's lactate. 5 cc of each one of these solutions at 37°C were injected intraluminally as in the HCl stimulations. A total of 6 instillations with each concentration (10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, 10^{-2}) were performed in two different dogs. Much to our surprise xylocaine itself was observed to stimulate a motor response which appeared to be of a magnitude roughly proportional to the concentration. The response itself appeared very similar to the response produced by HCl with the presence of a time lag followed by a motor response (Figure 24).

Figure 24.

THE RESPONSE TO THE INJECTION OF 5 cc OF XYLOCAINE AT VARIOUS CONCENTRATIONS.



Stimulation with HCl was attempted at various intervals of time ranging from one to five minutes after the injection of xylocaine. In every case no blockade was observed. This might be due to dilution of the xylocaine in the intestinal secretions, absorption and quick dissipation in the blood flow or propulsion further down in the intestine and absorption. To avoid these disadvantages perfusion studies were undertaken.

b) <u>The effect of a perfusion of Ringer's lactate, 0.1 N HCl, and xylocaine</u>.

These experiments were carried out in four different dogs in the following manner. A single lumen tube was used and after its insertion into the jejunostomy, 5 minutes were allowed to elapse for adaptation. A 10 minute strip was then recorded for base line activity. Stimulation with o.1 N HCl was carried out as usual. 8 minutes after the last stimulation (3 minute interval for the estimation of the response + 5 minutes "rest"), a perfusion with Ringer's lactate, 0.1 N HCl, or xylocaine was started with a Havard pump at the rate of 1.225 ml/min. An extremely low flow was chosen in order to avoid any volume distention effect while still exposing the mucosa to the studied chemical. The perfusate passed through a tubing coil placed in a water bath at 37°C. The perfusion lasted 10 minutes. 1 minute

Table XII.

PERFUSION STUDIES.

perfusate	Fr.	Mx.A.	N.Ctr.	Me.A.
none (base-line)	13.5 ± 1.0 (4)	91.0 ± 21.0 (4)	110.8 ± 21.7 (4)	34.7 ± 13.8 (4)
Ringer's lactate	12.8 ± 0.5 (4)	100.3 ± 22.6 (4)	96.8 ± 13.3 (4)	33.9 ± 6.4 (4)
0.1 N HCl	13.0 ± 0.8 (4)	111.0 ± 44.3 (4)	64.0 ± 19.3 (4)	29.1 ± 12.7 (4)
p value			$p < 0.02$	
xylocaine (10^{-2})	13.3 ± 1.0 (4)	62.0 ± 26.2 (4)	44.8 ± 36.1 (4)	29.2 ± 17.2 (4)
p value			$p < 0.025$	

Data presented as mean ± SD.
(n): number of experiments.
Fr.: frequency, number of waves/minute.
Mx.A.: maximum amplitude, pressure in cm of water.
N.Ctr.: number of contractions.
Me.A.: mean amplitude, pressure in cm of water.

p value: obtained by Student's t test; comparison with the base line. Comparison was also made with the measurements obtained during Ringer's lactate perfusion, but the p values were of no significance and are consequently omitted.

after the end of the perfusion a train of 3 stimulations with HCl was performed. The motility during the different perfusions was compared with the 10 minute base line strip and with the motility observed during Ringer's lactate perfusion. Similarly the responses to HCl stimulation after the different types of perfusion were submitted to statistical analysis and compared with each other.

When compared with the resting activity the main effect of HCl perfusion seems to be a reduction of the number of contractions. This is statistically significant for $p < 0.02$. The other values do not show any significant change (Table XII). Surprisingly there is no statistical difference between the values measured during Ringer's lactate and HCl perfusion. Simple visual observation gave the impression that the motility was more active during the first 5 minutes of HCl perfusion as compared with the following 5 minutes. However it is not confirmed by the Student's t test (Table XIII).

It was decided to study the effect of xylocaine at the concentration of 10^{-2} after pilot evaluation had shown in a couple of dogs that little or no change had to be expected with lower concentrations. Xylocaine 10^{-2}, as expected, has an inhibitory action; but only the number of contractions is significantly decreased when compared to the resting activity. If the comparison is made with the activity during Ringer's lactate perfusion, the

Table XIII.

ANALYSIS OF THE PERFUSION WITH 0.1 N HCl: FIRST AND SECOND 5 MINUTES.

	Fr.	Mx.A.	N.Ctr.	Me.A.
1st 5 min.	13.0 ± 0.8 (4)	98.5 ± 26.3 (4)	38.3 ± 16.8 (4)	37.3 ± 17.6 (4)
2nd 5 min.	13.3 ± 1.0 (4)	65.5 ± 39.4 (4)	25.8 ± 3.5 (4)	27.1 ± 18.0 (4)

Data presented as mean ± SD.
(n): number of experiments.
Fr.: frequency, number of waves/minute.
Mx.A.: maximum amplitude, pressure in cm of water.
N.Ctr.: number of contractions.
Me.A.: mean amplitude, pressure in cm of water.

changes are less apparent and lose their statistical significance. However the comparison of the first 5 minutes of xylocaine 10^{-2} perfusion with the following 5 minutes shows that almost all the activity is concentrated during the first 5 minutes in 3 out of 4 dogs. The second period of 5 minutes is thus characterised by total inhibition in these animals (Table XIV).

After each perfusion a train of 3 stimulations with HCl was carried out. Results are given in tables XV and XVI. The responses after Ringer's lactate perfusion appear to be essentially

Table XIV.

ANALYSIS OF THE PERFUSION WITH XYLOCAINE 10^{-2}: FIRST AND SECOND 5 MINUTES.

	Fr.		Mx.A.		N.Ctr.		Me.A.	
dog	5 min.	10 min.	5 min.	10 min.	5 min.	10 min.	5 min.	10 min.
1	14	0	48	0	25	0	19.4	0
2	12	0	84	0	40	0	39.5	0
3	13	12	164	64	63	34	62.9	23.4
4	14	0	32	0	17	0	11.0	0

Data presented as absolute values.
Fr.: frequency, number of waves/minute.
Mx.A.: maximum amplitude, pressure in cm of water.
N.Ctr.: number of contractions.
Me.A.: mean amplitude, pressure in cm of water.

normal. Xylocaine 10^{-2} perfusion decreases significantly the number of contractions during the 3 minute period following stimulation and the time lag is lengthened. However, when present, all the responses occured within 3 minutes. HCl perfusion seems to have a similar influence though less pronounced. Recovery of the responses to normal after xylocaine perfusion takes place after 8 to 20 minutes. The responses to the second stimulation show already some improvement and reversion to normal is almost complete by the time of the third stimulation.

Table XV.

THE INCIDENCE OF RESPONSES TO 0.1 N HCl AFTER THE EXPOSURE OF THE INTESTINAL MUCOSA TO VARIOUS PERFUSATES FOR 10 MINUTES.

perfusate	number of experiments	number of responses within 3 minutes	number of responses after 3 minutes	no response
base line	12	12	0	0
Ringer's lactate	12	12	0	0
0.1 N HCl	12	12	0	0
xylocaine (10^{-2})	12	9 (75%)	0	3 (25%)

Table XVI.

THE RESPONSE TO HCl AFTER EXPOSURE OF THE INTESTINAL MUCOSA TO VARIOUS PERFUSATES FOR 10 MINUTES.

perfusate	T.L.	Fr.	Mx.A.	N.Ctr.	Me.A.
none (base line)	24.9 ± 4.0 (12)	13.1 ± 0.6 (12)	96.3 ± 36.6 (12)	30.7 ± 3.6 (12)	52.8 ± 22.0 (12)
Ringer's lactate	35.5 ± 9.2 (12)	13.0 ± 0.2 (12)	110.0 ± 45.3 (12)	24.8 ± 9.3 (12)	54.2 ± 22.1 (12)
0.1 N HCl	45.6 ± 20.4 (12)	13.3 ± 0.7 (12)	73.9 ± 10.3 (12)	20.3 ± 5.2 (12)	32.4 ± 7.4 (12)
p value				p 0.02	
xylocaine 10^{-2}	56.9 ± 14.2 (9)	13.3 ± 0.8 (9)	73.8 ± 25.2 (9)	22.0 ± 4.6 (9)	34.3 ± 6.0 (9)
p value	p 0.01			p 0.025	

Data presented as mean ± SD.
(n): number of experiments.
T.L.: time lag, seconds.
Fr.: frequency, number of waves/minute.
Mx.A.: maximum amplitude, pressure in cm of water.
N.Ctr.: number of contractions.
Me.A.: mean amplitude, pressure in cm of water.

p value: obtained by Student's t test; comparison with the base line.

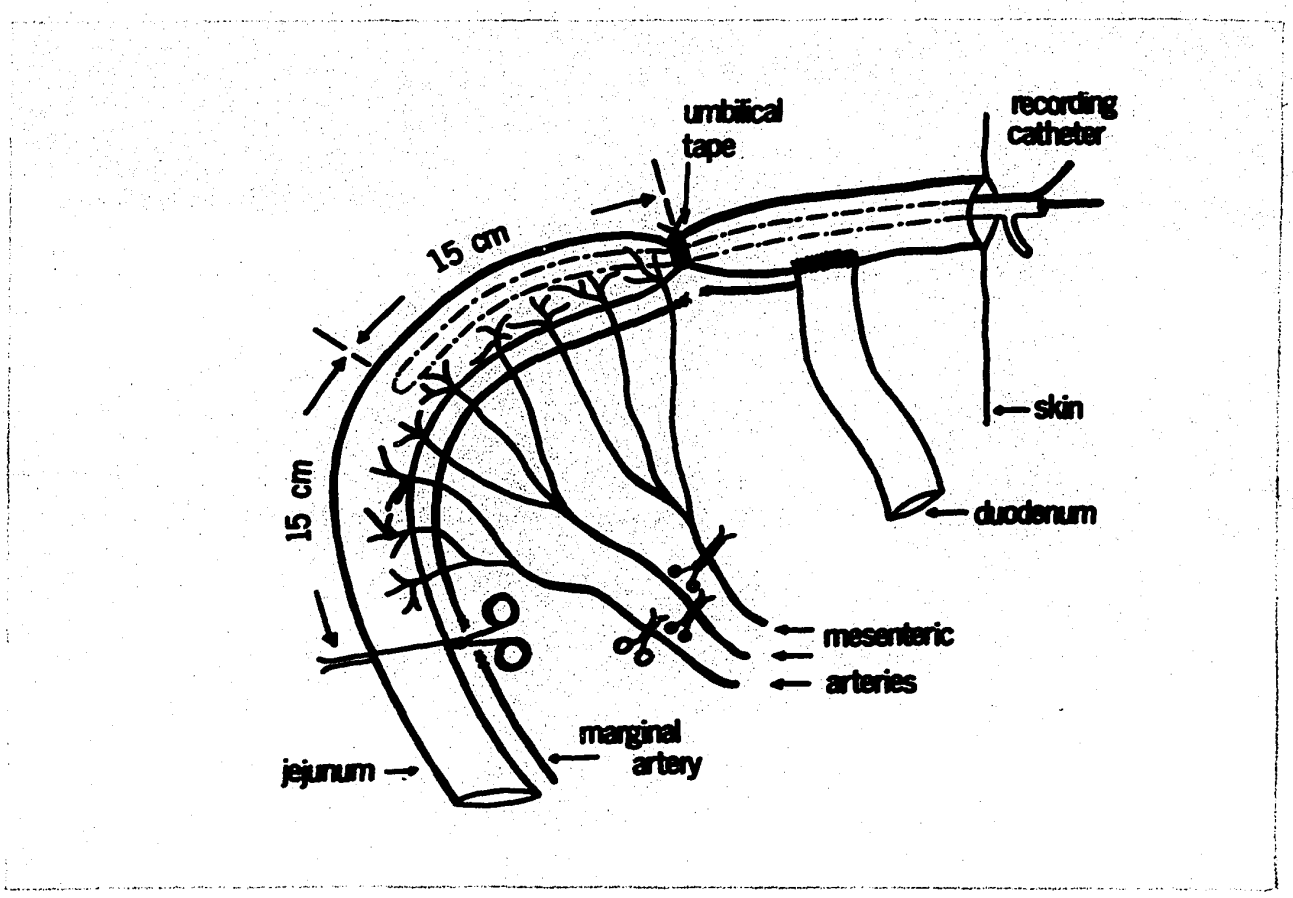
4. THE EFFECT OF ACUTE ISCHEMIA AND THE RESULTING MUCOSAL SLOUGHING ON THE INTESTINAL MOTILITY.

The effect of acute ischemia and shock on the intestinal mucosa have been described in details in chapter I, paragraph 11. In this set of experiments mucosal damage and shedding was produced in a segment of proximal jejunum by an episode of acute ischemia and its effect on motility was recorded during the period of recovery. This experiment was designed to study the influence of disrupted mucosal integrity upon intestinal motor activity.

Two groups of 4 dogs each were considered, one forming the experimental group and the other the controls. As for all the other experiments the dogs were fasted for a minimum period of 18 hours prior to the measurements. The intestinal motility was recorded with the double lumen catheter. 5 minutes were allowed to elapse for adaptation after insertion of the recording tube. Then a 10 minute strip was obtained for basal activity. A train of 3 stimulations with 0.1 N HCl were carried out for base line purposes. A number 16 intravenous canula (Intracath, Abbott) was inserted in one of the front legs and an intravenous infusion of Ringer's lactate was started. The dogs were kept fasting and intravenous administration of this solution was maintained during the entire length of the experiment, i.e. 24 to 48 hours.

Figure 25.

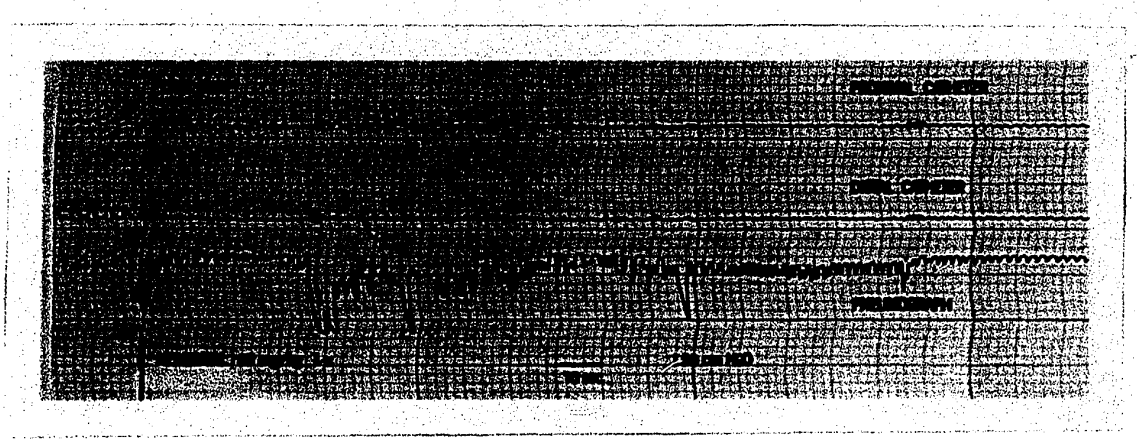
THE CLAMPING PROCEDURE.



Each animal received an average of 1500 ml to 2500 ml of Ringer's lactate per day. They were then anesthetized with intravenous Nembutal and the abdomen was shaved and prepared with Metaphen tincture. Laparotomy was performed through a midline incision and the loop of intestine containing the recording catheter was extracted out of the peritoneal cavity. The marginal vessels were interrupted and tied 15 cm above and 15 cm below the tip of the recording catheter. The mesentery was slit at this level as far down as possible. The arteries supplying the segment of jejunum so isolated were dissected carefully as close to their point of origin as possible. A ligature of umbilical tape was passed around the intestine containing the recording tube at the level of the proximal end of the segment and a soft clamp coated with a piece of rubber tubing was applied at the distal end. Bulldog vascular clamps were delicately closed on the arteries leading to the isolated segment of bowel, but the venous drainage and the nerves were left intact (Figure 25). The clamping period lasted 1 hour. A biopsy was then taken from the antimesenteric border at a level distal to the tip of the recording catheter and the defect was oversewn. The umbilical tape ligature and the soft clamp were removed, and the intestine was replaced into the peritoneal cavity. Abdominal closure was performed the same way as for the jejunostomy operation. Recordings were obtained 3 hours, 6 hours, 12 hours, 24 hours and in 2 dogs of each group

Figure 26.

THE EFFECT OF AN INTRAVENOUS INJECTION OF NEMBUTAL ON THE SPONTANEOUS MOTILITY.



48 hours after closure. At each recording session a 10 minute strip was obtained for evaluation of the spontaneous motility before a train of 3 stimulations with 0.1 N HCl was carried out. After completion of the experiment the dogs were sacrificed, autopsy was carried out, and a specimen of clamped and unclamped bowel was removed for histological examination.

The above protocol was also applied to the control dogs, but a "sham" operation was performed. It was identical to the operative procedure described in page 118, but the mesenteric arteries supplying the isolated segment of jejunum were not clamped. They were also cautiously dissected as in the experimental group of animals, and, with extreme care not to damage the accompanying veins or nerves, bulldog vascular clamps were also placed around them, but not closed and immediately removed. 1 hour was allowed to elapse as if clamping was taking place and then abdominal closure was performed as in the experimental group of dogs. Thus in the control group of dogs the mesenteric circulation of the studied jejunal loop was never interrupted.

a) The effect of Nembutal.

As the dogs were still under the influence of Nembutal anesthesia for a period of varying duration after the end of the operative procedure, the influence of the drug on intestinal motility was evaluated in 5 dogs. After a train of 3 stimulations with HCl for base line estimation, 25 mg to 35 mg of Nembutal per kilogram were administered intravenously. 5 minutes later a train of stimulations with HCl was attempted. This was repeated 40 and 80 minutes after the injection. Almost immediately after the injection the spontaneous motility of the intestine came to a complete standstill (Figure 26). This persisted as long as the dog was asleep. During the wake-up period the dogs manifested irregular spells of semi-consciousness followed by episodes of persisting unconsciousness. These spells would often be accompanied by a temporary resurgence of spontaneous motility. The normal pattern reappeared only with complete recovery of consciousness.

Attempts to stimulate intestinal motility with HCl were met with a considerable increased failure rate with moderate improvement as time elapsed (Table XVII). The time lag was significantly prolonged after the stimulations performed at 40 and 80 minutes. Similarly the number of contractions occurring within 3 minutes after the stimulation was equally reduced and a certain

Table XVII.

THE INCIDENCE OF RESPONSES TO HCl UNDER NEMBUTAL ANESTHESIA.

time after Nembutal	number of experiments	number of responses within 3 minutes	number of responses after 3 minutes	no response
base line	15	15	0	0
5 min.	14	7 (50%)	0	7 (50%)
40 min.	14	6 (42.8%)	3 (21.4%)	5 (35.7%)
80 min.	14	7 (50%)	2 (14.3%)	5 (35.7%)

number of responses were delayed past the 3 minutes mark. The maximum amplitude was also significantly reduced in the responses to the train of stimulations performed 5 and 40 minutes after the onset of anesthesia. There was no evidence of improvement of the characteristics of the responses occurring within 3 minutes after the stimulation during the period of study. The characteristics of the responses which were delayed beyond 3 minutes were not suitable for statistical comparison. In addition to the prolonged time lag, the maximum amplitude of these delayed responses tended to be reduced. These figures are reported in tables XVII, XVIII, and XIX.

Table XVIII.

THE RESPONSES TO 0.1 N HCl UNDER NEMBUTAL ANESTHESIA.

time	T.L.	Fr.	Mx.A.	N.Ctr.	Me.A.
base line (before Nembutal)	30.7 ± 14.5 (15)	13.6 ± 0.6 (15)	96.5 ± 30.2 (15)	27.4 ± 5.7 (15)	47.2 ± 19.1 (15)
5 min. after Nembutal	63.0 ± 49.3 (7)	14.1 ± 0.8 (7)	45.2 ± 25.0 (7)	16.6 ± 12.4 (7)	27.6 ± 20.7 (7)
p value			$p < 0.05$		
40 min. after Nembutal	100.1 ± 44.2 (6)	13.5 ± 1.2 (6)	27.5 ± 18.7 (6)	11.8 ± 5.4 (6)	20.2 ± 14.8 (6)
p value	$p < 0.025$		$p < 0.01$	$p < 0.01$	
80 min. after Nembutal	86.3 ± 18.8 (7)	14.1 ± 1.4 (7)	43.8 ± 28.7 (7)	14.2 ± 0.7 (7)	27.7 ± 21.0 (7)
p value	$p < 0.01$			$p < 0.005$	

Data presented as mean ± SD.
(n): number of responses occurring within 3 minutes after the stimulation.
T.L.: time lag, seconds.
Fr.: frequency, number of waves/minute.
Mx.A.: maximum amplitude, pressure in cm of water.
N.Ctr.: number of contractions.
Me.A.: mean amplitude, pressure in cm of water.

p value: obtained by Student's t test; comparison with the base line.

Table XIX.

THE DELAYED RESPONSES TO 0.1 N HCl STIMULATION (OCCURRING AFTER OVER 3 MINUTES).

time after Nembutal	T.L.	Fr.	Mx.A.
40 min.	240.0 ± 42.4 (3)	13.5 ± 2.1 (3)	44.0 ± 11.3 (3)
80 min.	287.0 ± 145.7 (2)	12.0 ± 1.4 (2)	28.0 ± 22.6 (2)

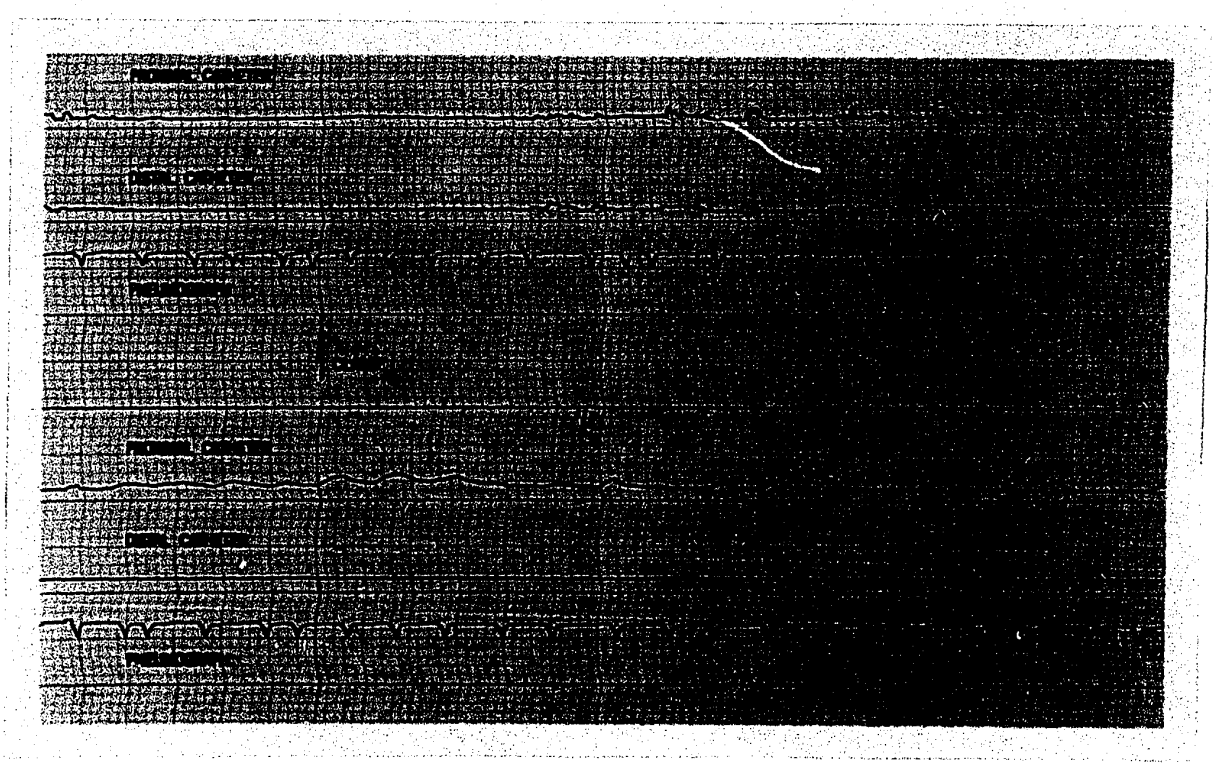
Data presented as mean ± SD.
(n): number of experiments.
T.L.: time lag, seconds.
Fr.: frequency, number of waves/minute.
Mx.A.: maximum amplitude, pressure in cm of water.

b) The motility of an intestinal segment with ischemic mucosal damage.

Immediately after clamping of its arterial blood supply the segment of intestine under study became extremely pale and underwent a succession of vigorous contractions lasting for several minutes. These contractions then progressively diminished until complete standstill occurred. Immediately after the reestablishment of the blood supply the reverse change in colour was obser-

Figure 27.

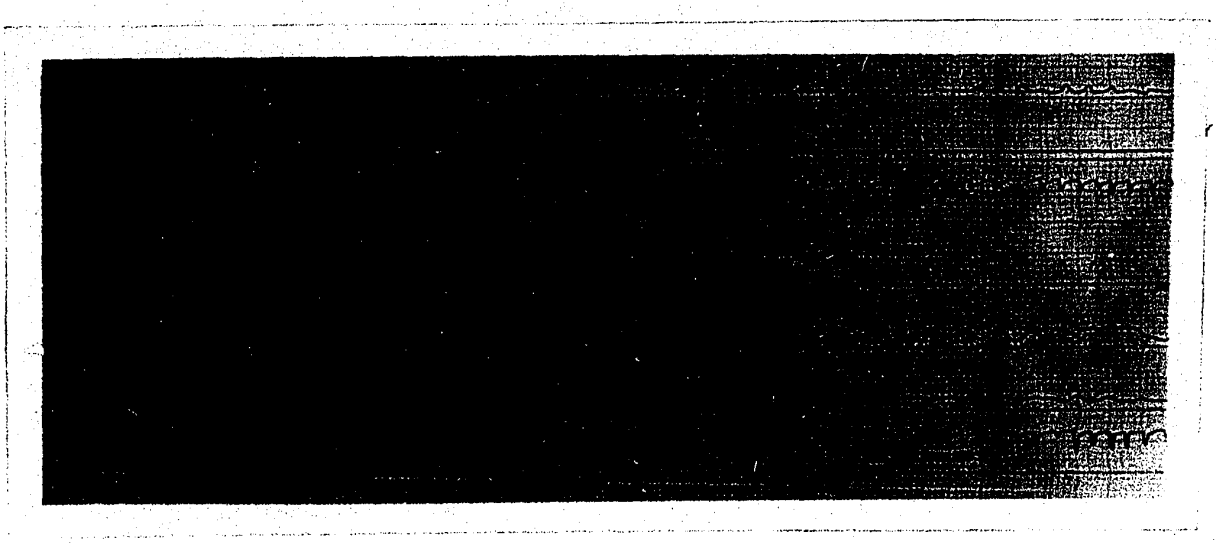
SPASTIC CONTRACTIONS FOLLOWED OCCLUSION OF ARTERIAL BLOOD SUPPLY.



(The lower portion of the graph is the continuation of the upper part).

Figure 28.

IRREGULAR SPASTIC CONTRACTIONS TOOK PLACE AFTER THE REESTABLISHMENT OF BLOOD FLOW.



(The lower portion of the graph is the continuation of the upper part).

ved as the intestine became vivid pink in colour due to reactive hyperemia. Irregular spastic contractions took place for a few minutes but this motor activity did not propagate to the distal healthy intestine (Figure 27, 28). The biopsy taken distally to the recording catheter showed consistently severe damage corresponding to the grade III or IV of the classification presented in Chapter I, paragraph 11. The mucosa of many villi was completely sloughed off with accumulation of the debris into the lumen. In others mucosal lifting and separation without complete detachment was evident (Figure 29, 30, 31). Careful examination of the neural ganglia of the myenteric and submucous plexuses revealed no evidence of damage on light microscopy. The Nissl granules had a normal appearance and there was no suggestion of cytoplasmic vacuolisation. The nucleus of the neurones seemed unaltered. At laparotomy 24 hours later the segment of clamped intestine and its mesentery appeared severely edematous. The clamped intestine was darker than the normal loops and the markedly swollen mesentery was covered by a film of opalescent fibrin. However normal arterial pulsation was observed. At 48 hours the changes were essentially similar, but less severe. The arteries were examined carefully for the presence of a thrombus, but none was found. However there were a few clots around the dissected arteries of dog 8809. The villi of the clamped intestine were almost entirely covered by a fragile layer of cuboid

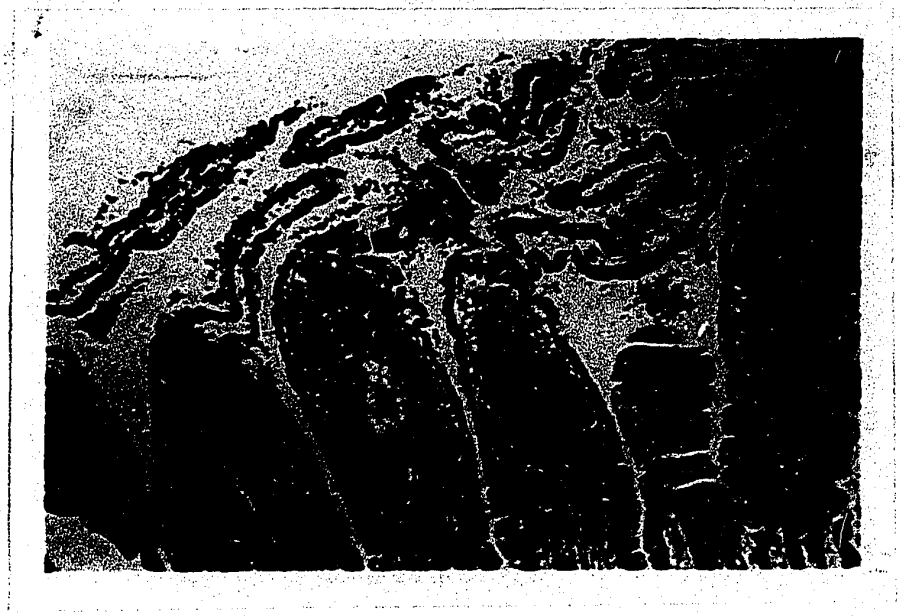
Figure 29.

THE INTESTINAL MUCOSAL LESION AFTER THE INTERRUPTION OF ARTERIAL BLOOD FLOW FOR 1 HOUR. GRADE IV DAMAGE.

The mucosa is completely sloughed into the intestinal lumen.

Figure 30.

THE INTESTINAL MUCOSAL LESION AFTER THE INTERRUPTION OF ARTERIAL BLOOD FLOW FOR 1 HOUR. GRADE III DAMAGE.



The mucosa is completely shed but still attached to the villi.

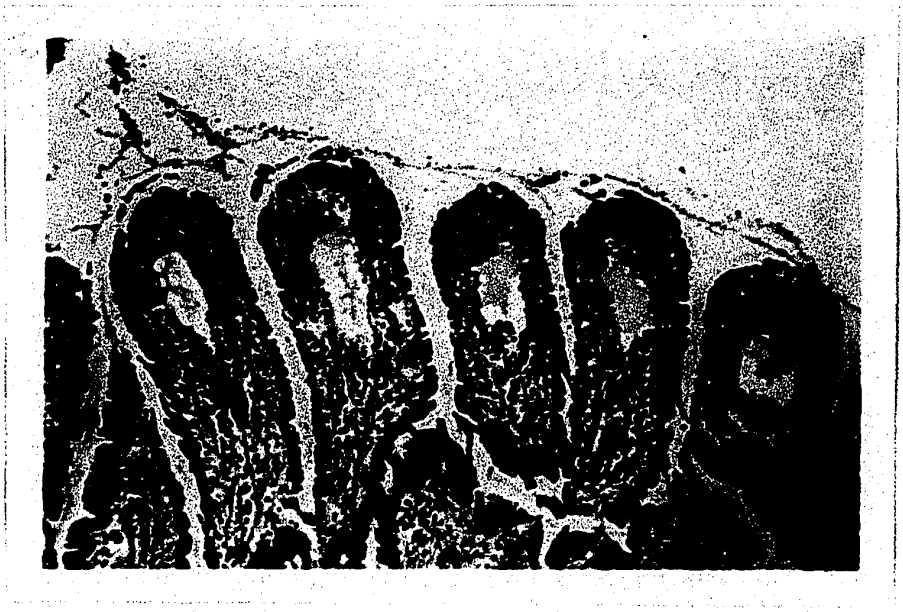
Figure 31.

THE INTESTINAL MUCOSA IMMEDIATELY AFTER A "SHAM" CLAMPING OPERATION.

Control of the lesions shown in Figure 29 and 30.

Figure 32.

THE INTESTINAL MUCOSA 24 HOURS AFTER THE CLAMPING OPERATION.



The villi are partially covered by friable cuboid cells.

Figure 33.

THE INTESTINAL MUCOSA OF THE CONTROLS 24 HOURS AFTER THE "SHAM" OPERATION.

The tip of the villi presents a round cells infiltrate with occasional discrete epithelial lesions.

Figure 34.

THE INTESTINAL MUCOSA OF THE CONTROLS 24 HOURS AFTER THE "SHAM" OPERATION.

The tip of the villi presents a round cells infiltrate with occasional discrete epithelial lesions.

Figure 35.

THE INTESTINAL MUCOSA 48 HOURS AFTER THE CLAMPING OPERATION.

The villi are completely reepithelialized with persistence of an occasional defect at the tip. A diffuse infiltrate is still present.

Figure 36.

THE INTESTINAL MUCOSA OF THE CONTROLS 48 HOURS AFTER THE "SHAM" OPERATION.

Persistence of an infiltrate at the tip of the villi.

cells by 24 hours. These cells were extremely friable and often the tips of such villi were devoid of any cellular covering layer (Figure 32). In the control dogs the main feature observed at the end of 24 hours was an infiltrate of mononuclear cells in the stroma of the tip of the villi. Often there were small defects in the continuity of the mucosa at the tip of the villi with occasional areas of mild lifting of surface cells (Figure 33, 34). At 48 hours the mucosa of the clamped and unclamped bowel was almost identical in appearance with a few scattered small defects at the tip of the villi (Figure 35, 36).

The spontaneous motility of the control and clamped segment is described for each dog of both groups in table XX a, b, & c, and in figures 37 to 44. Measurements at 48 hours post-operatively were performed on 2 dogs only in each group as the 2 others were sacrificed at 24 hours in order to follow the progress of healing of the mucosa in the clamped segment of intestine.

When the maximum amplitude, the mean amplitude and the number of contractions are considered, the general trend in the control dogs is obvious. There was no spontaneous motility three hours after closure in all of the control dogs. In 3 out of 4 dogs this complete standstill extended up to the sixth and twelfth hour. One of the animals showed signs of recovery at the sixth hour while for the others recuperation was not detected before the twelfth hour. Beyond 12 hours post-operatively a pro-

Table XX a.

THE SPONTANEOUS MOTILITY IN THE CONTROL AND CLAMPED INTESTINE.

time	wave charac-	dog number, controls				dog number, clamped			
	teristic	1	2	3	4	5	6	7	8
pre-op.	Fr.	15.0	13.7	14.7	14.0	15.0	0.0	13.0	0.0
	Mx.A.	72.0	60.0	40.0	80.0	84.0	0.0	120.0	0.0
	N.Ctr.	112.0	44.0	29.0	80.0	101.0	0.0	115.0	0.0
	Me.A.	20.4	24.4	10.3	22.4	29.0	0.0	39.4	0.0
3 hours	Fr.	0.0	0.0	0.0	0.0	14.0	13.0	0.0	13.0
post-op.	Mx.A.	0.0	0.0	0.0	0.0	20.0	10.0	0.0	80.0
	N.Ctr.	0.0	0.0	0.0	0.0	55.0	58.0	0.0	28.0
	Me.A.	0.0	0.0	0.0	0.0	7.0	5.0	0.0	27.9

Data presented as absolute values.
Fr.: frequency, number of waves/minute.
Mx.A.: maximum amplitude, pressure in cm of water.
N.Ctr.: number of contractions.
Me.A.: mean amplitude, pressure in cm of water.

Table XX b.

THE SPONTANEOUS MOTILITY IN THE CONTROL AND CLAMPED INTESTINE.

time	wave charac-	dog number, controls				dog number, clamped			
	teristic	1	2	3	4	5	6	7	8
6 hours post-op.	Fr.	0.0	0.0	0.0	16.0	0.0	0.0	16.0	0.0
	Mx.A.	0.0	0.0	0.0	32.0	0.0	0.0	16.0	0.0
	N.Ctr.	0.0	0.0	0.0	34.0	0.0	0.0	10.0	0.0
	Me.A.	0.0	0.0	0.0	15.5	0.0	0.0	8.8	0.0
12 hours	Fr.	12.6	0.0	0.0	0.0	14.0	13.0	14.0	13.0
	Mx.A.	32.0	0.0	0.0	0.0	60.0	8.0	80.0	36.0
	N.Ctr.	43.0	0.0	0.0	0.0	48.0	18.0	47.0	13.0
	Me.A.	10.0	0.0	0.0	0.0	18.7	7.3	33.7	22.2

Data presented as absolute values.
Fr.: frequency, number of waves/minute.
Mx.A.: maximum amplitude, pressure in cm of water.
N.Ctr.: number of contractions.
Me.A.: mean amplitude, pressure in cm of water.

Table XX c.

THE SPONTANEOUS MOTILITY IN THE CONTROL AND CLAMPED INTESTINE.

time	wave charac-	dog number, controls				dog number, clamped			
	teristic	1	2	3	4	5	6	7	8
24 hours	Fr.	14.0	12.0	14.5	11.0	15.0	13.0	14.0	0.0
post-op.	Mx.A.	60.0	32.0	12.0	24.0	100.0	20.0	52.0	0.0
	N.Ctr.	102.0	39.0	32.0	47.0	60.0	22.0	14.0	0.0
	Me.A.	16.0	11.3	6.4	11.8	44.3	5.8	31.1	0.0
48 hours	Fr.	14.0	12.0	-.-	-.-	14.0	14.0	-.-	-.-
post-op.	Mx.A.	180.0	32.0	-.-	-.-	40.0	20.0	-.-	-.-
	N.Ctr.	132.0	94.0	-.-	-.-	56.0	50.0	-.-	-.-
	Me.A.	50.0	11.7	-.-	-.-	13.7	8.2	-.-	-.-

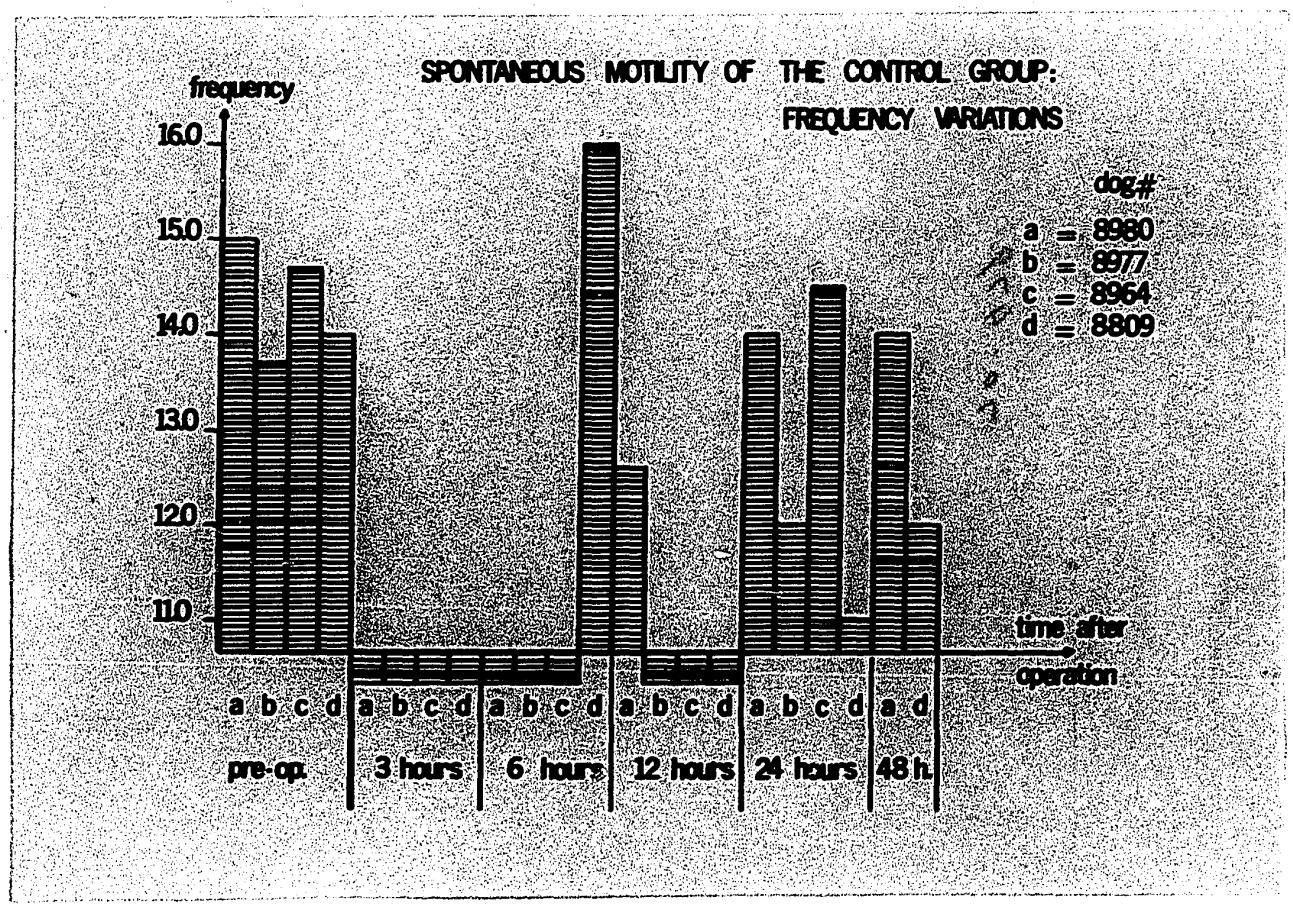
Data presented as absolute values.
Fr.: frequency, number of waves/minute.
Mx.A.: maximum amplitude, pressure in cm of water.
N.Ctr.: number of contractions.
Me.A.: mean amplitude, pressure in cm of water.

gressive improvement in motility was generally observed in the control animals. The variations in frequency are more difficult to interpret as no value can be estimated in the absence of any motor activity. Consequently the sequence of events is difficult to follow until the twenty fourth hour when the motility resumes. At the twenty fourth hour all the values are decreased when compared with the pre-operative level. The only value obtained in the twelfth hour is similarly decreased. By contrast the only dog which presented any motor activity at the sixth hour postoperatively had an increased frequency. But the measurements performed on this animal later on were in agreement with the general trend. It should be emphasized that no statistical evaluation is really possible when dealing with the spontaneous motility because of the significant number of zeros observed. However the situation is different when the responses to HCl are considered, because they are categorized in different groups according to presence or absence of a response and the value of the time lag. Thus homogeneous sets of results obtained in different circumstances can be compared. Consequently, if the general trend of the spontaneous motility is indicated, the significance of these variations in the statistical sense of the term is unknown. The same reasoning applies to the spontaneous motility of the clamped intestine to be presented below.

In the clamped intestine some spontaneous motility was pre-

Figure 37.

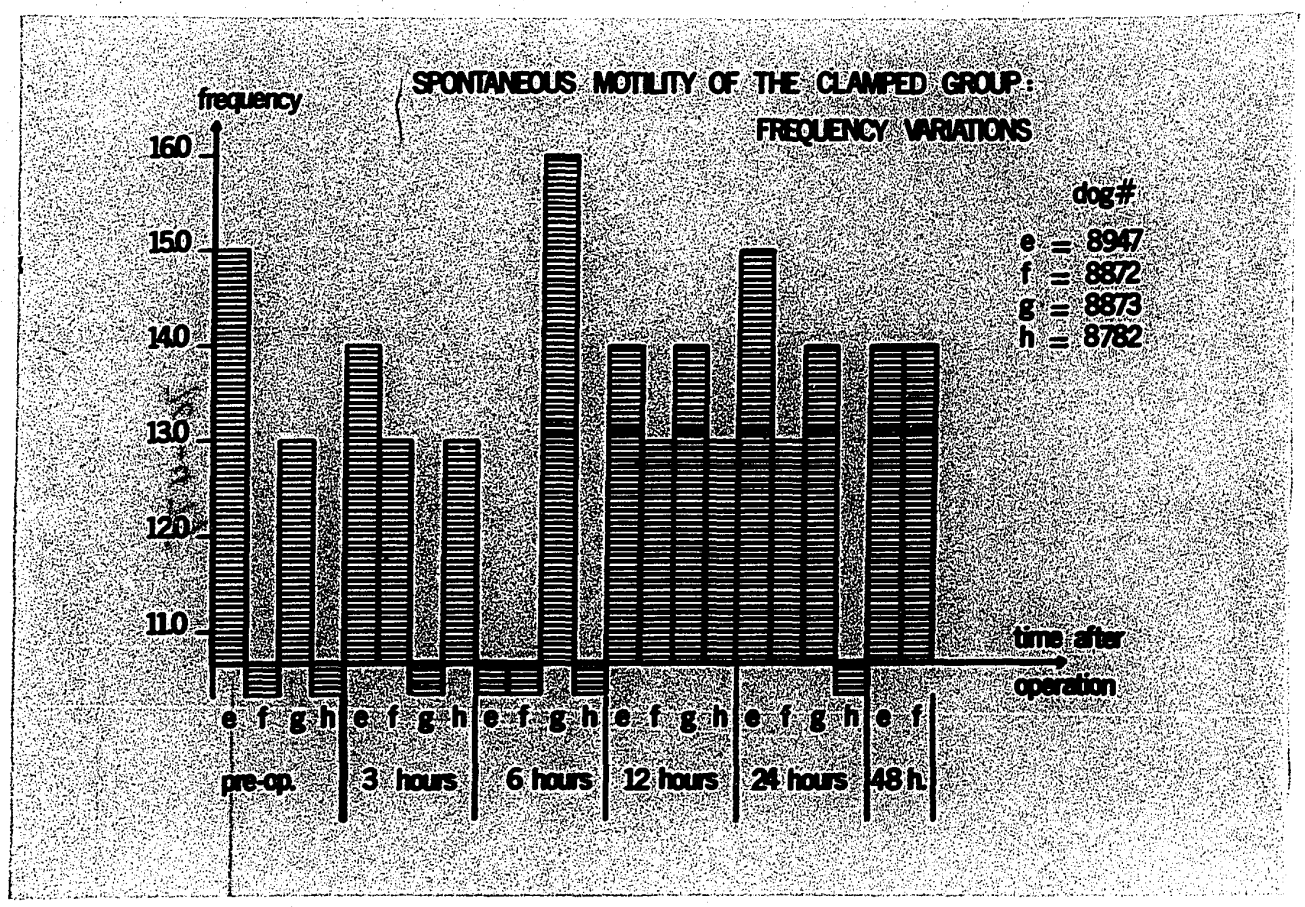
SPONTANEOUS MOTILITY OF THE CONTROL GROUP: FREQUENCY VARIATIONS.



The frequency is expressed in terms of "number of waves per minute". The zeros are represented by a small square below the base line.

Figure 38.

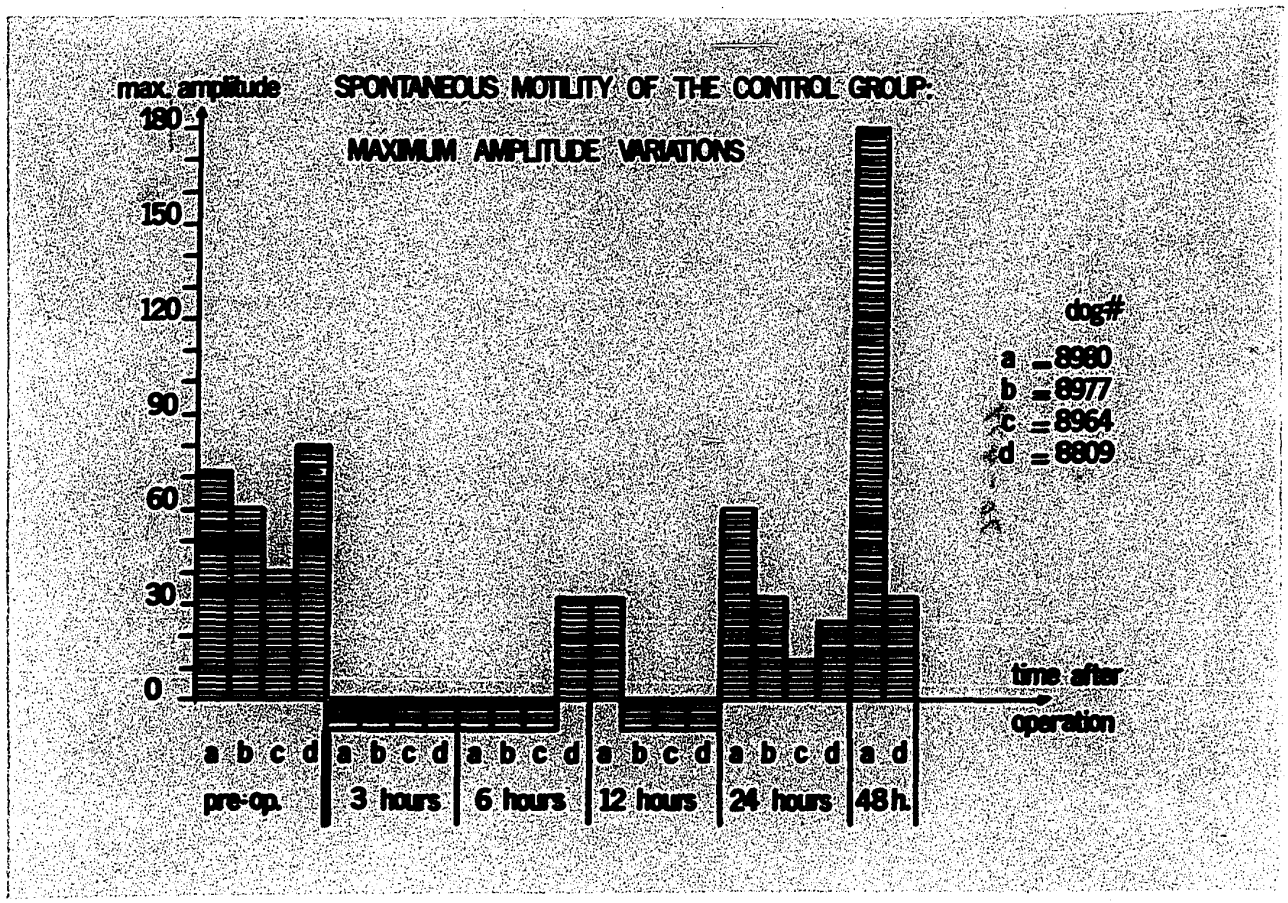
SPONTANEOUS MOTILITY OF THE CLAMPED GROUP: FREQUENCY VARIATIONS.



The frequency is expressed in terms of "number of waves per minute". The zeros are represented by a small square below the base line.

Figure 39.

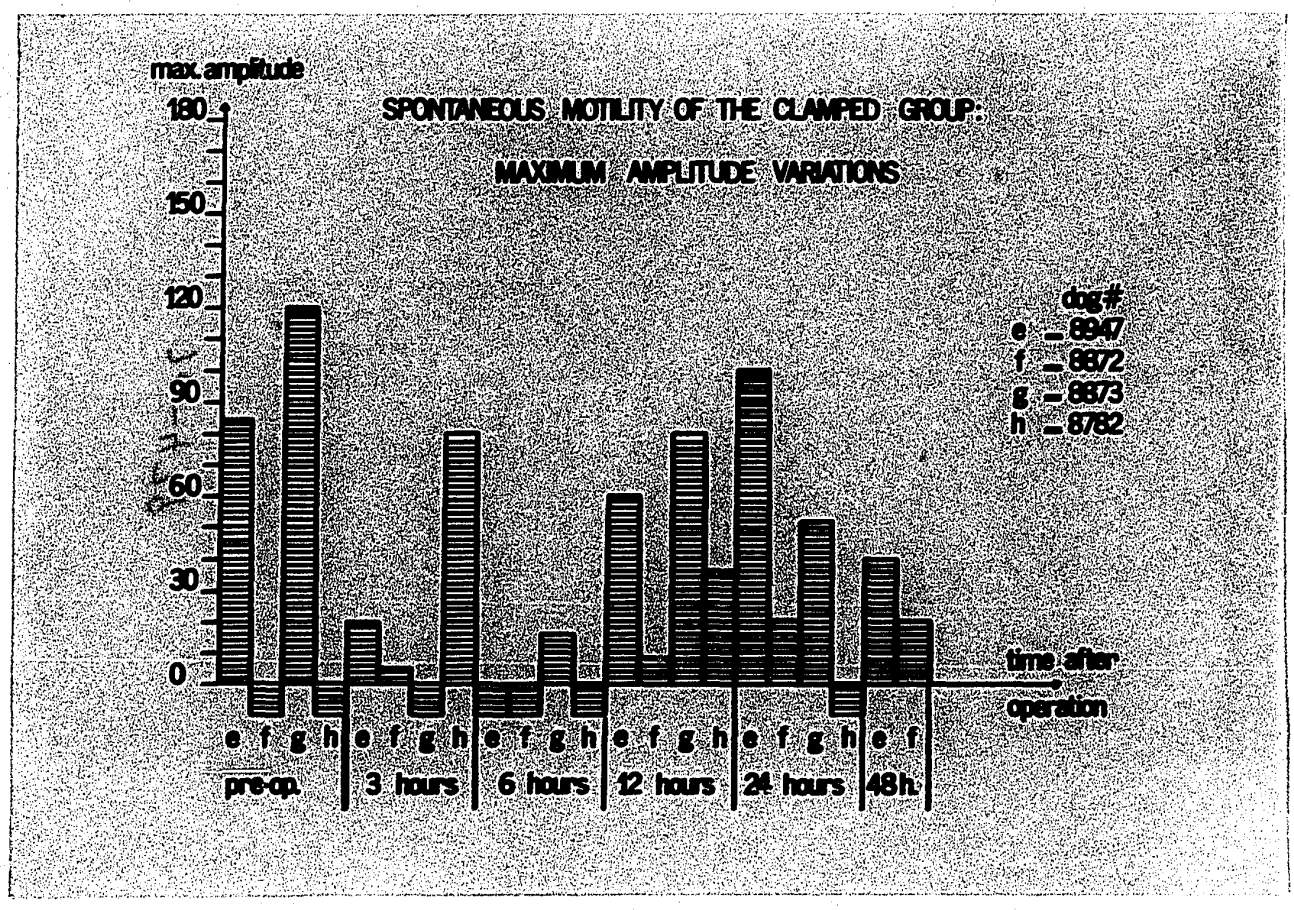
SPONTANEOUS MOTILITY OF THE CONTROL GROUP: MAXIMUM AMPLITUDE VARIATIONS.



The maximum amplitude is expressed in cm of water. The zeros are represented by a small square below the base line.

Figure 40.

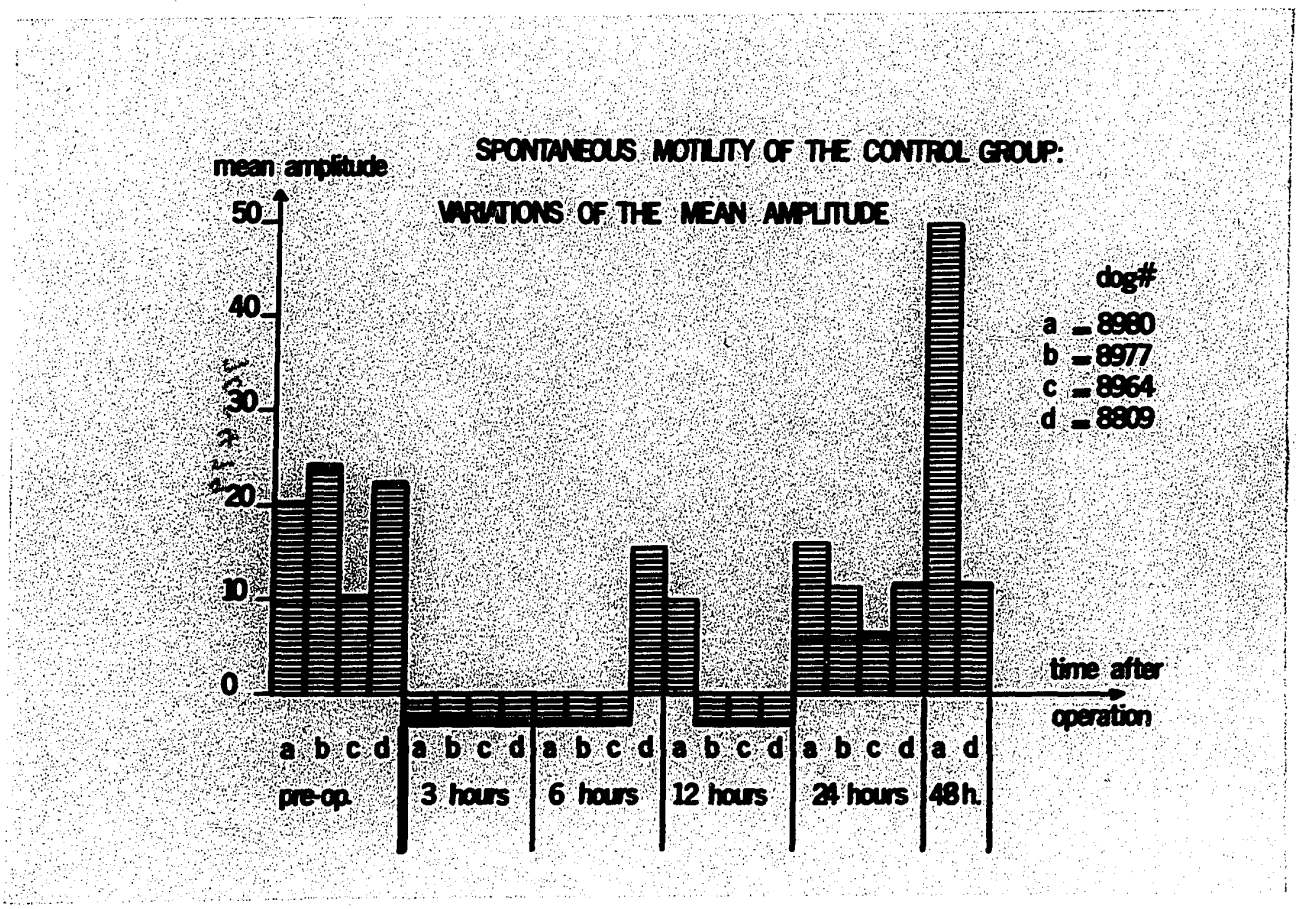
SPONTANEOUS MOTILITY OF THE CLAMPED GROUP: MAXIMUM AMPLITUDE VARIATIONS.



The maximum amplitude is expressed in cm of water. The zeros are represented by a small square below the base line.

Figure 41.

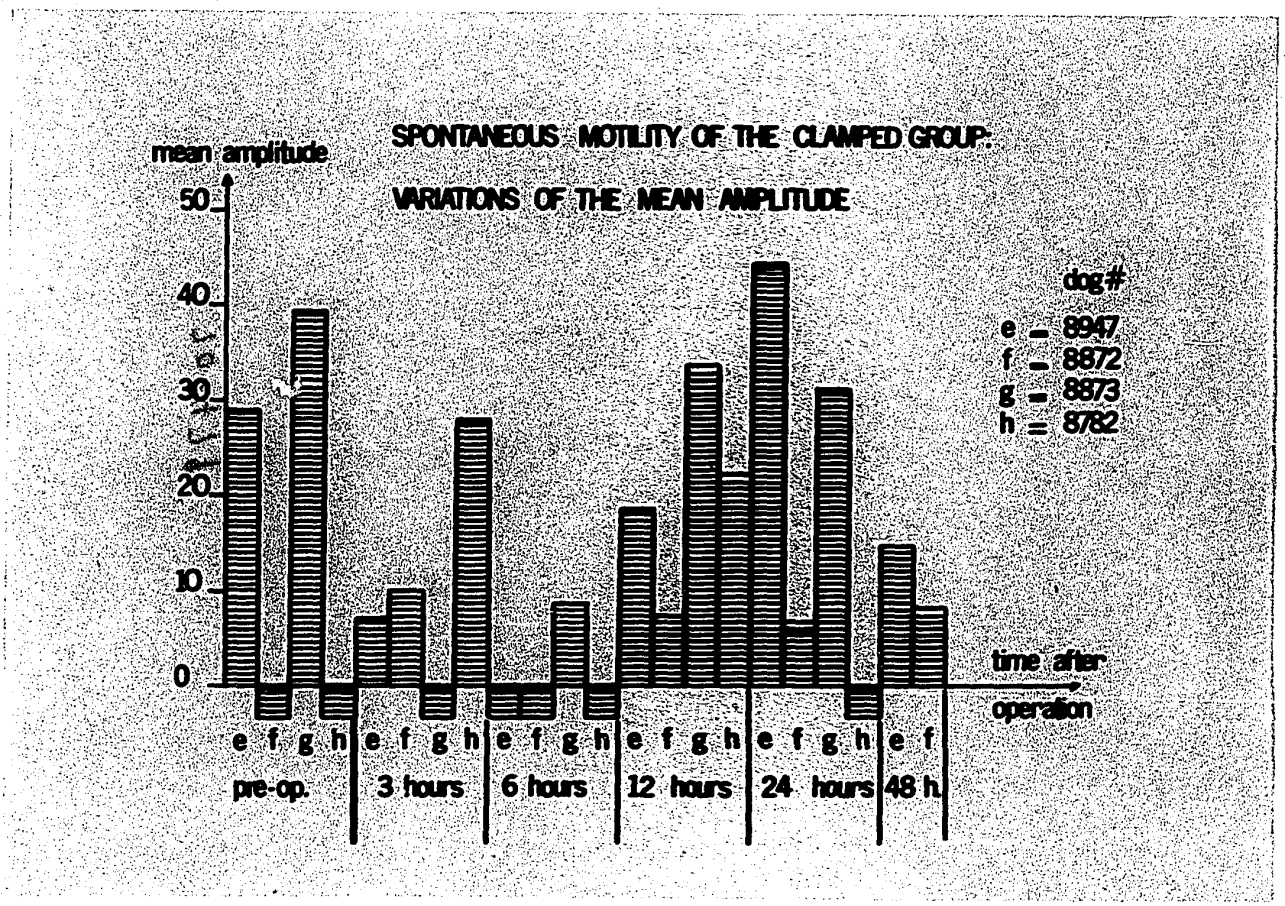
SPONTANEOUS MOTILITY OF THE CONTROL GROUP: VARIATIONS OF THE MEAN AMPLITUDE.



The mean amplitude is expressed in cm of water. The zeros are represented by a small square below the base line.

Figure 42.

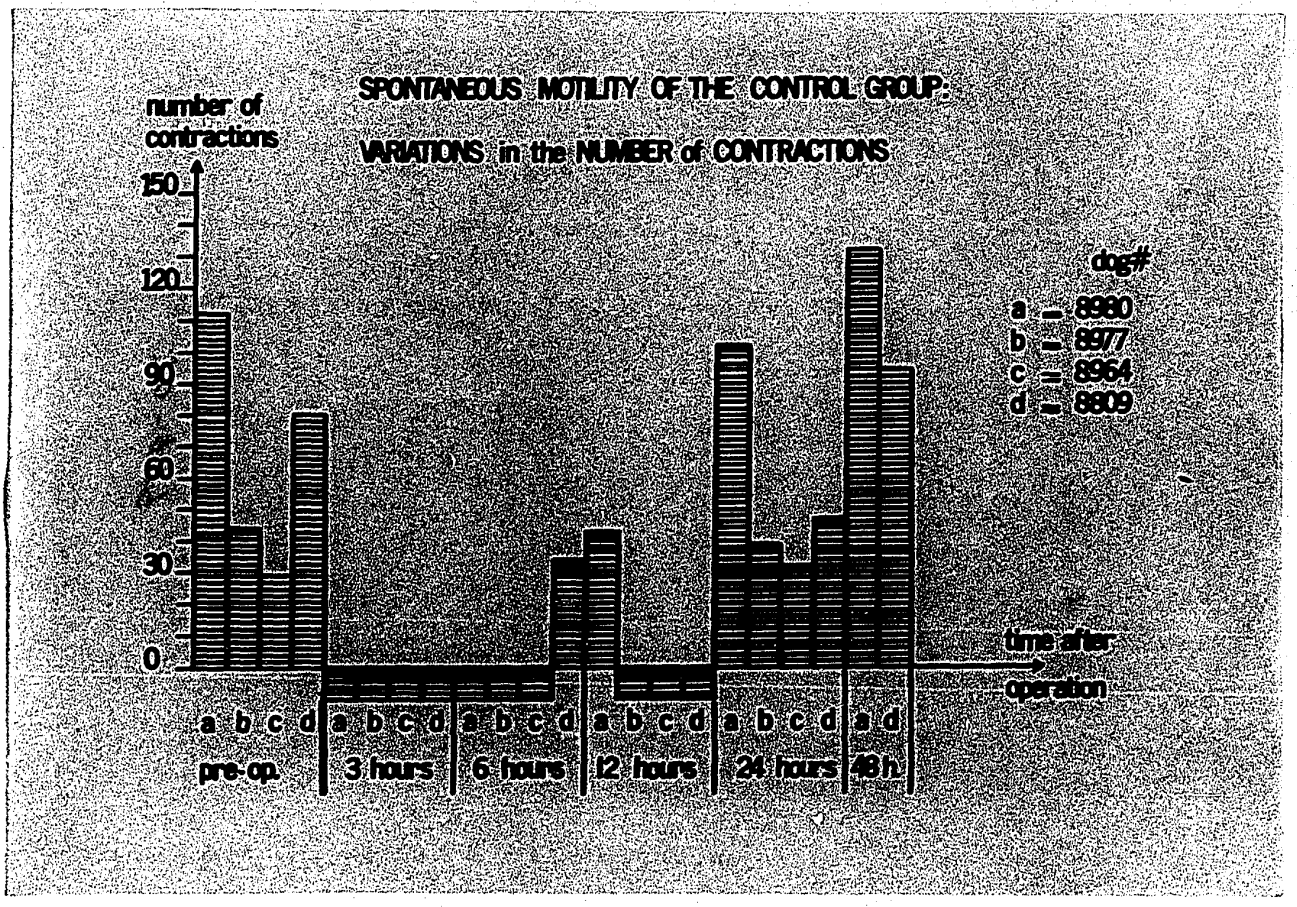
SPONTANEOUS MOTILITY OF THE CLAMPED GROUP: VARIATIONS OF THE MEAN AMPLITUDE.



The mean amplitude is expressed in cm of water. The zeros are represented by a small square below the base line.

Figure 43.

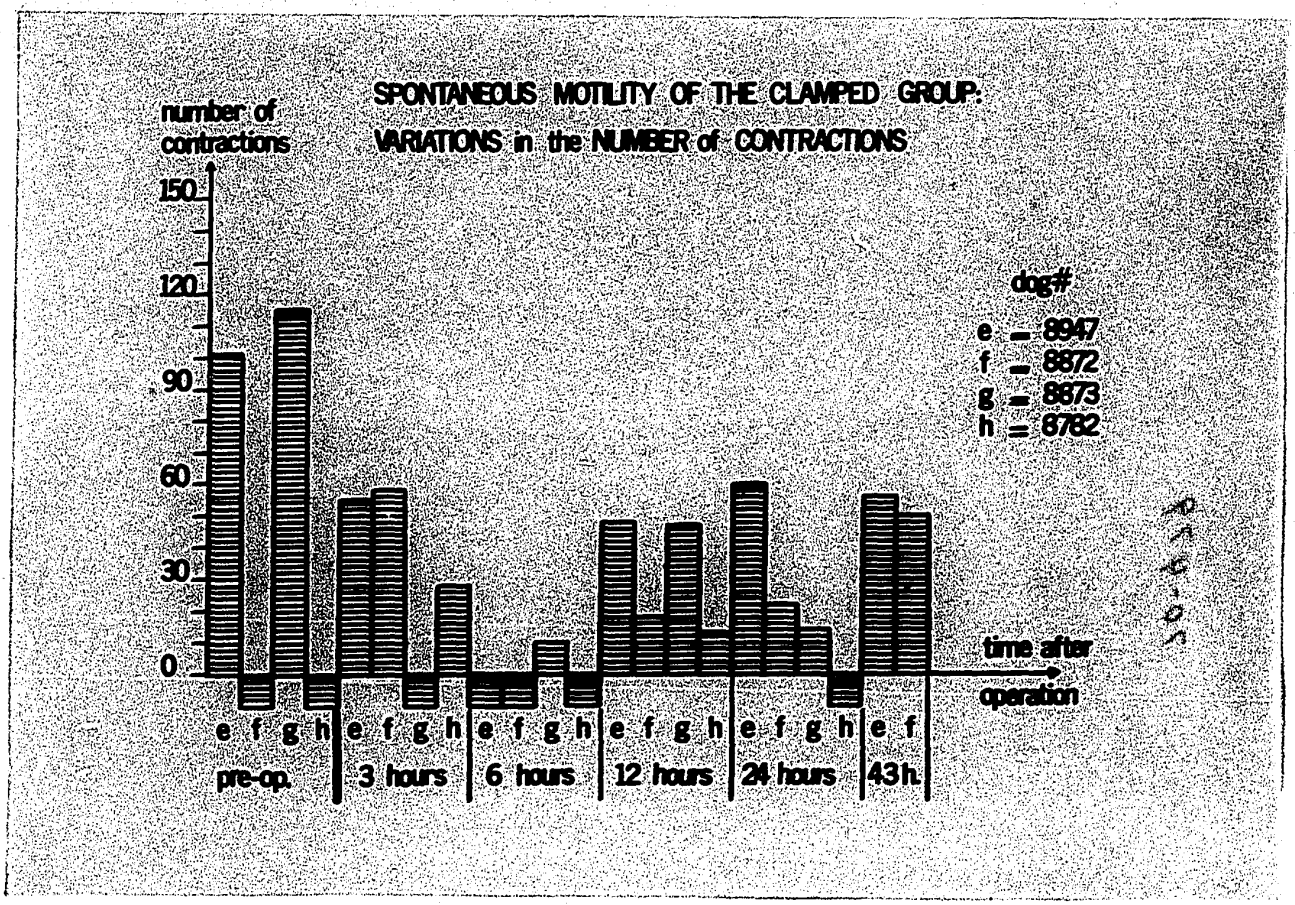
SPONTANEOUS MOTILITY OF THE CONTROL GROUP: VARIATIONS IN THE NUMBER OF CONTRACTIONS.



The zeros are represented by a small square below the base line.

Figure 44.

SPONTANEOUS MOTILITY OF THE CLAMPED GROUP: VARIATIONS IN THE NUMBER OF CONTRACTIONS.



The zeros are represented by a small square below the base line.

sent in only 2 out of 4 dogs pre-operatively, but in 3 out of 4 dogs 3 hours after the procedure. Curiously at 6 hours the figure is reversed with no activity in 3 out of 4 dogs. However some motile activity was present in all the animals by the twelfth hour. This was not followed by the general trend of improvement observed in the control animals. Thus the spontaneous motor activity of the clamped intestine consisted of an irregular swinging pattern characterized by episodes of activity early in the post-operative period.

The incidence of responses to HCl in both the clamped and the control groups at the different recording sessions is reported in table XXI a & b. While the control dogs demonstrated a relatively constant progression toward recovery, the animals with the clamped intestine manifested an irregular pattern characterized by the persistance of a certain number of failures of response during the whole first 24 hours except at the third hour when a striking 100% rate of responses was obtained. However this was followed by an increased failure rate at the sixth and twelfth hour with a progressive improvement thereafter (Figure 45). The characteristics of the responses occurring within 3 minutes after stimulation are reported in tables XXII a to e and in figures 46 to 50.

In the control group the comparison with the pre-operative level (p1 value; indicated in the tables only when significant)

Table XXI a.

THE INCIDENCE OF RESPONSES TO STIMULATION WITH 0.1 N HCl IN THE CONTROL AND CLAMPED INTESTINE.

time and type of experiment		number of experiments	number of responses within 3 min.	number of responses after 3 min.	no response
pre-op.	control	12	12 (100%)	0	0
	clamped	12	12 (100%)	0	0
immediately post-op.	control	12	2 (16.7%)	4 (33.3%)	6 (50%)
	clamped	12	6 (50%)	1 (8.3%)	5 (41.7%)
3 hours post-op.	control	11	7 (58.3%)	1 (9.1%)	3 (27.3%)
	clamped	12	12 (100%)	0	0
6 hours post-op.	control	12	4 (33.3%)	1 (8.3%)	7 (58.3%)
	clamped	11	8 (72.7%)	0	3 (27.3%)

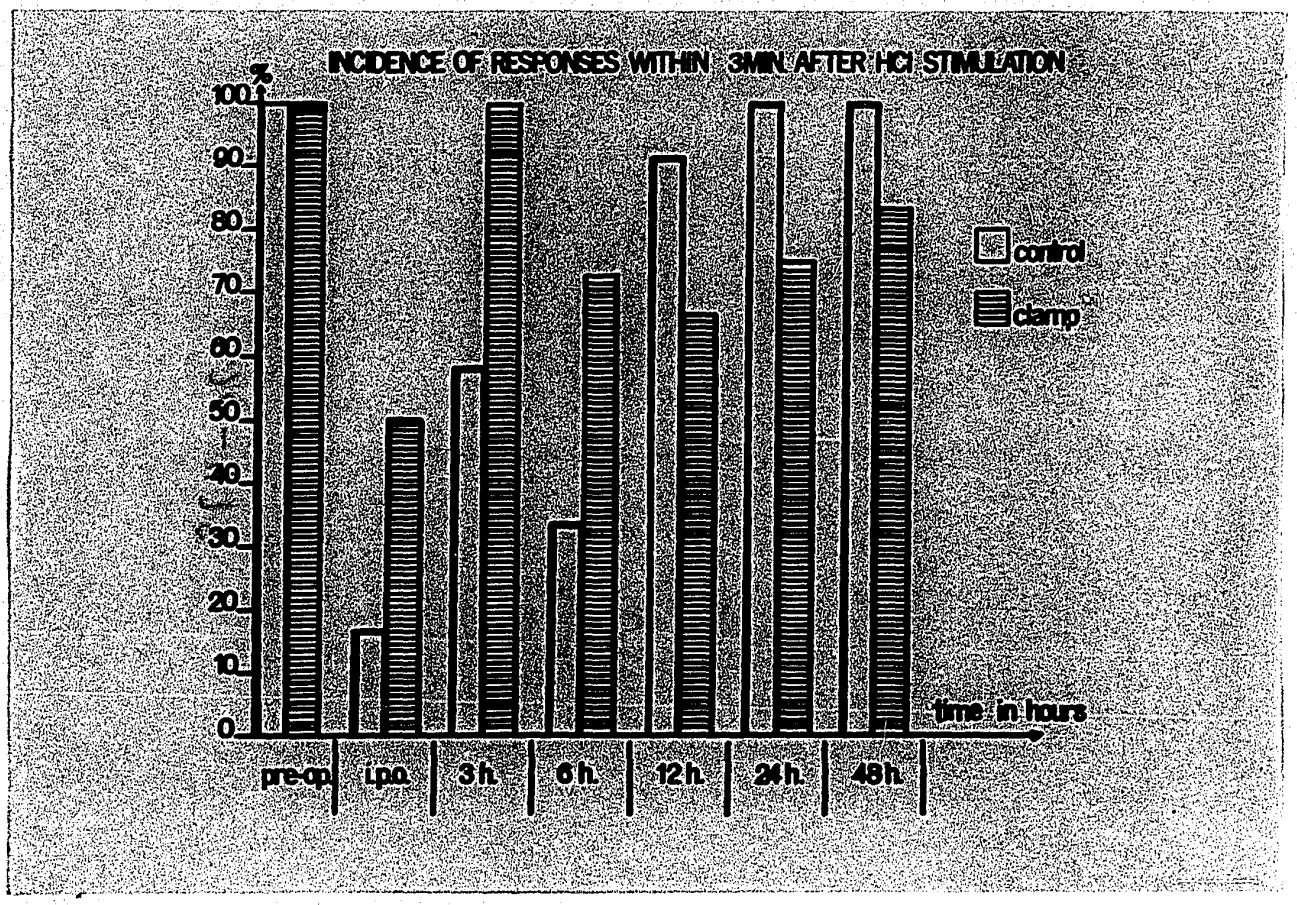
Table XXI b.

THE INCIDENCE OF RESPONSES TO STIMULATION WITH 0.1 N HCl IN THE CONTROL AND CLAMPED INTESTINE.

time and type of experiment		number of experiments	number of responses within 3 min.	number of responses after 3 min.	no response
12 hours post-op.	control	12	11 (91.7%)	1 (8.3%)	0
	clamped	12	8 (66.7%)	2 (16.7%)	2 (16.7%)
24 hours post-op.	control	12	12 (100%)	0	0
	clamped	12	9 (75%)	2 (16.7%)	1 (8.3%)
48 hours post-op.	control	6	6 (100%)	0	0
	clamped	6	5 (83.3%)	1 (16.7%)	0

Figure 45.

INCIDENCE OF RESPONSES WITHIN 3 MINUTES AFTER HCl STIMULATION.



i.p.o. = immediately after operation.

Table XXII a.

ANALYSIS OF THE RESPONSES OCCURRING WITHIN 3 MINUTES AFTER STIMULATION WITH 0.1 N HCl IN THE CONTROL AND CLAMPED INTESTINE;

a) TIME LAG.

time	T.L. control	T.L. clamped	p2 value
pre-op.	40.7 ± 10.6 (12)	39.7 ± 31.5 (12)	
immediately post-op.	110.0 ± 28.3 (2) p1 < 0.05	133.1 ± 14.9 (6) p1 < 0.001	
3 hours post-op.	100.3 ± 9.7 (7) p1 < 0.001	82.4 ± 48.6 (12)	
6 hours post-op.	124.0 ± 59.1 (4) p1 < 0.05	73.2 ± 28.7 (8)	
12 hours post-op.	104.2 ± 37.7 (11) p1 < 0.02	88.3 ± 35.9 (8)	
24 hours post-op.	53.7 ± 16.9 (12)	77.8 ± 48.0 (9)	
48 hours post-op.	74.7 ± 12.2 (6)	64.9 ± 39.8 (5)	

Data presented as mean ± SD in seconds.

(n): number of responses occurring within 3 minutes after stimulation.

T.L.: time lag in seconds.

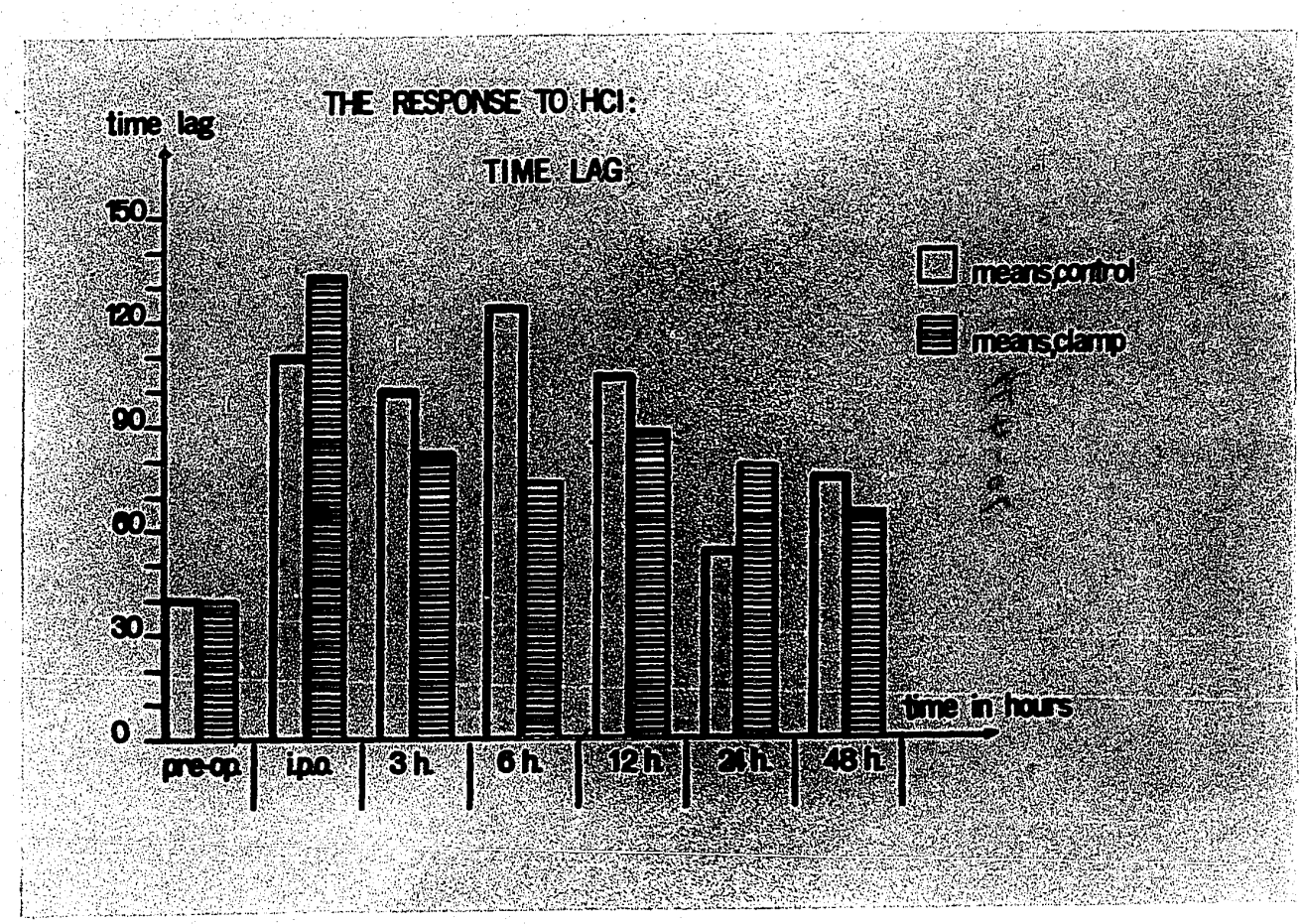
p1 value: obtained by Student's t test; comparison with the pre-operative value of each respective group.

p2 value: obtained by Student's t test; comparison between the control and the clamped group. In the cas of the time lag none is significant.

Figure 46.

THE RESPONSE TO HCl IN THE CONTROL AND CLAMPED GROUP:

TIME LAG.



The time lag is indicated in seconds.

i.p.o. = immediately post-operatively.

Table XXII b.

ANALYSIS OF THE RESPONSES OCCURRING WITHIN 3 MINUTES AFTER STIMULATION WITH 0.1 N HCl IN THE CONTROL AND CLAMPED INTESTINE;

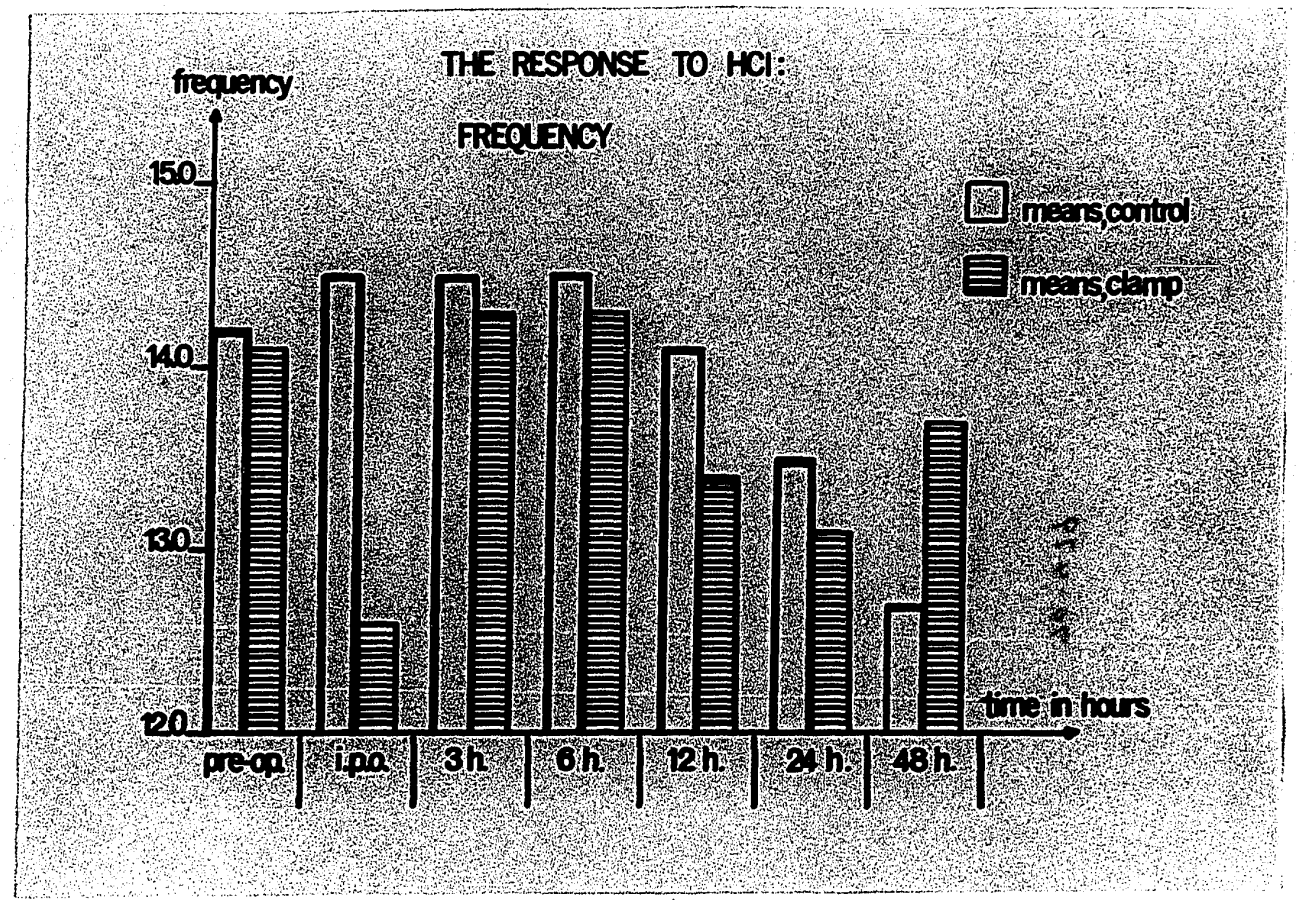
b) FREQUENCY.

time	Fr. control	Fr. clamped	p2 value
pre-op.	14.2 ± 1.1 (12)	14.1 ± 1.1 (12)	
Immediate-post-op	14.5 ± 0.5 (2)	12.6 ± 1.0 (6)	
3 hours post-op	14.5 ± 0.4 (7)	14.3 ± 1.1 (12)	
6 hours post-op.	14.5 ± 0.6 (4)	14.3 ± 0.9 (8)	
12 hours post-op.	14.1 ± 1.6 (11)	13.4 ± 0.7 (8)	
24 hours post-op.	13.5 ± 2.4 (12)	13.1 ± 1.5 (9)	
48 hours post-op.	12.7 ± 0.5 (6)	13.7 ± 0.3 (5)	

Data presented as mean ± SD, number of waves/minute.
(n): number of responses occurring within 3 minutes.
Fr.: frequency, number of waves/minute.
p2 value obtained by Student's t test; comparison between the control and the clamped group. In the case of frequency none is significant.

Figure 47.

THE RESPONSE TO HCl IN THE CONTROL AND CLAMPED GROUP: FREQUENCY.



The frequency is expressed in terms of "number of waves per minute".

i.p.o. = immediately post-operatively.

Table XXII.c.

ANALYSIS OF THE RESPONSES OCCURRING WITHIN 3 MINUTES AFTER STIMULATION WITH 0.1 N HCl IN THE CONTROL AND CLAMPED INTESTINE;

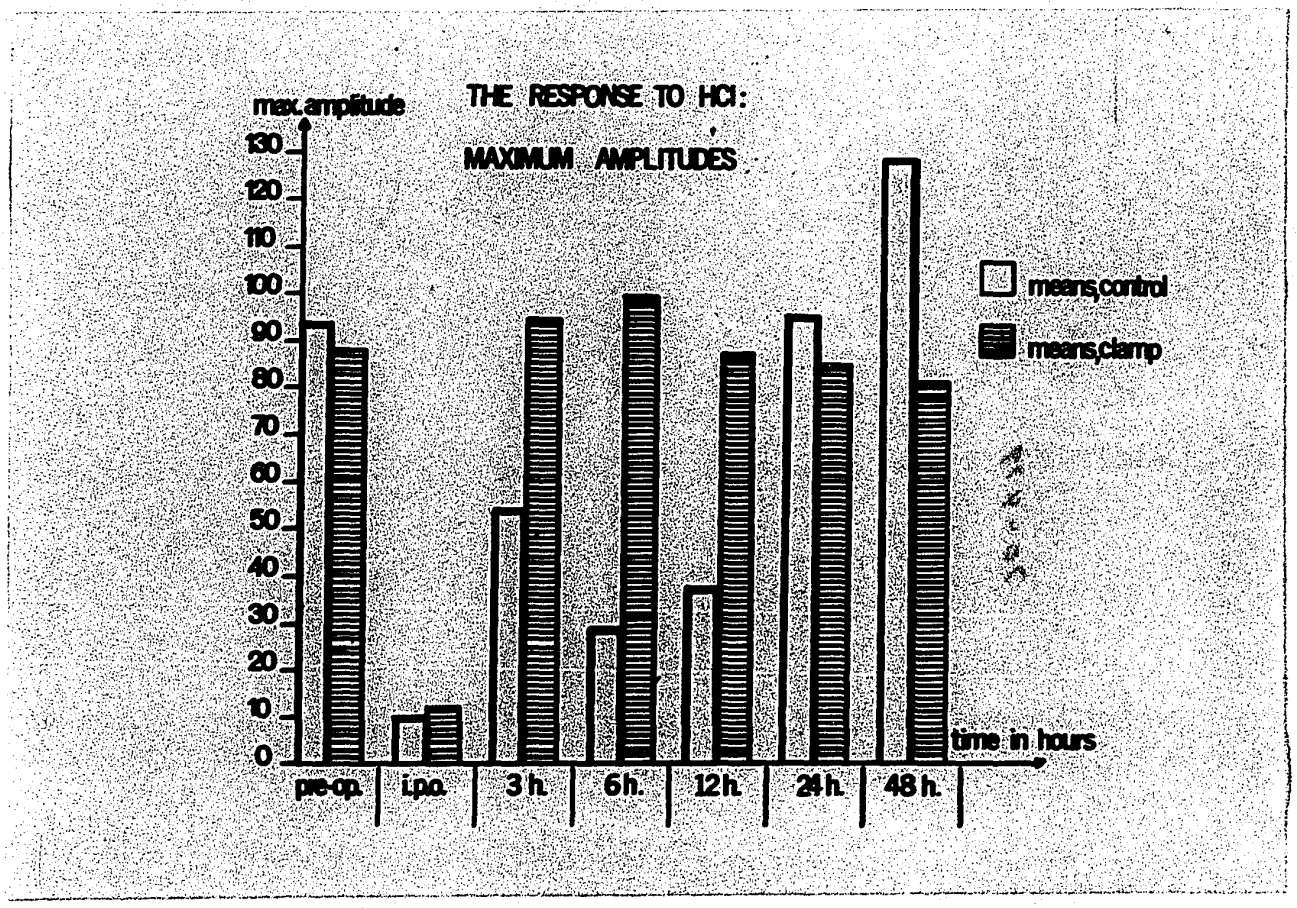
c) MAXIMUM AMPLITUDE.

time	Mx.A. control	Mx.A. clamped	p2 value
pre-op.	93.3 ± 29.8 (12)	88.0 ± 36.1 (12)	
immediately post-op.	10.0 ± 2.8 (2) p1 < 0.01	11.7 ± 2.4 (6) p1 < 0.01	
3 hours post-op.	53.5 ± 42.1 (7)	94.4 ± 36.2 (12)	
6 hours post-op.	29.0 ± 47.4 (4)	99.5 ± 16.4 (8)	p2 < 0.05
12 hours post-op.	37.7 ± 10.2 (11) p1 < 0.02	87.1 ± 6.6 (8)	p2 < 0.001
24 hours post-op.	94.7 ± 38.6 (12)	85.0 ± 11.9 (9)	
48 hours post-op.	129.2 ± 73.5 (6)	81.6 ± 44.7 (5)	

Data presented as mean ± SD in cm of water.
(n): number of responses occurring within 3 minutes.
Mx.A.: maximum amplitude, pressure in cm of water.
p1 value obtained by Student's t test; comparison with the pre-operative value of each respective group.
p2 value obtained by Student's t test; comparison between the control and the clamped group.

Figure 48.

THE RESPONSE TO HCl IN THE CONTROL AND CLAMPED GROUP: MAXIMUM AMPLITUDE.



The maximum amplitude is expressed in cm of water.

i.p.o. = immediately post-operatively.

Table XXII d.

ANALYSIS OF THE RESPONSES OCCURRING WITHIN 3 MINUTES AFTER STIMULATION WITH 0.1 N HCl IN THE CONTROL AND CLAMPED INTESTINE;

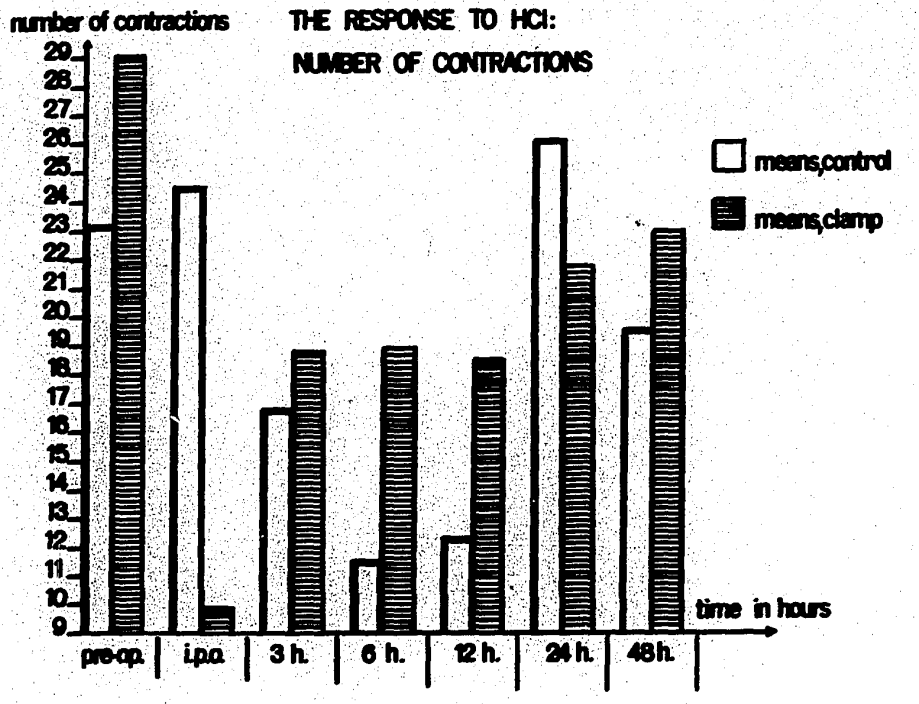
d) NUMBER OF CONTRACTIONS.

time	N.Ctr. control	N.Ctr. clamped	p2 value
pre-op.	23.2 ± 7.8 (12)	29.1 ± 6.8 (12)	
immediately post-op.	24.5 ± 17.7 (2)	9.9 ± 0.8 (6) p1 < 0.005	
3 hours post-op.	16.8 ± 4.7 (7)	18.8 ± 7.9 (12)	
6 hours post-op.	11.5 ± 6.2 (4)	18.9 ± 3.3 (8) p1 < 0.05	
12 hours post-op.	12.3 ± 8.3 (11)	18.5 ± 5.6 (8)	
24 hours post-op.	26.1 ± 9.8 (12)	21.7 ± 13.7 (9)	
48 hours post-op.	19.5 ± 5.4 (6)	22.9 ± 6.2 (5)	

Data presented as mean ± SD.
(n): number of responses occurring within 3 minutes.
N.Ctr.: number of contractions.
p1 value obtained by Student's t test; comparison with the pre-operative value of each respective group.
p2 value obtained by Student's t test; comparison between the control and the clamped group. In the case of the number of contractions none is significant.

Figure 49.

THE RESPONSE TO HCl IN THE CONTROL AND CLAMPED GROUP: NUMBER OF CONTRACTIONS.



i.p.o. = immediately post-operatively.

Table XXII e.

ANALYSIS OF THE RESPONSES OCCURRING WITHIN 3 MINUTES AFTER STIMULATION WITH 0.1 N HCl IN THE CONTROL AND CLAMPED INTESTINE;

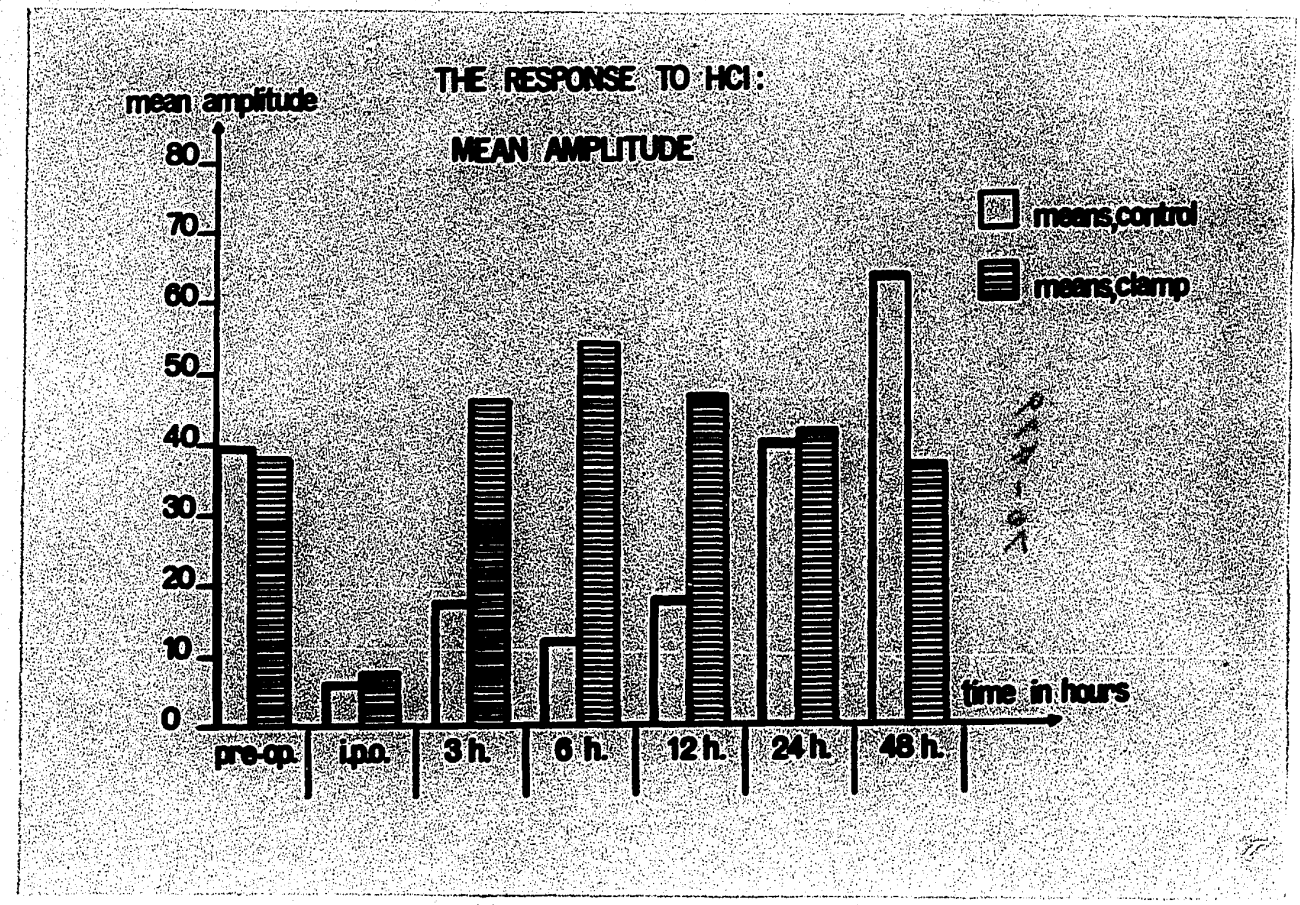
e) MEAN AMPLITUDE.

time	Me.A. control	Me.A. clamped	p2 value
pre-op.	39.5 ± 12.7 (12)	38.1 ± 11.8 (12)	
immediately post-op.	5.9 ± 0.2 (2) p1 < 0.01	7.7 ± 0.9 (6) p1 < 0.005	p2 < 0.025
3 hours post-op.	17.6 ± 11.1 (7) p1 < 0.05	46.2 ± 12.7 (12)	p2 < 0.02
6 hours post-op.	11.9 ± 13.3 (4) p1 < 0.05	54.0 ± 8.7 (8)	p2 < 0.005
12 hours post-op.	17.8 ± 11.5 (11) p1 < 0.05	46.5 ± 6.1 (8)	p2 < 0.01
24 hours post-op.	40.0 ± 12.1 (12)	41.3 ± 13.5 (9)	
48 hours post-op.	63.6 ± 34.5 (6) p1 < 0.05	36.8 ± 10.3 (5)	

Data presented as mean ± SD in cm of water.
(n): number of responses occurring within 3 minutes.
Me.A.: mean amplitude, pressure in cm of water.
p1 value obtained by Student's t test; comparison with the pre-operative value of each respective group.
p2 value obtained by Student's t test; comparison between the control and the clamped group.

Figure 50.

THE RESPONSE TO HCl IN THE CONTROL AND CLAMPED GROUP: MEAN AMPLITUDE.



The mean amplitude is expressed in cm of water.

i.p.o. = immediately post-operatively.

indicates a significant lengthening of the time lag post-operatively in all the responses obtained except at 24 hours. The frequency is rather stable. The maximal amplitude is generally decreased in all the responses till the twelfth hour and particularly immediately after the operation. At 24 hours the maximal pressures are back to normal. The number of contractions appears to be decreased between the third and the twelfth hour; however this is not statistically significant. The mean amplitude is consistantly and significantly diminished until the twelfth hour, the latter being included. The recovery of the controls takes place between the twelfth and the twenty fourth hour. But it is to be noted that the time lag is increased at 48 hours.

In the clamped group comparison with the pre-operative levels shows a distinctly different pattern. Immediately after the operation all the parameters are significantly decreased except for the frequency for which statistical confirmation is lacking. Later on all the responses obtained within 3 minutes after the stimulation showed rather normal characteristics except for a tendency toward a decreased number of contractions. It is statistically significant at 6 hours.

When the control and the clamped group are compared, the parameter which is affected by the most significant difference is the amplitude. The maximum amplitude is generally lower in the control group than in the clamped group until the twelfth

hour. It is of interest to note that it is particularly significantly so at 6 and 12 hours with the best performance at 3 hours. The number of contractions have a similar variation in both groups. It is therefore not very surprising that the control group presents a mean amplitude which is also consistantly and significantly reduced when compared with the clamped group until the twelfth hour.

The parameters describing the responses occurring after 3 minutes after the stimulation seem in no way different from the responses occurring within 3 minutes after the stimulation at the same recording session except for a much lengthened time lag. Their values are reported in table XXIII.

Table XXIII.

THE DELAYED RESPONSE TO HCl: CONTROL AND CLAMPED GROUPS.

time and type of experiment		T.L.	Fr.	Mx.A.
immediately post-op.	control	250.0 ± 14.1 (2)	13.5 ± 0.7 (2)	10.0 ± 8.4 (2)
	clamped	240.0 (1)	12.0 (1)	16.0 (1)
3 hours post-op.	control	300.0 (1)	14.0 (1)	56.0 (1)
	clamped	-.-	-.-	-.-
6 hours post-op.	control	186.0 (1)	13.7 (1)	16.0 (1)
	clamped	-.-	-.-	-.-
12 hours post-op.	control	220.0 (1)	15.0 (1)	12.0 (1)
	clamped	245.0 ± 35.4 (2)	13.0 ± 1.4 (2)	24.0 ± 5.7 (2)
24 hours post-op.	control	-.-	-.-	-.-
	clamped	198.0 ± 11.3 (2)	12.5 ± 2.1 (2)	38.0 ± 42.4 (2)
48 hours post-op.	control	-.-	-.-	-.-
	clamped	186.0 (1)	14.0 (1)	40.0 (1)

Data presented as mean ± SD, as absolute values when n = 1.
(n): number of responses delayed past 3 minutes after HCl stimulation.
T.L.: time lag, seconds.
Fr.: frequency, number of waves/minute.
Mx.A.: maximum amplitude, pressure in cm of water.

CHAPTER III. GENERAL DISCUSSION.

1. CHARACTERISTICS OF INTRINSIC WAVE PATTERNS OF INTESTINAL MOTILITY.

a) Technical considerations.

Recording the intestinal motility with open tipped catheters is a well established method [52]. The necessity of interrupting the bowel continuity in animal experiments and the bulk of the recording tube are the main disadvantages of this technique. A direct influence on motility by such a foreign body lying within the intestinal lumen cannot be excluded. Our double lumen tube is somewhat unusual in that a different pattern of waves is recorded with the proximal catheter lying on the side of the tube from that recorded with the distal catheter which is inserted inside the Foley. The shape of the waves recorded with the proximal catheter is generally blunter and often the pressures recorded are not as high when compared with the distal catheter recording (Figure 17, 18). This difference has been interpreted in the following manner. It was noted that simple plugging of the recording catheters would cause the recording of a pressure equivalent to the height of the microdrip fluid column. The catheter attached to the side of the tube could be

easily plugged by simple contact with the mucosa of the intestine. Thus rather than measuring true intraluminal pressures, it would reflect the presence of contractions in pure mechanical terms. On the other hand the catheter encased inside the Foley catheter was prevented from any direct contact with the mucosa, thereby avoiding simple plugging. The presence of two large openings on each side of the tip of the outer tube facilitated the measurement and recording of intraluminal pressures. The recordings from the distal catheter would thus be a truer reflection of intraluminal pressures as evidenced by taller peaks and the abscence of dampening. This interpretation was supported by observations during the clamping procedure. Shortly after occlusion of the mesenteric arteries multiple contractions were visually observed and were recorded by the proximal catheter. However the tracing of the distal catheter remained flat indicating that probably no effective pressures were developed within the segment of intestine by these contractions. More powerful contractions followed the reestablishment of blood flow. These were more efficient and variations in the intraluminal pressure were recorded by both distal and proximal catheter (Figure 27, 28). For these reasons the quantitation of the motility was always performed on the tracing recorded by the distal catheter.

Our calibration of 5 mm for 20 cm of water makes it diffi-

cult to record the basal rhythm with pressure variations of a few cm of water only. Pressures lower than 4 cm of water are actually not detectable, and low pressures are easily obscured by movements or panting of the dog. Such a calibration was rendered necessary by the extremely high pressures developed during HCl stimulation. Peaks reaching more than 190 cm of water were occasionally recorded and pressures of the order of 100 cm to 150 cm of water were quite common.

The choice of the dog as the experimental animal model is not devoid of major shortcomings. The intestine of the dog presents a very thick muscularis layer and consequently is unlikely to become distended and develop the clinical features inherent to the condition of paralytic ileus in man. Schamaun claims that the intestine of dogs subjected to arterial clamping of variable duration presented the typical pathological picture of paralytic ileus [131]. Similarly Streeten described the occurrence of experimental paralytic ileus in the dog following potassium depletion [18]. Obviously the use of the term "paralytic" or "adynamic" ileus is improper if one refers to the clinical course of dogs submitted to severe intestinal injury. In the control group of the clamping procedure the intestine was quiescent for a period lasting between 12 and 24 hours after operation. However this was of self-limiting duration with progressive recovery of relatively normal intestinal motility. Further more such a pe-

riod of quiescence was not observed in the animals whose intestine had been clamped. In this group no mortality was recorded and only mild distention was present at autopsy when the animals were sacrificed. All the dogs of the clamped group recovered clinically as quickly than the controls and were able to walk around 12 hours post-operatively. The sick look of the mechanically obstructed dog was never observed in the animals used for this study. Thus the clinical observations made on the dog cannot be transposed to the human. However the model is useful for the study of the peristaltic reflex and presents definite advantages for a study performed in vivo and without anesthesia as the animal can be trained.

b) Spontaneous and stimulated motility.

Whether the Miller-Abbott tube, open tipped catheters or the radiotelemetric capsule were used to estimate intestinal motility, the majority of studies performed in the past were limited to the observation and assessment of spontaneous motility. Code emphasized how erratic and irregular this type of intestinal motor action can be and recommended prolonged recording sessions for satisfactory estimation [50]. Deinke also noted the variable behavior of each individual dog [53]. We made the same observation (Table XX). Very little is known of the physiological

significance of the spontaneous motility. However the propulsive action of the peristaltic reflex is relatively well documented and has been the object of multiple in vitro experimentation [40, 78, 80 - 85, 100, 101, 103, 105, 148]. It was felt that an evaluation of the peristaltic reflex would be a more direct appraisal of the functional status of the intestine than the simple recording of spontaneous motility, and that the difficulties related to the variability of the latter phenomenon would also be avoided. Further this investigation was also directed toward the possible definition of the role of the mucosa in the pathogenesis of post-operative ileus. The reasons for such a postulate have been exposed earlier in Chapter II, paragraph 1. In this perspective it is evident that the spontaneous motility does not constitute the only primary relevant parameter.

2. INTESTINAL MOTOR RESPONSES TO VARIOUS CHEMICAL STIMULI.

A few authors have elicited the peristaltic reflex with 0.1 N HCl and other chemicals in the past. Thomas injected 2 - 4 cc of 0.1 N HCl in the intestine of unanesthetized dogs and recorded the motility with a double balloon recording system. He reported frequent failures of stimulation and confirmed the easy fatiguability of the reflex previously described by Bayliss and Starling [239, 4]. When successful, injection of the solution between the two balloons caused inhibition below and excitation above. Hukuhara used pieces of filter paper soaked in 0.1 N HCl to elicit the mucosal reflex in denervated loops of dog intestine in vivo [81]. The recording was also performed by the balloon method. Like other writers, he reported an excitatory response above and an inhibitory response below the level of stimulation. HCl was also used by Brink, Schlegel and Code to study the motility of the gastro-duodenal junction [240]. The instillation of 0.1 N HCl in the duodenum at the rate of 6 ml per minute caused a significant rise in the duodenal motility.

In our experience, we did not observe the high rate of failures reported by Thomas. In the normal dog a response was obtained within 3 minutes after stimulation in 93.3% of the cases. Fatiguability was also a problem if the stimulations were carried out too frequently. For this reason a protocol was adopted

in which the stimulations were spaced by intervals of 8 minutes. As described in the previous chapter, the response is peristaltic in character in that the contractions elicited are propagated. The response consists of two phases. There is first a period of inhibition, the time lag, which is followed by a burst of increased activity. Our experiment was not designed to analyse the significance of these two phases, but in conformity with the available literature, it is probable that the injection of acid caused an inhibition below and a stimulation above the injection site. Thus the recording catheter located below the site of injection would be affected first by a wave of inhibition lasting until the peristaltic wave of excitation reaches it. If this concept is valid, the time lag would represent an indirect measurement of propagation velocity. The normal response is quite variable from animal to animal, each dog having his own range of values. Thus the time lag varied from 22 to 47.3 seconds, the maximum amplitude between 53.2 and 141.2 cm of water, the number of contractions during the 3 minute period following the stimulation varied between 16.3 and 34.7 and the mean amplitude during the same period was in a range of 22.4 to 78.8 cm of water. The frequencies varied from 13.1 to 15.0 waves per minute. All these quoted ranges represent the mean of 3 responses to 3 different stimulations spaced by 8 minute intervals in the same individual dog. Curiously enough and despite the widespread use

of the dog as a laboratory animal, the available literature is rather elusive on the normal range of canine intestinal intraluminal pressures. Most recent evaluations have been performed with extraluminal transducers and are reported in gram-force [53]. They are consequently not directly comparable with our results. Price reports pressures in the upper jejunum with peaks well over 40 mm Hg [243]. Hiatt obtained pressures reaching 200 mm Hg in Thiry-Vella ileal segments [86]. Our own recordings are in a similar range to those mentionned. The frequencies mentionned above are in close agreement with the figures measured by other workers on the dog intestine below a duodeno-jejunal anastomosis [237].

When compared with the spontaneous motility, it appeared that the maximal amplitude of the response to HCl was in the same range (Table VI). This indicates that HCl does not cause "supercontractions" and that the pressures developed during the response were in the physiological range.

No change in the frequency of contraction was noted following HCl stimulation (Table VI). This is in contradiction with previous reports where the basic electrical rhythm was found to be increased by the injection of HCl in the duodenum [244]. However our method of estimating the frequencies was less sensitive and therefore less accurate that only marked changes could have been appreciated.

The effect of the injection of a bolus of 5 cc 0.1 N HCl was plotted against the results obtained following a similar injection of Ringer's lactate. What was felt to be a response after Ringer's lactate appeared in 23.8% of the cases. In all the others no change was recorded at all whether the intestine was active before or not. A "volume distention effect" cannot be excluded in the tracings presenting the features of a response, i.e. the presence of a time lag followed by a motor activity. However comparison with the HCl response shows that the maximum amplitudes are significantly lower. If the time lags are considered (Table VII), the tendency is toward a lengthening though it is not statistically significant. Thus despite a volume effect, the chemical action of HCl is reflected by a higher predictable incidence of responses, a higher maximum amplitude and perhaps a shorter time lag. Fukuhara demonstrated recently that the propagation velocity is related to the magnitude of the intraluminal pressure [245]. According to this concept a shorter time lag after HCl stimulation would be anticipated.

Cooling the duodenum results in a decrease in the rate of basic intestinal rhythmic contractions [222]. Decrease in total body temperature has the same effect as shown by Daniel [150]. A recent report described the inhibition of esophageal peristalsis by a cold bolus [246]. In the experimental situation described in this study, it is reasonable to postulate that the injection of

5 cc of a solution at 20°C might cause sudden cooling of the mucosa and thus a certain degree of inhibition. This is supported by the increased failure rate observed (15%). However as mentioned earlier these failures occurred all in the same animal and are consequently of doubtful significance. The responses recorded after stimulation with cold HCl have a tendency to have a higher maximum amplitude and a higher mean amplitude. No satisfactory explanation could be found for this trend which is actually not statistically significant.

Despite its variability the response to HCl is probably a more direct and more reliable way of testing the motor function of the intestine than the simple recording of the spontaneous motility. Food is a major determinant of intestinal motility [53, 151, 237]; conversely an empty intestine is relatively quiescent. Thus stimulation studies are possibly a more logical approach to the understanding of intestinal function since the stimulus can be standardized and the response quantitated.

This concept finds some support in our observations on the relationships between the spontaneous motility and the responsiveness to HCl stimulation. Total absence of any spontaneous motility gives no indication of potential intrinsic responsiveness: a response might or might not occur. Thus absence of spontaneous motility does not reflect the functional state of the intestine. However the presence of spontaneous contractions is usually

associated with responsiveness. This is well illustrated by the recordings of the clamping experiment (Figure 37, 38, 41, 43, 45). In the clamped group, no spontaneous motility was recorded pre-operatively in 2 out of 4 dogs. However they all responded spectacularly to HCl (Table XXI).

The analysis of the different components of the response to HCl appear to be only moderatly informative. The increase in the time lag, the decrease in the number of contractions and in the height of the maximum and mean amplitude all parallel grossly the variations of the rate of failure to elicit responses (Figure 45, 46, 48, 50). Thus the estimation of the failure rates alone provides a fairly good indication of the performance which can be expected from the intestine.

3. INFLUENCE OF VARIOUS DRUGS ON SPONTANEOUS AND STIMULATED MOTILITY.

a) Perfusion studies and the effect of local anesthetics.

The perfusions were performed at an extremely slow rate in order to avoid any volume distention effect. The aim was mainly to bathe the mucosa with different solutions under study. In these experimental conditions it is not very surprising that a balanced buffered solution such as Ringer's lactate has no detectable effect. However perfusion with 0.1 N HCl decreased significantly the number of contractions when compared with the base line recordings of the spontaneous motility. The effect is not statistically significant when the comparison is made with the perfusion with Ringer's lactate, but still the trend is the same. This suggests an inhibitory action of HCl when perfused during a 10 minute period. Brink et al. observed an increase in duodenal motility during HCl perfusion. But he used a much greater perfusion rate, 6 ml per minute during 8 minutes [240]. These technical differences and the physiological differences between the duodenum and the upper jejunum might explain our failure to reproduce his results. Also it is possible that slow perfusion of HCl may allow more rapid neutralization of the acid thus neutralizing its stimulant capability.

It is interesting to note that the response to a bolus of HCl was not depressed after perfusion with HCl (Table XVI). Thus the intestine reacts differently depending on whether the acid is slowly infused or injected rapidly as a bolus.

Perfusion with xylocaine 10^{-2} was followed by what seemed to be a biphasic effect. The first 5 minutes of perfusion are followed by a normal or perhaps an increased motor activity. The second 5 minutes are characterized by a complete inhibition. The overall result is a significant decrease in the number of contractions. The recorded maximum amplitudes were also generally decreased, but this trend did not receive statistical confirmation. As for HCl this definite inhibition following xylocaine 10^{-2} perfusion contrasts with the stimulation caused by a bolus of this solution (Table XII, XIV, XV, and Figure 24).

Xylocaine 10^{-2} perfusion results in a definite inhibition of the response to 5 cc of 0.1 N HCl. The failure rate of HCl stimulation is increased to 25% after xylocaine perfusion, and half the failures took place 5 minutes after the end of the perfusion (Table XV, XVI).

The experiment does not allow any conclusions on the mechanism of action of either xylocaine or HCl. Xylocaine is probably absorbed [247] and the inhibition involves probably both the smooth muscle and the intramural nervous structures in a non specific fashion. However the following explanation can be sugges-

ted. Local anesthetics such as procaine act in a biphasic fashion. They first cause depolarisation and then hyperpolarisation of the membranes [248]. The depolarisation phase is associated with an hyperexcitable state which might be reflected by the persisting or increased motility of the first minutes of perfusion. Once hyperpolarisation is established, complete block results.

Xylocaine is known to be able to stimulate directly smooth muscle [249, 250]. This could also explain the motility pattern observed during the first few minutes of perfusion.

Xylocaine is usually under the hydrochloride salt form. Thus HCl could be liberated and have a stimulatory effect until the base has become effective.

We are unable to offer any satisfactory explanation for the apparently opposite effect of the perfusion and of a bolus of xylocaine. Not enough experiments have been performed with a bolus injection of local anesthetic to ascertain the stimulatory effect. However these observations suggest a similarity between the effect of HCl and xylocaine. It is possible that HCl has a very weak local anesthetic effect.

b) <u>The effect of Nembutal (Pentobarbital)</u>.

Oxybarbiturates tend to reduce the tonus and the amplitude

of rhythmic contractions. This is due to a peripheral as well as to a central effect. The peripheral effect involves a mild local anesthetic action on the cell membranes and possibly the release of noradrenaline from the adrenergic nerve endings. An hypermotility state has been suggested on emergence of barbiturate induced sleep [248, 251].

In our own experience, immediate inhibition of spontaneous motility was noticed after intravenous injection of pentobarbital. Similarly a very poor response to HCl stimulation was elicited under Nembutal anesthesia with minimal improvement as time elapsed. The effect is mainly characterized by an increase in the failure rate of the responses to HCl stimulation. The response itself, if present, shows a much lengthened time lag, a decreased maximum amplitude, and a smaller number of contractions (Table XVIII). Nembutal anesthesia appears to significantly influence intestinal motility the early hours after operation until the dogs are completely awake. It certainly plays a role in the depression of intestinal motility immediately after the operation and might be responsible for the period of decreased motility which is apparent in the control group of the clamping experiment 3 hours post-operatively.

4. RELATIONSHIP BETWEEN MUCOSAL INTEGRITY AND INTESTINAL MOTILITY.

a) The effect of acute ischemia and destruction of the intestinal mucosa on motility.

Sudden acute ischemia by occlusion of the mesenteric arteries was followed by the onset of spastic contractions. Similar observations have been reported in the past by Schamaun, Job, and others [130, 131, 252, 253]. Reestablishment of blood flow was associated with slow spastic contractions which persisted longer than after the onset of ischemia. This is in accordance with a previous report by Zfass [132].

The post-operative pattern of the motility in the control and clamped group is very different. If both the spontaneous motility and the response to HCl are considered at 3 hours, all the controls show a severe depression of activity, while most of the clamped segments are spontaneously active and present a normal response to HCl. Thus an hypermotility state is present in the clamped group, influencing all the parameters of the motility measured in this study: spontaneous motility, incidence of responses to HCl and the characteristics of the response to HCl (Figure 39 - 46, 48 - 50).

A decrease in the frequency (the parameter usually least

influenced in this study) of the contractions was noted in the clamped group immediately after operation. Although not statistically significant in our study, the reduction of frequency is a recognized effect of ischemia which has been thoroughly investigated by Schamaun [131] and is believed to be due to functional alterations in the intramural plexuses [148, 149]. After a short period of ischemia recovery is rapid and the frequencies recorded at 3 hours were all normal. Curiously the frequency of the control dogs dropped 2 days after the operation, an observation which we are unable to explain. Rinecker described an unstable frequency pattern following laparotomy in the dog [254]. Except for the observations just mentioned, the frequency pattern of the control dogs does not confirm this report. It is felt however that an irregular pattern was present in the clamped group (Figure 47). These interpretations should be accepted with reservation because of the limited number of dogs studied and because of the presence of depressed motility in the first hours post-operatively which limits the number of possible measurements.

The origin of the hyperexcitability state is unknown and our experiment does not suggest any explanation. Depression of the metabolic processes might interfere with the ionic movements across the cell membranes, thus altering the excitability [146, 255]. Such an effect on the intramural neurones has been noted

early during ischemia by Job and was proposed as an explanation for the spasms which follow the interruption of blood flow [252]. However whether a prolonged instability of membrane excitability is part of the recovery process is unknown.

No direct relationship could be established between the lesion of the mucosa and the spontaneous motility or the response to HCl. The destruction of the mucosa up to the grade III or IV described before was followed by a complete recovery within 48 hours (Figure 29, 30, 35). At 24 hours the villi were generally covered by a thin friable epithelium composed of cuboid cells (Figure 32). The functional capacity of these cells is probably decreased though this has not been proved. These results are in agreement with previous studies [162, 256]. Three hours after the establishment of the mucosal damage the intestine manifested a normal response to HCl (Figure 45 - 50). Thus the peristaltic reflex could still be elicited despite complete destruction of the mucosa. Our observations fall in agreement with those of Diament [83]. Obviously the ischemic process affects the whole intestinal wall. Although alterations of the mucosa appear to be the only morphological changes apparent on light microscopy, other structures of the bowel wall may be functionally affected. The hyperexcitable state which results from ischemic injury may very well mask a more subtle change in motility regulation which could be a consequence of specific mucosal damage.

b) The mode of action of intraluminal HCl.

Our experiments provide very little information on the mechanism of action of HCl in provoking a motor response in the canine intestine. Mukuhara describes the peristaltic reflex obtained with such a stimulus as a "mucosal" reflex as opposed to the "muscular" reflex which is elicited by stimulation of the muscularis from the serosal side [81]. The term is somewhat misleading because there is no evidence that HCl acts specifically on the mucosal cells. Data accumulated in this laboratory have shown that the H^+ ions deposited into a closed loop of canine jejunum in vivo are rapidly exchanged for sodium, and this is accompanied by a widespread hemorrhagic enteritis. The H^+ ions are thus possibly resorbed and might have an action on deeper structures of the bowel wall. An hemorrhagic enteritis was not observed in our study, probably because of the limited amount of acid used and its quick dispersion throughout the gut.

A similarity between the action of HCl and local anesthetics has been previously suggested. In both cases continous perfusion causes a varying degree of inhibition while injection of a bolus is associated with a motor response, suggesting a similar mechanism of action. Xylocaine modifies the membrane excitability. An exchange between H^+ and other intracellular ions might be followed by a similar effect.

Our experiments did not demonstrate any selective action of HCl upon the mucosa. Mucosal blockade with local anesthetics and mucosal destruction both failed to prevent the motor response of the intestine to HCl stimulation. Furthermore our studies demonstrated that HCl can be effective in provoking a motor response even in the absence of intact epithelium. Whether this is linked to the ischemic injury of the deeper structures of the intestine is unknown.

5. PERSPECTIVES.

The physiological integration of the different anatomical components of the intestinal wall is still poorly understood despite numerous studies using various techniques. The basic mechanisms regulating the peristaltic reflex and the modulation of one layer of muscularis over the other have been described only recently with in vitro experiments and pharmacological analysis. However the alterations which might affect these mechanisms in disease are still completely unknown. Attempts to isolate anatomically and functionaly one structure of the intestine without damaging the others involve enormous technical difficulties and explain this lack of information.

The inadequacy of the presently available animal models have been a major drawback in the understanding of the pathogenesis of paralytic ileus. The anatomical characteristics of the carnivorous intestine precludes the development of intestinal distention as seen in man. The long and thin walled intestine of herbivorous or omnivorous animals possibly may simulate intestinal abnormalities similar to that seen in human disease. Unfortunately the paucity of the data concerning these species and their cost have prevented their more extensive use in the laboratory. Future efforts should probably be directed toward the development of a proper animal model of post-operative

paralytic ileus if further progress in the understanding of its pathophysiology is to be expected.

6. CONCLUSIONS.

1. A reproducible response to the stimulation of small intestinal peristalsis could be obtained through the injection of 5 cc of 0.1 N HCl in the lumen of the upper jejunum in the dog. Comparison with control injections of Ringer's lactate indicate that the response is due to the chemical action of HCl.

2. The functional abilities of the intestine can be estimated by the study of the incidence or failure rate of its response to HCl injection in different experimental circumstances. More detailed information can be obtained in this respect by the analysis of the characteristics of the intestinal motor response itself. The wave pattern of the motor response can be quantitated by measuring the following parameters: the frequency, the amplitude in terms of the intraluminal pressure developed, both maximum and mean, the number of contractions, and perhaps most important of all, the time lag or period of inhibition, because the latter reflects the propagation velocity of the peristaltic waves. The variations in the failure rate of the response were observed to parallel the variations of the various parameters mentioned above. The failure rate of the response alone thus appears to be a fair index of the functional condition of the intestine as far as motility is concerned.

3. The response to the injection of 5 cc of 0.1 N HCl is

significantly inhibited by previous perfusion with xylocaine 10^{-2}, by intravenous injection of Nembutal (Pentobarbital), or following laparotomy and dissection of the vessels supplying the studied segment of intestine without impediment to blood flow.

4. In one experiment the integrity of the intestinal mucosa in a segment of upper jejunum was disrupted by a period of acute arterial ischemia lasting for 1 hour. The motility of this segment was plotted against control measurements determined in a group of animals which underwent a "sham" operation. The control dogs developed intestinal adynamia for a period lasting between 12 and 24 hours post-operatively. This inhibition of the motility was self limited and cannot be compared to the physiological changes and consequences of paralytic ileus in man. In the ischemic segment of intestine, the more severe degree of injury was not reflected by a comparable increase in the degree or duration of inhibition of intestinal motility, but rather by an hyperexcitable state followed by a period of irregular recovery of motor activity.

5. The experiments failed to demonstrate any selective action of intraluminal HCl on the intestinal mucosa. The study did not identify any specific role of the mucosa in the regulation of intestinal motility or in the pathogenesis of paralytic ileus.

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