THE NEURO-HUMORAL ASPECTS OF ULCER FORMATION

BY

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INTRODUCTION

In spite of the early and brilliant observations of clinical pathologists, notably Rokitansky, who first called attention to the association of brain damage and pathological changes in the stomach, suggesting a neurogenic basis for ulcer formation, this concept was for many decades overshadowed by the views of Virchow and his followers who held that peptic ulcer was essentially a local disease.

Although the neurogenic concept was later supported by both experimental and clinical studies, it was not until the publication of Cushing's Balfour Lecture, relating peptic ulcer to disturbances in the interbrain, that the interest in this aspect of ulcer formation was revived. In the years that followed, there has been an increase in both clinical and experimental reports indicating that the initiation and the maintenance of chronic peptic ulcer in man may be mediated through a substratum of the nervous activity.

The emotional and psychic aspects of the ulcer problem have been stressed in the past, but it is only in recent years that psychiatrists in their exacting analysis of the features of the personality which predominate in patients with peptic ulcer, have reinforced the concept that peptic ulcer may be a psychosomatic disease, induced by an imbalance of the autonomic nervous system resulting from sustained emotional conflicts. The benefits thus far derived from vagotomy in the treatment of peptic ulcer tends to support this view.

During the course of other experiments conducted in this laboratory

it had been observed that following single injections of mecholyl into dogs, marked bloody diarrhoea was produced, and the post-mortem examination of the stomach and intestines of these dogs revealed the mucosa to be markedly hemorrhagic, edematous with numerous grossly visible gastric and duodenal hemorrhages and erosions.

Mecholyl (acetyl - B - methylcholine) is a choline ester which closely resembles acetylcholine, but it is less readily destroyed by the cholin-esterase and therefore has a more prolonged effect. It has been shown to have a more powerful muscarine-like action, and a less marked nicotinic-like effect than that produced by acetylcholine (366). According to Gray and Ivy (360), mecholyl was one of the most suitable choline esters for the stimulation of gastric secretion, being from 100 to 200 times more potent in this respect than acetylcholine when the two were given subcutaneous-ly. The secretion evoked by mecholyl closely resembled that produced by the action of vagus nerves on the gastric glands of the stomach. The special physiological and pharmacological properties of mecholyl, therefore, make it a choice drug for this study.

This investigation was undertaken to determine whether the mucosal hemorrhages and erosions induced by a single dose of mecholyl would eventually progress to gastro-intestinal ulcerations after daily repeated injections of mecholyl over a prolonged period of time. Although the main interest was to observe the lesions produced in the stomach and duodenum, several interesting pathological changes have been noted in the colon and pancreas, which will be included in this thesis.

Early History Of The Neurogenic Doctrine To Harvey Cushing

Over a century ago, Kammerer (1) in 1823 and Rokitansky (2) in 1841 first called attention to the association of brain damage and changes in the stomach. Rokitansky described two types of lesions in the stomach, the first, a gelatinous softening usually seen in infancy associated with demonstrable pathological changes of the brain. He thought that, "the proximate cause may be looked for in the diseased innervation of the stomach, owing to a morbid condition of the vagus, and to the extreme acidification of the gastric juice". The second form, which occurred both in children and adults as a result of meningitis, especially when it involved the base of the brain, was ascribed to a reflex action of the oesophagael and gastric branches of the vagi.

Several years later, Schiff (3) reported the interesting observation that experimentally produced intracranial lesions in dogs and rabbits which involved the optic thalamus or the cerebral peduncles regularly led to hyperemia with blood stasis, erosions, or softening and occasionally to actual perforations of the stomach.

Damage to other parts of the brain in front of or above the cerebral peduncles and the optic thalamus produced no effect on the gastric mucosa. Lesions in the pons or the medulla also gave rise to similar pathological changes in the stomach, but not as consistently. From these observations, Schiff concluded that the patchy erosions and softening of the stomach were due to a neuroparalytic hyperemia produced by injury of the central pathway of the vasomotor nerves to the stomach.

Schiff's observations were repeated and confirmed by Brown-Sequard (4), Ebstein (5) and Pomorski (6).

In spite of these early and brilliant observations, this concept of a neurogenic basis for gastric lesions was for many years overshadowed by the views of Virchow (7), who held that a gastric ulcer was essentially a local disease resulting from a local vascular disturbance, such as an embolus etc., leading to local ischaemia and destruction of the gastric mucous membrane by the acid gastric juice. In 1885, Welch (8) lecturing on the genesis of gastric ulcer stated, "that the neurogenic theory of the origin of gastric ulcer is altogether speculative and has never gained wide acceptance".

Virchow's postulate that gastric ulcer is essentially a local disease continued to influence investigators for many generations. They made use of varied techniques, such as interference with the local blood supply to the stomach, or local application of chemical, mechanical, toxic and bacterial irritants. They soon found however, that although they could occasionally produce acute lesions and even acute gastric ulcers, such lesions healed rapidly and never became chronic. Accounts of this earlier work may be found in the reviews by Greggio (9) and McCann (10). In 1932, Cushing (11) wrote,"Out of this work has come the highly unprofitable research for a primary cause in the walls of the stomach itself, a search beset by many pitfalls and contradictions".

Although most experimentalists of this epoch paid little or no attention to the neurogenic aspects of the ulcer problem, from time to time the neurogenic theory was reviewed and isolated investigators attempted to extend the work of Kammerer, Rokitansky, Schiff and others.

A new approach to the understanding of certain types of clinical functional disorders was opened by Eppinger and Hess (12) in their monograph on "Vagotonia". Hitherto patients presenting themselves with long-standing complaints, especially referable to the heart or gastro-intestinal tract, in whom no anatomical or pathological basis for the complaints could be established, were labelled as neurotics. According to Eppinger and Hess, such individuals should be classified as 'Vagotonic'. They react with sweating and salivation to small doses of pilocarpine; they are apt to be asthenic, to have cardiac irregularities, bradycardia, and to show increased gastric motility and acidity. All these symptoms indicate a state of increased tonicity of the autonomic nervous system. Furthermore, such conditions as troublesome salivation, pylorospasm, the discomfort of hyperacidity, bronchial asthma, cardiospasm and hunger pains, to which vagotonic persons are prone, are frequently made worse by injection of pilocarpine and relieved by atropine. Such vagotonic individuals were believed to be constitutionally disposed to react differently and with greater intensity to various stimuli than normal persons (12).

Although Eppinger and Hess (12) discussed briefly the relation of vagotonia to gastric ulcer, they did not state definitely that vagotonia predisposes to ulcer, but their concept of autonomic imbalance, particularly regarding the vagus was enlarged upon by Von Bergmann (13) who believed that hyperactivity of the vagus evoked a spastic contraction of the stomach, leading to strangulation of the incoming vessels and producing thereby local ischaemia and necrosis. The ischaemic areas being digested by the

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gastric juice, erosions and ulcers result. Such patients, Von Bergmann believed, were benefited by atropine.

Pharmacological support to this view was supplied by the observation of Westphal (14), that subcutaneous administration of pilocarpine frequently led to mucosal hemorrhages and erosions in the rabbit. This work was confirmed by Friedman (15) and Underhill and Freiheit (16). Cushing (1931) injected pilocarpine and posterior pituitary extract (Pituitrin) into the cerebral ventricles of patients and found that in susceptible (or vagotonic) individuals it produced parasympathetic effects, such as sweating, flushing, lachrymation and excessive vomiting which was occasionally blood tinged.

These effects could be checked by atropine or by barbiturates, (which are known to depress the hypothalamic centres). These observations led to the assumption that the parasympathetic as well as the sympathetic systems had a primary nuclear representation in the interbrain. The effect of pilocarpine injected into the ventricles was soon confirmed by Bishop, Kendall and Light (18). At this time Beattie (19) reported the observation that electrical stimulation of the tuberal nuclei in the hypothalamus caused increased peristalsis and gastric secretion and led to gastric mucosal hemorrhages and erosions. These effects were abolished with section of the vagi.

In 1932, Cushing (11) reviewed the evidence on hand in support of the neurogenic basis of ulcer formation and concluded that "direct stimulation of the tuber nuclei in the hypothalamus or its descending tracts, or what theoretically amounts to the same thing, a functional release of the vagus

from paralysis of the antagonistic sympathetic fibres leads to hypersecretion hyperchlorhydria and hypermotility, especially marked in the pyloric segment. By the spasmodic contractions of the musculature, possibly supplemented by accompanying local spasma of the terminal blood vessels, small areas of ischaemia or hemorrhagic erosions are produced, leaving the overlying mucous exposed to the digestive effects of its own hyperacid juices". This re-affirmed and stated more concisely the earlier views of Rokitansky (2), Schiff (3), Von Bergmann (13) and others.

Cushing's work created a new interest in the subject, and in the years following his paper there has been an increase in both clinical and experimental reports which tend to support the neurogenic basis for ulcer formation.

Pathological Criteria for the Diagnosis of Ulcer

In reviewing the literature, it has been noted that many authors have made no attempt to differentiate clearly between erosions and true ulcers, and in their discussion have frequently referred to ulcers, when only erosions were present. This has only added to the confusion that already existed. In order to provide a basis for comparison, the terms erosions and ulcers as referred to in this paper may be defined as follows: An erosion is a break in the continuity of mucous membrane. It may be associated with hemorrhage. It may be superficial or deep; if it is deep, then it may be referred to as a crater. An ulcer is also an interruption in the continuity of the mucous membrane, but is in addition, always accompanied by an inflammatory reaction (Karsner (20), Boyd (21)). This kind of ulcer may be appropriately termed an acute ulcer; it may occur anywhere in the stomach or duodenum and may be multiple. A chronic ulcer, of the type usually seen in man, is more localized, and is most often limited to the first part of the duodenum, or to the lesser curvature of the stomach, and posterior wall, particularly in the pyloric region. Grossly a chronic ulcer reveals a sharply defined crater with overhanging edges of mucous membrane and a necrotic and indurated base. Microscopically, four zones can be distinguished in the floor of the ulcer (Boyd (21)); 1. an inflammatory zone consisting of fibrin and polymorphonuclear leucocytes, 2. a zone of necrotic granulation tissue, 3. a zone of living granulation tissue, and 4. a zone of dense scar tissue, which forms one of the most important features of the chronic ulcer.

Acute ulcers may either heal completely and leave no scars, or may heal and show evidence of cicatrization or scarring. The presence of a healed ulcer with cicatrization has often been incorrectly referred to as evidence of chronicity.

Clinical-Pathological Evidence for the Association of Gastric and Duodenal Lesions with Intracranial Disorders.

Reports by Arndt (22), Von Eiselberg (23), Beneke (24) Hart (25) Mogilnitsky (26) and Korst (27), have demonstrated clearly the association of gastric and duodenal lesions with lesions of the brain. Cushing (11), reported 11 cases of intracranial lesions accompanied by gastric and duodenal lesions which varied from hemorrhagic erosions to actual perforations. In 6 of the 11 patients, the lesions involved the posterior cranial fossa. One case, a child in whom a mid-line cerebellar tumor was verified, lived for two years and at autopsy a chronic duodenal ulcer was found.

Following Cushing's paper, there has been an increased number of reports illustrating the clinical-pathological correlation of gastric and duodenal lesions with affections of the brain and spinal cord. Gastric and duodenal lesions have been associated with a large variety of intracranial disorders, including such conditions as acute meningitis, (Masten and Bants) (29); Hartung and Workang (301); encephalitis, Masten and Bants (29); brain tumors, Grant (31), Masten and Bants (29), Boles and Riggs (42); pituitary tumors, Comroe (32); Swan and Stephenson (33); Foley, Snell and Craig (34); vascular lesions of the brain, Davies (25); Ask-upmark (36); Masten and Bants (29); Dott (37), and brain trauma (Vanzant and Brown (38)); Ask-upmark (36).

It has been shown that melena in infancy (6) was frequently due to intracranial lesions occurring at birth, and was especially noted after prolonged and difficult labors (28). Acute gastric and duodenal erosions

have also been associated with lesions of the upper spinal cord, Riddock (39) and Moolton (41). Parsons, Plummer et al (40), studied the occurrence of peptic ulcer in syphylis of the central nervous system. They found peptic ulcer occurred in 10,5 percent of 200 cases of neurosyphylis, while among 400 controls, the incidence of ulcer was only 3 percent.

Summary

Nearly all of the gastro-intestinal lesions discovered to be associated with the intracranial and spinal cord lesions were of the acute type, usually multiple and with no special preference for localization. The pathological changes observed were nearly all of the hemorrhagic type of erosion with edema of the mucous membrane. Craters were only occasionally noted and true acute ulcers with or without perforation were rare. Only in the single case reported by Cushing (11), was there any evidence of the association of a brain lesion with a chronic peptic ulcer.

In almost all the cases reviewed, gastric bleeding or perforation indicating a gastric or duodenal lesion, was noted very shortly after the brain injury or soon after the operative interference, usually within 24-72 hours. In most instances, the patients were not fed for at least 24 hours or longer prior to operation, and for 24 hours or longer after operation. These patients all had stormy post-operative courses, associated with shock-like conditions. Many patients were comatose for 24 hours or longer prior to death, and lesions were discovered only at autopsy.

Ask-upmark (36), analyzed the fasting gastric secretions in 10 cases of

intracranial tumors pre-operatively, and found the acidity of the gastric juice may be unaffected, reduced, or enhanced. Dragstedt (154), reported that immediately following brain operations, patients exhibited a large increase in the volume and acidity of the total night gastric secretion.

The majority of intracranial lesions accompanied by gastric or duodenal changes reported in the literature reviewed above, were located in the neighbourhood of the third and fourth ventricles, while tumors involving the basal ganglia, mid-brain, or upper portions of the cord were less frequently associated with gastro-intestinal pathology.

Although the association of brain lesions and gastric or duodenal pathological changes seems well established, it is significant that such a low incidence of gastro-intestinal lesions were reported following brain disorders. Since it was only those cases with clinical evidence of hematemesis, melena or tarry stools and those accidentally discovered at autopsy which have been reported, it is very possible that many more cases with post-operative gastric mucosal hemorrhages or erosions have remained undiagnosed because they did not show any of the outward signs of bleeding. With improvement in clinical conditions, the resumption of a proper diet, and aided by the rapid regenerative powers of the gastro-intestinal mucosa, many of these acute lesions may heal completely, leaving no trace at the site of the lesion. It would be interesting to observe the number of patients with intracranial lesions who show no outward clinical signs of gastro-intestinal pathology, but in whom occult blood may be found in the stools.

Experimental Data Relating The Hypothalamus To The Function Of The Gastro-Intestinal Tract And To Peptic Ulcer.

A. Effects of Stimulation of the Hypothalamus.

The existence of a cerebral diencephalic centre for the sympathetic nervous system was indicated when, in 1909, Karplus and Kreidl (43) first showed experimentally that electrical stimulation of the hypothalamus caused a sympathetic-like response, e.g., pupillary dilation, sweating, lachrymation and salivation. Since then experimental reports have confirmed Karplus and Kreidl's work and have linked the hypothalamus with the control of such common autonomic functions as carbohydrate metabolism, water metabolism, heat regulation, sleep and cardio-vascular regulation (47). The researches of Cannon and Britton (44), Bard (45), and Fulton and Ingraham (46), have indicated that when the hypothalamus is released from cortical control, primitive behavior reactions in animals may be elicited. This quasi-emotional state is often called 'sham-rage', and is accompanied by a mass discharge of the sympathico-adrenal system. Similar reactions have been noted in man in association with hypothalamic lesions (48).

The first description of the change in the gastro-intestinal tract following stimulation of the hypothalamus was given by Beattie in 1932 (19). Stimulating the lateral margins of the infundibulum under direct vision, he noted increased peristalsis and secretion in the stomach. (Bipolar electrodes were used with a current just subminimal for contraction of the fibres of the temporal muscle). The secretion was watery, contained some

free hydrochloric acid, pepsin, etc., and in general, resembled that obtained by stimulation of the vagus nerves. When the stimulation was continued for one half hour, small patches of hyperemic mucous membrane were seen near the lesser curvature of the stomach. Section of the vagi abolished the response.

In an address on hypothalamic mechanisms, Beattie (31) presented the following hypothesis of hypothalamic function which seemed to fit all the experimental data. He suggested that an anterior hypothalamic complex consisting of the supra-optic and tuberal regions acted as a parasympathetic centre, while a posterior hypothalamic complex situated in the mammillary region of the hypothalamus served as a sympathetic centre. He believed that all the evidence was against the existance of a series of discrete 'centres' in the anterior or posterior complexes, but favoured the view that one or other complex gave rise to more generalized "mass reactions".

This hypothesis received some direct experimental support from the work of Beattie and Sheehan (52), who found that stimulation of the tuber region resulted in a rise of the intragastric pressure varying from 10 to 50mm H_2O, after a latent period of approximately 30 seconds. In no case was it as marked as that produced by stimulation of the peripheral end of the cut vagus. The rise of the intra-gastric pressure was accompanied by a fall in blood pressure and by a subsequent increase in the peristaltic movements of the stomach. Section of the vagi, abolished these effects. Stimulation of the posterior hypothalamus, caused a slight fall in the intragastric pressure, accompanied by a rise in the blood-pressure and by complete obliteration of all gastric motility. Section of the vagi did not affect these results.

Heslop (53), using more accurate methods of stimulating the hypothalamus and recording gastric motility repeated and confirmed the work of Beattie and Sheehan (52). He found that stimulation of the anterior hypothalamus produced a marked increase in gastric tone and motility; posterior hypothalamic stimulation only caused a transient relaxation of the pyloric end of the stomach.

Heslop (54) found also that stimulation of the anterior hypothalamic region produced an increase in gastric secretion and a marked rise in the free and total acid. Stimulation of the posterior region, resulted in the production of a marked increase in the amount of mucous and a tendency to diminish the rate of flow and acidity.

Kabat, Anson, Magoun and Ranson (55), (using cats at least two and one-half hours after ether anaesthetic was discontinued), found that stimulation of the hypothalamus with the Horsley-Clarke stereotaxic instrument always caused cessation of peristalsis and loss of tone of the stomach and small intestine, after a short latent period of one second. Gastro-intestinal motility was never increased. Accompanying the diminished activity of the gut were marked dilation of the pupils, increased rate and amplitude of respiration, erection of hair, etc., which has been referred to as a "sympathetic discharge".

These observers thus found no evidence of a "parasympathetic centre" for gastro-intestinal activity as described by Beattie, but their results indicated that there is a hypothalamic centre which inhibits gastro-intestinal activity. Although the exact localization was not certain, the

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lateral hypothalamus was chiefly involved since stimulation of this region always resulted in gastro-intestinal inhibition. Since inhibition was always accompanied by a "sympathetic discharge", they believed that one centre is concerned in all responses, though their respective thresholds differ, that for gastro-intestinal inhibition being the highest of all. Stimulation of the thalamus, internal capsule, anterior commissure, septum pellucidum and infundibular stalk with the same strenght of current produced no change in gastro-intestinal motility.

The results of Masserman and Haertig (56), offer a possible explanation for the differences in results obtained by Beattie and Ranson et al. These authors found that when the anterior hypothalamus was stimulated with a weak current (too weak to induce typical marked emotional mimetic response) increased gastro-intestinal activity resulted. Enteromotor effects were also obtained when the dorsal portion of the supramammillary decussation and the mammillary bodies were stimulated. When any portion of the hypothalamus was stimulated with currents intense enough to elicit diffuse sympathetic discharges, intestinal activity was definitely reduced or stopped. Thus it may be that motor responses of the gastro-intestinal tract are only elicited by weaker stimuli.

Sheehan (49) in his excellent review of this subject called attention to three other facts, (a) that Ranson et al never stimulated the supra-optic area from which Beattie claimed to obtain increased enteromotor effects, (b) that variability in results may be due to differences in frequency as well as in strength of stimulation. Because of the lack of uniformity in methods of stimulation, it was impossible to compare the

strength or the nature of the stimulation used by various workers, (c) that the significant differences which existed in the latent period between the motor responses which followed anterior (30 sec.) and posterior (approx. 1 sec.) hypothalamic stimulation indicated that there may be some fundamental difference between the mechanisms of the two responses.

More recently Wang, Clark, Dey and Ranson (57) found that when the anterior hypothalamus was stimulated, there was occasionally a slight inhibition, but usually a marked delayed excitatory response of the intestine, colon, and stomach occurred after a latent period of 40-60 seconds (average 52 seconds). The response was always gradual in onset, reaching a maximum in one or two seconds and slowly diminishing, making a total duration of 2-7 minutes. Bilateral vagotomy did not abolish the delayed excitatory response. Vagal effects on the gut were also obtained when the hypothalamus at or behind the infundibular level was stimulated. Such responses were elicited in chronic spinal cats and were abolished after bilateral vagotomy. These responses were prompt; the latent period never exceeded 7 seconds and closely resembled the responses obtained by Beattie (19) and Masserman and Haertig (56). The delayed type of responses were similar to the responses of the stomach obtained by Beattie and Sheehan (52), and Heslop (53) where the latent period was at least 30 seconds. Wang (57) et al were unable to obtain this delayed response in spinal, but vagus-intact cats and believed that it was not a simple vagal effect.

Although the experimental findings are contradictory and incomplete,

Sheehan (49) believed there were adequate grounds for accepting a sympathetic centre regulating gastro-intestinal activity, located in the hypothalamus, more particularly in the lateral hypothalamic area. The posterior or the mammillary region appeared to be particularly responsive.

The evidence for the existence of a parasympathetic centre in the anterior hypothalamus as postulated by Beattie, is still very much in dispute. Sheehan (49), has considered the possibility that stimulation of the anterior hypothalamic area may activate the cortical inhibitory fibres to the sympathetic centre and thus the enteromotor results may be due to inhibition of the more posteriorly situated sympathetic centre.

More recently Hare and Geohegan (58) and Bronk, Pitts and Larrabee (59) have called attention to the influence of the frequency of hypothalamic stimulation upon the response. Hare and Geohegan (58) found that in cats, stimulation of the hypothalamus with low frequencies produced a parasympathetic response characterized by fall of blood-pressure, constriction of pupils, etc., while stimulation of the same area at a higher frequency caused a rise in blood pressure, dilation of the pupils, etc., i.e. a sympathetic response.

Bronk et al (59), found that stimulation of a point in the tuberal region at a frequency of 20 per sec. produced an increased discharge of impulses in the inferior cardiac nerve and a rise of blood-pressure. Then stimulation at exactly the same point with a frequency of 2 per second, inhibited the existing sympathetic activity with a resultant fall of blood-pressure.

Due to the lack of uniformity in methods of hypothalamic stimulation used by the different workers, it is not possible to compare the strength

or frequency of stimulation utilized, but it may well be that the conflicting results obtained by Beattie (19) and Ranson et al (55) may be due to the differences in frequency as well as in the strength of the hypothalamic stimulation (56).

In 1941 Gellhorn, Carlson and Darrow (274) experimenting on cats, concluded that hypothalamic stimulation led to an excitation of the sympathetic and parasympathetic systems, occasionally to an inhibition of the parasympathetic and that excitation of both systems may result from stimulation of the same part of the hypothalamus. These results were further supported by the observation of Feldman, Cortell and Gellhorn (275), and Gellhorn, Cortell and Feldman (272) who showed that central excitation of the autonomic centres by anoxia, metrazol, rage and 'sham rage' produced by stimulation of the hypothalamus, activated the parasympathetic and sympathetic centres at the same time, resulting in a simultaneous sympathico-adrenal and vago-insulin discharge; with a slight predominance of the former. From these observations they concluded that it was not justified to apply the concept of reciprocal innervation to central autonomic processes (275).

Summary

In view of the more recent findings, all attempts to localize sympathetic and parasympathetic centres in the hypothalamus may prove futile, for the division between the sympathetic and parasympathetic systems may no longer be considered anatomically or functionally complete. When the hypothalamus is stimulated electrically, the state of strict reciprocity of the two autonomic centres is suspended and both centres discharge simultaneously with the sympathetic response predominating.

Effects of Hypothalamic Lesions

The first experiments designed to disclose the effects of hypothalamic lesions on the gastro-intestinal tract were performed by Burdenko and Mogilnitzki (60) in 1926. Placing lesions behind the infundibular stalk, they noticed gastric mucosal hemorrhages, erosions, occasionally perforations with peritonitis, and cicatrization of some ulcers in a few of their animals which survived the operation for several months. Post-mortem study of the brains of such animals showed that the tuberal region was extensively destroyed in most of the cases.

As a control, lesions were made in other parts of the brain, but these were without effect, Burdenko and Mogilnitzki then concluded that the destruction of a sympathetic vasoconstrictor centre in the mammillary and tuberal regions of the hypothalamus resulted in dilation of blood vessels, mucosal hemorrhages and necrosis, the necrotic areas undergoing digestion by the acid gastric juice.

In 1933, Keller, Hare and D'Amour (61), made a preliminary report on a series of 50 cats and 40 dogs in which experimental lesions in the upper brain stem resulted in acute gastro-intestinal changes in a relatively small number of animals. In 12 dogs, mucosal hemorrhages and hyperemia were noted in the body of the stomach at death which occurred 7 to 24 hours after operation. These were often associated with hyperemia of duodenal and jejunal mucosa, becoming less pronounced as the distal ileum approached. In the 8 dogs in which erosions were noted, however, lesions existed in the anterior hypothalamus at the level of the chiasma.

Watts and Fulton (62) produced extensive lesions in the hypothalamus of

monkeys and were unable to find a definite relationship between destruction of any single group of hypothalamic nuclei (supra-optic, tuber or paraventricular) and pathological changes in the gastro-intestinal tract. Out of 17 animals in which the lesions involved the tuberal, supra-optic and paraventricular nuclei, only 7 revealed any gastro-intestinal pathology. Erosions of the stomach were found in 4 animals, free blood in the lumen in two cases and a duodenal perforation in 1 case. Several animals with similar hypothalamic lesions showed no evidence of gastro-intestinal pathology. Posterior hypothalamic lesions did not result in gastric or duodenal changes.

In a control series of 63 monkeys, which had undergone operations upon some other part of the brain or spinal cord, 19 per cent showed multiple punctate mucosal hemorrhages, unaccompanied by erosions in the stomach or small and large intestines. In only 3 animals was free blood noted in the lumen of the gut, twice in monkeys with mid-thoracic transection of the cord, and once in an animal in which both premotor areas had been destroyed. It was concluded that these lesions were due to hyperactivity of the sympathetic centre, either by a release or an irritation, which led to vasoconstriction of the blood vessels of the gut, local ischemia and necrosis.

As the observations of Watts and Fulton were based on relatively long term experiments, this work was continued by Hoff and Sheehan (63) and studies were made on animals which were sacrificed earlier, in order to determine whether any earlier lesions had been missed.

In their study of 19 monkeys, 3 of which died during the operation, 5 of the remaining 16 showed acute mucosal erosions. These were confined mainly to the body of the stomach and showed no predilection for the pylorus or lesser curvature of the stomach. The erosions were always multiple, many

had a punched out appearance and were a half a centimeter square. They were superficial and never involved the muscularis.

Histological examination of the hypothalamic injuries revealed that in all 5 animals showing gastric lesions at autopsy, the lesions were small and confined to the tuberal nuclei. Lesions in the posterior hypothalamus were never followed by changes in the gut. In only one out of 5 monkeys was the track of the lesion hemorrhagic, and in all 5 cases the base of the 3rd. ventricle had been opened, but other hypothalamic nuclei were not injured. Thus it was found that lesions restricted to the tuberal nuclei led to hematemesis and multiple erosions in the body of the stomach, although similarly placed lesions were as often unassociated with gastro-intestinal changes. It is of special interest that of those 5 animals which showed erosions, 2 died on the first day after a stormy post-operative course, and another on the second day, while the other 2, which were sacrificed on the 3rd. day, showed a marked disinclination to eat during the three-day survival period.

In a control series of 50 animals subjected to various non-hypothalamic cerebral lesions, autopsy examinations revealed only 1 case of a gastro-intestinal lesion, in an animal in which both the right and left motor and premotor areas had been extirpated 5 months prior to 2 transections of the spinal cord.

Although the number of positive findings were small, Hoff and Sheehan concluded that the consistently negative findings in the control experiments as well as those of Watts and Fulton appeared to lend some significance to the association of gastro-intestinal lesions with injury to the hypothalamus or interruptions of the descending autonomic pathways, especially those lesions

in the tuberal region.

A large series of 200 dogs with a varied distribution of brain stem lesions, approximately one half of which were located in or near the hypothalamus was reviewed by Keller (64) in 1936. Included in this series were 6 dogs with massive prechiasmal lesions, 3 with extensive transverse chiasmal damage, 20 with less extensive unilateral hypothalamic lesions and 33 dogs in which there was almost complete destruction of the hypothalamus. Of the whole series of 200 dogs, 19 showed hemorrhagic states and 11 revealed craters or erosions at autopsy. Of those with hemorrhagic states the fundic portion of the stomach was most frequently involved, often with a sharp line of demarcation from the blanched pyloric or cardiac end. Occasionally these lesions of stomach and duodenum revealed engorgement of capillaries and localized areas of mucosal hemorrhages, and in no instance was there any cellular inflammatory reaction noted in these lesions.

It is of special interest to note that of these 20 animals which showed lesions, 12 died in 24 hours or less; 4 died in less than 48 hours; and 4 within 72 hours of the operation. In several instances, bloody vomiting and bloody diarrhoea were noted soon after operation and blood was found in the lumen at autopsy 8 to 12 hours after operation. Of the 19 dogs with gastro-intestinal pathology, 14 had lesions in the anterior hypothalamus at the level of the optic chiasma. In 3 animals the lesion encroached upon the tuberal nuclei; in no instance was the posterior hypothalamus involved, and in all but one, the lesions extended into the third ventricle.

In 11 dogs with gastric craters or erosions, 8 had transverse chiasmal lesions, involving mainly the rostral portion of the anterior hypothalamus (supra-optic region) the remaining 3 had pontine lesions. Again, 5 of these

animals died within 84 hours after operation; one died on the 15th. day and the remaining 2 were sacrificed on the 26th. day. These erosions were not associated with hemorrhagic states and mainly involved the surface mucosa, but in several instances extended down to the muscularis. In no instance was there any resemblance to a chronic ulcer as seen in man.

Keller noted particularly that hemorrhagic states usually occurred after complete destruction of the anterior hypothalamus and were associated with absence of free acid in the gastric content at autopsy, whereas the craters were noted only when part of the anterior part of the hypothalamus was intact, and at autopsy the presence of craters was associated with free acid in gastric contents. Keller (65) then submitted 24 dogs to bilateral vagotomy prior to producing a chiasmal lesion, and typical hemorrhagic states but no erosions were precipitated in 9 of these animals. On the other hand, bilateral removal of the thoracic and lumbar sympathetic chains prior to making the hypothalamic lesions resulted in erosions, without hemorrhage in 14 out of 29 dogs.

Keller and D'Amour (65) next reported the production of hemorrhagic lesions and erosions in 5 out of 23 animals following removal of the hypophysis. They felt that the lesions were precipitated because of a neighbouring neural derangement, possibly intraventricular stimulation as a result of opening into the third ventricle or incidental damage to the hypothalamus.

Martin and Schnedorf (67), on the other hand, found no changes in gastro-intestinal motility or secretion following hypothalamic lesions in cats and monkeys. In no instance was there any gastric or duodenal lesion found, in any of the animals which were sacrificed after 42 to 190 days,

even though in all the monkeys and in 10 cats, the lesions were made in the tuber region in an effort to parallel the results of Hoff and Sheehan.

Ingram (47) also reported that he found no significant evidence of gastro-intestinal lesions in some hundreds of animals without hypothalamic lesions.

DISCUSSION

Although the experimental lesions of the hypothalamus produced gastro-intestinal lesions more frequently than did lesions placed elsewhere in the central nervous system, it did not follow that all hypothalamic lesions resulted in such changes in the gut. Indeed, as Sheehan (49) has pointed out in a study of the collected data of Watts and Fulton, Hoff and Sheehan, Keller and Martin and Schnedorf, changes in the gastro-intestinal tract occurred in less than one third of all the experimental hypothalamic lesions.

The positive findings indicate that the gut lesions were associated mainly with injuries of the anterior hypothalamus, the supra-optic and tuberal regions, especially the latter. As has already been noted above, the tuber region was believed to be part of a generalized sympathetic centre influencing, among the other visceral functions, the motility and secretory activity of the gut.

In general, lesions such as were found were of an acute variety, varying from mucosal hemorrhages, erosions and craters, but never were chronic ulcers produced of the type seen in man. The lesions produced occurred in the fundic portion of the stomach, were multiple and showed no predilection

for the pylorus, lesser curvature of the stomach or duodenum, as in man.

It is of interest that similarly placed lesions frequently gave negative findings, and that small, carefully localized lesions placed in all parts of the hypothalamus, especially in the tuberal regions by Martin and Schnedorf (67) completely failed to produce pathological changes in the gut. The lesion of the gut appeared to be mainly associated with the large extreme hypothalamic lesions as produced by Watts and Fulton (62), Hoff and Sheehan (63) and Keller (64,65). These were made with a blunt probe, and the lesions frequently extended into the third ventricle. Martin and Schnedorf (67), felt that the unintentional trauma to the surrounding tissues with uncontrolled side actions may well have accounted for a fair number of the gastric changes. Keller (64) for a while supported the view that changes in the gastro-intestinal tract may possibly be due to a disturbance of the cerebro-spinal fluid circulation from debris or blood, making its way into the ventricles, but further experiments did not support this view. Hoff and Sheehan (63) found that extensive lesions, with hemorrhage into the ventricles frequently resulted in negative findings in the gut.

The balance of facts indicates, however, that damage to the hypothalamus may precipitate lesions, but by what mechanism is unknown. It has been suggested that hyperactivity of the sympathetic centre, either by a release or an irritation, leads to spasm of the terminal vessela in the submucosa of the gastro-intestinal tract with the production of local ischemia in the mucosa and the digestion of the necrostic tissue by the acid gastric secretions (Schiff (3), Watts and Fulton (62)).

It is not known at present whether overactivity of the sympathetic is brought about by the destruction of the inhibitory pathways in the more

anterior parts of the hypothalamus or due to irritation of the sympathetic centre from an adjacent injury. Hoff and Sheehan (63) were more inclined to favour the latter view. The fact that lesions in the posterior hypothalamus were never associated with gastro-intestinal lesions would tend to support this view.

Cushing(11) and others (12, 13, 14) appeared to favour the view of the hyperactivity of the parasympathetic system as the cause of ulcer formation. They believed that stimulation of the parasympathetic centre of the hypothalamus or of its descending tracts led to hypermotility, hypersecretion with resultant focal ischemic necrosis and digestion of the damaged areas by the increased acid secretion.

Hoff and Sheehan (63), thought that probably there is no real difference in the two views expressed above, since the gastro-intestinal lesions may have resulted because of a complex imbalance between the two autonomic systems.

More recently Wolf and Wolff (254) (271), observed profound physiological changes in human gastric mucosa in response to certain emotional disturbances. Emotional states of fear, depression and other feelings involving a desire for withdrawal, were always accompanied by a sympathetic response on the stomach consisting of hyposecretion, hypomotility, mucosal pallor, and decreased mucin production. Reactions and emotions involving conflict, hostility, resentment and anxiety were found to be associated with hyperemia, hypersecretion, hypermotility increased mucin production, which were predominantly parasympathetic effects. Where conflict involving both fear and resentment existed, a dissociated response was observed resulting in increased parasympathetic activity, namely hyperemia, hypersecretion and hypermotility. Gellhorn and his associates have noted that in some states of stress, and

hypothalamic stimulation, strict reciprocity of both centres was suspended and the parasympathetic and sympathetic systems discharged simultaneously (272, 274, 275).

Banting et al (85 & 86) and Wener (276), have also observed that when acetycholine (85,86) or mecholyl (276) were administered to animals, there was a direct parasympathetic effect and an indirect compensatory sympathetic response, again indicating that both divisions of the autonomic nervous system responded together.

Summary

Thus from the evidence presented it may not be justifiable to interpret the types of response obtained from hypothalamic lesions as purely sympathetic or parasympathetic, for evidently both systems were frequently activated simultaneously. It therefore seems more correct to consider that lesions placed in the hypothalamus upset the autonomic regulating mechanism, thereby setting up a state of autonomic imbalance resulting in vasomotor changes in the gut, which may be severe enough in some cases to cause mucosal hemorrhages, erosions and occasionally acute ulceration.

These vasomotor changes may have been aggravated by the shock-like conditions which accompanied the operations. In most instances where the lesions did occur, the animals were moribund and died soon after operation, within the first 24 to 96 hours. Selye (277-279) has reported the occurrence of acute gastro-intestinal erosions which he believed were characteristic of the shock-phase of the alarm reaction.

Mann (280, 281) Elliott, T.R. (83) have also reported the occurrence

of acute mucosal hemorrhages and erosions associated with the moribund condition of animals following bilateral adrenalectomy.

In the experiments of Martin and Schnedorf (67), the animals received very careful pre-operative and post-operative care and most of them survived the operation and were sacrificed only after 40 days or more. It may very well be that had some of these animals been examined in the first few days after the operation, some gastro-intestinal lesions would have been noted, but as the animals recovered any acute lesions that may have existed had time to heal leaving no traces at autopsy at the later date.

From the experimental evidence thus far submitted, it is clearly evident that hypothalamic lesions and lesions of the pons, medulla and upper spinal cord, by causing derangement of the autonomic centres or interfering with the descending pathways, may initiate acute gastro-duodenal lesions, but no evidence exists that these lesions can or ever have gone on to form chronic ulcers of the type seen in man.

The Effect Of Lesions Of The Peripheral Nerves Of The Stomach

A. Vagus

Kammerer (1) was probably the first to observe gastric lesions in rabbits following injury to the vagus and splanchnic nerves. It was not, however until the latter part of the ninteenth century that experimental work was attempted along similar lines. In 1893, Lorenzi (69) reported that following section of the vagi, either in the neck or below the diaphragm in rabbits, mucosal hemorrhages were noted, and if the animals survived 24 hours or longer, hemorrhagic erosions developed. Saitta (70), performed bilateral vagotomy in the neck and observed mucosal hemorrhages and erosions in 7 out of 10 rabbits. In 4 rabbits, following bilateral vagotomy, he administered three per cent HCL solution repeatedly by mouth and found multiple ulcers. Finzi (71) and Keppich (72) found hemorrhagic necrosis and acute and subacute ulcers in the stomach of animals subjected to bilateral cervical vagotomy; according to Greggio (73) negative results were noted by other workers following cervical vagotomy.

Van Yzeren (74) cut both vagi subdiaphragmatically in 20 rabbits and in 10 of them claimed he found single chronic ulcers in the pyloric region; the earliest was observed in 5 days and the oldest after 269 days.

Entirely negative results following subdiaphragmatic vagotomy were obtained by Donati who believed the positive results claimed by others were incidental and that vagotomy had no effect on the mucous membrane of the stomach. On the other hand, Ophuls (76) repeated and confirmed the work of Van Yzeren, but in only 6 out of 30 rabbits did he produce ulcers which he claimed resembled those seen in man. These did not appear before the 24th. day and the last one on the 18th. day. Examination of these ulcers shows them to

be acute erosions in no way resembling ulcers seen in man. Ophuls concluded that the lesions were neurotrophic and that trophic influences were necessary to preserve the normal resistance of the mucous membrane to the digestive action of the gastric juice. Latzel (77) noted hemorrhagic erosions and ulcers in 10 dogs, 12 days following subdiaphragmatic vagotomy.

Greggio (73) who performed numerous cervical and subdiaphragmatic vagotomies in rabbits and dogs, found among acute ulcers only one lesion which resembled a chronic ulcer, 30 days following the operation. These animals were sacrificed from 15 to 150 days post-operatively, and at autopsy only occasional gastric mucosal hemorrhages or erosions were seen. In spite of the paucity of positive results, Greggio concluded that altered gastric motility and modification of the gastro-pancreatic juices play a role in the etiology of ulcer. McCrea (286) noted that after vagotomy ulcers occurred in approximately 50 per cent of his rabbits, but none in cats or dogs.

More recently, Ferguson (78) found erosions in 2 animals which had been subjected to vagotomy; one animal died from perforation on the 20th. day.

Beazell and Ivy (79) claimed an increased incidence of chronic ulcers in rabbits and dogs placed on a rough diet following subdiaphragmatic vagotomy. Ulcers developed in 12 out of 29 animals, and the maximum incidence was noted about the 50th. to 60th. day. The incidence of ulcer decreased by one half in another group placed on a soft diet. Ulcer did not occur in 60 dogs which were subjected to bilateral vagotomy above the diaphragm and fed a soft diet. Meek (80) also reported that ulcers appeared in 2 out of 13 vagotomized dogs which were on a rough diet. It should be pointed out that adequate histological evidence to confirm the existence of ulceration was

not submitted by Beazell and Ivy (79) and Meek (80).

Keller (65) found that acute mucosal hemorrhages and erosions were precipitated in the gastric mucosa in a high percentage of vagotomized dogs which were subjected to yard conditions during the winter months. In a few instances such lesions healed with extensive scarring. Such lesions were never encountered in animals under a cage regime. Berg (81) found no evidence of ulcer in 6 dogs sacrificed 30 to 90 days after subdiaphragmatic vagotomy.

Results obtained by stimulation of the vagi have been equally contradictory. Keppich (84) claimed to produce chronic gastric ulcers in 10 out of 11 rabbits by placing electrodes on the vagi near the cardia. The nerves were stimulated with faradic current for 10 minutes daily for 5 to 25 days. Stahnke (82) stimulated the vagi in dogs near the cardia by placing the electrodes into the lumen of the lower oesophagus, with resultant hypermotility, hypersecretion, pylorospasm, chronic gastritis and erosions but no ulcers. According to McCann (19), negative results were obtained by Gundelfinger, Korte and Donati. Best and Orator (294) found they could not produce ulcers by direct stimulation of the vagus with magnesium, and that it did not prolong ulcer already present. Ettinger, Hall and Banting (85), by repeated and prolonged vagal stimulation in the dog, produced congestion of the mucosa of the upper gastro-intestinal tract, but no erosions or ulcers. The following year, Manning, Hall and Banting (86) using continuous vagal stimulation in dogs (31 to 74 hours) produced congestion and hemorrhage in upper gastro-intestinal tract, but when eserine was added, small acute ulcerations in the pyloric region and duodenum were noted in one dog. Since the microscopic description of these lesions were not fully reported, it is not known whether these lesions were merely acute erosions or true ulcers.

section of the splanchnic nerves with removal of the first lumbar ganglion yielded good results in 14 out of 25 cases with gastro-duodenal ulcer.

Celiac Plexus

According to Greggio (73), lesions of the celiac plexus were found to produce ulcers and mucosal hemorrhages by Vedova, Kawamura, Lilla and Gebelli. Greggio (73) also reported that Pincus and Samuel, and Popielski noted hyperemia, mucosal hemorrhages and ulcers following extirpation of the celiac plexus, while Adrian, Budge Lustig and others constantly observed negative results in dogs and rabbits. Latzell (77) also reported that gastro-intestinal lesions did not occur following removal of the celiac plexus.

According to Ivy (90), section of both vagi and splanchnic nerves occasionally produced petechial hemorrhages of the pyloric and duodenal mucous membrane, but in 10 dogs which were killed from 1 week to 4 months following double vagotomy and splanchnotomy with extirpation of the celiac plexus, no gastric or duodenal lesions were observed. This confirmed the findings of Donati. However, Auer (91) has claimed that ulcers developed after complete denervation of the stomach.

DISCUSSION

From the contradictory evidence submitted, it is evident that although many investigators have produced gastric or duodenal lesions by interfering with the nerve supply to the stomach, only rarely, if at all, has it

stomach. Vagus fibres have been found to be present in the splanchnic nerve of the cat. (Rasmussen and Duncan (92)); Iwama (93); Duncan (94). Inhibitory effects have been obtained by stimulation of the vagus and motor effects on stimulation of the sympathetic nerves. (Wheelan and Thomas (95)). The latter authors also noted a decrease in tonus following stimulation of the vagus with a weak current and motor effects were obtained when the current was increased in 2 cases. Heslop (54) observed that stimulation of the splanchnic nerves caused increased secretion of acid gastric juices, even when the vagi were cut.

McCrea, McSwiney and Stopford (96) concluded that the effects of section of the nerves of the stomach may be divided into 2 stages, a temporary or immediate effect of initial paresis and gastric dilation, probably due to shock, lasting 7 to 10 days, followed after an interval by a return to normal function. The permanent effect was a decrease in initial emptying of the stomach.

It was also shown by McCrea et al (98) that stimulation of the peripheral end of the cut vagus may either initiate movement, if the organ be in a state of rest or hypotonus, or if movements are present, augment and sometimes accelerate them. If hypertonus, or activity exists, stimulation of the cut end of the vagi is followed by inhibition and relaxation, but ultimately increased contractions occur. The results were not altered by anaesthetics, decerebration or splanchnic nerve section.

According to McSwiney (97) and others, the immediate effects of vagotomy, splanchnectomy and denervation of the stomach are quite similar, namely retardation of function. At a later date, the peripheral intrinsic nervous mechanism takes over the control of the stomach and only one important

abnormality in motor function persists, namely a decrease in the initial emptying time of the stomach. After carefully reviewing the extensive and contradictory literature on the innervation of the stomach, McSwiney (97) concluded that the experimental evidence indicated the presence of motor inhibitory fibres in the vagus and splanchnic nerves.

From the results of vagotomy for duodenal ulcer thus far reported, it has become apparent that the decreased tonus and diminished amplitude of the contractions of the stomach wall which were invariably noted after vagotomy, were not permanent. In many patients, the motor activity of the resting stomach was practically normal in less than a year after operation (309, 312, 320). Most observers have agreed that the initial delay in emptying of the stomach after vagotomy gradually disappeared after several months to a year (309, 312, 313, 318, 320, 337). However, several instances have occurred in which the gastric retention was of such a severe nature that many patients required subsequent gastro-enterostomy (312, 324). Another minor complication of vagotomy has been the development of diarrhoea, which was usually found to be transient and mild in character, but in some cases it persisted for many months and became very troublesome (312, 320). Although the period of post-operative observation is still too short, there is every indication that in most instances bilateral vagotomy in man causes only transitory upset in the motor activity of the gut which gradually returns to normal or nearly normal, with only a slight delay in the emptying time of the stomach persisting. Thus it is evident that in man the effects of vagotomy closely resemble those found in animals as was shown by McCrea, McSwiney and others (96, 97, 98).

The functional and anatomical division between the sympathetic and parasympathetic systems can no longer be considered as complete, at least in so far as the gastro-intestinal tract is concerned. It is believed that the vagus and sympathetic nerves can no longer be considered to be antagonistic, but that their actions supplement each other to control and regulate the activity of the stomach. When either the vagi or splanchnics or both are sectioned, a state of imbalance results, which alters the motility of the gut and vasomotor state of the blood vessels, and leads to local ischemia, necrosis and erosions. It is believed that this altered state is temporary and soon the control is taken over by the intrinsic nervous system and the remaining system, leading to a normal functional activity. Such a view receives support from the clinical observations of the numerous individuals who have had bilateral extensive sympathectomy for hypertension and vagotomy for chronic ulcers. Thus far, except for the temporary upsets in motility, distension of the stomach, diarrhoea, etc., no permanent disabilities as to gastric functions have been reported in such individuals. By this concept, one can more readily explain the relatively high incidence of acute gastro-duodenal lesions (erosions, mucosal hemorrhages, acute ulcers, etc.,) which have been noted soon after vagotomy or splanchnectomy in experimental animals and why these rarely go on to chronicity.

However, it is still difficult to account for the absence of gastric or duodenal lesions following vagotomy in man. It may be possible that following vagotomy gastric mucosal hemorrhages and erosions do occur, but since they caused no outward signs have not been clinically recognised. With the rapid return to normal activity, these lesions heal over leaving no scars.

Summary

The studies on vagotomies and splanchnectomies along with the work done on damaging the hypothalamus in experimental animals have thus far only partly solved the problem of ulcer pathogenesis. They have shown that by creating an imbalance in the autonomic innervation of the gut, the resulting alterations in gastro-intestinal motility, secretion and vasomotor state of the blood vessels of the mucosa, especially the vascular changes may, if severe enough produce acute mucosal hemorrhages, erosions and acute ulcerations which rarely, if ever, have gone on to chronicity. It is thus evident that other unknown factors are necessary to make these acute lesions persist and go on to form chronic ulcers of the type seen in man. This will be discussed more fully below.

Physiology Of Gastric Secretion

One of the earliest investigators to note the effect of vagotomy on gastric secretion was Brodie (100), who observed that lethal doses of arsenic given intravenously to dogs always caused copious watery and mucous gastric secretions, while if the vagi had been sectioned previously, secretions were absent. From these experiments he concluded that gastric secretions were under nervous control. These observations were later confirmed by Wood (101). Although the results of Bidder and Schmidt (102), Richet (103), Contejean (104) and others also indicated that the vagus nerves were important in regulating gastric secretion, it was not until 1910 that it was definitely established by Pavlov (105) that the vagi conveyed secretory fibres to the gastric glands. Pavlov's findings were later confirmed by Farrell (106).

Beaumont (107) and others (105) had recognised that the gastric glands could be directly stimulated by mechanical or chemical (food) stimuli and Pavlov demonstrated the importance of psychic stimuli on gastric secretion. Further studies on this subject by numerous investigators made it clear that the digestive period of secretion could be divided into three phases, the cephalic, the gastric and the intestinal (108-121).

The cephalic or psychic phase, under nervous control of the vagi, is characterized by the appearance of a highly acid juice rich in pepsin and organic matter. This secretion is abolished by section of the vagi and by the administration of atropine. The gastric and intestinal phases are controlled by humoral mechanism and are not affected by section of the vagi or administration of atropine. The gastric juice secreted during the

latter two phases of digestion is highly acid, but contains smaller amounts of enzymes and organic matter than that evoked by the vagi (115).

Pavlov (105), Babkin (114) and others (121-124) have stressed the comparative potency of various foods as stimuli of gastric secretion. Thus the volume and the qualitative character of the gastric juice is affected by food ingested. Babkin has shown that the "qualitative changes in the gastric juice under different secretory conditions are chiefly due to the unequal quantitative activity of the different groups of glandular cells constituting the gastric mucous membrane". (115)

Another important phase of stomach secretion occurs in the absence of food and is commonly called the inter-digestive or continuous secretory phase. Pavlov (105) denied the existence of continuous secretion, for he found that gastric secretion was intermittent in dogs, and any secretion that did take place in the inter-digestive phase could be attributed to psychic factors. In man, however, the existence of a continuous secretion had been observed by Carlson (120-121), Ivy (125), Dragstedt and others (156) even during periods of prolonged fasting. According to Babkin (116, 154), Winkelstein (165, 273), Dragstedt (200-203) and Mears (204) and others, this continuous secretion is neurogenic in origin.

Variations In Gastric Secretion In Normal Subjects

Following the introduction of the method of fractional analysis by Rehfuss in 1914 (127), numerous studies have been carried out which indicated that volume and the acidity of gastric secretion in healthy persons varied greatly (128-156). The free hydrochloric acid of the gastric juice appeared to increase rapidly from childhood up to the age of 20 years when adult values were obtained (130), and has tended to decrease with increasing age (130) (148) (134). The incidence of achlorhydria increased steadily from youth to old age (130, 134).

The fluid content of the empty stomach has been shown to vary in volume from 0 to 150cc, with an average of 50-60cc (120,121,143,144,145,150). The acidity of the empty stomach content may vary from almost zero to full gastric juice acidity (121).

Variations in the peptic power of the fasting gastric contents were observed by Vanzant, Osterberg, Alvarez and Rivers (146). Babkin (154) believed that one of the reasons for the discrepancies in the composition of the morning fasting contents might perhaps be due to the variable degree of excitability of the gastric glandular apparatus.

The cephalic or appetite secretion in man has been shown to vary from 50-150cc in 20 minutes (121,125,135), and was found to be transitory, ceasing usually within 15-20 minutes after completion of mastication (121) (153). The rate of this secretion has varied directly with the palatability of the food and the degree of hunger and appetite, but the quality of this secretion is independent of the character of the food (121).

The rate of secretion in man during the gastric and intestinal phases of digestive secretion can be roughly approximated only, owing to the extreme

difficulty of making accurate measurements (125,155), but it has been estimated to be 45-70cc per hour during the gastric phase and approximately 45-85cc per hour in the intestinal phase (125,157).

Normal healthy subjects may react differently to the same standard test meal at various times (128,129,144,150,191), and these variants may be so great that a single gastric analysis determination could easily give a misleading impression regarding the secretory activity of an individual. Vanzant, Alvarez and Berkson (131), found no definite relationship between gastric acidity and the weight and height in man. Vanzant and Alvarez reported a cyclic variation in gastric acidity after an Ewald-type test meal in a large series of men and women. They found that there was a tendency towards higher acid values in Spring, Autumn and Mid-Winter (132). The influence of drugs, tobacco, alcohol, nutritional disturbances and other abnormal factors has been recently reviewed by Schiffren and Ivy (155).

Carlson (121), Ihre (135), Ivy (125) and others have shown that the continuous secretion varies between 10 to 117 cc per hour. Hellebrandt, Tepper, Grant, and Catherwood (205) found that the acidity of the fasting secretion rises and falls intermittently, in the absence of an interval stimulation, and that the acidity of the fasting secretion obtained during the night was higher than that produced in the day time.

Summary

Because of the wide variations in free and total acidity of the gastric juice found in apparently healthy individuals, no rigid limit of normality can be maintained. Thus when considering what range of acidity is normal for any one individual, many factors, especially the age and sex of the individual must be taken into account.

Gastric Secretion In Relation To Peptic Ulcer

When the method of fractional gastric analysis was applied to the study of gastric secretion in patients with peptic ulcer, it was generally recognised that higher percentage of such individuals showed elevated free and total acid than do normal people. Vanzant (133) and his associates reported an average increase of approximately 12 units above 'normal' in the cases of duodenal ulcer, while the cases of gastric ulcer was 6 units below 'normal'. Sagal, Marks and Kantor (134) also found higher values than normal in patients with ulcer, particularly in cases of duodenal ulcer. The hypersecretion associated with duodenal ulcer and the slightly elevated, but more frequently normal secretion found in cases of gastric ulcer have been observed by others (135) (141) (159).

More recently Page (160) reported that there was no real difference in the fasting free acidity between 137 patients with X-Ray evidence of peptic ulcer and 109 controls, and that both groups revealed approximately similar degrees of free acidity after a fractional test meal. Similar observations were reported by Glenn (192), following a histamine test meal.

Berk, Thomas and Rehfuss (185, 222), found that the fasting duodenal acidity and the acidity after an Ewald test meal was higher in patients with duodenal ulcer than in normal persons. Similar observations were made by others (186,187,220).

Necheles and Maskin (153) showed that although there was no significant difference in basal acidity between ulcer and healthy persons, the cephalic secretion contained more free acid in the ulcer patients than in the controls. However they concluded that since this appetite secretion was of such small

volume, of short duration and only of moderate acidity, it did not merit an important role in the genesis of ulcer. On the other hand Babkin (161) and Winkelstein (162-164) have frequently emphasised that an exaggeration of the cephalic secretory mechanism was of considerable importance in the production of peptic ulcer.

Although, a higher percentage of patients show a free acidity of more than 40 units and a total gastric acidity of more than 60 units, these values do not always indicate hyperacidity, as the extreme degree of variation of freed total gastric acidity in normal subjects has already been noted above. The range of the hydrochloric acid concentration found in the gastric secretion of ulcer patients following a test meal, rarely exceeds that found in healthy subjects.

Although the frequent association of free and total gastric acidity with peptic ulcer has led many observers (155,165,167,273), to adhere to Schwartz's (166) dictum of "no acid, no ulcer", numerous instances have been cited in the literature where peptic ulcer has been found in the presence of low acidity or achlorhydria (168-178). Vanzant and his associates (133) have found the presence of achlorhydria in their series of ulcer patients, but the incidence was approximately half of that observed in normal persons. Palmer (179) has strongly questioned the existence of chronic ulcers and achlorhydria and in reviewing a group of cases reported by others, and in a study of over a 1000 cases of peptic ulcer found no conclusive evidence that chronic gastric or duodenal ulcers occurred in the complete absence of acid gastric juice. In a later study, Palmer and Nutter (180) concluded that small and subacute gastric ulcers may occur in the presence of achlorhydria as proved by the histamine test, but that chronic gastric ulcers

only occur in the presence of acid gastric juice.

For a long time, clinicians have realized the importance of the continuous night secretion in ulcer patients, and the experiments of Exalto (183), Mann and Williamson (184), and the "sham-feeding" production of erosions by Silbermann (193), further emphasized the significance of the continuous acid secretion, specially in a fasting stomach. Sippy (194), Chalfen (195), Henning and Norpoth (196), Winkelstein (197), Palmer (198), Val Dez (199) and others have reported that ulcer patients have greater volume and acidity in their nocturnal secretions than were found in normal subjects. The ulcer diets recommended by Sippy (194) and Winkelstein (162) were directed to overcome this increased acid secretion.

Dragstedt, Palmer (167,208) and Winkelstein (203) and their associates (200,202), have re-emphasized the importance of the continuous secretion, especially the nocturnal secretion in the initiation and the persistence of chronic ulcers in man.

More recently Sandweiss et al (206,207) have reported that they found no statistically significant difference in the volume and acidity of the nocturnal gastric secretion between normal patients and patients with uncomplicated duodenal ulcers. These results differ considerably from those reported by other workers (197,199,204). The cases studied by Sandweiss et al were ambulatory and comparatively free from any distress, whereas the cases studied by Winkelstein, Ivy Dragstedt and others were complicated cases associated with more distress.

Summary

Although the main body of evidence at present indicates that the nocturnal gastric secretion of ulcer patients are generally greater in volume

The Role Of The Gastric Secretion In The Pathogenesis Of Ulcer

It had been suspected for a long time that the digestive powers of the gastric secretions bore some important etiological relationship to the production of peptic ulcer. The question naturally arose, "Why did the gastric secretions not dissolve the stomach in situ?" This thought had occupied the attention of many workers, one of the earliest of whom was John Hunter. In 1772, Hunter (209) concluded that the resistance of the gastro-intestinal mucosa to the digestive action of its own secretions was primarily due to an inherent property of the living cell. Pavy (210) in 1863 believed that the alkalinity of the blood in the gastric tubules prevented the digestion through a neutralization of the hydrochloric acid of the gastric juice. He believed it was possible for the acidity of the gastric secretion to be so increased that this mechanism would no longer neutralize the juice and thus lead to digestion of the stomach wall. The view that peptic ulcer was in some way due to a local loss of resistance of the mucous membrane to the digestive activity of the gastric juice was slowly gaining additional support, and in 1910, Schwartz enunciated the theory of "no acid, no ulcer", a view strongly supported to-day.

Attempts to produce chronic peptic ulcer experimentally in animals by the repeated administration of hydrochloric acid by mouth (211,212,217,326), or by perfusion of the intestine with acid alone (213) were not successful, even when far greater than physiological amounts of hydrochloric acid were employed. When 0.4 per cent hydrochloric acid was slowly administered by a continuous drip for 8 hours daily, Mann (211) observed that such animals

began to lose weight rapidly after 2 weeks, and in about 4 weeks subacute or chronic ulcers appeared. However, once an acute gastric or duodenal lesion was produced by other means, the presence of acid did delay the healing of the lesion and even caused it to spread (211,214,215,217,218). Bloomfield and French (219) have found no correlation between degrees of acidity and speed of healing of gastric or duodenal ulcers. More recently Wolf and Wolff (216) have shown that prolonged exposure of a gastric erosion to acid gastric juice in man resulted in delayed healing and extension of the lesion. Brown and Dolkart (252), found no relationship of gastric acidity to the onset of recurrences in patients with ulcer.

In 1924, Dragstedt and Vaughan (223) demonstrated that the resistance to the digestive action of the normal gastric contents was not limited to the gastric and duodenal mucosa alone, but jejunum, ileum, colon, spleen, pancreas, and kidneys were able to resist gastric digestion for months with little or no pathological changes.

The usual gastric contents consist of a mixture of swallowed food, saliva, acid secreted by the parietal cells, mucous and varying amounts of regurgitated alkaline duodenal juices. However, when living tissues were exposed to pure gastric juice, digestion of the tissue occurred. Matthews and Dragstedt (224) permitted the secretion from a small Heidenhain or Pavlov pouch to drain into the jejunum or the ileum and observed a large perforating ulcer in the intestinal mucosa adjacent to the anastomosis with the accessory pouch. The pure undiluted secretion from these pouches consist almost entirely of a watery solution of hydrochloric acid and pepsin (225). These experiments by Dragstedt and his collaborators clearly demonstrated the marked digestive action of pure gastric juice as compared to the relative

inactivity of normal gastric contents on gastro-intestinal tissues. Thus it is believed that under normal conditions the gastric wall is not digested away because it is not exposed to pure gastric juice (226).

Carlson (121) and others have repeatedly emphasized that the acidity of the gastric contents found in patients with duodenal or gastric ulcers only rarely approaches that of pure gastric juice. Carlson also believed that since so-called hyperacidity was commonly seen in normal persons, gastric or duodenal ulcers do not per se alter the activity of the gastric glands. Hardt (227) has shown that in dogs, gastric or duodenal ulcers produced experimentally may or may not result in a continuous or digestive hypersecretion.

The concept of hyperacidity of the gastric secretion slowly gave way to the newer and more modern idea that the hypersecretion of the stomach was the prime etiological factor in peptic ulcer. (This newer view was based largely on the experiments of Exalto (183), Mann and Williamson (184), Silberman (193) and Wangensteen and his associates (234-237).

The importance of the prolonged action of acid chyme on the intestinal mucosa was clearly shown by Mann and Williamson (184), who by diverting the alkaline intestinal juices away from the stomach, consistently produced ulcers in the intestinal mucosa adjacent to the anastomosis with the gastric mucosa. These ulcers were relatively large, 4-15 mim. in diameter, usually single and grossly and microscopically resembled the subacute and chronic gastro-jejunal ulcers seen in man following gastroenterostomy. These observations have been repeatedly and consistently reproduced by other workers

and also suggest the possibility of a failure of the neutralizing mechanism as an etiological factor in ulcer production.

In 1927, Silbermann (193) reported the production of ulcers in dogs which were "sham-fed" 40 to 60 minutes three times a day. The ulcers reported were usually multiple, shallow and were either erosions or shallow acute superficial ulcers, in no way resembling those found in man. These experiments were repeated by Schmidt and Fogelson (228) and no ulcers or erosions were found. The same authors augmented the acid irritation of the gastro-intestinal mucosa by the addition of 300cc 0.36 per cent HCL into the stomach of some dogs and still no lesions were noted. Similar experiments repeated in Dragstedt's laboratory also gave negative results (202).

Although some observers reported the production of gastric ulcer in rats (229), cats (245) following the administration of subcutaneous injections of histamine, Orndorff, Bergh and Ivy (231) failed to find erosions or ulcers after repeated injections of histamine in dogs, every 2 hours for 60 days. Heinlein and Kastrup also reported the failure to produce ulcers in cats with histamine (238). The healing of artificially produced ulcers was found to be delayed by the subcutaneous injections of histamine (230, 233). More recently, Code, Varco, Wangensteen, Walpole and Hay claimed to have produced acute, subacute and a few chronic ulcers in dogs, rabbits, and other animals by the injection of a slowly absorbable mixture of histamine and beeswax (234-237). This they have attributed mainly to the prolonged acid secretion resulting from the histamine and beeswax injections.

Careful examinations of the gross and the microphotographs of the lesions published by these workers show these lesions to be chiefly erosions

and superficial acute ulceration, some of which are in the subacute stage and have invaded the muscularis. Because of the lack of adequate histological detail and the lack of any of the fibrous changes characteristic of chronic ulcers, these ulcers in no way resemble the chronic peptic ulcers seen in man. Moreover it has been shown that histamine through its action on blood vessels, especially the capillaries may produce a prolonged stasis in the gastric mucous membrane with resultant local ischemic necrosis, resembling small infarcts (see Babkin (154), pp. 479-481). It seems more likely therefore, that the excess histamine produced local circulatory disturbances with resultant focal areas of necrosis, erosions, which were aggravated or prevented from healing by the prolonged and copious secretion of the acid gastric juice. The fact that many of their animals were anemic due to the frequent rectal bleeding, may have been another contributing factor.

The observations of Wangensteen et al renewed the interest in the continuous secretion, and Dragstedt and his associates re-affirmed that the nocturnal secretion in ulcer patients was more acid and more copious than in normal subjects, and repeatedly emphasized the role of this secretion in the initiation and persistence of chronic ulceration (226).

More recently, Sandweiss et al (206,207), found that the nocturnal secretions of patients with duodenal ulcer were not significantly different from that of normal subjects. However they believe that while ulcer patients did not secrete more gastric juice or show hyperacidity, their data indicated that ulcer patients retained more of this juice in their stomach and therefore during the night, the hydrochloric acid of the juice secreted might be

harmful since it was not properly neutralized due to the absence of food.

Summary

Thus it is evident that the experimental evidence of Silbermann, Wangensteen, Code, Varco et al, which numerous investigators have repeatedly quoted as evidence of the hypersecretion of acid as the prime factor in ulcer pathogenesis are as yet not convincing. Further observations are also necessary to determine the significance of the nocturnal secretions in cases of ulcer.

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The Role of Pepsin in Ulcer Production

The role of pepsin in ulcer production has been emphasized by Schiffrin (247) Schiffrin and Ivy (155), Schiffrin and Warren (248) and others. Although the pepsin was increased in some groups of patients with duodenal ulcer (146,251), Vanzant et al (146,249) found normal values in gastric ulcer patients, and reported that there was no consistent difference between ulcer patients and normal persons, or neurotic individuals, and contrary to what one might expect in a study of recurrences of ulcer following gastroenterostomy, the pepsin values were lower than those found in patients who did well following operation (250). Wangensteen in 1945, stressed the interrelationship between the vascular and the acid-peptic digestive factors in the etiology of ulcer. (237).

Summary

Although pepsin plays some role in the pathogenesis of ulcer, Dragstedt and Vaughn (223) and others (269,327), have shown that active pepsin is not the important digestive factor, but that the acid must injure the tissue before it can be dissolved by the acid pepsin secretions.

Failure of adequate neutralization as a cause of ulcer

While food is undoubtedly the most effective factor in neutralizing the acid of the gastric juice, considerable evidence has been presented to show that the mucous secretion (3,105,107,113,114,253,254), the inorganic compounds of the gastric juice (154), and the alkaline pancreatic, bile and

duodenal juices (184,185,186,222,255,256) play an important part in neutralizing the hydrochloric acid of the gastric juice. The significance of the neutralizing effect of the duodenal, bile and pancreatic juices in preventing the formation of duodenal ulcers in dogs has been clearly shown by Mann and Williamson (184), when they consistently produced chronic jejunal ulcers by diverting the alkaline intestinal juices away from the stomach. Although ulcers have been produced experimentally in animals with various modifications of the Mann-Williamson operation, whereby the bile, pancreatic and duodenal juices have been diverted from the stomach, except on rare occasions (257), there is no evidence that the absence or a deficiency of these secretions are the cause of ulcer in man (202). Mann and Bollman (255), and more recently Berk, Rehfuss and Thomas (222) and others have shown that in patients with ulcer, there was a deficiency in the capacity of the duodenal contents to neutralize the acid in the stomach and in the duodenal bulb. Comfort and Osterberg have shown the fasting contents in 10 cases of duodenal ulcer were similar to those in normal persons (270).

The neutralizing and protecting property of mucous and its capacity to absorb acid has been shown to be important in regulating the acidity of the gastric juice at the beginning and the end of the secretory period (253, 254,258,259,260,261,262). Anderson and Fogelson have reported that ulcer patients have a relative mucin deficiency per cc of gastric contents in response to an alcohol test meal, as compared with that of normal subjects (265).

Summary

Although there is no absolute evidence that the absence or deficiency of intestinal secretions or mucous are responsible for the production of

ulcer in man, yet a relative deficiency of the neutralizing capacity of these secretions may be some importance in ulcer pathogenesis, especially in instances of hypersecretion when the stomach is empty.

Most observers are of the opinion that gastric hypersecretion, rather than hyperacidity is the important factor in ulcer pathogenesis. It has been shown by Dragstedt et al that although stomach and intestinal mucosa could withstand the continued action of the normal gastric contents, they were immediately digested by pure gastric juice. Under ordinary circumstances the gastric and duodenal mucosa are protected from the action of the acid juice mainly by the buffering action of the ingested food and secondarily by the neutralizing action of the mucous and alkaline intestinal secretions. Although Carlson has repeatedly emphasized that the acidity of the gastric contents of ulcer patients only rarely reaches the level of pure gastric juice, it is very possible, as has been frequently stated by Winkelstein, Dragstedt and others, that the excessive secretion, particularly when the stomach is empty, may so overpower the neutralizing mechanism, that it may exert a deleterious effect upon the gastric or duodenal mucous membranes. Although there is no good evidence that the increased action of acid alone may lead to ulcer production, it has been indicated in animals and in man, that the prolonged action of acid can delay healing or cause extension of any pre-existing lesions in the stomach and duodenum.

The Effects Of Vagotomy On Gastric Secretion And Peptic Ulcer

A. Vagotomy in Animals

From a review of the observations of other workers and from his own experimental findings, McCrea (286) concluded that vagotomy prevented psychic secretion, but that an active gastric juice was still secreted, since the chemical phase of secretion had not been abolished. He pointed out moreover, that after sectioning either the vagi or splanchnics, the majority of animals appeared to lead normal lives, except in the case of some rabbits. In 1930, Hartzell (287) reported that transthoracic vagotomy in dogs resulted in a marked reduction in both free and total acidity, and that after transabdominal vagus section, the quantity of free hydrochloric acid occasionally returned to the pre-operative level. If the vagotomy was incomplete, no decrease in acid secretion resulted. Studying 4 of Hartzell's dogs which had survived, Vanzant (288) found that acidity returned to normal after 1 to 2 years. A return of the gastric acidity to normal in 4 to 6 weeks after vagotomy and subtotal gastrectomy was observed by Shapiro and Berg (289,293). Friedenwald and Feldman (290) found only a negligible decrease in acidity following section of the left vagus in dogs, while section of the right vagus resulted in little or no secretion. Thompson (291) also reported that bilateral vagotomy in the pylorectomized stomach in dogs decreased gastric secretion. Contrary to the findings of Shapiro and Berg, Wilhelmj et al (295) noted a marked decrease in acidity following partial gastrectomy and transthoracic vagotomy in dogs, which persisted for at least 3 months, the duration of the study.

On the other hand Ferguson (292) found no reduction in gastric acidity following vagotomy in monkeys. More recently Komarov and Shay (325),

observed in acute experiments, that bilateral vagotomy almost completely abolished the interdigestive phase in unanesthetized rats, while unilateral vagotomy reduced the rate of secretion by approximately 50 per cent without affecting acidity, total chloride or pepsin. Experiments in chronic vagotomized rats revealed that the secretion remained at very low levels for approximately 3 months.

B. Vagotomy in Man

Although vagotomy was attempted many years ago by Latarjet (296) Schiassi (297) and others, with only temporary success, it is only in recent years that vagotomy has become popular in the treatment of chronic gastric and duodenal ulcer. Its reintroduction has been stimulated in large measure by the high incidence of complications and recurrences following partial gastrectomy or gastro-enterostomy. Following the observation by Winkelstein (298) that marginal ulcers occurred after partial gastrectomy only when the secretion of a highly acid gastric juice persisted, and that this secretion was inhibited by the administration of atropine, indicating that the vagus might be responsible for the persistence of this acid secretion, Klein (299) suggested that left vagus section should be performed along with subtotal gastrectomy for duodenal ulcer with a high pre-operative acidity. The following year Berg (300) reported the results obtained after division of left vagus along with a partial gastrectomy in 8 patients with duodenal ulcer who had high gastric acidity prior to operation. Whereas only approximately 25 per cent of patients became anacid after subtotal gastrectomy alone, all of the 8 cases were anacid in 2 weeks to several months after operation. Further successes in reduction of gastric acidity with the combination of

vagotomy plus partial gastrectomy or gastro-enterostomy were reported in man (301,302) and in dogs (295).

Colp, Dragstedt and their associates who favoured the view that the hypersecretion, particularly of the interdigestive and nocturnal phases of gastric secretion was of nervous origin pioneered in the application of bilateral vagotomy alone in the treatment of peptic ulcer. In 1944, Weinstein, Colps et al (305) reported that none of their 6 cases had benefited greatly from either supra- or infradiaphragmatic vagotomy. The acid secretion was only slightly reduced and because of the ill effects on gastric motility with its resultant increase in operative risk and post-operative morbidity, they concluded that vagotomy alone was not to be recommended in ulcer therapy. The results of Dragstedt and his associates appeared to be more favourable however, and it was largely to their enthusiasm that the application of vagotomy in peptic ulcer became popular and as widespread as it is to-day. Their first reports showed that a marked reduction in free and total acidity, as well as a decrease in nocturnal secretion was to be expected after the operation (200) (303). They also noticed a decrease in gastric tonus and hunger contractions in the empty stomach (201). These earlier successes with vagotomy have been confirmed on a large series of ulcer patients by Dragstedt and his co-workers (304,306,324).

From the large number of recent reports on the post-operative effects of vagotomy in man (304-323) several facts have become evident. It is generally agreed that following vagotomy most of the patients experienced an immediate and complete relief of their ulcer symptoms, and the evidence indicates that the ulcers healed promptly after vagotomy. Recurrences of ulcer have been reported, but up to the present, the incidence of recurrence

has been small.

In general vagotomy has led to a marked reduction in volume and acidity of gastric secretion; especially important has been the reduction in the volume of the night secretion. Although vagotomy abolished the cephalic phase of secretion in most instances the digestive phase was rarely influenced. The secretory response to insulin was usually abolished if vagotomy was complete but the response to histamine and caffeine was unaffected. Several reports have indicated that the early post-operative reduction in volume and acidity of gastric secretion usually noted after vagotomy has shown a tendency to return to normal values, thus confirming the earlier experiences in animals (288,289,293,337).

DISCUSSION

Although vagotomy has yielded immediate relief of ulcer symptoms, and has allowed the ulcers to heal promptly, the post-operative period of observation has thus far been too brief to know whether the benefits derived will be lasting.

The immediate benefits brought about by vagotomy may have been due to the initial decrease in gastric motility and acid secretion, but although it has already been noted that there is a tendency for the gastric motility and the volume and acidity of the gastric secretion to return to almost pre-operative levels in many cases, there has not been a recurrence of ulcer or symptoms of ulcer in such patients. In the light of these observations, it is difficult to evaluate the concept that hypermotility and hypersecretion was the important etiological factor in the development of ulcer.

More recently, it has been shown by Wolf and Andrus (316) that gastric

hyperemia and engorgement of the stomach mucosa due to vascular congestion induced by feelings of anger and resentment in a patient with gastrostomy, failed to occur after vagotomy. Thus, as has been suggested by Bockus (318), any permanent benefits which may be derived from vagotomy may be due to the interruption of the cephalic impulses caused by certain threatening situations which are known (254) to give rise to profound vascular changes in the stomach.

Experimental Production Of Gastro-Intestinal Lesions By The Administration Of Chemicals Or Drugs

A. Hydrochloric Acid.

Frequent attempts to produce chronic peptic ulcer experimentally in animals by the repeated administration of hydrochloric acid by mouth (211,212, 217,326) or by perfusion of the intestine with acid alone (213) were not successful, even when far greater than physiological amounts of hydrochloric acid were employed. Although Ochsner, Gage and Hosoi (326) and others had observed that repeated hydrochloric acid feeding resulted in multiple acute gastro-intestinal lesions, such as petechiae, erosions and shallow acute ulcers, chronic ulcers were never obtained even after the prolonged administration of the acid. When the acid (.4 hydrochloric acid) was administered slowly by a continuous drip for 8 hours daily, Mann (211) observed that such animals began to lose weight rapidly after 2 weeks, and in about 4 weeks subacute or chronic ulcers appeared, which he related to an apparent exhaustion of the neutralizing mechanism of the stomach and duodenum.

B. Pilocarpine

Basing his experiments on the clinical assumption that hypertonicity of the vagus results in the development of gastric or duodenal ulcers, as put forth by Eppinger and Hess (12) and Von Bergmann (13), Westphal (14) injected pilocarpine subcutaneously into animals and recorded the formation of multiple mucosal hemorrhages and erosions in the stomach and duodenum. From these observations he concluded that pilocarpine, by its action on the smooth muscle of the gut, produced gastric and duodenal spasm which occluded the mucosal

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end vessels, leading to ischemia, necrosis and ulceration. Friedman (15) repeated and confirmed the observations by Westphal (14) and in addition found a higher frequency of duodenal lesions when pilocarpine and adrenaline were given simultaneously to rabbits. The lesions produced by Westphal (14) and Friedman (15) were mainly acute mucosal hemorrhages and erosions, and there was no evidence submitted to support their claims for the production of acute ulcers, in accordance with our definitions. All attempts to produce chronic ulceration failed.

These experiments were repeated and extended by Underhill and Freiheit (16) who stated that subcutaneous injections of pilocarpine with or without adrenaline, led to production of mucosal hemorrhages or erosions in the stomach and duodenum, but in no instance could a chronic ulcer be formed. These investigations showed that the production of the lesions were not due to changes in acidity alone, but was mainly related to the localized areas of ischemic necrosis which were associated with cyanosis of the whole stomach, and the subsequent action of the gastric juice on these damaged areas. Subcutaneous injections of pilocarpine into the cat and the rat did not evoke gastro-intestinal changes and Underhill and Freiheit (16) concluded that the action of pilocarpine in the production of the lesion was not specific, but due to a species peculiarity.

Following Cushing's (17) observations that the injection of a small dose of pilocarpine into the lateral ventricles of humans was soon followed by a parasympathetic response which included retching, vomiting which was at times blood tinged, indicating a central effect via the vagus Bishop, Kendall and Light (18) attempted to reproduce these effects in rabbits. They noted that the injection of 10 mg. doses of pilocarpine into the lateral ventricles

of rabbits produced gastric lesions in 94 per cent of their animals. Microscopic study of these pathological gastric changes revealed early acute mucosal hemorrhages with superficial necrosis, which at times extended down to the level of the muscularis mucosae, but rarely deeper. The capillaries in these pale areas were usually contracted and empty in contrast to the partially filled capillaries of the unaffected tissue on either side. The lesions which were produced within $2\frac{1}{2}$ hours after the injection of pilocarpine, were mainly areas of superficial focal necrosis, without any evidence of leucocytic or lymphocytic infiltration and in no instance was there any evidence of true acute or chronic ulceration. It was concluded that pilocarpine acted by stimulating the higher autonomic centres, and that the focal gastric necrosis was the result of vascular damage due either to active vaso-constriction or to mechanical obstruction by the increased contractions of the stomach musculature. Indirect evidence for the concept that stimulation of the higher autonomic regions may result in gastric or duodenal lesions was seen in these results. On the other hand, Ferguson (292) reported that the administration of over 100 intraventricular injections of pilocarpine in doses 0.15 to 17.1 mg. per kilo in 15 monkeys yielded no evidence of gastro-intestinal lesions.

C. Acetylcholine

Following the observation of Dale and Feldberg (328) that acetylcholine was the chemical transmitter of vagus effects to the stomach, Necheles and his associates (329-331) demonstrated that small doses of acetylcholine, comparable to those liberated when the vagi were stimulated (328), caused diminished blood flow through the stomach of dogs and of humans, indicating

a vasoconstrictor effect. These observations led Necheles (332) to advance the theory that overproduction or the continuous formation of acetylcholine may produce areas of focal necrosis which when acted upon by the acid-pepsin contents of the stomach leads to formation of peptic ulcers. Thus far, this theory has received very little support from further animal experiments or clinical observations.

Hall, Ettinger and Banting (333) and Horswell (335) have noted a generalized hyperemia of the gastro-intestinal tract, with focal mucosal hemorrhages and erosions following prolonged daily administration (50-600mg.) of acetylcholine intravenously in dogs. Although many of the dogs received 100 to 200 or more injections which were frequently accompanied by bloody diarrhoea or bloody stools, no acute or chronic peptic ulcers resulted. Similar observations were made by Necheles and Masur (334) after the continuous injections of acetylcholine for 28 to 51 hours in 3 dogs, and daily injections over a period of 3 to 6 days with a total injection time of 18 to 37 hours in another group of 3 dogs. Although some of the animals had gross gastric and intestinal hemorrhages, no ulcers were found.

D. Adrenaline

After repeated injections of epinephrine, duodenal erosions and acute ulcers were observed by Friedman in dogs (338) and rabbits (339). It was also reported by Friedman (15) and Underhill and Freiheit (16) that the administration of adrenaline with pilocarpine resulted in a higher incidence of gastro-intestinal erosions and acute ulcers than was noted after giving pilocarpine alone to rabbits. Acute phlegmonous ulcerations of the small and large intestines of dogs, cats, rabbits and guinea pigs were noted following the

daily intraperitoneal injections of adrenaline by Penner and Bernheim (282). Baronofsky and Wangensteen (237) (349), also found that the implantation of epinephrine in beeswax into dogs invoked multiple erosions, mucosal hemorrhages of the stomach and duodenum and the intramuscular injection of aqueous adrenalin suspended in gelatin into 2 guinea pigs, led to gastric erosions and shallow acute ulceration of the stomach. Whereas it was noted that it was difficult to produce ulcers in rabbits with histamine in beeswax alone, the addition of epinephrine to the histamine in beeswax preparation increased the incidence of the formation of gastric and duodenal erosions and acute ulcers (237) (349). In man, Wolf and Wolff (254) observed that when epinephrine was applied locally to the stomach or given hypodermically, the initial pallor of the gastric mucous membrane was soon followed by a secondary hyperemia and an increase in acid secretion. It was generally agreed that the effects observed following the administration of adrenalin were due mainly to its ability to produce vasoconstriction, causing tissue anoxemia, and focal necrosis.

E. Pitressin

Severe extensive hyperemia with focal areas of superficial necrosis of the fundic portion of the stomach was first reported by Dodds et al (340) following a single injection of posterior pituitary lobe extract into laboratory animals. The following year, Dodds and his associates (341) using larger and repeated doses of the acetone picric acid extract of the pituitary gland, claimed to have produced chronic peptic ulcers in rabbits resembling those seen in man, but no microscopic data concerning these ulcers were found in their report. They also found that injection of the extract caused

a temporary inhibition of HCL secretion, in such a way that the stomach would not react to histamine for a period of 6 hours. These observations were confirmed and extended by Nedzel (342-344), Berg (89,345) Necheles and Masur (334) and Metz (348) who subjected dogs and rabbits to repeated and continuous doses of pitressin (334).

The erosions produced in the gastro-intestinal tract varied from small mucosal hemorrhages to superficial and deep mucosal erosions, and superficial acute ulcerations, and in no instance was a chronic lesion formed. It was generally agreed that the initial spasm of the vessels which was soon followed by intense hyperemia produced by the pitressin, and the spasm resulting indirectly from the increased muscular contractions, interfered with local nutrition and led to focal ischemic necrosis. The necrotic areas were further acted upon by the acid-pepsin content of the stomach resulting in ulceration.

More recently Wolf and Wolff (254) observed that local application of pitressin administered intravenously or hypodermically in man, resulted in a transitory pallor of the mucous membrane, which was soon followed by a secondary intense hyperemia, increased motility and increased acid secretion, thus confirming the observations of Nedzel and Berg in their experiments on dogs and rabbits.

Although large doses of pitressin caused acute gastro-intestinal lesions, smaller doses inhibited the gastric motility and secretion and Metz et al (346,347) and others have reported some success in the treatment of ulcer patients with small amounts of posterior pituitary extract.

Although the experimental lesions in no way resembled the chronic peptic ulcer commonly seen in man, they do call attention to the possible importance of vascular spasm and hyperemia in the production of ulcer.

F. Histamine

The action of histamine on gastric secretion was first studied by Popielski (239) who observed an increased flow of gastric juice in dogs following the administration of subcutaneous injections of histamine. Vagotomy or administration of atropine did not affect this secretion, indicating that histamine acted directly on the glands.

Babkin and his associates have shown that histamine activates chiefly the parietal cells of the gastric glands and to a much lesser extent the peptic and mucoid cells of the stomach, giving a secretion rich in hydrochloric acid, but somewhat deficient in enzymes and organic substances (240-244). This juice closely resembled that obtained by stimulation of the vagi. From the many observations of Babkin and his associates (154,161), it was concluded that histamine was liberated during the normal secretory process in the stomach and therefore was part of the normal secretory mechanism. Babkin (161) in 1938 presented a theory that some pathological derangement of this normal secretory mechanism, whereby excessive amounts of histamine were liberated could give rise to peptic ulcer formation.

The action of the excess histamine liberated was believed to be twofold. Firstly, by acting on the parietal cells it produced excessive quantities of extremely acid juice; secondly, because of the action of histamine on the capillaries, a prolonged stasis with increased capillary permiability occurred resulting in local tissue anoxia and necrosis, which when acted upon by the copious acid juice of the stomach produced erosions and ulceration (154) (161).

Although some observers have reported the production of gastric ulcer in rats (229), cats (245) following the administration of subcutaneous injections of histamine, Orndorff, Berg and Ivy (231) failed to find erosions or ulcers in the gastro-intestinal tract of dogs after repeated injections of histamine

every 2 hours for 60 days. Heinlein and Kastrup (238) also failed to produce lesions in cats with histamine. The healing of artificially produced ulcers was found to be delayed by subcutaneous injections of histamine (230,233). More recently, Code, Varco, Wangensteen, Walpole and Hay claimed to have produced acute, subacute and a few chronic ulcers in the stomach and duodenum in dogs, rabbits and other animals by the injection of a slowly absorbable mixture of histamine and beeswax (234-237). These lesions were not prevented by vagotomy prior to the administration of the histamine and beeswax (246). The formation of these ulcers has been attributed mainly to the prolonged effects of the hypersecretion and hyperacidity of the gastric juice which were induced by the histamine in beeswax injections.

Careful study of the gross and microphotographs of the lesions published by these workers show these to be chiefly erosions and superficial acute ulcerations, some of which are in the subacute stage and have invaded the muscularis. Because of the lack of adequate histological detail, and the lack of any of the fibrous changes characteristic of chronic ulcers, these in no way resemble the chronic peptic ulcers seen in man.

DISCUSSION

The gastric and duodenal erosions and acute ulcerations produced by histamine lend some evidence in support of Babkin's theory that excess histamine production may be the cause of ulcer formation in some cases. Although this theory is a plausible one and deserves serious consideration, it requires additional evidence to support its claims. Since as Babkin (154) has indicated the action of the excess histamine is two-fold, acting both on the blood vessels and the parietal cells of the stomach, it cannot be

assumed that the lesions were produced by the prolonged action of the acid juice alone, as has been claimed by Wangensteen et al and others. It seems as likely that the excess histamine produced local circulatory disturbances with resultant focal areas of necrosis, and erosions, which were aggravated or prevented from healing by the prolonged and copious secretion of the acid gastric juice.

G. Caffeine

Recent studies reported by Judd (350) demonstrated that daily intramuscular injections of caffeine in beeswax were capable of inducing shallow acute gastric or duodenal lesions in guinea pigs and rats in approximately 4.5 days and 15 days respectively. These observations were soon confirmed by Roth and Ivy (351) who also observed that following the daily implantation of caffeine in beeswax, 50 per cent of their cats developed mucosal erosions, acute or subacute gastric ulcerations. It was subsequently found that caffeine stimulated gastric secretion in cats and man, but not in dogs (350,352,353). Bilateral vagotomy or the administration of atropine did not abolish the secretory response to caffeine in cats; neither did the administration of 1 mg. of atropine sulphate affect the secretory response to caffeine in man (354). Giddings et al (355) found that the daily administration of 75 mg. caffeine per kilo body weight by stomach tube to cats for 21 days, failed to produce any pathological changes in the stomach or duodenum. Although daily injections of the same amount of caffeine in a beeswax and oil mixture likewise filed to produce gastro- or duodenal lesions, acute erosions and "ulcers" were noted when large doses of caffeine in beeswax (similar to those used by Roth and Ivy) were given.

Attempts to produce ulcer in dogs by repeated daily intramuscular injections of caffeine in beeswax were not successful, indicating a species difference to the response to caffeine (356). According to Roth and Ivy (356) the caffeine initiated marked hyperemia of the gastric mucosa which was followed by a period of cyanosis in the cat. Sections of the mucosa following the administration of caffeine showed marked hyperemia and congestion of the blood vessels and scattered foci of serous transudate and extravascular collections of red blood cells. From these observations it was concluded that the vascular changes induced by caffeine produced local nutritional disturbances in the gastric mucosa and the resultant ischemic areas were more susceptible to the digestion of the acid-pepsin secretions of the gastric contents. Although gastric lesions have followed the injection of caffeine in cats and guinea pigs, thus far there is no evidence that such lesions were provoked in dogs or in man.

Summary

The numerous experimental studies have shown that the repeated administration of pilocarpine, adrenaline, acetylcholine, histamine, pitressin and caffeine had frequently led to the production of gastro-intestinal lesions, which were mainly of the acute type. These lesions were usually multiple, involving the fundus of the stomach, more often than the pylorus or the duodenum, and consisted mainly of mucosal hemorrhages, erosions, superficial acute ulcerations and occasionally subacute ulcers were seen. In general, the pathological changes observed were secondary to profound vascular disturbances in the gastric or duodenal mucous membrane, vasoconstriction, spasm or marked hyperemia with capillary stasis, which resulted in local

tissue anoxemia, and ischemic necrosis of the mucous membrane. These necrotic areas presumably became more susceptible to the digestive action of the acid-pepsin contents of the stomach, leading to ulceration in many instances, which rarely, if ever became chronic. The administration of acid alone rarely led to ulcer formation, but once a lesion was produced artificially in the gastric or duodenal mucous membrane, the presence of acid definitely delayed the healing of the ulcer and even caused it to spread.

Although the gastro-duodenal lesions produced, in no way resemble the chronic peptic ulcers seen in man, they do stress the importance of repeated and of prolonged circulatory disturbances, (capillary spasm or profound vasodilation with stasis) as a factor in the initiation of such lesions, which may be further aggravated by the presence of the acid-pepsin contents of the stomach.

The Effect Of Mecholyl And Beeswax On Gastric Secretion

Introduction

Earlier studies on the effects of acetyl - B - methylcholine (mecholyl) have yielded contradictory results. When small doses were injected into humans, an increased acid response was noted by Abbott (358) in most of his cases. An alkaline gastric secretion, with increased mucin, was obtained in response to subcutaneous administration of mecholyl, in monkeys by Ferguson and Smith (357) and in man by Myerson, Rinkel and Damashek (359). According to Gray and Ivy (360) who investigated the effects of mecholyl on secretion in dogs with a Pavlov pouch or a pouch of the entire stomach, small doses of mecholyl .04 to .20 mg., increased the volume and acidity of the gastric juice and the secretion obtained resembled that produced by the action of the vagus on the parietal cells of the stomach. The same authors produced a continuous secretion from an entire stomach pouch by repeated doses of mecholyl every 10 minutes, and they noted that after reaching a maximum, the secretion declined in spite of the continued injections of mecholyl, indicating that the secretory mechanism had become refractory to the drug. This was recently confirmed by others (367). Gray and Ivy (360) also noted that whereas smaller doses of mecholyl augmented, larger doses inhibited the histamine secretion, and both effects were abolished by atropine. Following the injection of .5 to 1 mg. of mecholyl every 10 minutes in a total pouch dog, no acid was secreted. The juice obtained was scanty, mucoid and alkaline.

Necheles et al (361) experimenting on dogs with Heidenhain pouches, confirmed Gray's findings (360) of potent stimulation of gastric secretion by

small repeated doses of mecholyl, but although they found no evidence of exhaustion even when doses of 1 mg. of mecholyl were given every 30 minutes for 3½ hours, the volume of the secretion obtained was very small, 1.5 to 3.5 cc. per hour. When larger doses were injected, the secretions obtained were scanty (.5 to 2 cc. per hour) and of low acidity. Free acid was absent in the secretion for the first 60-75 minutes, but later returned, never exceeding 50 acid units. Flexner and Wright (365) found that absence of free HCL in the fasting contents of cats' stomach, persisted after the subcutaneous injections of 2-10 mg. of mecholyl, and that doses of 25 mg. administered to humans generally caused a slight to a marked rise in free and total acidity, when proper care was taken to prevent the swallowing of the excess saliva. The administration of mecholyl by iontophoresis resulted in an alkaline mucoid gastric secretion (364).

More recently Stravraky (362) studying the effects of mecholyl on gastric secretion in dogs with Heidenhain pouches, and in acute experiments in dogs and cats under nembutal anaesthesia, or under a mixture of chloralose and urethane (1:10) confirmed the previous observations of others (360,361), that mecholyl stimulated the secretion of acid gastric juice, and also demonstrated that it was a strong stimulant for the secretion of pepsin. It was also shown that a large single dose of mecholyl caused a scanty mucoid secretion of low acidity and that mecholyl increased the secretion of the alkaline mucous from the pyloric portion of the stomach.

Following the administration of acetyl - B - methylbromide in doses of 100 to 600 mg. in man, Wolf and Wolff reported an increased acid secretion which became maximum in 30-45 minutes after the ingestion of the drug and then the acid output quickly fell to its control level. They also observed

that a moderate transitory hyperemia of the stomach, which at times was marked, was usually associated with the increased secretory activity. The effects obtained did not appear to depend on the size of the dose given (254).

In the present series of experiments, in an attempt to obtain a prolonged and continuous action, the mecholyl was embedded in a beeswax-mineral oil mixture, according to the method devised by Code and Varco (234) for prolonging the action of histamine, and given by intramuscular injection. Since mecholyl had not been administered in beeswax before, this study was undertaken to determine the effects of this mixture upon gastric secretion as compared to those obtained with large single doses of mecholyl in aqueous solution injected subcutaneously.

Methods

A total of 23 experiments were performed on 21 dogs which weighed 6 to 35 kg. Three of the experiments were carried out on a dog with a permanent gastric fistula; the remainder were acute experiments on dogs which had been specially prepared. For the acute experiment, 20 dogs under nembutal anaesthesia (25 mg. per kg.) or under a mixture of chloralose and urethane (1:10 dissolved in 60 cc. of saline and given 3 cc. per kg.) were used in which the oesophagus and pylorus were ligated and a metal fistula was inserted into the most dependent portion of the stomach. The dogs were fasted for at least 18 hours prior to the experiment to be sure that the stomach was empty at the onset of the experiment.

In every instance, the fasting secretion, if any, was collected for 30 minutes prior to the injection of mecholyl. The pH of the gastric secretions before and after the administration of the drug was determined on the

Beckman pH meter. Two different preparations of mecholyl were employed and each was administered by a different route.

A. Subcutaneous Injection Of Mecholyl In Aqueous Solution

One gram of dry powdered mecholyl chloride (merck & Co.) was dissolved in 100 cc. of distilled water or saline, resulting in a concentration of 10mg. per cc. The mecholyl was then given by subcutaneous injection in doses which varied from 15 to 35 mg. The size of the dose was determined through experience to be the maximum the animal could tolerate without going into shock or state of collapse. This 'sub-shock' dose depended partly on the size and the weight of each dog. These dosage levels were generally much higher than that used by previous investigators. The gastric secretions were collected every 15 or 30 minutes at the start of each experiment and later at half-hourly or hourly intervals.

The effects of the subcutaneous injections of mecholyl were studied on 4 dogs under anaesthesia and on one with a permanent gastric fistula. The dogs in this series weighed 6 to 20 kg. In several experiments, the same dose of mecholyl or 2 doses (.5 mg. histamine) 10 minutes apart, were injected subcutaneously into dogs when the initial mecholyl secretion had declined.

B. The Injection Of Mecholyl In Beeswax-Mineral Oil Mixture

The mecholyl in beeswax mixture was prepared in small quantities using 1 gram of mecholyl chloride (Merck & Co) to 8 cc. of 4.8 per cent beeswax in mineral oil mixture (supplied by Ayerst, McKenn, Harrison). Special care was taken to see that the mecholyl was kept dry since it was very hygroscopic. The mecholyl was finely ground in a martar and to it was added 8 cc. of the molten 4.8 per cent beeswax-mineral oil mixture. The contents of the mortar

were again mixed until the mixture was homogeneous. The molten preparation was then drawn into 1 cc. tuberculin syringes and when the mixture cooled to room temperature, the semi-solid mass was injected through 18 gauge needles. The mixture of mecholyl in beeswax thus obtained contained approximately 90-100 mg. of mecholyl chloride per cc.

This mixture was then injected intramuscularly in doses which varied from 0.2 to 2.0 cc. with dogs weighing 7 to 35 kg. Here again the size of the dose was the maximum the dog could tolerate or the 'sub-shock' dose. The gastric secretions were collected at 15 to 30 minute periods at the start of each experiment and later at 30 to 60 minute intervals.

RESULTS

A. The Effect Of Subcutaneous Injection Of Mecholyl

The typical response obtained following a single subcutaneous injection of mecholyl (in aqueous solution) are illustrated in Grs. 1 and 2. It can be seen that following the administration of large doses of this drug a rapid secretory effect was obtained which was accompanied by the immediate onset of salivation, lachrymation and increased gastro-intestinal motility. The secretory response reached its maximum within the first half-hour and then declined rapidly, lasting a total of 45 to 90 minutes. This juice was mucoid in consistency and of low acidity (pH 4.25-6.66). In the acute experiments the volume of the gastric secretion varied from 2 cc. to 17 cc. per hour. A similar response to mecholyl was obtained in a dog with a chronic gastric fistula, but the swallowed saliva and the regurgitation of bile interfered with

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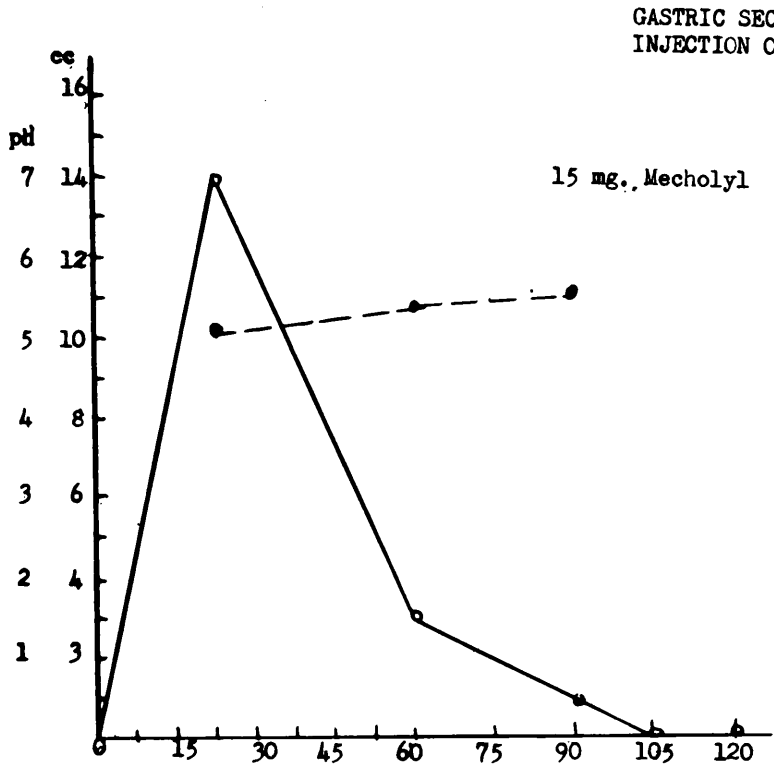
GASTRIC SECRETION IN RESPONSE TO A SINGLE INJECTION OF MECHOLYL IN AQUEOUS SOLUTION.



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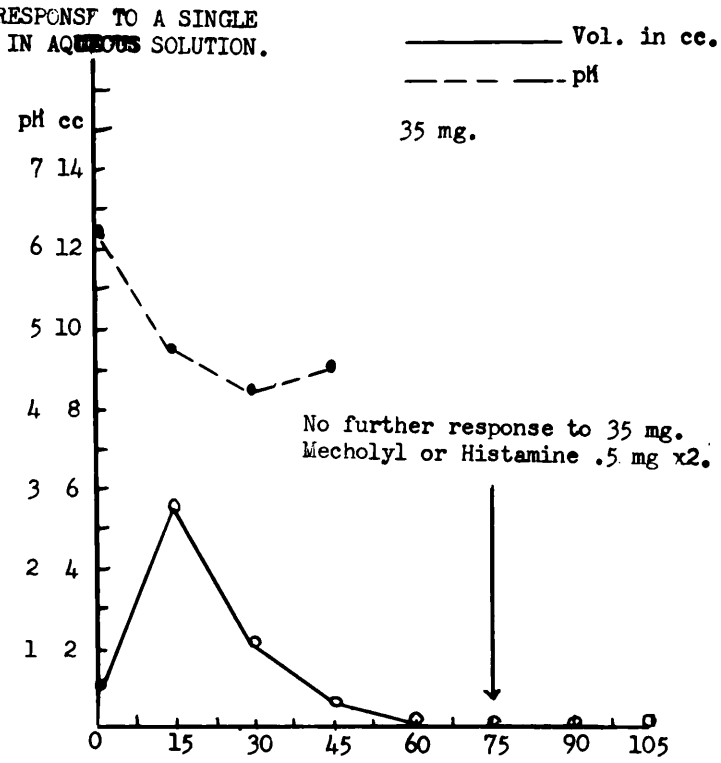


2

Grs. 1 & 2 The gastric secretory response to single injections of mecholyl in dogs #12 (10kg) and #17 (15kg) respectively. Note the immediate response, rapid decline and the low acidity of the juice obtained.

the accurate determination of the results.

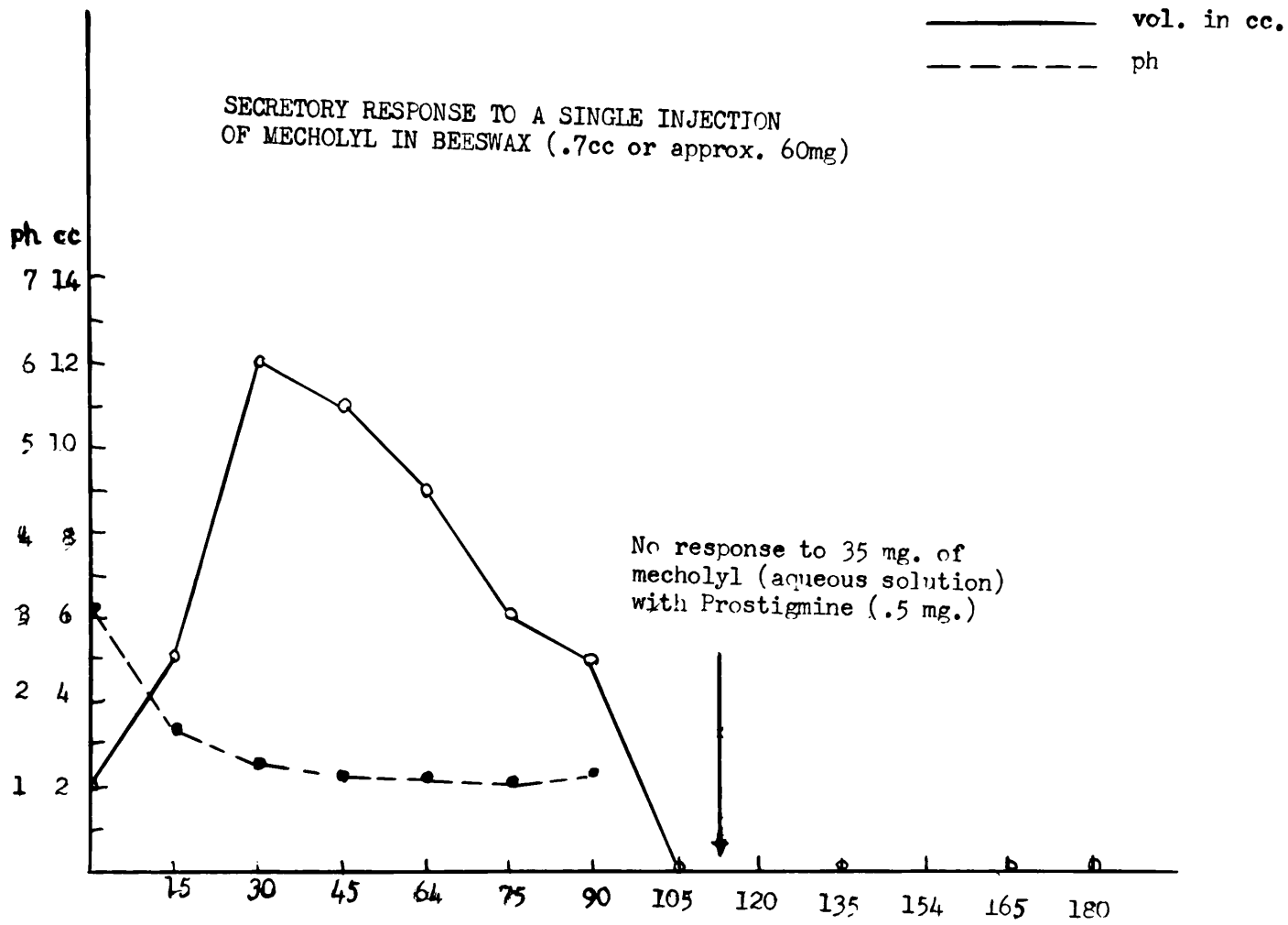
In 1 dog, the injection of a similar dose of mecholyl after the response to the initial dose had declined, failed to elicit an additional secretory response, and subsequent injections of histamine were also without effect. Another animal was found to be completely refractory to the initial dose of mecholyl and to repeated injections of histamine.

B. The Effects Of Mecholyl In Beeswax

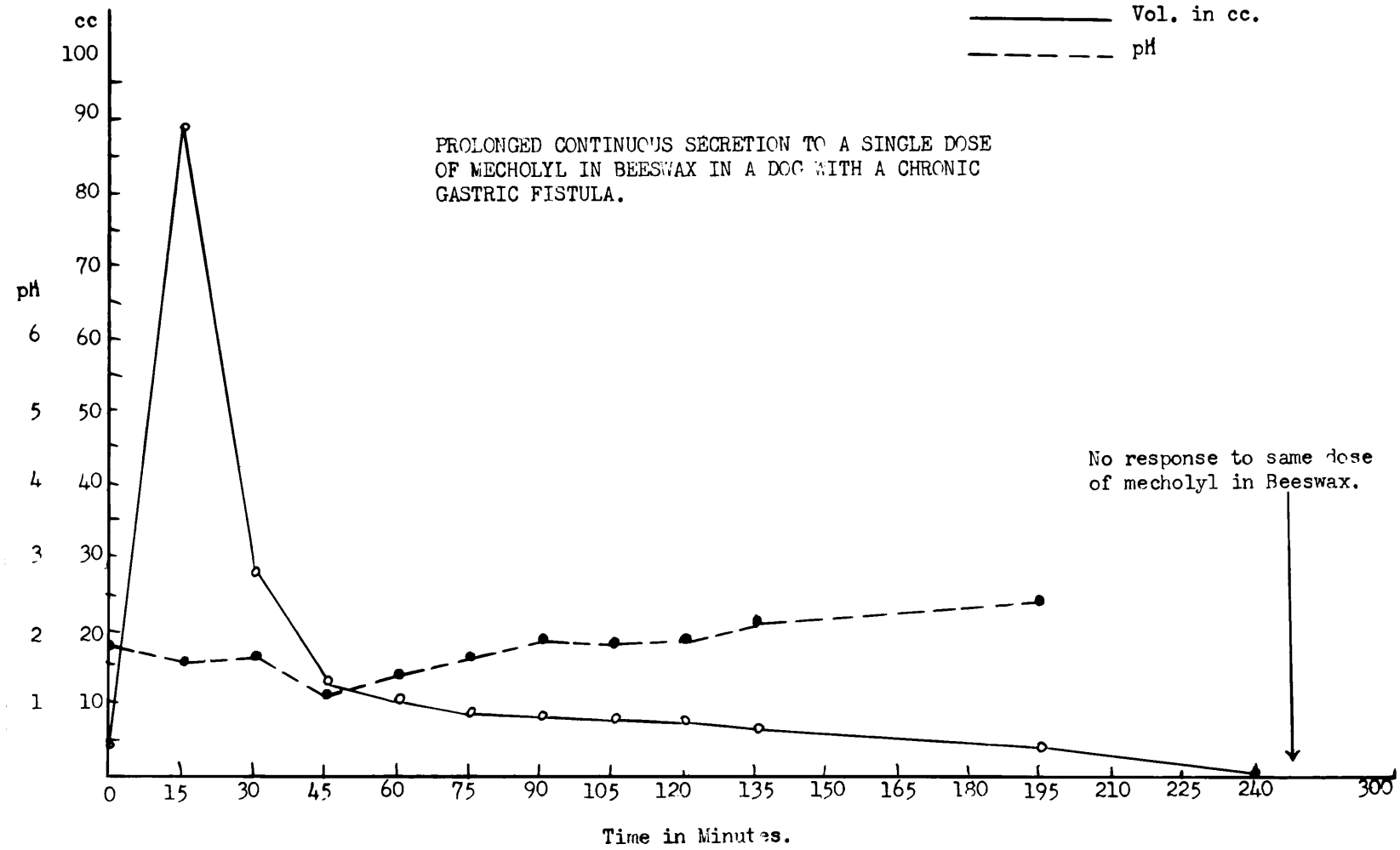
Grs. 3,4,5 and 6 illustrate the type of secretory response evoked by the single intramuscular injections of mecholyl in beeswax. The gastric secretion obtained in 12 out of the 18 dogs following the administration of the mecholyl in beeswax-mineral oil mixture was of greater volume and higher acidity than that observed after the injection of mecholyl in aqueous solution, and in 6 of the animals the secretion was definitely prolonged (Grs. 3,4,5).

In the remaining 6 dogs no response or a scanty mucoid alkaline secretion was noted after the implantation of the mecholyl in beeswax.

Although the amounts of mecholyl injected with the beeswax (20-200 mg.) were in most instances greater than the lethal subcutaneous dose for these animals, being from 2 to 4 times greater than that given by the subcutaneous injections of the aqueous solution of mecholyl, no untoward effects were noticed. In all instances, the salivation, lachrymation and the increased gastro-intestinal motility commenced 2-5 minutes following the injections and lasted longer than the gastric secretory response. The general effects to mecholyl were also observed in the dogs in which no gastric secretion was obtained, indicating that the implantation of the mecholyl in beeswax definitely prolonged the mecholyl effect in all the experiments, even in the absence of a secretory response.



Gr. 3 The secretory response of .7cc or (approximately 60mg) of mecholyl in beeswax in dog #1 (12kg). Note the continuous secretion and the high acidity of the juice obtained; no further response to 35mg of mecholyl (aqueous solution), with prostigmine .5mg x 2.



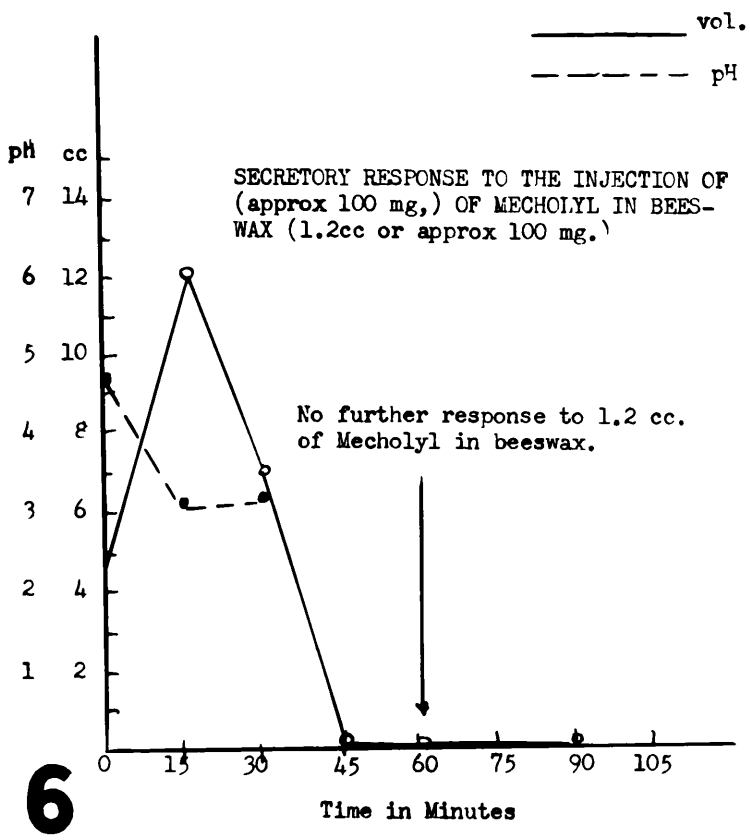
Gr. 5 The effect of 50mg mecholyl in beeswax on the gastric secretion in a dog with a chronic fistula (#15 - 22k). Note the prolongation of the secretory response and the high acidity of the juice obtained.

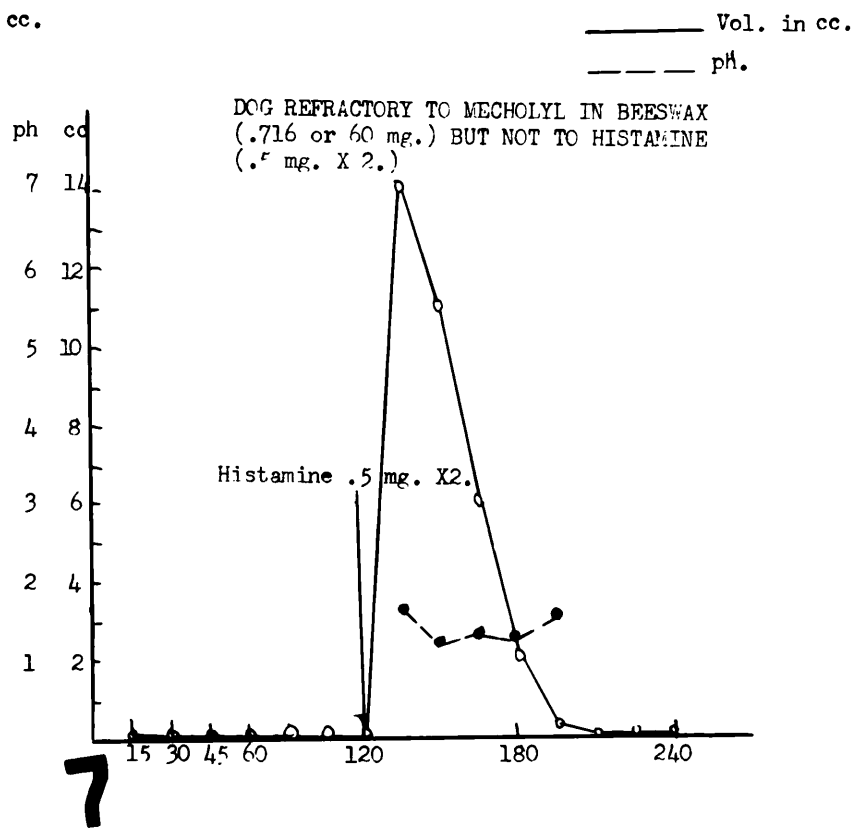
In the dogs in which a gastric secretion was obtained, it usually commenced 5-10 minutes after the injection, reached its maximum in 15-30 minutes and lasted 30 minutes to 6 hours. In only 6 dogs did the secretion last from 1½ to 6 hours, (Grs. 3,4,5) and in the remainder, the secretory response declined rapidly in 30 to 60 minutes (Gr. 6). The juice obtained was watery to mucoid in character of very high acidity (pH 1.0 - 3.5) and closely resembled that seen after vagal stimulation (Grs. 3,4,5,6). In the acute experiments the volume of gastric secretion during the first hour varied from 14 to 37.0 cc. (Grs. 3,4,6). In the chronic fistula dog, a more copious secretion was obtained in the first hour, which was partly due to the swallowed excess saliva, although the pH varied from 1.28 to 1.80 (Gr. 5).

When the mecholyl secretion had declined, the second injection of a similar dose of mecholyl in beeswax produced no further effects in 4 of the dogs, (Grs. 3,4,5,6), and in 2 of these the further addition of prostigmine (.5mg.), 10 minutes later also failed to elicit a secretory response (Gr. 3 & 6) although an increase in salivation was noticed.

When a second dose of mecholyl in beeswax was given the 3 dogs which showed no secretion following the first injection of mecholyl mixture, no effect was obtained. Two of these animals were also refractory to histamine injections, while a profuse watery highly acid secretion was obtained in the third following the histamine injection (Gr. 7).

The 3 dogs in which a scanty alkaline secretion was obtained following the mecholyl injection, were also refractory to subsequent doses of mecholyl or histamine. The response to the mecholyl in all these experiments were not directly related to the size of the doses injected.





Gr. 6 Although the character of this response resembles that seen with mecholyl above, the juice obtained here was more acid.

Gr. 7 Dog #6 (19kg.) did not secrete following injection of mecholyl in beeswax (.7cc), but copious watery highly acid secretion was obtained after subcutaneous histamine injection (.5mg x 2).

DISCUSSION

These experiments demonstrate that the injection of large single doses of mecholyl in aqueous solution or embedded in beeswax can stimulate an acid secretion in most of the dogs and that the administration of the mecholyl in beeswax can prolong the secretory response in at least one third of the animals tested.

The type of gastric secretion observed after single large doses of mecholyl in aqueous solution was in close agreement with the findings of others (360, 361,362) (Grs. 1 & 2), although the doses used in this investigation were generally much larger than those used by previous workers. The volume and the acidity of the juice provoked by the mecholyl in beeswax was definitely greater than that noted after the injection of the mecholyl alone, and was very similar to the type of secretion obtained by Gray and Ivy (360) and others (361,367), with repeated stimulation of small doses of mecholyl, indicating that the mecholyl suspended in the beeswax was being slowly absorbed (Grs. 3,4,5). The watery mucoid character and the extremely high acidity of this secretion closely resembled that obtained by stimulation of the vagi in dogs (368).

The failure to obtain a second response with the same dose of mecholyl (either in aqueous solution or in the beeswax) or to histamine (Grs.2,3,4,5,6), suggests that the secretory apparatus has become refractory not only to mecholyl, as previously shown by Gray and Ivy (360) and others (367), but to histamine as well. Although the exact reason for this refractory state after mecholyl is not definitely known, it may be due to the severe hyperemia, congestion and edema of the hemorrhagic gastric mucous membrane so frequently seen when the stomach is examined, both grossly and microscopically, after a single large dose of mecholyl.

In spite of the limited number of dogs used in this study, 4 or approximately 2o per cent of the series were completely refractory to mecholyl, while another 4 dogs, or 20 per cent responded with a scanty alkaline secretion. Nearly all of these 8 dogs were also refractory to subsequent injections of histamine. In only one dog (Gr. 7) did histamine elicit a marked secretory response of watery acid gastric secretion after no response to mecholyl.

The varied responses in gastric secretion to the administration of mecholyl in this study were very similar to the extreme variations in the volume and acidity of the gastric juice obtained after histamine or testmeals in monkeys (363) or in man (130,134,135,148,150).

The contradictory results of the effects of mecholyl on gastric secretion in a smaller series of dogs reported by different workers may perhaps be partly explained by the natural variability of the response of the animals to this drug. Thus it may be necessary to investigate a larger series of dogs before any final conclusions may be drawn.

CONCLUSIONS

1. The administration of large doses of mecholyl in aqueous solution, or embedded in beeswax produces an acid gastric secretion in most dogs.

2. The intramuscular injections of mecholyl in beeswax definitely prolonged the continuous secretion in 33 per cent of the dogs, and in approximately 70 per cent of the animals, the juice obtained was more acid and of greater volume than that obtained following the subcutaneous injection of mecholyl in aqueous solution.

3. The failure to elicit a secretory response to the same dose of mecholyl or histamine after the initial secretion had declined, suggested that the

secretory apparatus had become refractory to further mecholyl or histamine injections. A possible explanation for this state was discussed.

4. The variations in response to mecholyl in dogs were similar to those observed by others following the injection of histamine or test meals in monkeys and in man.

The Effects Of The Prolonged Administration Of Mecholyl

Experimental Data

Methods

In this study, the effects of the repeated injections of mecholyl were studied on two groups of dogs. In the first group (29 dogs), weighing from 7.7 to 20 kg., the aqueous solution was injected subcutaneously daily in doses from 10 to 50 mg. The dosage levels were determined through experience to be the maximum each dog would tolerate without collapsing or going into shock. This 'sub-shock' dose which was then maintained for the duration of each experiment, depended largely on the size and weight of the animal (See Table 1). The daily injections were made at 9 A.M. and the animals were not fed, or given water till 4 P.M. The diet consisted of ground red beef and all animals were allowed free access to water after 4 P.M.. Seven of the dogs (See Table 1) were also given .25 to .5 mg. of prostigmine along with the mecholyl. All but 1 of the dogs (dog #51 - Table 1) died from the general effects of the drug.

In the second group animals (19 dogs), weighing 5.9 to 15.9 kg., the mecholyl was embedded in a beeswax-mineral oil mixture, in order to prolong the effects of the drug. The mecholyl in beeswax was prepared according to the method devised to prolong the action of histamine by Code and Varco (234). The method of preparing this mixture has already been described in detail in the previous chapter. This mecholyl in beeswax preparation gave approximately 90-100 mg. of mecholyl per cc.. The dosage levels were again determined through trial to be the maximum each dog could tolerate without going into

shock. In dogs weighing 6.5 to 15.9 kg., the doses given were varied as in Table 2, from 20 to 125 mg. per injection. The mecholyl mixture was injected alternately into the shoulder and thigh muscles and the injections were given daily at 9 A.M.. The diet and time of feeding were the same as for the dogs which received the subcutaneous injections of mecholyl alone. There was thus a period of 7 hours after each injection when the stomach was empty. All but 4 of the dogs died from the general toxic effects of this drug; the remainder were sacrificed.

Results

A. The Effects Of The Daily Repeated Subcutaneous Injections Of Mecholyl (Aqueous)

The experimental data are summarized in Table 1. It can readily be seen that following the mecholyl injections, a sequence of pathological changes occurred which consisted of marked hyperemia and engorgement of the vessels, interstitial mucosal hemorrhages with superficial necrosis, erosions, and acute or subacute ulcerations in the stomach and duodenum. The dogs were injected with 10 to 50 mg. of mecholyl daily over a period from 2 to 191 days, having received a total of 2 to 134 injections. Erosions or ulcers were found in 12 of the 29 animals studied.

In almost all instances, marked generalized parasympathetic responses accompained every injection of mecholyl, leading to an immediate collapse and death in the first few dogs injected, especially when prostigmine was injected along with this drug. (Exp. Nos. 1-8 Table 1). This state of collapse was immediately relieved by the subcutaneous injection of atropine.

TABLE I

* RECEIVED 0.5 mg. PROSTIGMINE

THE EFFECTS OF THE PROLONGED DAILY ADMINISTRATION OF MECHOLYL (AQUEOUS)

EXP. NO.	DOG NO.	WT.	DAILY DOSE OF	NO. OF DOSES	TIME	RESULTS				REMARKS.
						STOMACH	DUODENUM	COLON	PANCREAS	
		kg.	mg.		dys.					
I	27	I0	20-40	4	4	Severe Hyperemia	Severe Hyperemia	Hyperemis	Hyperemia	Died in 30 min. after last injection.
2	45	I5	40	5	7	"	"	"	"	Died I hour after last injection. Shock.
3	28	9.I	I0-I5*	2	2	Erosions	Erosions	Mucosal Hemorrhages	Interstitial Hemorrhage	Died 30 min. after last injection. Shock.
4	I7	8.8	I0-I2*	2	2	"	Hyperemia	"	Hyperemia	" "
5	I5	I9	20*	2	2	"	Mucosal Hemorrhages	Hyperemia	Interstitial Hemorrhage	" "
6	3	20	I0-I5	3	5	Hyperemia	Hyperemia	Mucosal Hemorrhages	No Change	Died 2 hours after last injection. Bronchopneumonia.
7	2I	I7	I0*	2	2	Mucosal Hemorrhages	Erosions	Severe Hyperemia	Hyperemia	Died 20 min. after last dose. G-I tract filled with blood.
8	I6	I5	I0*	3	5	"	Mucosal Hemorrhages	Mucosal Hemorrhages	Interstitial Hemorrhage	Died 30 min. after last injection,
9	46	I7.5	I0	8	I0	Slight Hyperemia	Slight Hyperemia	Slight Hyperemia	Focal acute pancreatitis	Died during the night.
I0	3I	I7	30-40	30	40	Erosions	Erosions	"	Hyperemia	Healed non-specific pancreatitis with adhesion to the liver.

TABLE I (cont'd)

EXP. NO.	DOG NO.	WT. kg.	DAILY DOSE mg.	NO. OF DOSES	TIME dys.	RESULTS STOMACH	DUODENUM	COLON	PANCREAS	REMARKS.
II	37	8.6	20-30	32	44	Craters & Erosions	Erosions	Focal acute colitis	No Changes	Stomach and intestines combained bloody fluid.
I2	44	I5.2	30-35	I7	23	Mucosal Hemorrhages	Hyperemia	"	"	Died 7 hours after last dose from massive G-I hemorrhage.
I3	35	8.I	40	6	8	Erosions	Erosions	Hyperemia	Hyperemia	Died from extensive G-I hemorrhages.
I4	29	I8.I	I0-20	28	38	Hyperemia	Hyperemia	Hyperemia	Focal acute pancreatitis	Peri-pancreatic and peri-gastric fat necrosis.
I5	I0	I6.I	I5-20	3I-	4I	No Changes	No Changes	No Changes	No Changes	Died from infection.
I6	II	I5	I5-20	26	34	Severe Hyperemia	Severe Hyperemia	Hyperemia	Hyperemia	Died in 30 min. after last dose. Shock.
I7	33	I6.8	35	4	4	No Changes	No Changes	No Changes	No Changes	Died during the night; bronchopneumonia.
I8	34	20	20-30	II	I2	"	"	"	"	" "
I9	52	I5.9	30-40	I2	I3	"	"	"	"	" "
20	6	I4.2	20-35	4I	49	Hyperemia	Hyperemia	Hyperemia	Per- pancreatric fat necrosis	Died 7 hours after the last dose from severe rectal bleeding

TABLE I (cont'd)

EXP. NO.	DOG NO.	WT.	DAILY DOSE mg.	T.	TIME dys.	POST MORTEM STOMACH	POST MORTEM	POST MORTEM COLON	POST MORTEM PANCREAS	REMARKS.
21	7	[illegible]	15-20	52	68	Erosions	Hyperemia	[illegible]	Hyperemia	Died from extensive G-I bleeding.
22	6	14	15-25	72	96	No Change	No Change	No Change	No Change	Died during the night; bilateral adrenal hemorrhage
23	39	15	[illegible]-30	82	96	Erosions	Subacute ulcers	Erosions	[illegible]	Died 20 min. after last dose. Debilitated.
24	50	7.7	5-10	15	10	No Change	No Change	No Change	No Change	Encephalomyelitis.
25	49	7.7	10-15	5	5	"	"	Focal Ulcerative Colitis	"	Died during the night.
26	50	10	20-40	96	104	Craters & Erosions	Mucosal Hemorrhages	Hyperemia	Hyperemia	Died during the night; hemorrhage into the adrenals.
27	45	16.8	15-30	III	120	Erosions	"	"	"	Peri-duodenal fat necrosis. Died from extensive G-I bleeding.
28	51	20	20-30 *	114	154	Subacute ulcers	Erosions	No Change	No Change	Sacrificed; debilitated.
29	13	23.5	30-50 *	134	174	Erosions	"	Acute Hemorrhagic Colitis	Hyperemia	Died of extensive G-I bleeding. No malnutrition.

Within 1 to 2 minutes after the drug was given, sweating, panting, salivation, lachrymation, retching and excessive vomiting were noticed.

The vomitus was frequently blood-tinged and occasionally massive hematemesis occurred. Mecholyl also stimulated the contractions of urinary bladder and caused increased gastro-intestinal motility which resulted in immediate urination and defecation. The stools were well formed at first and of normal color and consistency, but within 10 to 15 minutes, subsequent bowel movements were looser and blood-tinged and eventually led to watery mucoid bloody diarrhoea of the type commonly seen in human cases of acute ulcerative colitis.

The bloody diarrhoea was usually over in most dogs in 1-2 hours after the injection, and within 8 to 24 hours the stools became formed again, of normal consistency, but tarry in color. In numerous instances (Expts. 11, 12, 13, 20, 21, 25, 27, 29, - Table 1) after repeated injections, the dogs continued to have frequent bloody stools and rectal bleeding for 12 to 18 hours after injection and finally such animals died from the extensive hemorrhages into the gastro-intestinal tract. On post-mortem examination of such dogs, the stomach and intestines were filled with varying amounts of blood and the gross appearance of the gut in most instances was similar to that shown in Fig. 1A & B.

The stomach was usually diffusely hemorrhagic, with multiple mucosal hemorrhages and focal areas of superficial necrosis and erosions. This hyperemic discoloration of the stomach was most severe in the fundic portion of the stomach, which was sharply demarcated from the paler pyloric region as seen in Fig. 1A & B. Beginning sharply at the most proximal end portion of the duodenum, this hemorrhagic involvement of the mucosa extended throughout the whole intestine with decreasing severity as the ileum approached

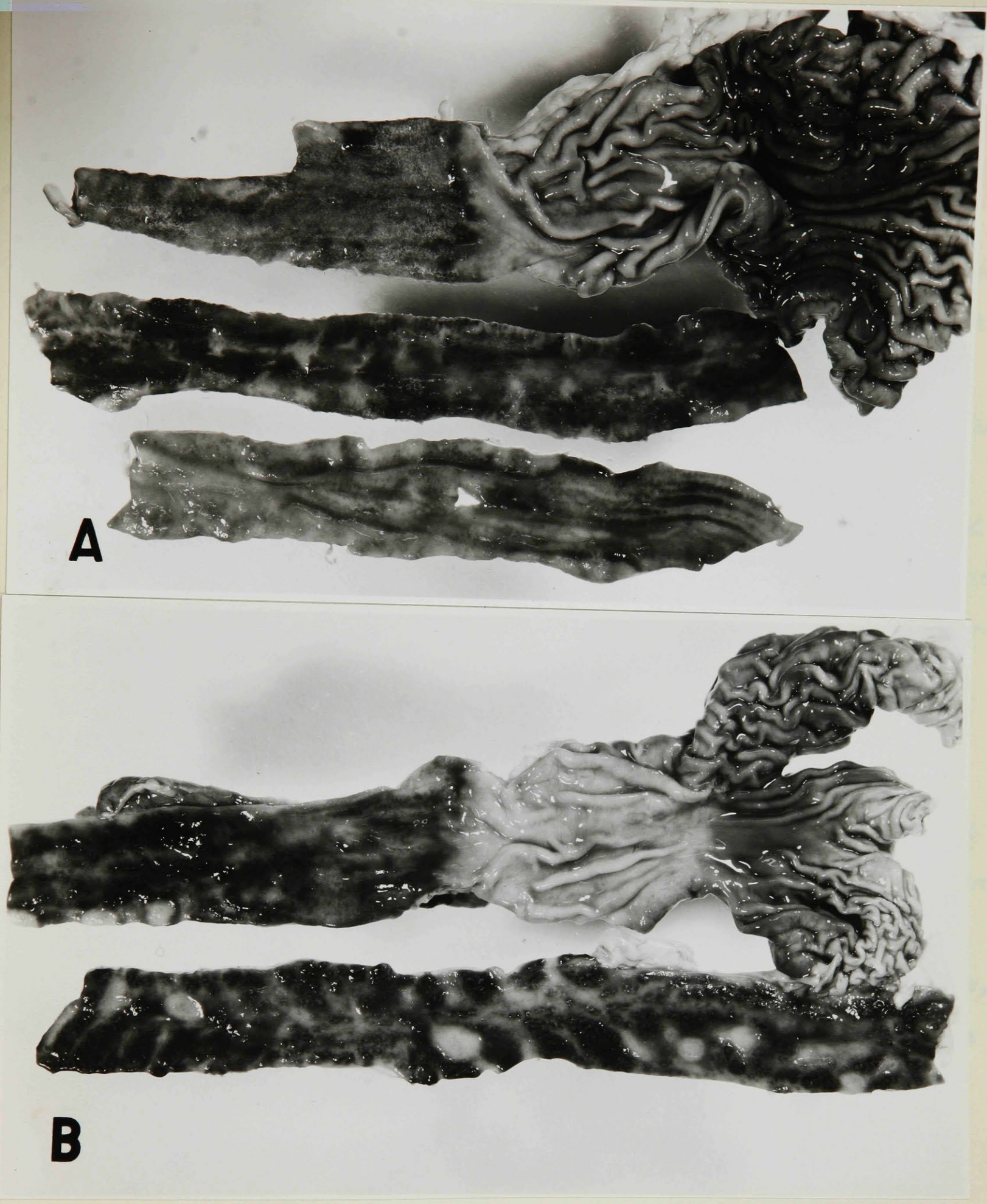


Fig. 1

A & B, severe and extensive hyperemia of the gastro-intestinal mucosa with multiple small mucosal hemorrhages and focal necrosis, in dogs #28 and #17, following the injections of mecholyl. Note that the hemorrhagic appearance is more extensive in Fig. B.

(See Fig. 1A & B).

The severity of the hemorrhagic changes and superficial necrosis observed at autopsy depended mainly on the time of death of the animal after the last injection. In most instances the mucosal alterations were most pronounced within the first 3 hours after the last dose of mecholyl and in those animals which died from the effects of the drug, other than hemorrhage, 12-18 hours after the last injection no changes, or only slight hyperemia could be found in the gut, indicating the rapid regenerative capacity of the gastro-intestinal mucosa (Table 1 Exp. 10,17,18,19,22,24). Similar mucosal changes were observed in the large bowel of such animals (Fig. 11-15). The erosions were multiple and were usually confined to the fundic portion of the stomach and were less often seen in the pylorus and duodenum.

Histological examination of the hemorrhagic portions of the stomach and duodenum showed the presence of interstitial hemorrhage into the mucous membrane with necrosis of the most superficial layers of the mucosa (Fig. 2). The blood vessels were generally markedly hyperemic. In several of the sections, underlying a relatively intact mucous membrane, focal infiltrations of acute inflammatory cells were noted, indicating the presence of focal hemorrhagic gastritis or duodenitis. Multiple sections taken through the erosions seen in the gross revealed varying degrees of hemorrhage and necrosis of the mucous membrane, but the basal layers were intact (Fig. 3A)

In several instances the necrotic tissue was infiltrated by polymorphonuclear leucocytes (Fig. 3B).

Microscopic examination of several sections taken through the twin gastric lesions found in Dog #37 (Table 1, Exp. 11) which closely resembled true ulcers in the gross (Fig, 4A & B) showed them to be deep craters or erosions

Fig. 2

Showing interstitial hemorrhage into outer two-thirds of mucous membrane and superficial necrosis of outer third of the mucosa. X 35.

Fig. 3A

Superficial gastric erosion of the outer two-thirds of the mucosa, which is the seat of hemorrhage and necrosis (dog #15). Note that the basalar layers of the mucous membrane are intact. X 23.

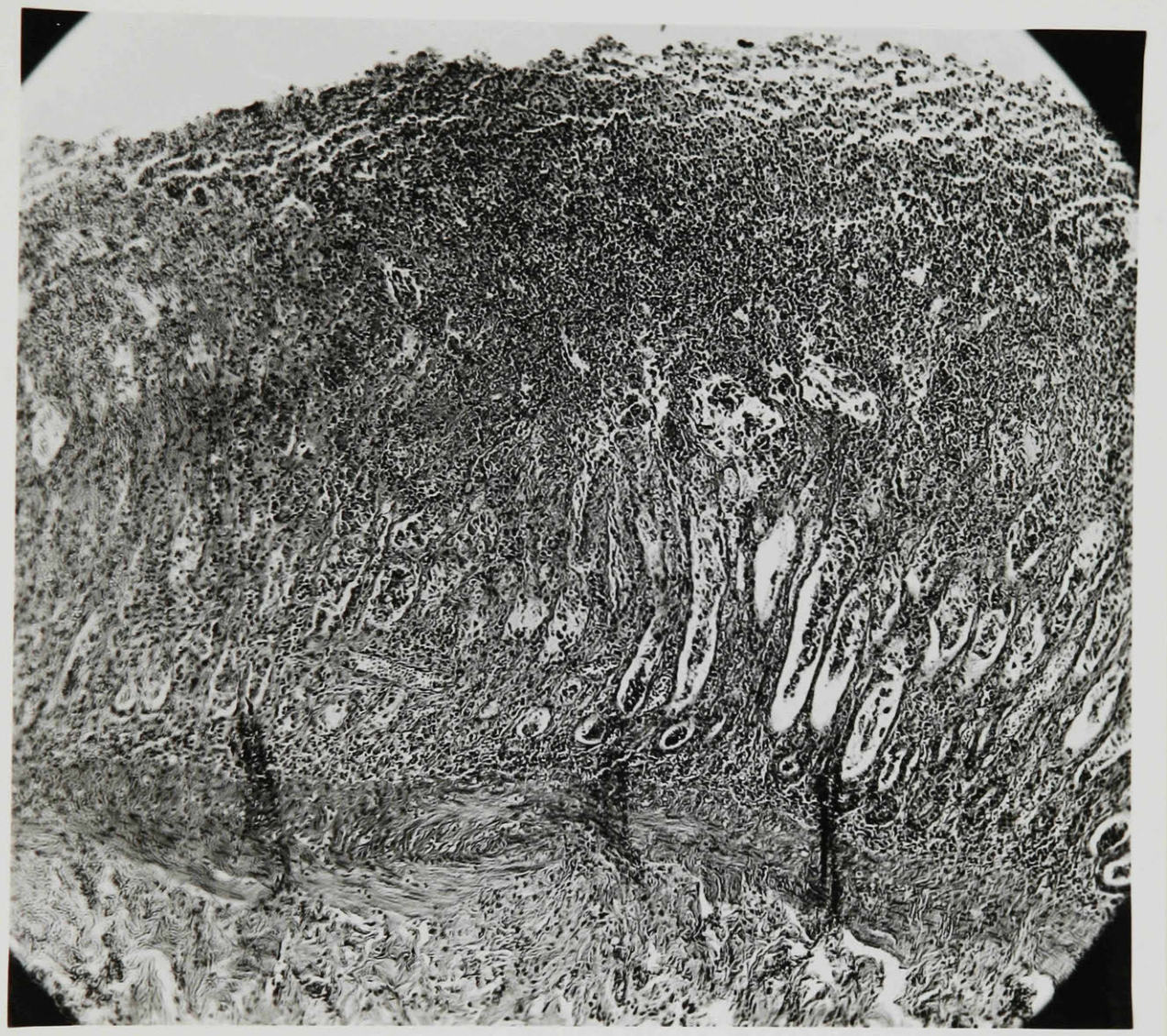


Fig. 3B

Higher power of deep erosions seen in section 3A., showing the remaining inner third of the gastric mucosa. Note that the necrotic tissue is infiltrated by polymorphonuclear leucocytes, but that there is a sparse number of inflammatory cells in the muscularis mucosa. X 84.

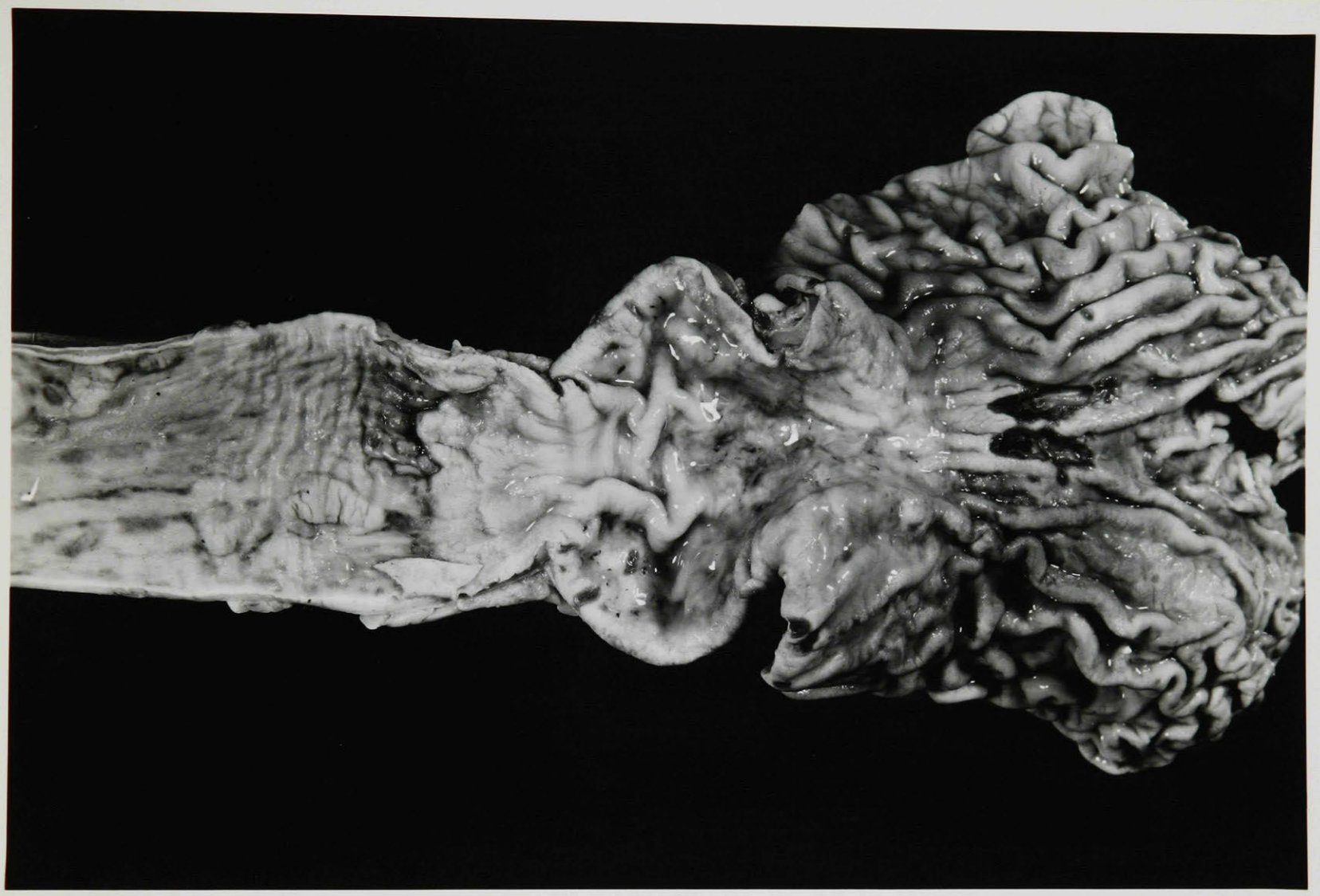


Fig. 4A

Twin gastric craters, and multiple scattered superficial erosions in dog #37 after repeated injections of mecholyl. Note the resemblance of these lesions to true ulcers.

Fig. 4B

Closer view of the craters seen in Fig. 4A, showing remnants of fresh clotted blood in their bases.

in which no inflammatory exudate was found either in the mucosa or submucosa (Fig. 5).

Acute or subacute gastric or duodenal ulcers were encountered in 2 animals. Two duodenal ulcers were found in the proximal portion of the duodenum of dog #39 (Table 1 Exp. 23) after 82 daily mecholyl injections of (20-30 mg.) during a period of 96 days (Fig. 6A & B). This animal exhibited profuse bloody diarrhoea daily after each injection for several weeks prior to death. This rectal bleeding became more prolonged after subsequent injections and finally the dog died during the night from extensive gastro-intestinal hemorrhages which continued for 18 hours after the last injection in a debilitated condition. Gross and microscopic examination of the duodenal lesions showed them to be subacute penetrating ulcers with overhanging edges and a necrotic inflammatory base. The blood vessels were hyperemic and the inflammatory exudate extended deep into the submucosa (Fig. 7A & 7B).

Multiple gastric ulcers in the pyloric region of the stomach along with numerous erosions in the fundus were found in dog #51 (Table 1 - Exp. 28) following 114 injections of mecholyl. Prostigmine in .5mg. doses were given along with the last 10 mecholyl injections. The dog had lost much weight and was sacrificed when in a debilitated condition. Fig. 10A & B shows a very acute small superficial ulcer, the base of which was infiltrated by polymorphonuclear leucocytes. The muscularis mucosa was necrotic and the adjacent submucosa was also infiltrated by the acute inflammatory cells. The microphotographs shown in Fig. 9A & B, reveal a definite subacute gastric ulcer with terraced edges and has penetrated to the submucosa. The inflammatory process, polymorphonuclear leucocytes and lymphocytes, has extended into the submucosa. Although many of the dogs died from extensive gastro-intestinal hemorrhages, most of the animals died from cardiac or pulmonary complications.

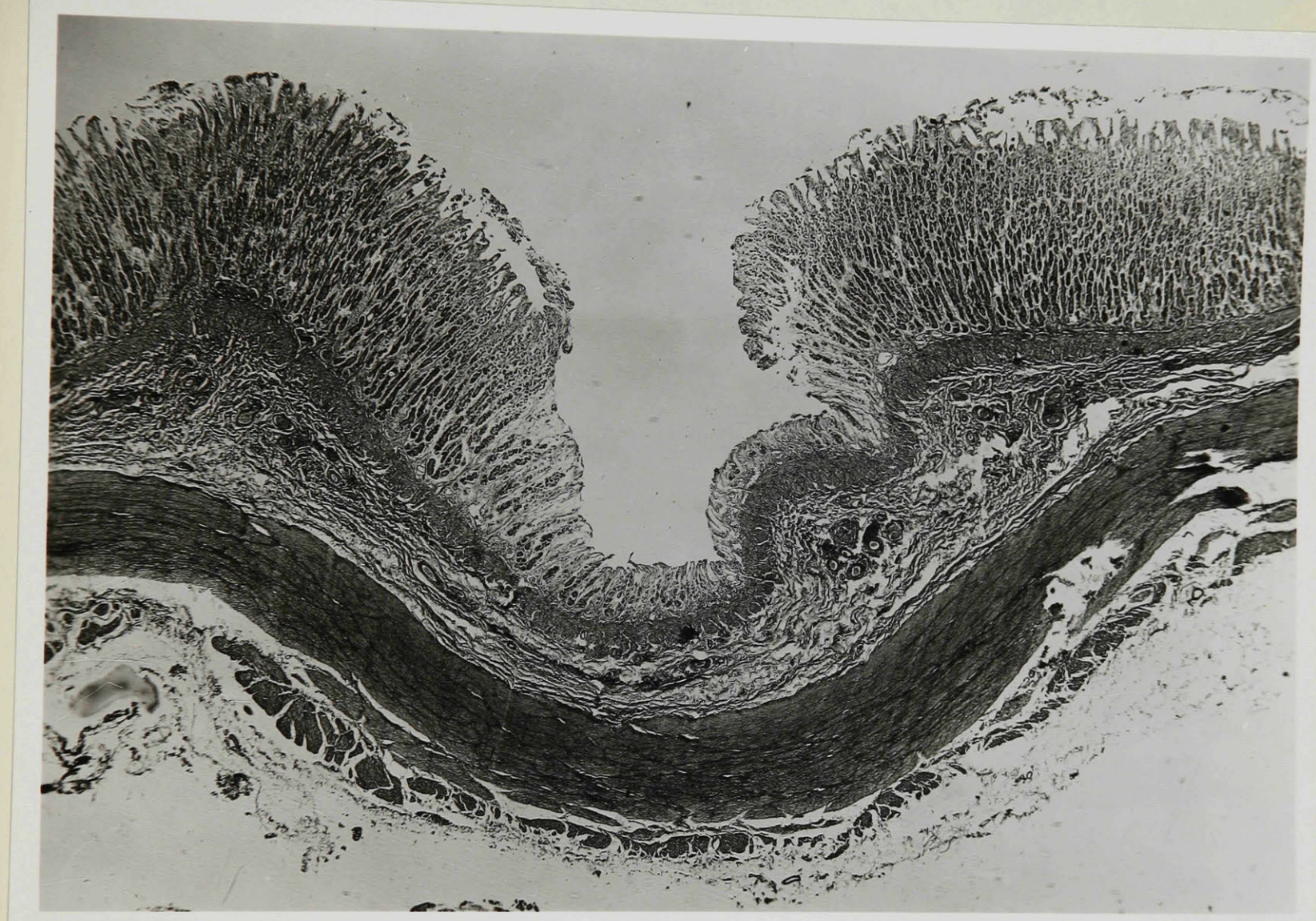


Fig. 5

Microphotograph of gastric craters seen in Fig. 4, showing the deep erosions, which in the gross could be mistaken for true ulcers. Note that residual mucosal glands still remain and that no inflammatory exudate is present in mucosa or submucosa. X 23.

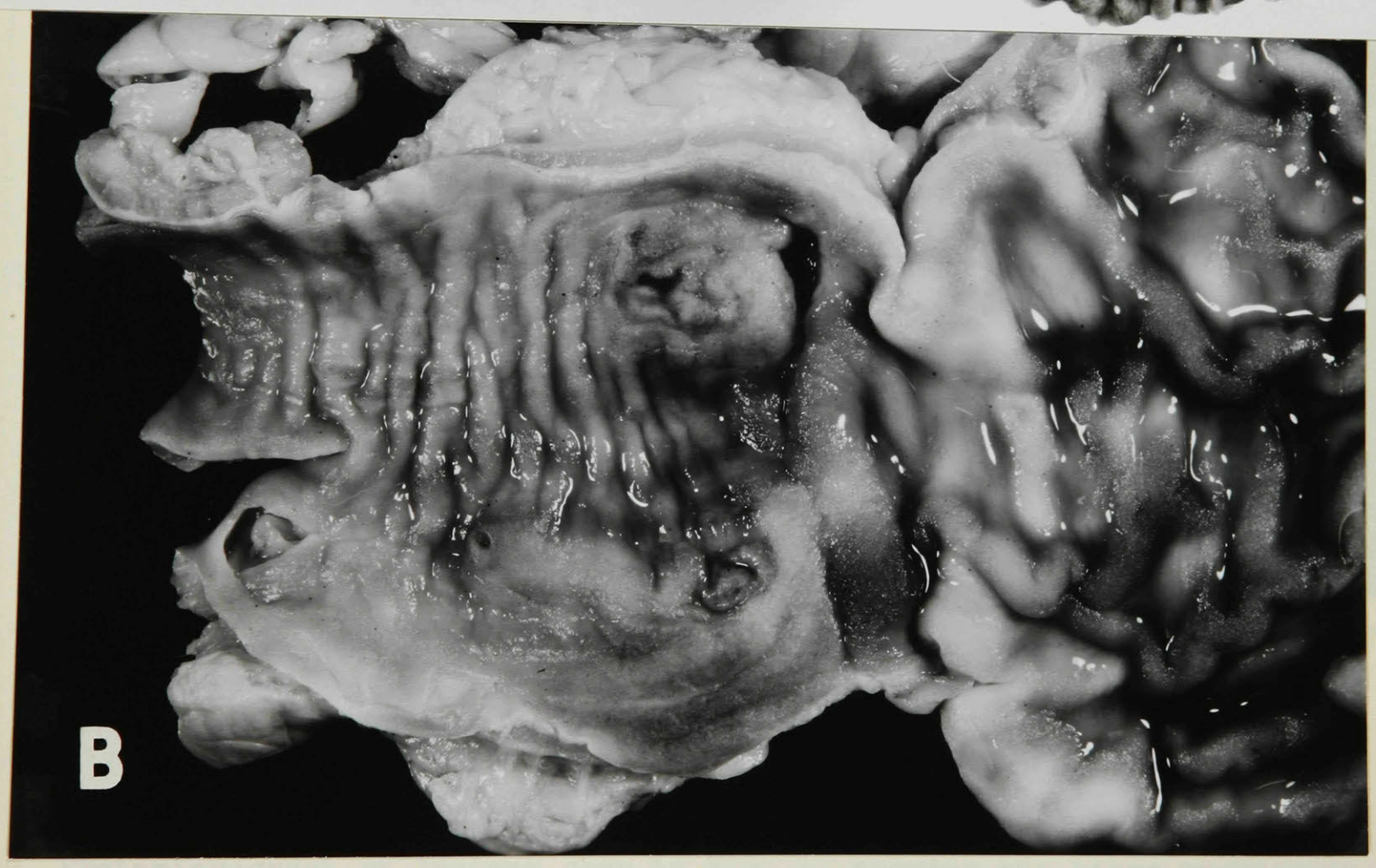


Fig. 6A

Two duodenal ulcers and multiple gastric erosions in dog #39 after 82 mecholyl injections. Note the hemorrhagic appearance of the gastric and duodenal mucosa.

B - Close up view of the duodenal ulcers showing the over-hanging edges. X 23.

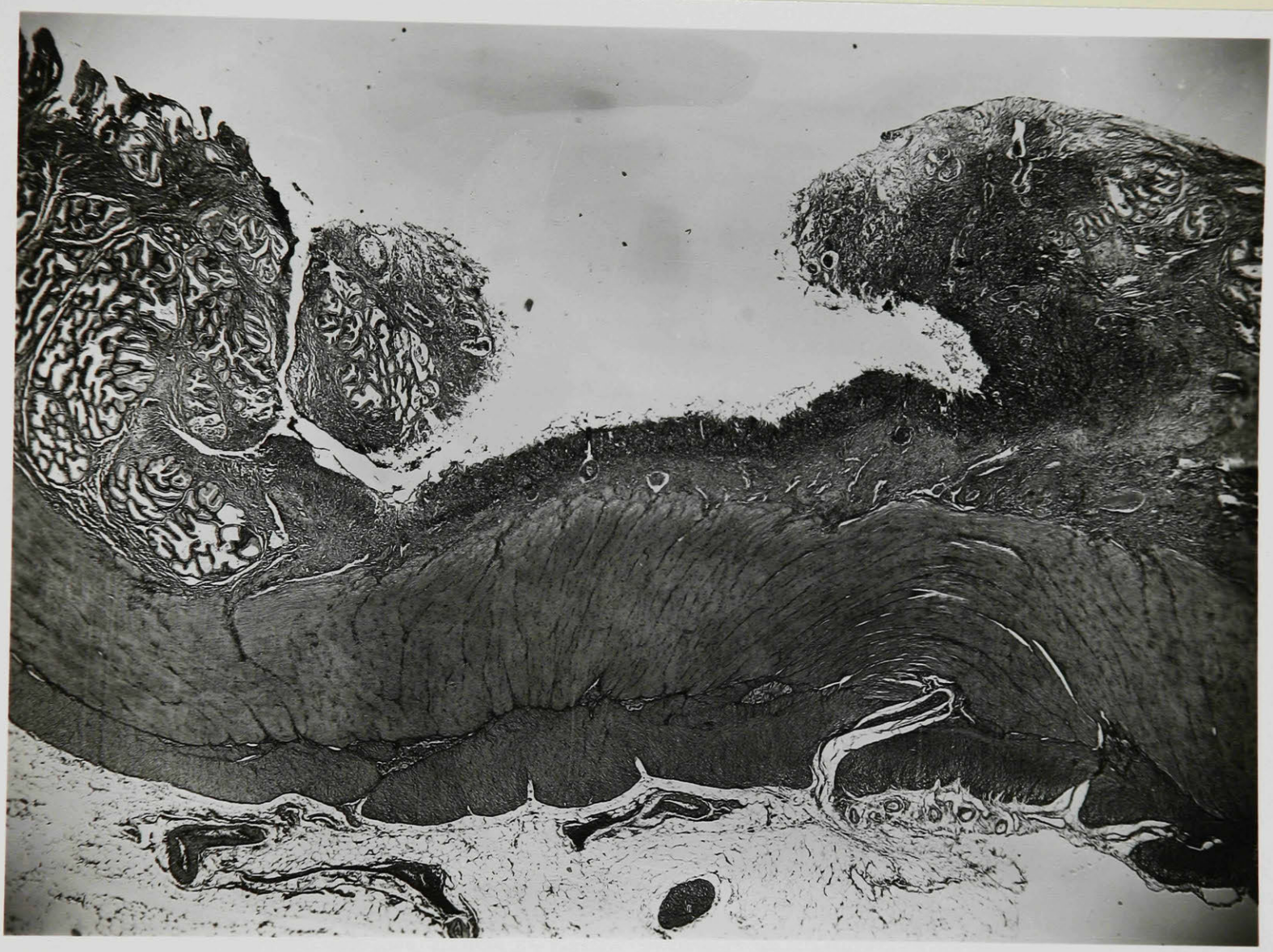


Fig. 7A

Photomicrograph of lesions seen in Fig. 6, showing the large penetrating subacute duodenal ulcer extending through the muscularis mucosa into the submucosa and superficially, at the left, into the muscularis. Note the over-hanging edges. X 20.

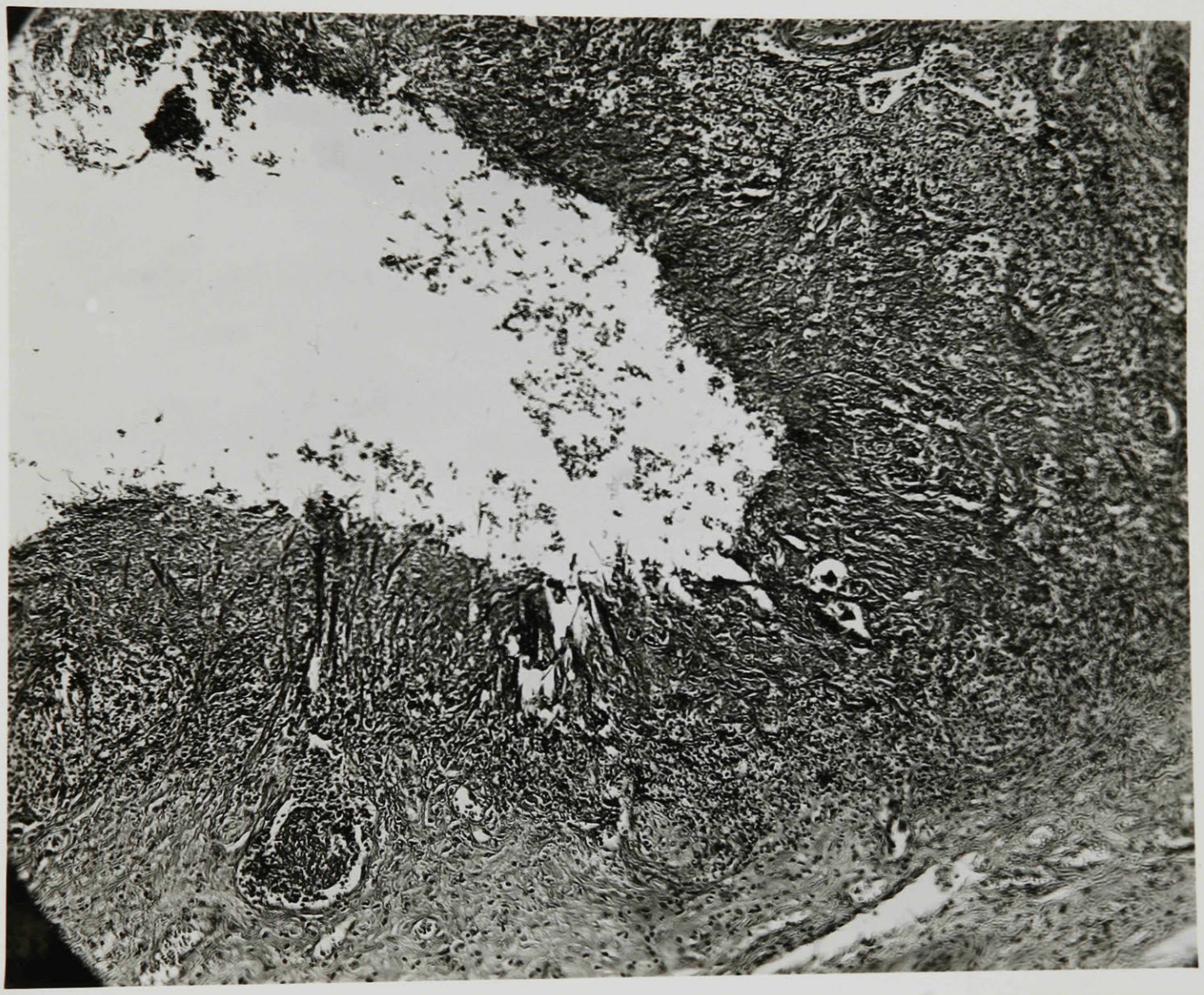


Fig. 7B

Higher power view of the base of the subacute duodenal ulcer seen in Fig. 7A, showing the over-hanging edge and the inflammatory exudate deep in the submucosa. Note the hyperemia of the vessel at the left, in the submucosa. X 101.

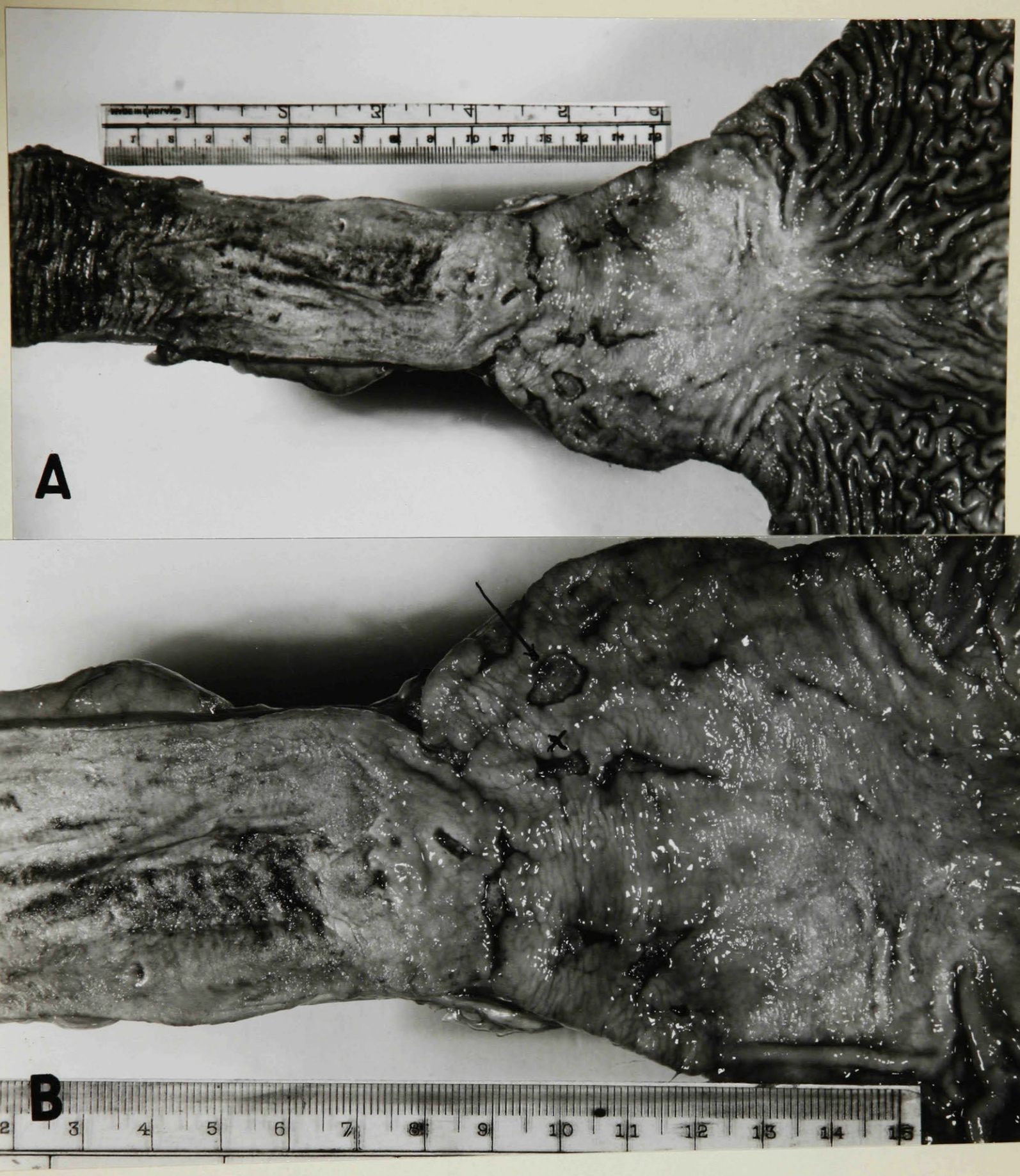


Fig. 8A & B

A. Multiple gastric ulcers in the pyloric portion of stomach and numerous gastric and duodenal erosions. Note the hemorrhagic appearance of the fundic portion of the stomach.

B. Closer view of the same lesions, showing the punched-out appearance of some of the larger gastric ulcers.

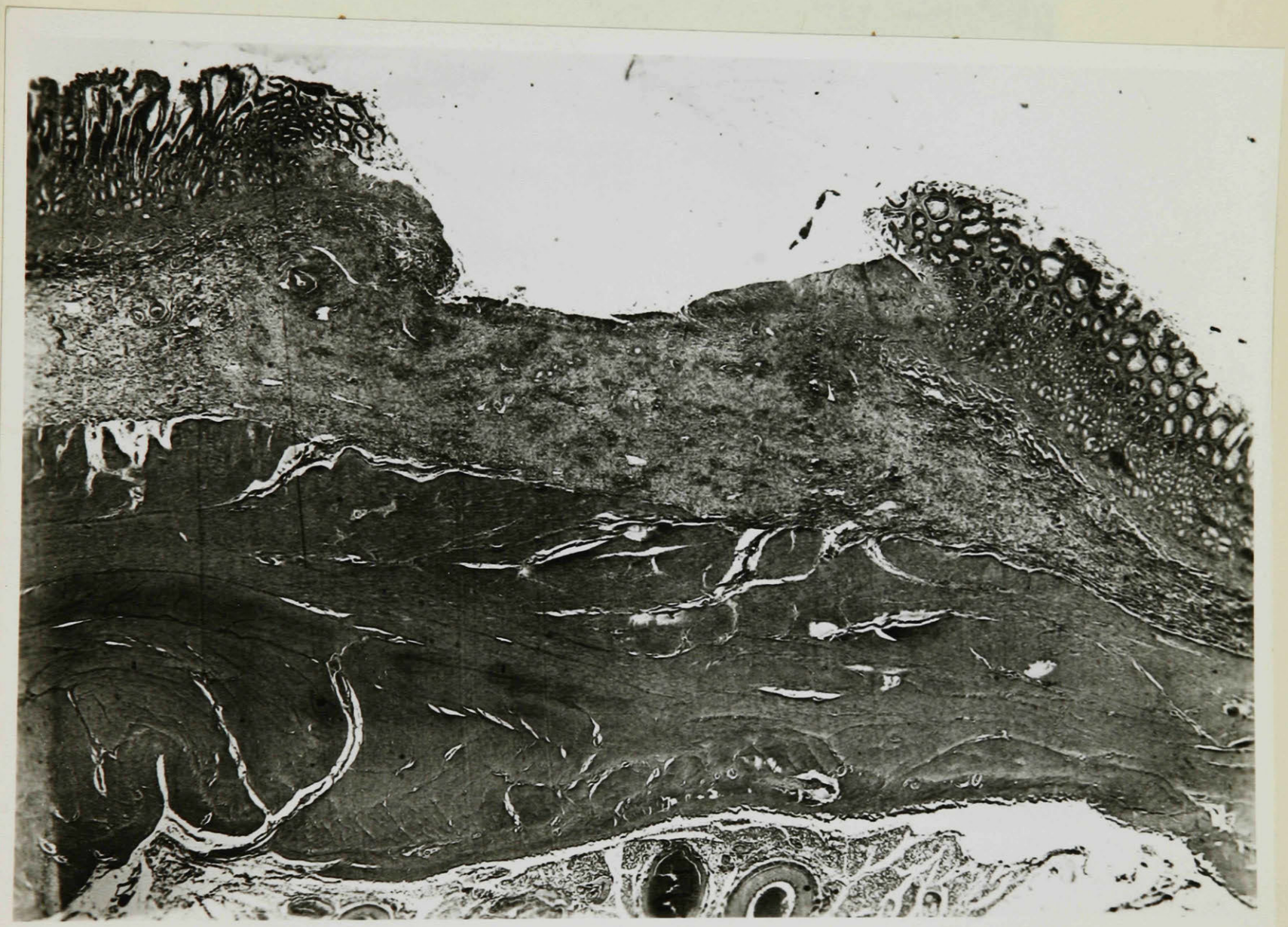


Fig. 9A

Microphotograph of the larger ulcer, indicated by the arrow in Fig. 8, showing a subacute penetrating gastric ulcer with extension into the submucosa. X 13.

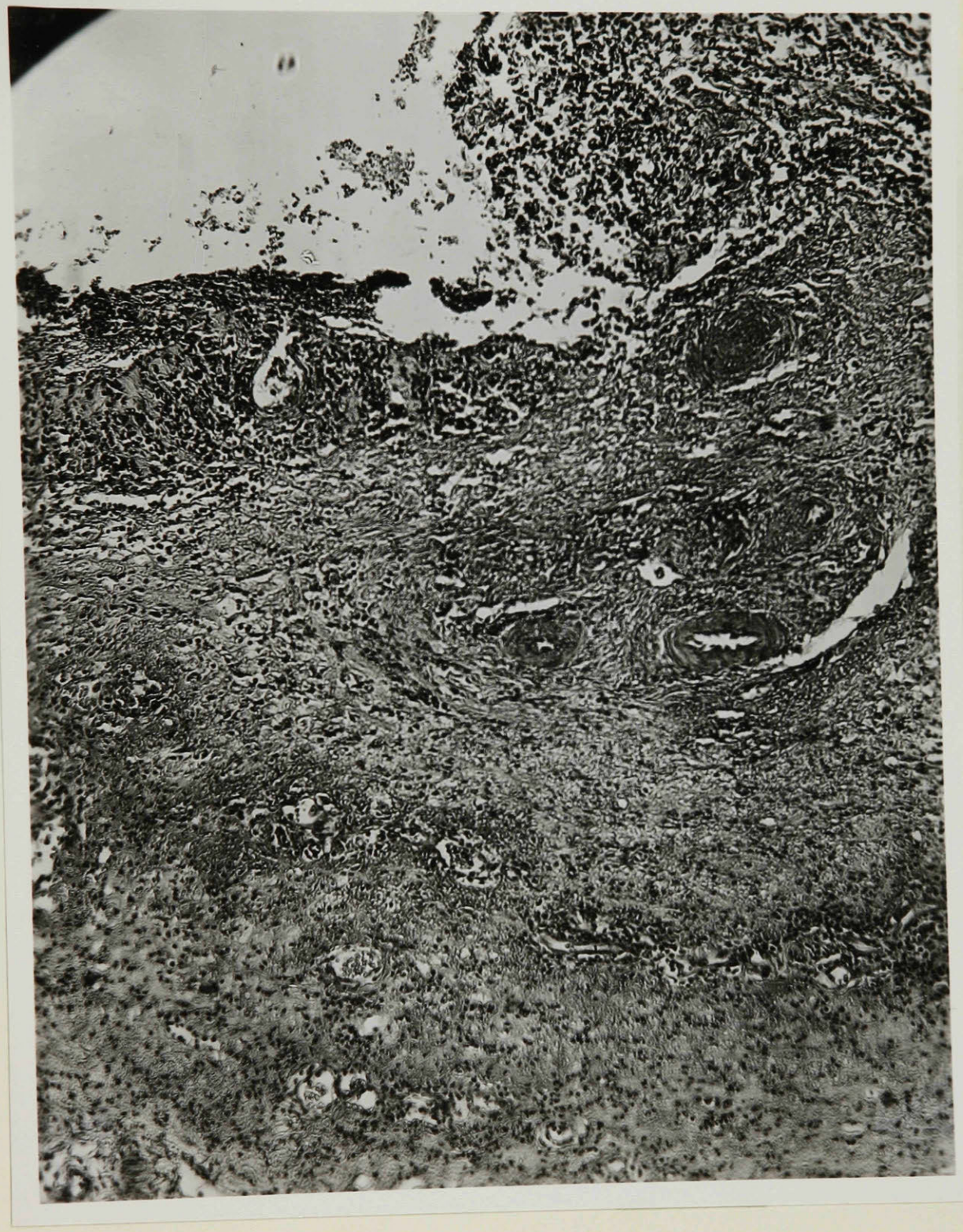


Fig. 9B

Higher power of the base and edge of the subacute gastric ulcer seen in Fig. 9A, showing the extension of the inflammatory process into the submucosa. Note also the thickened blood vessels, and marked edema in the submucous layer. X 110.

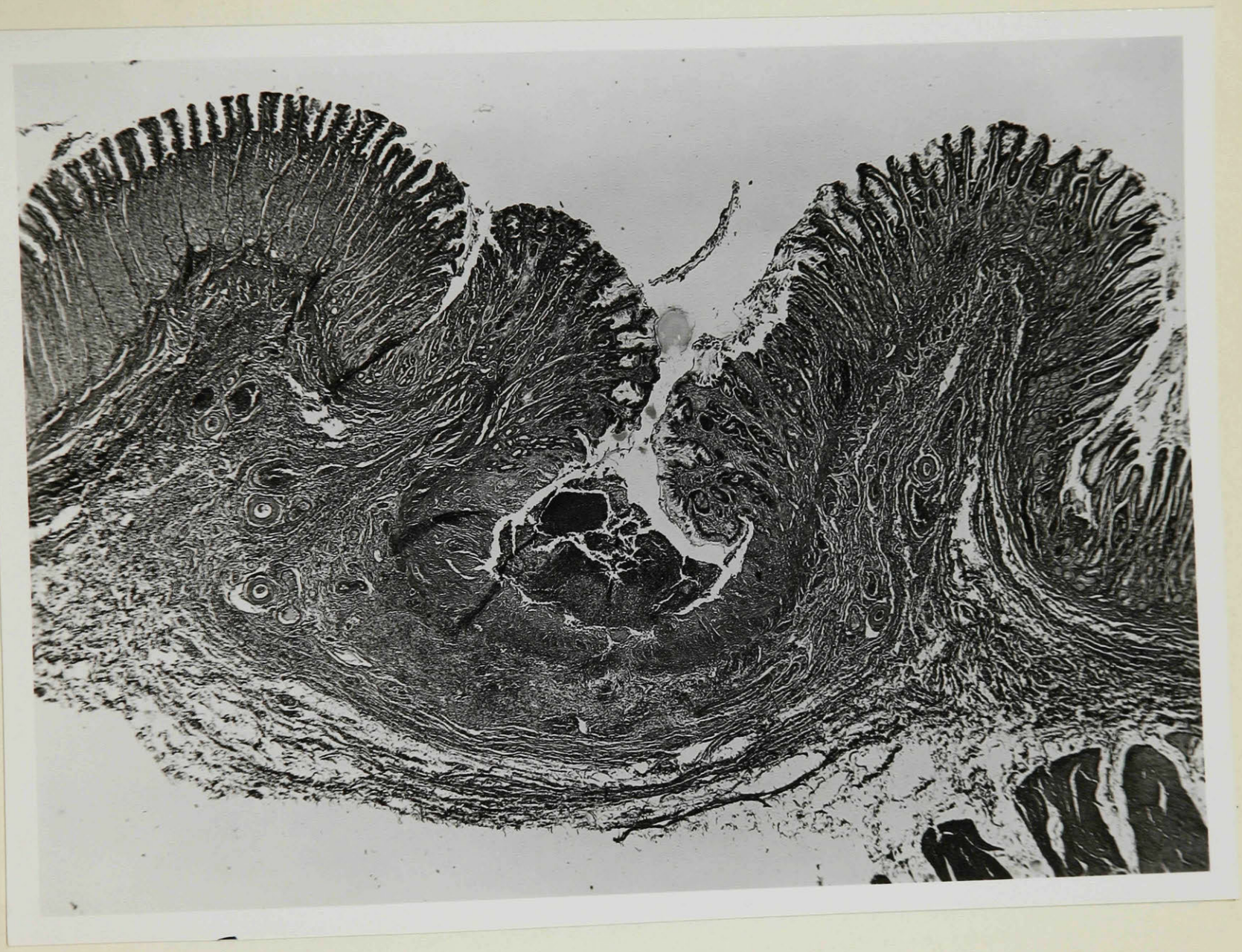


Fig. 10A

Microphotograph of gastric lesion indicated by X in Fig. 8, showing an early acute gastric ulcer. X 21.

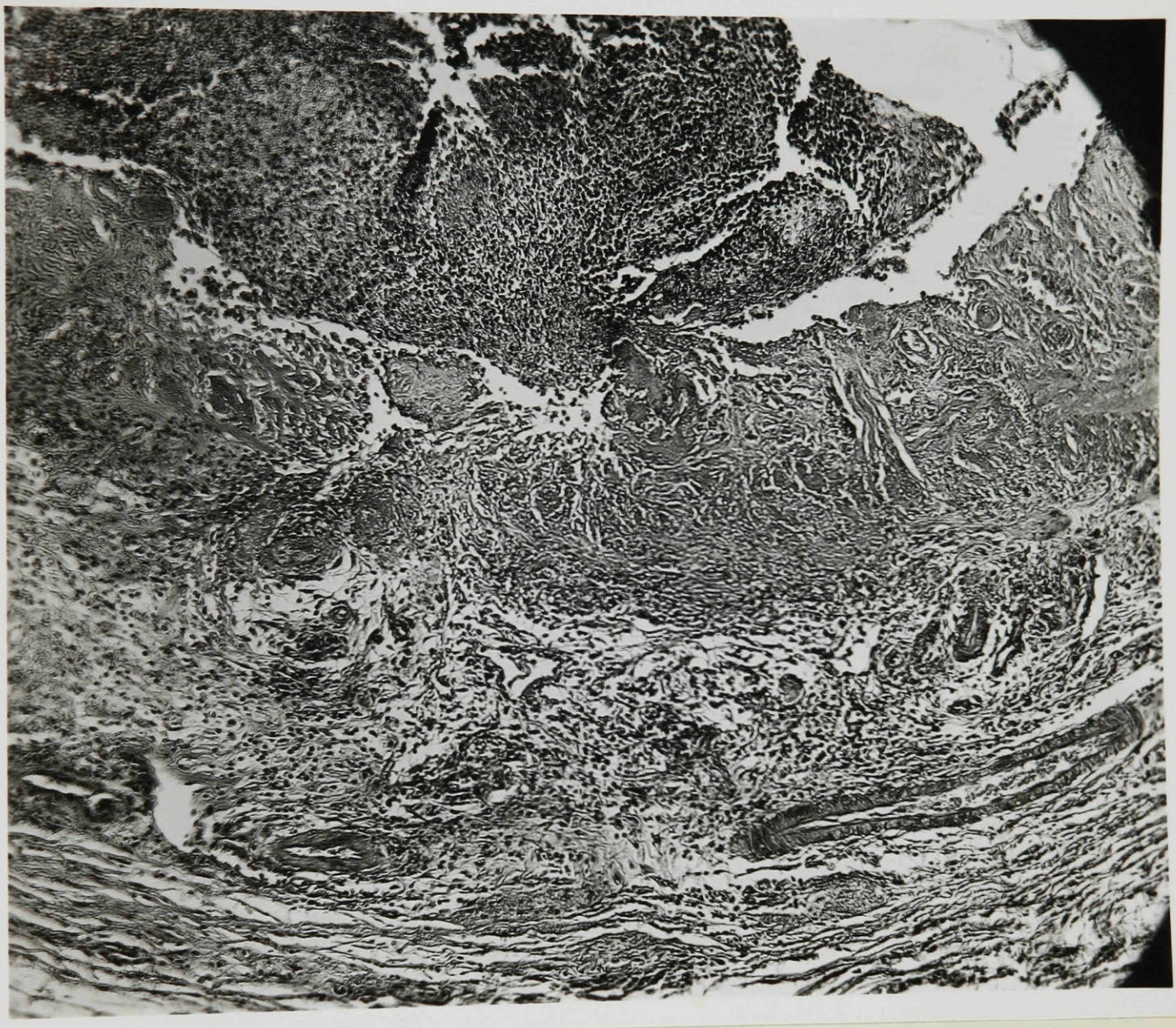


Fig. 10B

Higher power view of the base of the acute ulcer in Fig. 10A, showing complete loss of mucosa and infiltration of the submucosa and muscularis by inflammatory cells. X 101.

B. The Effects Of The Daily Intramuscular Injections Of Mecholyl In Beeswax

In Table 2 are summarized the experimental data following the prolonged administration of mecholyl in beeswax. The pathological changes in the stomach and intestines were pronounced and lasted longer than in the dogs which had received the mecholyl alone. Although no ulcers of the stomach and duodenum were encountered, this method of administration of the mecholyl resulted in acute and subacute ulcerations of the large bowel (Fig. 13,14,15). The mecholyl in beeswax mixture was injected intramuscularly in daily doses of 20 to 125 mg. into 19 dogs weighing 6.5 to 15.9 kg. The animals had received from 2 to 71 injections over a period of 2 to 73 days. Gastric or duodenal erosions were found in 8 of the 19 dogs injected (See Table 2).

Although the quantities of mecholyl injected with the beeswax (20-125 mg.) were in most instances greater than the subcutaneous lethal dose for these dogs, being from 2-4 times greater than that given by the subcutaneous injections of the mecholyl in aqueous solution, the general body parasympathetic responses to the drug were not as severe, and fewer dogs collapsed or died immediately after the injection than when mecholyl was given alone (Table 2). (In almost all the dogs the salivation, lachrymation, retching, vomitus and the increased activity of the bladder and gastro- intestinal tract commenced in 2-15 minutes following the injection, and lasted much longer than that following the subcutaneous injection of the aqueous solution of mecholyl).

In most cases the salivation commenced within 2-5 minutes following the injection and lasted from 1 to 4 hours, retching, vomiting, urination and defecation were slightly delayed, but commenced within 10 to 20 minutes after the drug was given. The character of the vomitus and the stools were

TABLE II

EFFECTS OF THE PROLONGED ADMINISTRATION OF MECHOLYL IN BEESWAX-MINERAL OIL MIXTURE.

EXP. NO.	DOG NO.	WT.	DAILY DOSE	NO. OF DOSES	TIME	RESULTS				REMARKS.
						STOMACH	DUODENUM	COLON	PANCREAS	
I	4I	kg. I4.5	mg. 80-90	3	dys. 3	Erosions	Erosions	Hyperemia	Acute Pancreatitis	Died IO min. after last dose.
2	42	8.5	25-60	5	I3	"	Mucosal Hemorrhages	"	No Change	Died during the night from G-I bleeding.
3	35	8.5	35-80	IO	I7	"	Hyperemia	"	Hyperemia	" "
4	36	I5.9	45-I25	6	6	"	Mucosal Hemorrhages	"	"	Died during the night; gut filled with blood. Pneumonia
5	3[illegible]	I5	45-I25	6	6	"	Hyperemia	"	"	Died during the right from extensive G-I bleeding,
6	44	IO	20	4	4	Hyperemia	"	"	No Change	Died during the night; pneumonia.
7	46	9	25-40	I2	I3	"	"	"	Hyperemia	Died during the night from extensive G-I bleeding.
8	47	8	30	IO	IO	No Change	No Change	No Change	No Change	Died during the night; pulmonary thrombosis.
9	30	7.2	20-25	8	IO	Erosions	Mucosal Hemorrhages	Erosion	No Change	Died during the night.
IO	32	IO.9	40-70	50	50	"	Hyperemia	acute focal colitis	"	Died 30 min. after last dose debilitated.

TABLE II (cont'd)

EXP. NO.	DOG NO.	WT.	DAILY DOSE	NO. OF DOSES	TIME	RESULTS				REMARKS.
						STOMACH	DUODENUM	COLON	PANCREAS	
		kg.	mg.		dys.					
II	33	I0	25-55	5I	5I	Erosions	Hyperemia	Subacute ulcers	Peri-pancreatic fat necrosis	Died during the night.
I2	34	6.7	50-70	2	2	Severe Hyperemia		Hyperemia	Hyperemia	Died from massive G-I Bleeding.
I3	22	6.7	35-50	7	7	"	"	"	"	" "
I4	27	I4	30-50	37	37	Hyperemia	Hyperemia	Acute Ulcers	Peri-pancreatic fat necrosis	Died 2 hours after last dose Fat necrosis in per-duodenal fat.
I5	I7	5.9	I0-35	7I	73	Severe Hyperemia	Hyperemia	Hyperemia	Hyperemia	Died I hour after last dose.
I6	23	7	30-90	69	74	No Changes	No Changes	No Changes	No Changes	Sacrificed.
I7	24	6,5	30-70	20	20	"	"	"	"	Sacrificed.
I8	25	8.5	80-90	5	5	Mucosal Hemorrhages	Hyperemia	Hyperemia	No Changes	Sacrificed I hour after last dose . Profuse rectal bleeding.
I9	26	9.5	80-90	5	5	"	"	"	"	" "

similar to that observed after the injection of mecholyl alone, but the bloody diarrhoea persisted much longer, leading to the death of 7-19 dogs from severe gastro-intestinal hemorrhage (Table 1 - Exp. 2,3,4,5,7,12,13).

The hemorrhagic character of the gastro-intestinal mucosa was more extensive and more severe than in the first group of dogs, but the gross and microscopic changes were essentially similar, although no gastric or duodenal ulcers were encountered in this group.

Here again, the death of 7 of the 19 dogs could be attributed to the profuse gastro-intestinal hemorrhages, of the remainder 4 were sacrificed and the others died of cardiac or pulmonary complications. The results obtained after the injections of mecholyl in both groups of dogs, did not appear to depend on the size of the dose given.

DISCUSSION

The essence of the ulcer problem consists of two distinct but closely related processes; that which initiates the ulcers and that which is responsible for the progression of these lesions to the chronic form. The experiments reported here have demonstrated that the repeated injections of mecholyl can produce a sequence of pathological changes ranging from mucosal interstitial hemorrhages to ulcer formation. The most striking feature of the observations has been the hemorrhagic appearance of the gut which was seen after each injection of mecholyl (Fig. 1).

The microscopic picture of the numerous sections taken from the gastro-intestinal tract points strongly to the fact that the extensive vasodilatory action of the mecholyl on the blood vessels was the main factor in the

pathogenesis of these lesions. From the gross and histological character of the lesions encountered in this study, the sequence of pathological events were probably as follows. The marked vascular engorgement and hyperemia gave rise to stasis, increased capillary permeability, transudation into the tissues and tissue anoxemia which resulted in focal extravasations of red blood cells into the mucosa with superficial necrosis of the overlying mucous membrane, erosions and eventually led to formation of true ulcers. Three additional factors, including trauma, acidity and that of malnutrition probably assisted in the production of the pathological changes observed. Trauma from the vigorous constriction of the stomach and intestines upon the friable engorged and hyperemic mucous membrane has induced mucosal hemorrhages or erosions in man (254). The acute mucosal hemorrhages and erosions which appeared after almost every mecholyl injection, healed rapidly even in the presence of the acid secretion provoked by this parasympathetic drug, and no ulcers were encountered in the group of dogs which had received mecholyl in beeswax injections, which have been shown to prolong the secretion of a highly acid juice in some animals. However after the prolonged repeated administration of mecholyl, the resistance and the regenerative powers of the anoxic mucosa may have been diminished so as to become more susceptible to the digestive action of the acid-pepsin contents of the gastric juice. The acid was therefore not of prime importance in the initiation of the erosions and ulcers, but may have delayed the healing or caused the spreading of mucosal lesions produced by the vascular disturbances.

The dogs in which the gastric or duodenal ulcers were found, were in a poorly nourished state terminally. Several dogs which had received a similar number of mecholyl injections, but were better preserved physically, did not

develop ulcers. These observations are in agreement with those of others (90,369,370,371), who have called attention to the importance of malnutrition in the development of experimental ulcers. It has also been suggested that dietary deficiencies or malnutrition may be important in the initiation and persistence of peptic ulcers in man (372-374).

These experimental results reinforce the concept of vascular changes as the basis of ulcer formation. This concept that the sequence of pathological changes resulting in the formation of erosions and ulcers, were initiated by the marked hyperemia and mucosal hemorrhages is in close agreement with that of Schindler (377), Wolf and Wolff (254) and others.

The results of this present study with mecholyl as well as the observations reported by others after prolonged vagal stimulation (85,86) and after the prolonged continuous administration of drugs which produce vascular spasm or marked vasodilation by direct action on the blood vessels, have demonstrated the importance of repeated profound circulatory disturbances as the main factor in the initiation of acute gastro-intestinal lesions.

The studies on the effects of vagotomy, splanchnectomy, hypothalamic damage in experimental animals, and the frequent association of gastro-intestinal lesions with intracranial disorders in man, have shown that by creating an imbalance of the component of the autonomic nervous system, the resulting alterations in gastro-intestinal motility and the vasomotor state of the blood vessels have produced such marked vascular changes in the mucosa, leading to hyperemia, mucosal hemorrhages, erosions and ulcerations, which rarely, if ever, have gone on to chronicity.

From the observations on their patient Tom, Wolf and Wolff (254,271), have reported that emotional conflicts involving anxiety, hostility and

resentment were accompanied by hyperacidity, hypermotility and hyperemia and engorgement of the gastric mucosa resembling that seen after mecholyl injections, but not as severe. This gastric hyperemia and engorgement became more pronounced and prolonged following intense sustained anxiety, and in this state mucosal hemorrhages and erosions were readily produced. More recently it has been shown by Wolf and Andrus (316) that the hyperemia and engorgement of the stomach mucosa induced by feelings of anger and resentment in a patient with a gastrostomy, failed to occur after vagotomy.

Thus far, the experimental results from this study and from the observations of the numerous investigations by others, have only partially answered the questions on the pathogenesis of chronic peptic ulcer. Although it has been clearly demonstrated that the vascular alterations, leading to local tissue anoxemia and necrosis were the most important factor in the initiation of erosions and ulcers, the lesions produced have rarely if ever gone on to chronicity. However the repeated vascular insults induced by the experimental methods employed by the numerous investigators, although severe enough, were relatively transitory in nature and thus far it has not been possible to produce the sustained reflex nervous disturbances in dogs, such as are known to occur in man dur to long lasting emotional conflicts. Although erosions or acute ulcers occur frequently in man, comparatively few people develop chronic peptic ulcer (375,376,377). Most of these lesions heal rapidly and it has also been shown that chronic peptic ulcers heal as rapidly as the acute ulcers, when the state of sustained emotional conflicts were removed (376).

These observations offer a physiological basis for the neurogenic concept of ulcer formation, and re-emphasize the importance of marked

circulatory disturbances, in the initiation of acute gastro-intestinal lesions, ranging from mucosal hemorrhages to erosions and ulcers. This also fits the psychosomatic concept of ulcer formation, which regards the appearance of ulcers as the pathological development incident to the imbalance of the autonomic nervous system created during sustained emotional conflicts.

CONCLUSIONS

1. It has been shown that erosions or acute and subacute gastric or duodenal ulcers can be produced by the prolonged continuous administration of mecholyl in dogs.

2. The most important factor in initiation of this sequence of pathological changes in the stomach and duodenum was the marked circulatory disturbances produced by the mecholyl which resulted in marked dilation, vascular stasis, mucosal hemorrhages, local tissue anoxemia, erosions and finally led to ulcers.

3. The acid factor was of secondary importance. True ulcers were rarely produced by acid alone, but the presence of acid may have in certain cases delayed the healing or caused spreading of the lesion, initiated by the profound circulatory alterations.

4. These experimental results reinforce the vascular concept of ulcer formation.

5. The observations of these experiments with mecholyl and the numerous and varied experimental observations on the neuro-humeral aspects of the ulcer problem, offer a physiological basis for the psychosomatic concept of ulcer formation.

Appendix A

The Effect Of The Repeated Injection Of Mecholyl On The Colon And Pancreas

Following the prolonged continuous administration of mecholyl, pathological lesions were encountered in the large bowel and the pancreas. Grossly, the mucosa of the colon appeared hemorrhagic and edematous throughout its entire length with focal areas of mucosal hemorrhages, erosions and areas of acute focal colitis (Fig. 11,12). Acute and subacute confluent ulcerations of the large bowel were found in 2 dogs which had received mecholyl in beeswax injections (Fig. 13,14,15). The sequence of pathological changes were thus similar to that observed in the stomach and duodenum, and the histological picture of the numerous sections taken through these lesions indicated that the marked vasodilatory effect produced by the mecholyl was the main factor in the initiation of these lesions.

Gross and microscopic study of the lesions produced in the pancreas revealed a sequence of pathological changes consisting of marked hyperemia, interstitial hemorrhages into the pancreas, focal areas of fat necrosis which eventually led to the production of acute hemorrhagic pancreatitis in 2 of the dogs (Fig. 16-21). The pancreatic changes were more marked after the administration of mecholyl embedded in the beeswax than after the mecholyl alone. The lesions were focal in nature and in several instances focal fat necrosis were encountered in the peri-duodenal, peri-gastric and peri-pancreatic fat without any demonstrable changes in the pancreatic sections taken (Fig. 22).

From the gross and histological character of the changes observed, it is strongly suggested that these lesions were also initiated by the profound

vascular changes produced by the mecholyl. The increase in the pancreatic secretions resulting from the administration of this parasympatheticomimetic drug may also have assisted in the pathogenesis of these lesions.

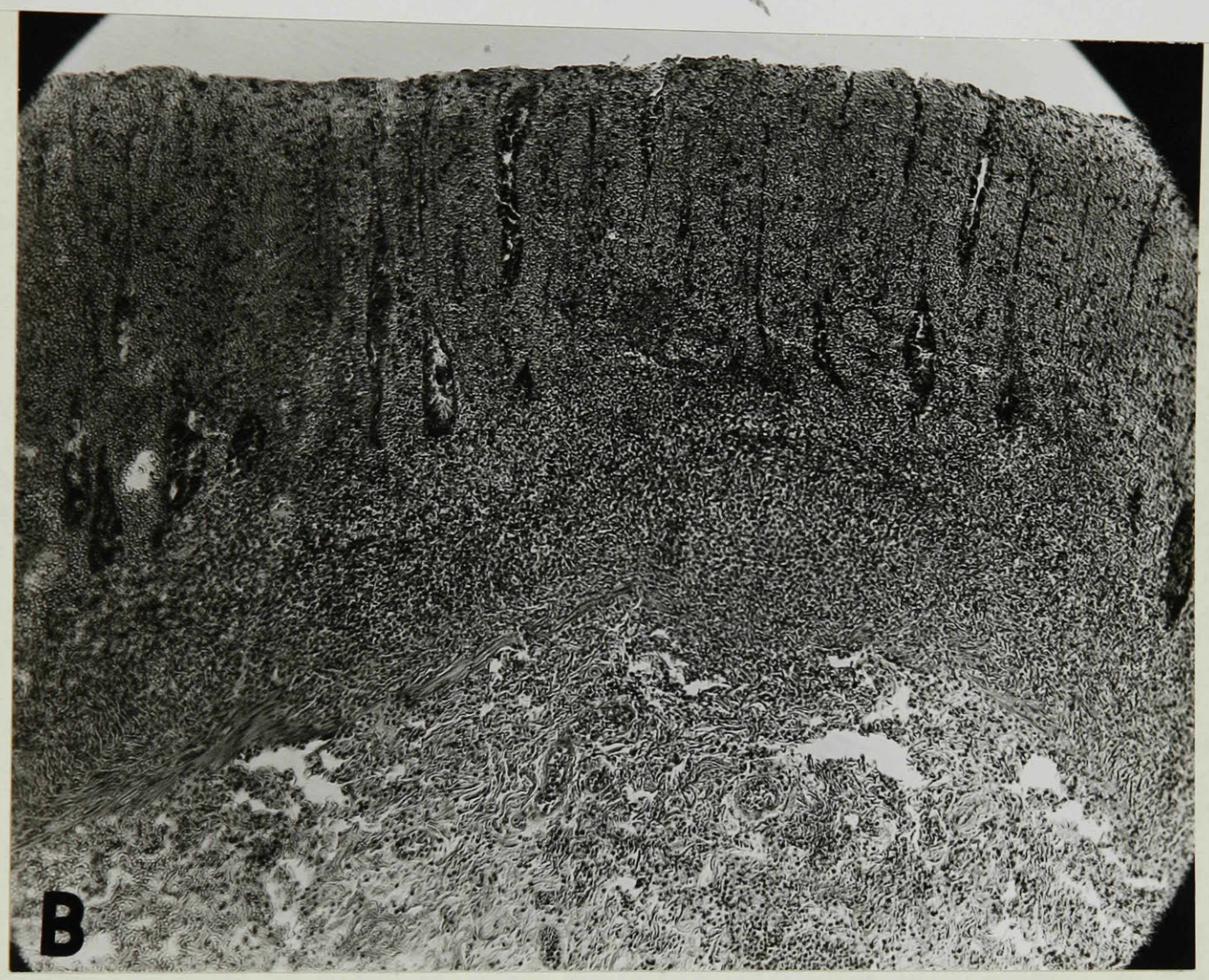


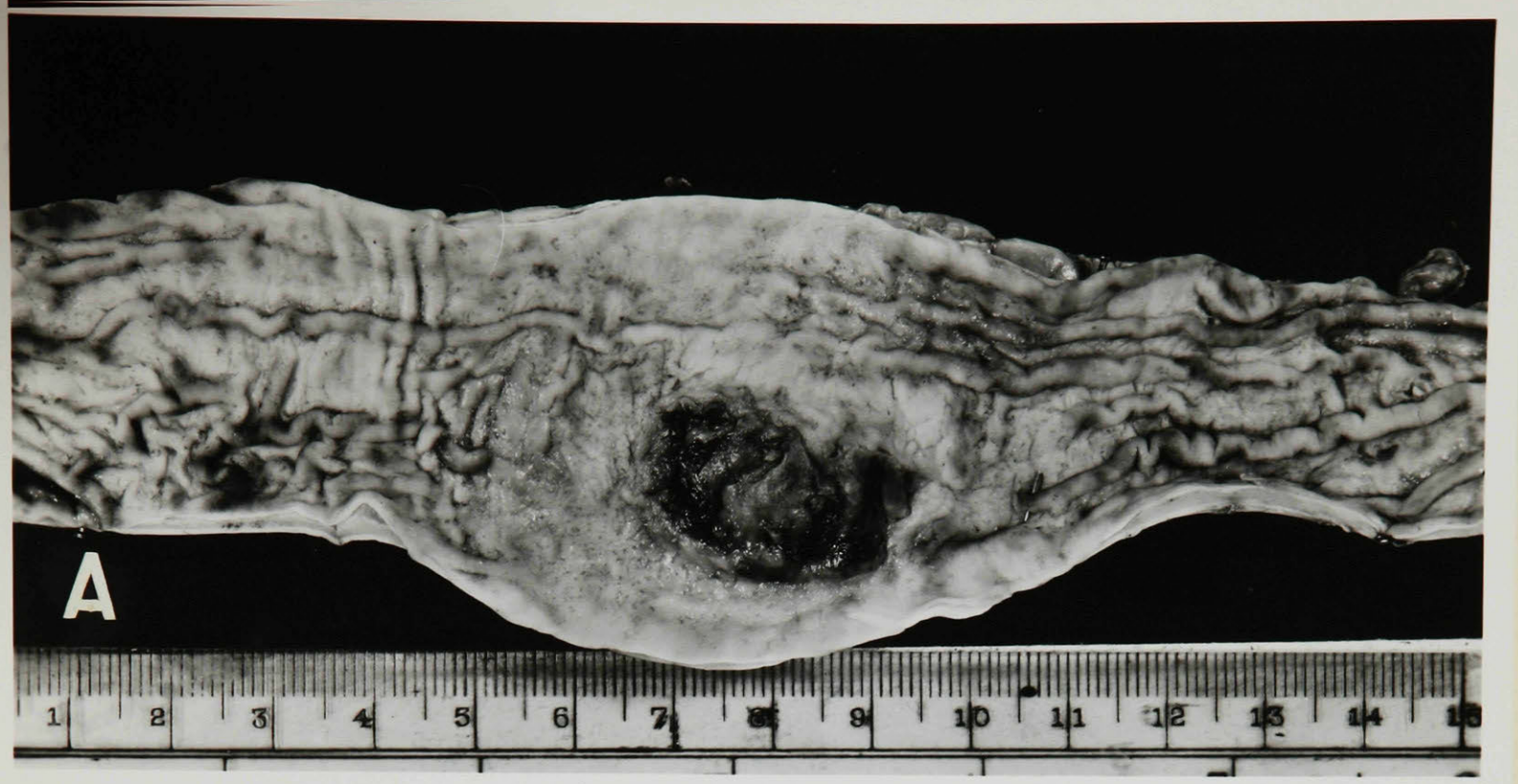
Fig. 11A &B.

A. Colon, showing extensive and massive hyperemia and interstitial hemorrhage. (Dog #13).

B. Microphotograph of portion of above colon showing extensive hemorrhage and necrosis of the mucosa with underlying acute exudative inflammation in the submucosa. Note that the polymorphonuclear infiltration extends through the muscularis mucosa into the edematous submucosa. X 90.

Fig. 12

Acute exudative focal colitis. Note that although the entire mucosa is infiltrated by inflammatory cells, true ulceration of the mucosa has not yet occurred. X 128.



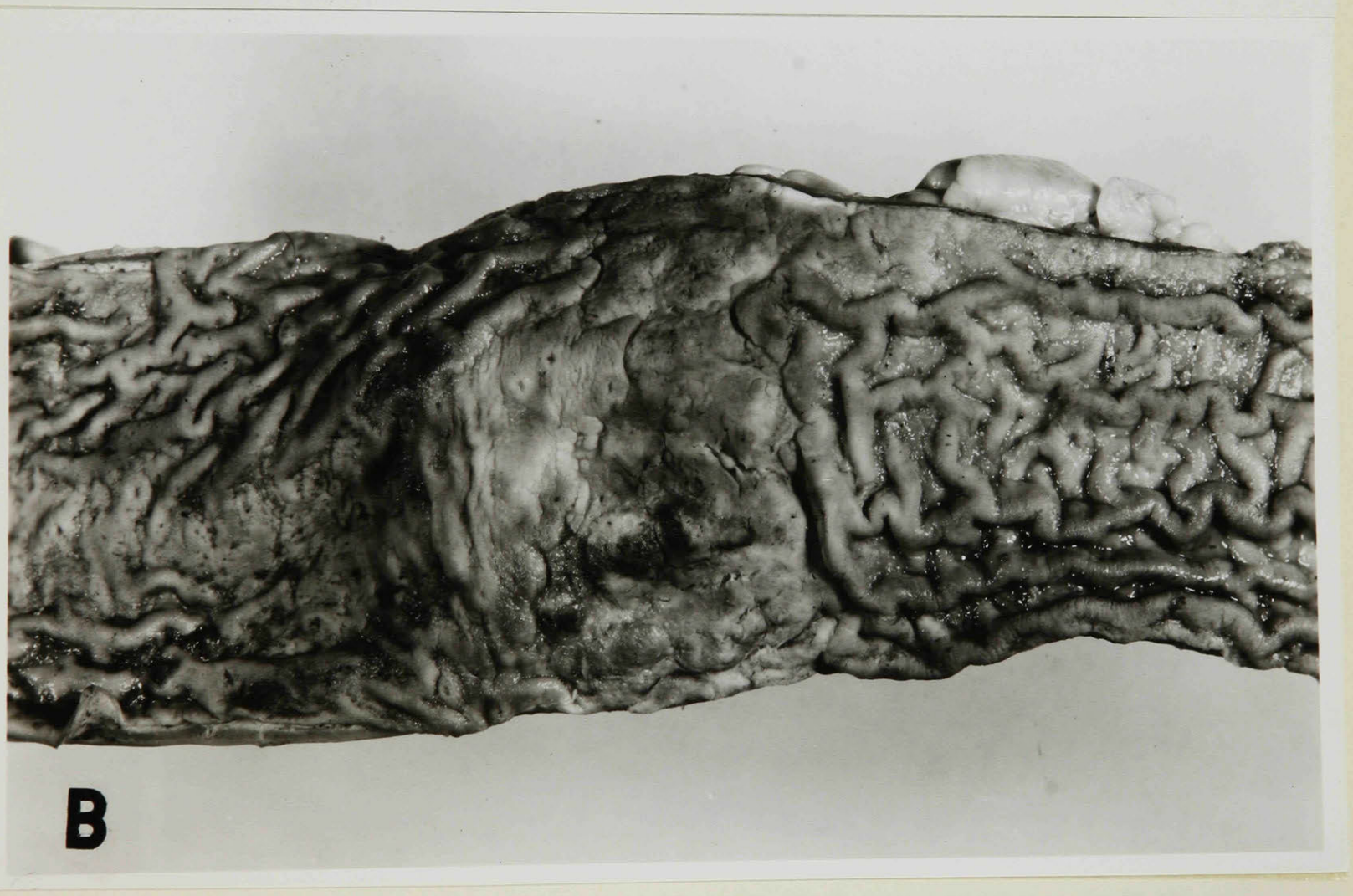


Fig. 13A & B

Distinct ulcers of large intestine, after repeated mecholyl in beeswax injections. (Dogs #44 and #27).

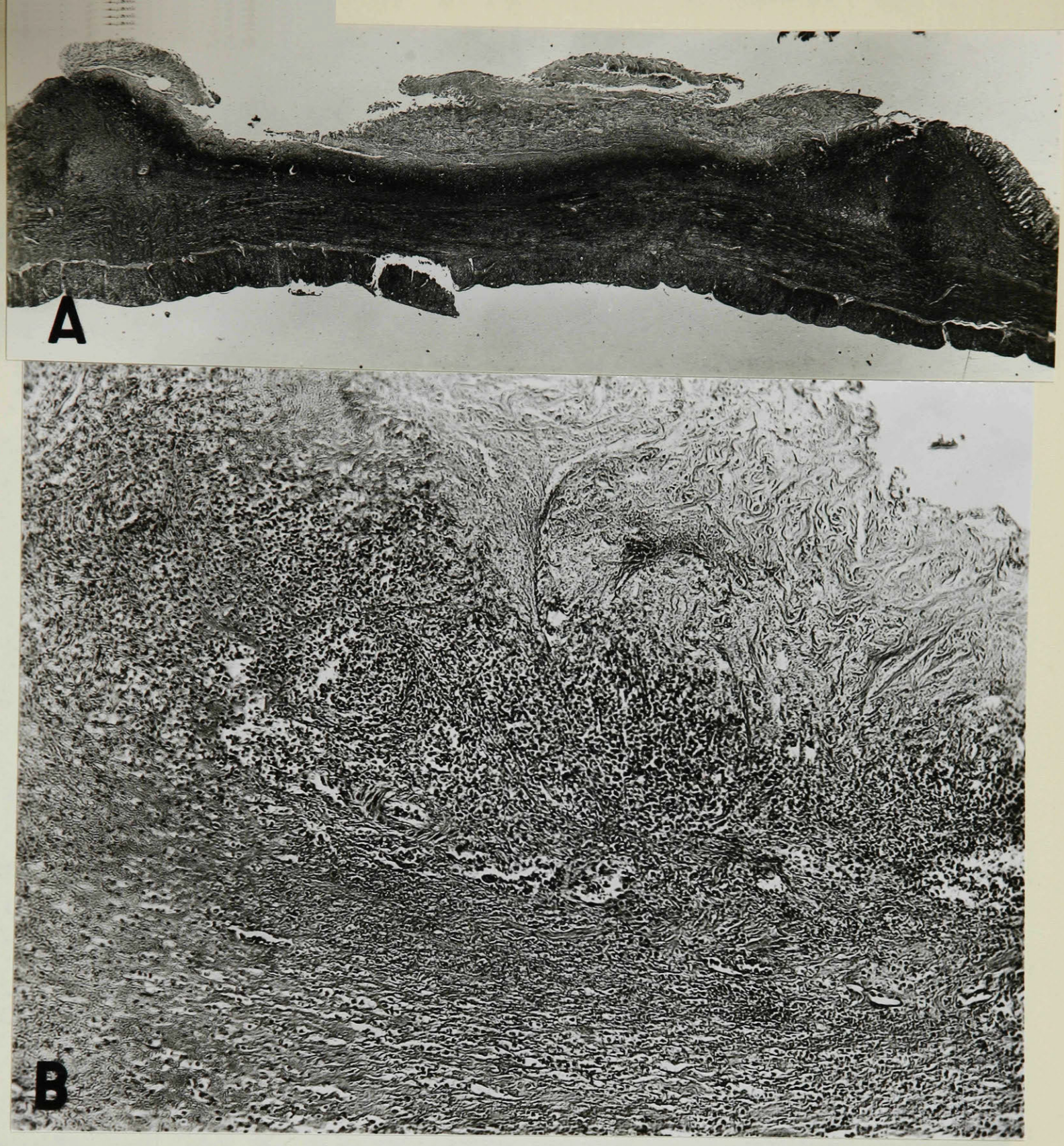


Fig. 14

A. Low power of large subacute ulcer of colon see Fig. 13A. Note that the base is covered with necrotic debris and that the diffuse infiltration of inflammatory cells has extended into the submucosa and muscularis. The ulcer has penetrated to the muscularis. X 7½.

B. Higher power of large ulcer base seen above, showing the extensive involvement by the inflammatory process. Note newly formed blood vessels, lower right. X 121.

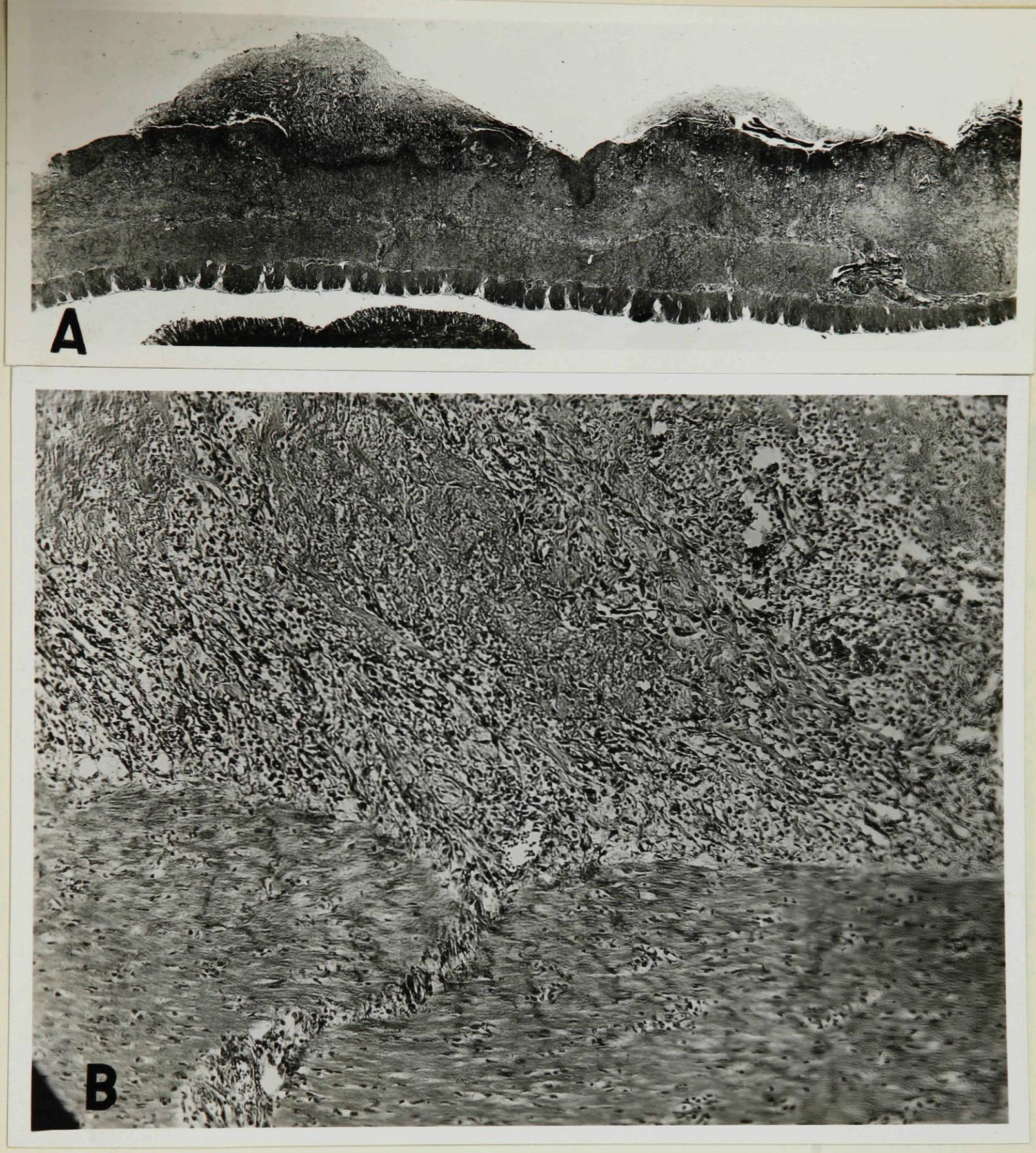


Fig. 15A & B.

A. Low power of large confluent penetrating sub-acute ulcers of colon seen in Fig. 13B. Note the necrotic debris and the diffuse infiltration of inflammatory cells at the base of the ulcer. The inflammatory process has extended to the deeper layers. X $6\frac{1}{2}$.

B. High power view of the base of the large subacute ulcer of colon. The inflammatory exudate occupies the entire submucosa and extends into the muscularis along the course of the penetrating blood vessels. X 110.

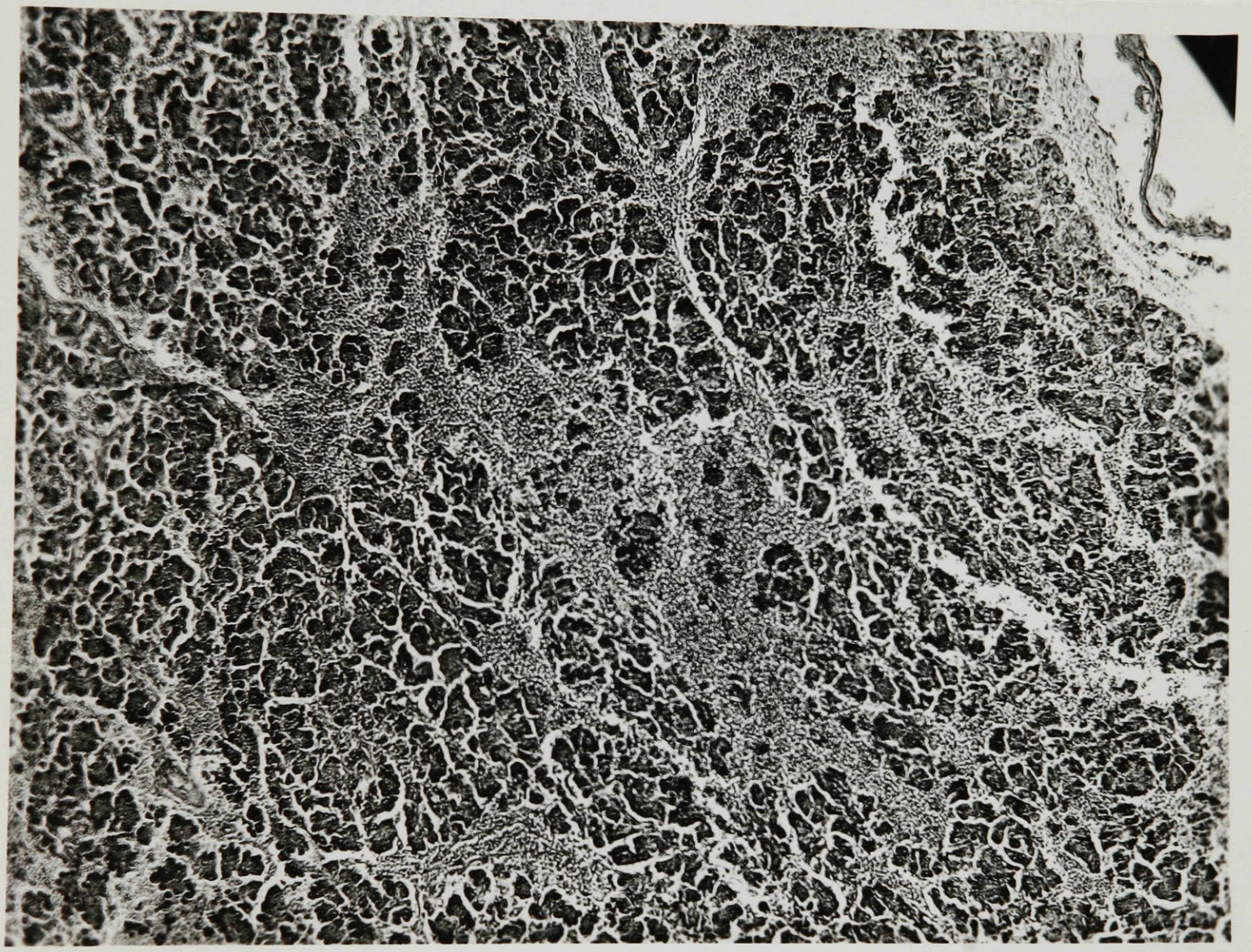


Fig. 16

Extensive recent interstitial hemorrhage into the pancreas. No inflammatory reaction is present and no fat necrosis was seen. (dog #10) X 101.

Fig. 17

Focal interstitial acute hemorrhagic pancreatitis (see arrow). Note the focal peri-pancreatic fat necrosis, upper left (dog #46). X 18.

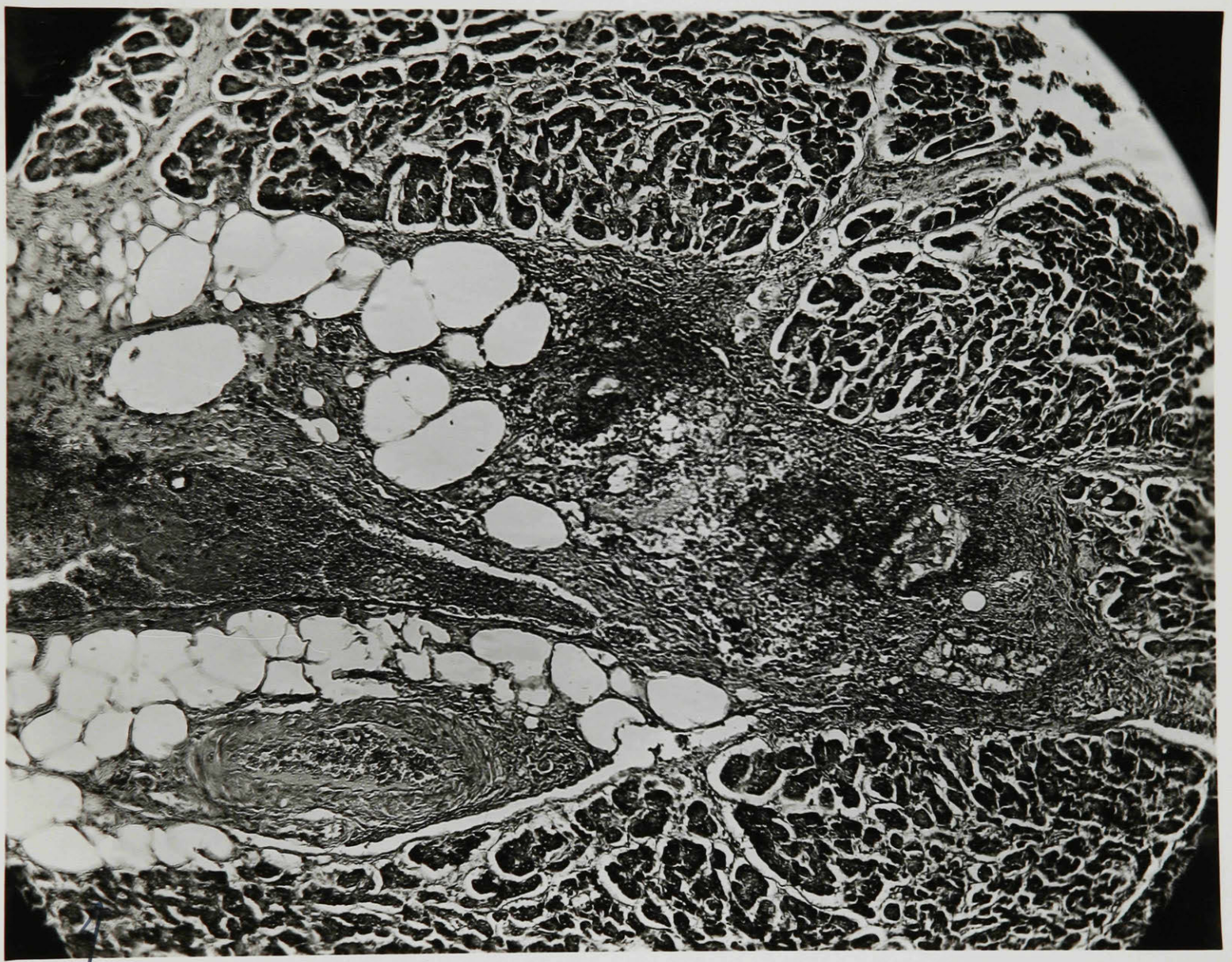


Fig. 18

Higher power view of segment of pancreas indicated by arrow in Fig. 17, showing the interstitial hemorrhagic acute pancreatitis. X 96.

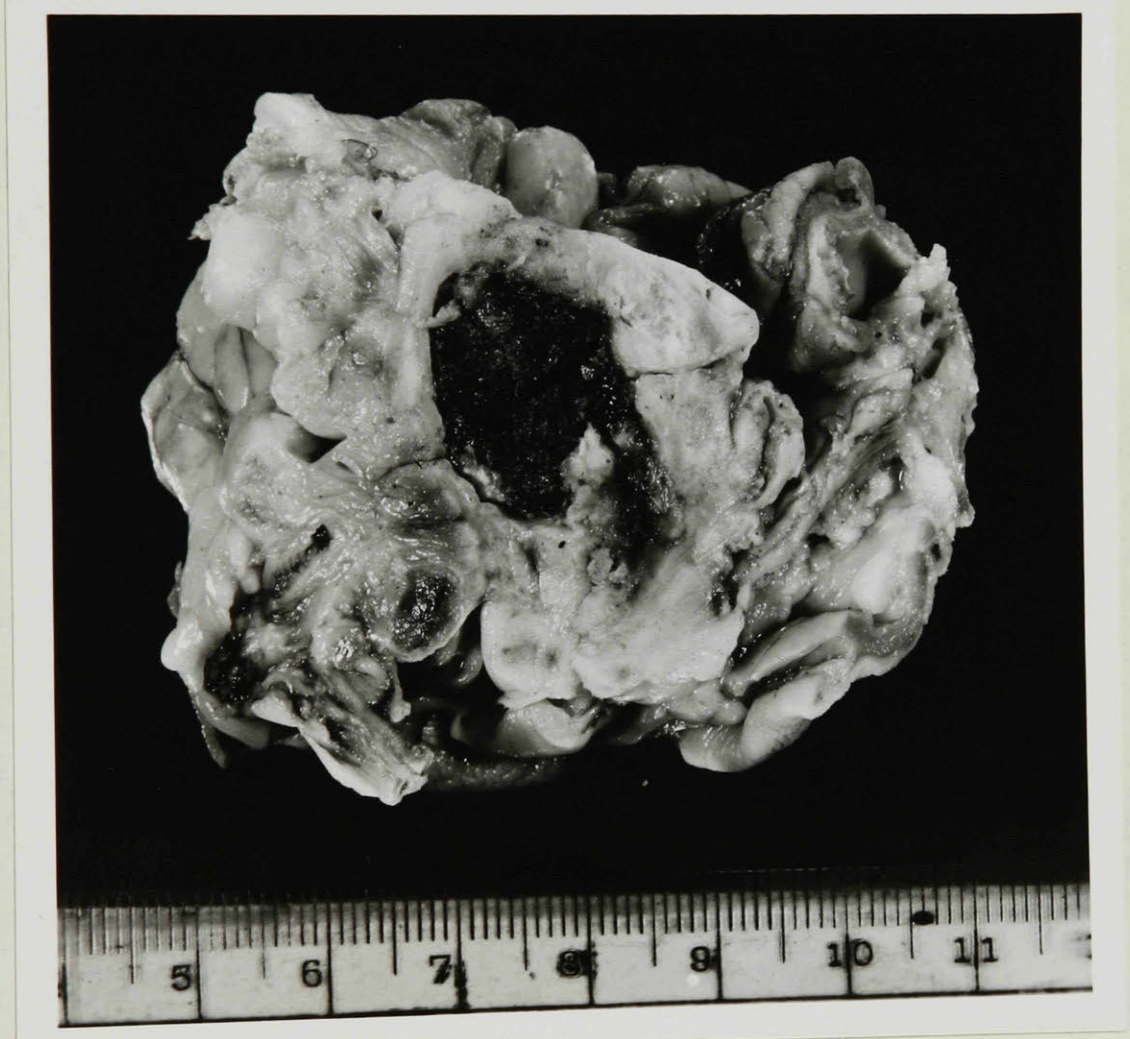


Fig. 19

Cross section of pancreas showing the extensive acute hemorrhagic pancreatitis (dog #41).

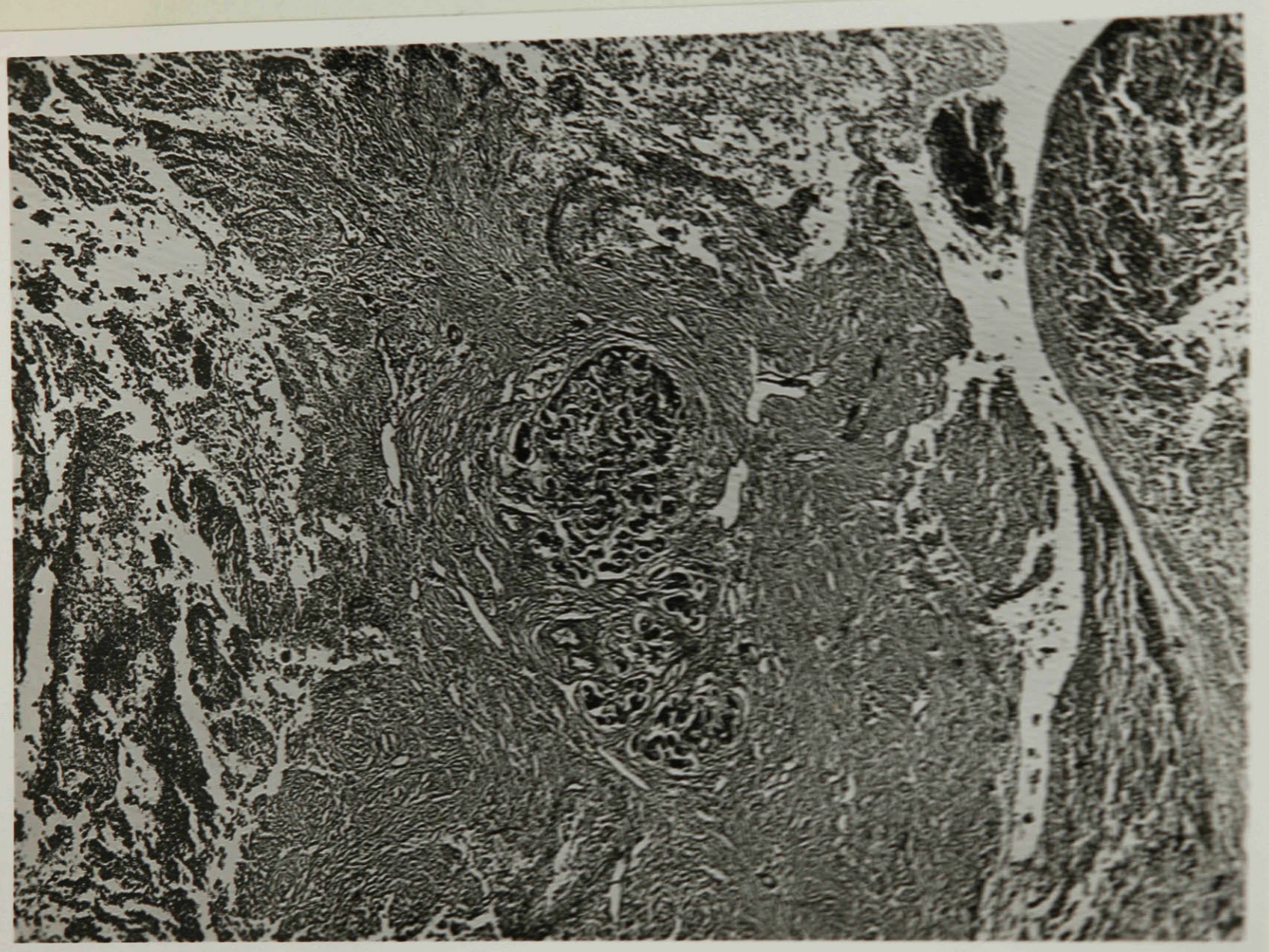


Fig. 21

Higher power of Fig. 20. Section of acute hemorrhagic pancreatic necrosis showing a few residual islands of pancreatic tissue. X 39.

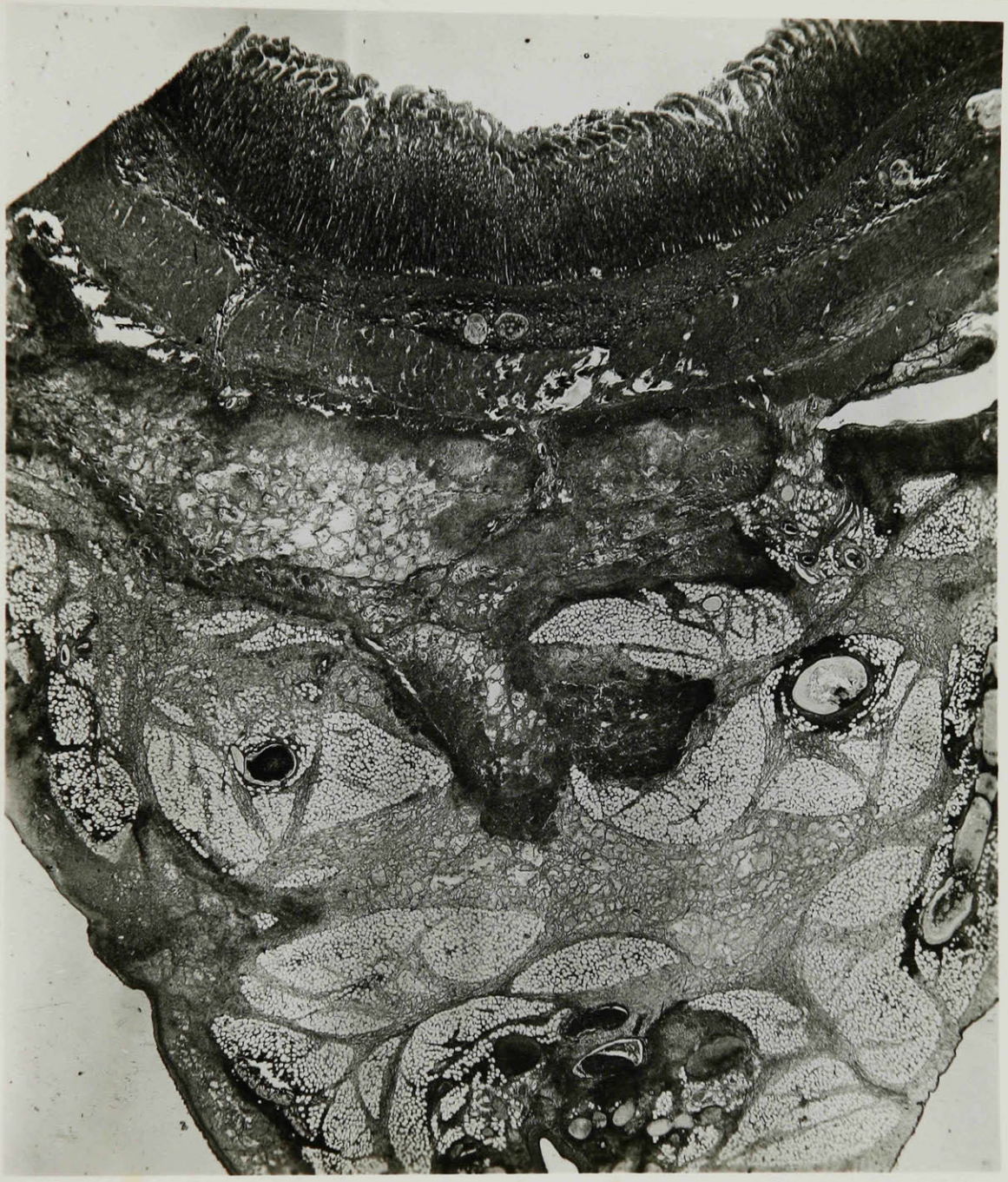


Fig. 22

Extensive fat necrosis in peri-gastric fat. Histological sections of pancreas in this case failed to reveal any pancreatic lesion (dog #29). X 8.

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