

Abdominal Postganglionic Sympathectomy: *

A Method for the Production of an Ulcerative Colitis-like State in Dogs

ROBERT L. BERGER, M.D., ROLF LIUM, M.D.**

*From the Third (Boston University) Surgical Service and Research Laboratory,
Boston City Hospital*

THE ETIOLOGY of chronic idiopathic ulcerative colitis is a multi-faceted, controversial and unsettled issue. In recent years it has been widely regarded as a psychosomatic illness, and autonomic nervous system imbalance has been postulated as a major factor in the causation of the pathologic changes found in the bowel. The precise role of the vegetative nervous system in the etiology of this disease is not clearly understood. One of the major handicaps to the elucidation of the factors and mechanisms important in the causation of ulcerative colitis has been the lack of an experimental model of the disease. To this time there has been no satisfactory reproduction, in laboratory animals, of the bowel changes encountered in the clinical disease.

Motor function and secretory activity in the gastro-intestinal tract is mediated largely via the autonomic nervous system. Clinical experience and experimental evidence suggest that harmonious balance between the sympathetic and parasympathetic divisions is essential for normal digestive and eliminative processes. Conversely, disruption in the equilibrium will result in functional disturbances and eventual organic changes in the gastro-intestinal tract. Popielski,¹¹ in 1903, reported that extirpation of the celiac plexus (sym-

pathetic) in dogs produced severe diarrhea and blood in stools. Laignel-Lavastine⁶ concluded that these changes are caused by the removal of sympathetic influences which normally exercise a restraining action on bowel motility. Cannon,² in 1929, repeated the procedure, but could not duplicate Popielski's results. He concluded that removal of abdominal sympathetic ganglia does not significantly alter digestive and eliminative habits. Lium,⁷ in his investigations of peptic ulceration, added inferior ganglionectomy to the procedure and obtained variable results; some animals exhibited little diarrhea while others had diarrhea to a marked degree.

These somewhat inconstant results obtained with surgical ganglionectomy required further study to perfect the technic in order to achieve a more uniformly reproducible laboratory model. It is our purpose to report our recent results obtained by an expanded, more meticulous, abdominal sympathetic ganglionectomy.

Methods

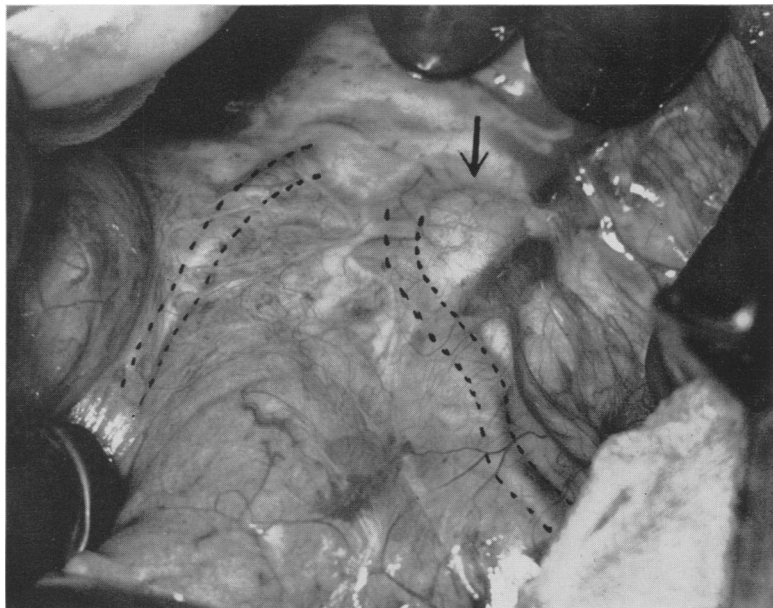
Healthy mongrel dogs of both sexes weighing between 10 to 15 kg. were observed for three days. Animals having diarrhea were excluded from the study. A single, inflated rubber balloon was inserted in the colon and then attached to a Sanborn Polyviso system for tracings of bowel motility. Recordings were obtained before, during, and at various intervals after operation. Several animals had con-

* Submitted for publication Nov. 13, 1959.

** Portsmouth, New Hampshire.

This study was supported in part by the United States Public Health Service (A3512).

FIG. 1. The operative field is exposed. The peritoneum is still intact. The celiac axis and superior mesenteric artery are outlined by interrupted lines. An arrow points to the left adrenal gland. Large interganglionic nerve fibers are seen near the proximal portion of the vessels.



tinuous recordings during the procedure. Intravenous sodium pentobarbital, 30 mg. per kilogram of body weight, was used for anesthesia. In two dogs open-drop ether was used as a control on the inhibitory effects of sodium pentobarbital on bowel motility. All operations were performed under sterile conditions and with endotracheal intubation. The femoral artery was cannulated with a polyethylene catheter and connected to a mercury manometer for continuous blood pressure readings.

With the animal lying on the right side, the incision was started on the left lower chest at a point three centimeters lateral to the spinous process of the twelfth dorsal vertebra. The incision was curved along the upper margin of the twelfth rib toward the mid-line of the abdomen, and hence directly caudad for another five centimeters. The abdominal cavity was entered, and once the bowel, stomach and spleen were packed away the left adrenal gland came into view (Fig. 1). The two most important landmarks, the superior mesenteric artery and the celiac axis, branch off the aorta retroperitoneally, just above the left adrenal gland. The posterior peri-

toneum overlying the two vessels was incised, thus exposing the celiac and superior mesenteric ganglia. They adhere closely to their respective arteries and communicate with each other through numerous fibers which are embedded in the intervening areolar tissues. The ganglia were separated from the arteries and excised together with the areolar tissues containing the sympathetic fibers. Then the superior mesenteric artery and the celiac axis were stripped of their periadventitial nerve fibers. The section of the aorta lying between the two vessels was cleared in a similar manner (Fig. 2).

Attention was turned next to the inferior mesenteric ganglion. The inferior mesenteric artery (posterior mesenteric artery in the dog) branches off the aorta at the level of the fourth lumbar vertebra and runs between the peritoneal leaves of the mesocolon. About four centimeters from its origin the artery is surrounded by the inferior mesenteric ganglion. The lumbar colonic nerve passes through the ganglion. Postganglionic fibers accompany the inferior mesenteric artery distally and supply the colon with sympathetic impulses. The peri-

toneum of the mesocolon was incised close to the colon. The nerve was separated from the artery, traced back to the ganglion, and then excised with the ganglion. At the completion of the procedure segments of the aorta, celiac axis, superior and inferior mesenteric arteries were stripped of their sympathetic periadventitial fibers and the superior mesenteric, inferior mesenteric, celiac and left adrenal ganglia were removed. The previously flaccid bowel assumed, at this stage, a sustained, rigid tone.

Technically the operation is difficult, time consuming, and it requires much practice to develop speed in execution. Utmost patience is demanded in the dissection, for it is very easy to mistake small blood vessels for nerves and to injure vital blood supply to the bowel. Operative mortality had been high during the initial period of our study, but the last 20 consecutive animals survived the operation.

Results

Following operation a fairly constant sequence of events could be observed in all of the 25 animals operated upon. Diarrhea began soon. Bowel movements occurred five to ten times a day and could be produced almost at will by feeding the

dogs. The discharge consisted of mahogany colored, mucus laden, mushy fecal material, or light yellow stools. On the third or fourth day diarrheal movements became more frequent, prolonged and bloody, reaching a peak during the third week. Then there was gradual subsidence and by the end of the fourth week diarrhea had diminished greatly or completely disappeared. The stools remained unformed, the daily fecal output exceeded that of a normal dog, but the discharge no longer contained mucous or blood.

Tenesmus was usually seen on the first postoperative day. It was associated with diarrhea and paralleled its course. When it was severe the animal strained in the position of defecation for as long as ten minutes at a time.

Blood in the stools appeared for the first time on the third or fourth postoperative day. It was usually preceded by tenesmus. The animals expelled a watery or mucous stool, they continued to strain and soon drops of bright red blood were mixed with the feces. Occasionally as much as ten to 20 milliliters of blood were lost with a single bowel movement.

Significant weight loss was another constant finding. The average weight loss aver-

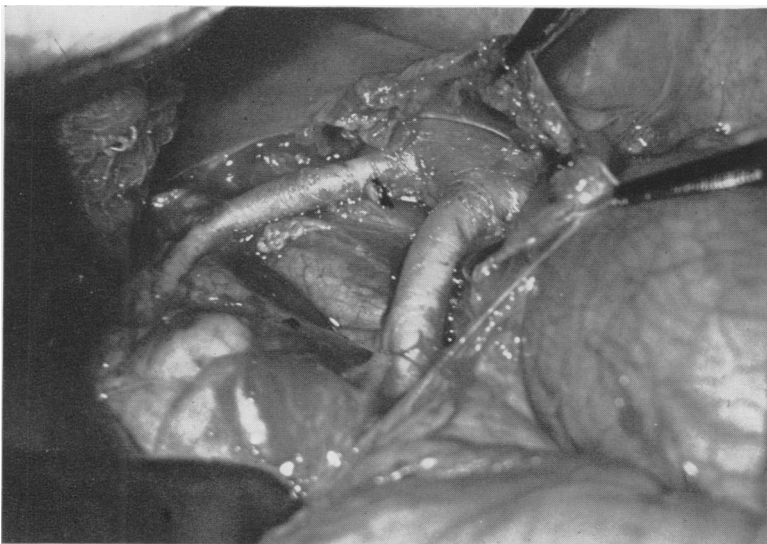
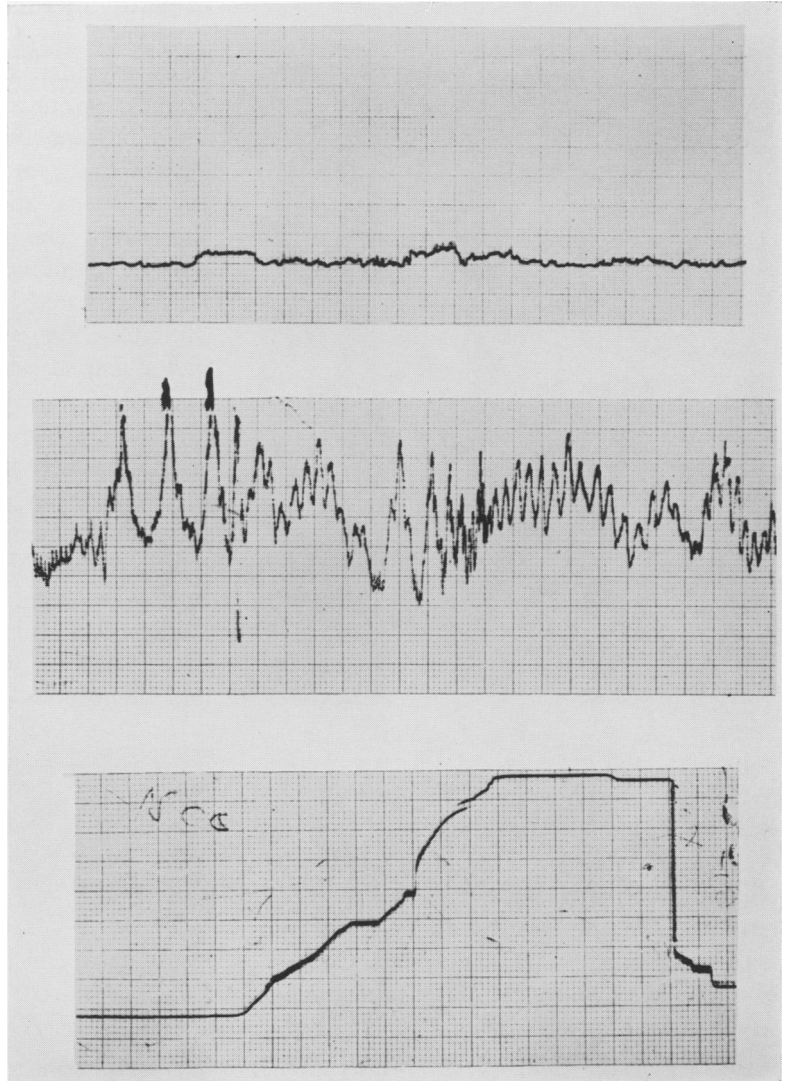


FIG. 2. The stripped portions of the celiac axis, superior mesenteric artery, and aorta are shown. The prevertebral ganglia and interganglionic nerve fibers have already been excised.

FIG. 3. Representative tracings of colonic motility studies. (Speed: 0.5 mm/sec.) Top: Tracing obtained from the colon of a normal dog shows simple waves of low magnitude (Type I). Middle: The baseline is elevated and the excursions are increased in amplitude (Type III). This is a postoperative tracing. Bottom: Another postoperative tracing corresponding to the expulsion of the recording balloon from the colon. The ascending limb represents the beginning of the contraction while the descending vertical line is synchronous with the appearance of the balloon at the anus.



aged 25 per cent of body weight in four weeks. Some of the dogs ate while others refused their food. However, all the dogs lost weight, and they gave the haggard appearance of very sick animals. Once the diarrhea subsided, the dogs seemed to come alive, but during the duration of the study they never regained their normal preoperative weights.

Increase in colonic motility, as measured by the balloon technic, was dramatic. Representative recordings are shown in Figure 3. Immediately following completion of the

ganglionectomy there was marked increase both in phasic and propulsive activity. Powerful propulsive contractions forcibly expelled the recording balloon from the colon repeatedly. Abnormal tracings were obtained for as long as two months after the operation.

No significant change in blood pressure occurred during and immediately following the ganglionectomy.

Pathologic changes were confined to the gastrointestinal tract. The gross lesions were observed through the sigmoidoscope

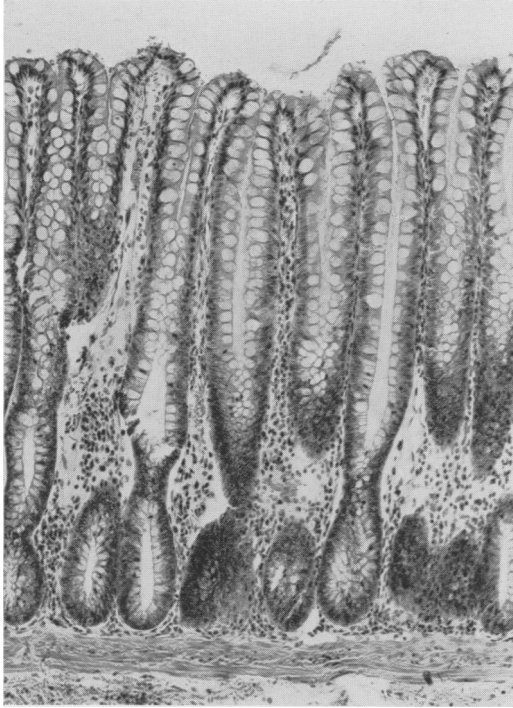


FIG. 4. Colonic mucosa of a normal dog.

and in the freshly removed specimen. The wall of the colon was edematous, the mucosa hyperemic, and it demonstrated petechial hemorrhages with minute superficial erosions. Microscopically, all layers of the wall were swollen and congested. Congestion was most marked in the mucosa and submucosa. Many of the smaller blood vessels ruptured intramurally or into the lumen of the colon (Fig. 5, 6). Occasional submucosal fibrin thrombi were also seen. The erosions were superficial and small with only minimal acute inflammatory reaction. The glands showed evidence of increased secretory activity, and there was marked patchy invasion by chronic inflammatory cells (Fig. 7, 8). Peptic ulceration was found only in one dog.

Discussion

That functional disturbances are often expressed via bowel disfunction and may result in eventual organic lesions is well known to the clinician. Integrative control

of gastro-intestinal functions is exercised on a cephalic level, but local activity is partially executed through the visceral autonomic nervous system. These experiments indicate that the splanchnic sympathetic system exercises a restraining influence on the secretory and the kinetic activities of the bowel. The pronounced changes in the bowel dynamics of these animals were probably facilitated by the sudden cessation of inhibitory sympathetic antagonism to the motor and secretory impulses of the vagus and sacral parasympathetics. We observed a striking spasm of the bowel and marked peristaltic activity immediately following the completion of the denervation procedure. Subsequently, this was manifested in tenesmus and diarrhea, and documented by the tracings obtained from the balloon studies. Abnormally high secretory activity was indicated by the mucus laden stools, and the widely dilated glands seen on tis-

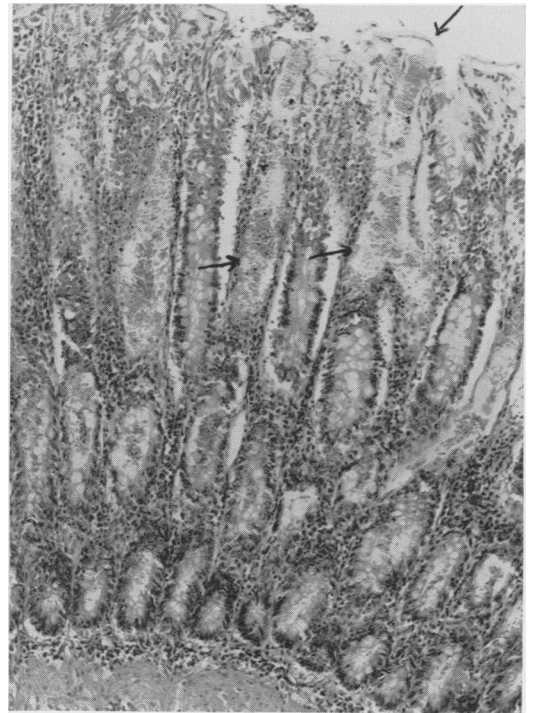


FIG. 5. Appearance of the mucosa one week after the operation. The mucosal blood vessels are dilated and congested. Intraluminal and intramucosal (arrow) hemorrhages are evident.

sue sections under the microscope. These sections also indicated that the blood in the stools originated from the ruptured small superficial mucosal vessels. It is our belief that spasm of the powerful longitudinal and circular muscle fibers allowed for arterial inflow but blocked venous egress. The resultant intermittent local blood pressure changes produced congestion and eventual rupture of small vessels.

The operation of prevertebral sympathectomy produced constant, uniform and predictable results in our laboratory. It provides a standardized experimental preparation for the study of gastro-intestinal diseases, the effects of antispasmodics and the role of the sympathetics in the control of the splanchnic vascular bed. In the appraisal of the preparation, however, there are two immediate problems confronting us.

1. This denervation is a postganglionic one and produces an effect quite distinct from that of a preganglionic sympathectomy. Splanchnicectomy performed by us on dogs and in patients studied by Bingham and associates,¹ did not significantly alter preoperative bowel habits.

2. Spontaneous recovery from the diarrhea occurred almost invariably within four to five weeks. Whether this was due to nerve regeneration, increased sensitivity of end plates to circulating epinephrine, or

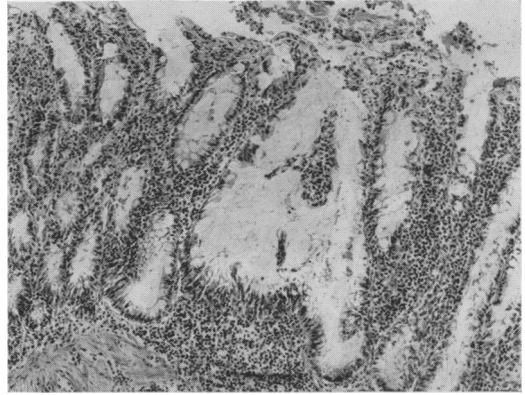


FIG. 7. Increased secretory activity is highlighted in this section. There is a moderate invasion by round cells.

development of an inherent tone by smooth muscle fibers is not clear.

The precise relationship of this experimentally produced illness in dogs to human ulcerative colitis remains to be evaluated. The dogs demonstrate several features which resemble strikingly the human disease. Clinically they experience, for a limited time, an ulcerative colitis-like syndrome, and the mechanism that we observed is compatible with the prevailing theories of pathogenesis. According to this, autonomic imbalance triggered by emotional factors result in abnormal gastro-intestinal motor, secretory, and vascular activity. The combined effects of these three altered factors produce the primary vascular lesion of early ulcerative colitis. Our observations suggest that the evolution of the vascular lesions are secondary to compression of blood vessels by spasm of mural musculature. Once the vascular lesions are established, other as yet unknown factors come into play, provoke the acute inflammatory reaction, and thereby contribute to the development of the chronic disease.

The work of several investigators is of interest in this connection. Grace, Wolff and Wolf⁴ observed the colons of patients with ulcerative colitis through colostomies. In stress situations the exposed colon exhibited sustained propulsive contractions,

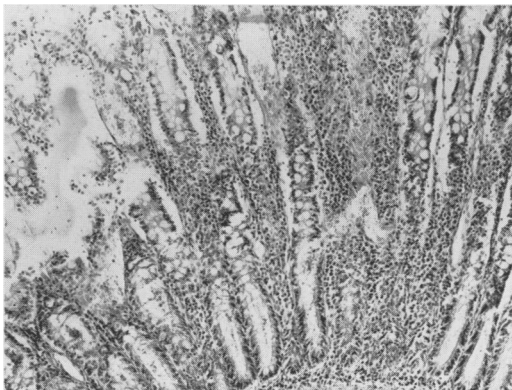


FIG. 6. Shows mucosal hemorrhages with considerable inflammatory reaction.

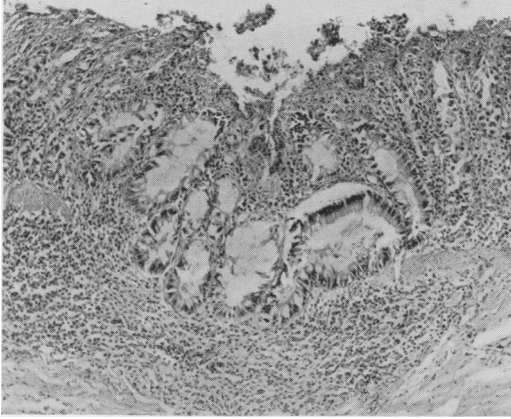


FIG. 8. Normal architecture is markedly altered by hypersecretion, inflammatory reaction, and superficial erosion.

hyperemia, and hypersecretion. Mucosal ulcerations and petechial hemorrhages were caused by prolonged hyperactivity. Wener and Polonsky¹³ studied a young woman with long standing ulcerative colitis by the same method. They noted that prolonged hyperemia, provoked by emotional stress, led to an edematous friable mucosa with petechial hemorrhages. Vigorous contractions, were followed by frank bleeding and superficial ulcerations. Lium's^{8,9} experimental observations substantiate the significance of spasm. He prepared viable colonic explants in dogs. Severe muscular spasms in the explants were induced by mechanical means, and this was invariably followed by copious mucous secretion, petechiae, bleeding and ulcerations. It is also known from pathological studies that ulcerative colitis usually begin in the rectosigmoid area where the strongest muscles of the colon are located. Furthermore, Monaghan,¹⁰ who followed the evolution of the lesions by serial sigmoidoscopy, noted only minimal edema and petechiae early in the disease. The edema progressed in severity, and ulcerations appeared at a later stage. Purulent ulcers indicated advanced disease. These observations again underline the fact that the initial lesion is a vascular one.

Observations on colonic motility also implicate disturbed autonomic activity in the pathological physiology of ulcerative colitis. Studies with the balloon recording system by several authors reveal three distinct patterns of activity in the distal colons of healthy subjects.^{3,12} Type I and II waves are nonpropulsive, simple contractions of low amplitude. Type III waves again represent churning contractions. They are composed of Types I and II, superimposed on a heightened baseline. In a large percentage of patients with ulcerative colitis these physiologic contractions are replaced by a powerful mass propulsive wave (Type IV).⁸ This pattern is not seen in normal individuals, but can be produced in both man and dogs by the injection of parasympathomimetic agents. The expulsion of the recording balloon from the dogs' colons in our experiment was accompanied by tracings similar to Type IV waves; another suggestion of kinship between the experimental and human disease.

As is often the case, artificially-induced conditions in animals can only at best simulate the naturally evolved diseases of man. Therefore, the insight into human diseases obtained in the laboratory is only partial, and not always valid. The problem is even more pronounced in the psychogenic illnesses. Furthermore, the canine colon differs from the human in that it is devoid of the longitudinal taeniae, possibly a crucial anatomical structure in the causation of ulcerative colitis. Nevertheless, these dogs exhibited an ulcerative colitis-like disease, as a result of artificially induced autonomic disturbances. Other still unestablished etiologic factors (infectious, allergic, biochemical) probably combine forces with the autonomic nervous system in the evolution of chronic idiopathic ulcerative colitis.

Summary

1. Bloody and mucous diarrhea, tenesmus, weight loss and structural changes

mainly in the colon were induced in dogs by operative prevertebral ganglionectomy.

2. The technic of prevertebral ganglionectomy is described.

3. The role of the autonomic nervous system in functional gastro-intestinal diseases and ulcerative colitis is discussed.

Acknowledgment

We are indebted to Dr. John J. Byrne, Director, Third (Boston University) Surgical Service and Research Laboratory for his assistance and guidance.

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