AGNOGENIC VENOUS MESENTERIC THROMBOSIS*

FRANK B. BERRY, M.D., AND JAMES A. BOUGAS, M.D.

NEW YORK, N. Y.

FROM THE DEPARTMENT OF SURGERY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK

WITH THE INTRODUCTION OF THE ANTICOAGULANTS, surgery acquired valuable agents in the prevention and treatment of accidents and conditions associated with increased coagulability of the blood. Mesenteric thrombosis, always a terrifying abdominal emergency, usually finds both patient and surgeon unprepared for surgery of great magnitude, but its high operative mortality is still considerably lower than when operation is not performed. Diagnosis is difficult, and surgery frequently too long delayed, and this hesitancy still persists in spite of the advance in therapy afforded by the anticoagulants. In the past, authors have considered both the arterial and venous forms together. We wish, however, to focus entirely upon the venous variety and have restricted this still further so as to exclude all venous thromboses with known cause, which are quite distinct from primary agnogenic venous mesenteric thrombosis.

HISTORICAL REVIEW

Mesenteric thrombosis was first described by Antonio Beniviene in Florence in the latter part of the 15th century,[1] and although Joseph Hodgson reported a case from Guys Hospital in 1815,[2] it was not until Tiedman,[3] in 1843, and Virchow,[4] in 1847 and 1854, described this condition that the medical profession really became interested. In 1895, J. W. Elliot[5] of the Massachusetts General Hospital, Boston, reported the recovery of a patient following the "operative relief of gangrene of intestine due to occlusion of the mesenteric vessels." Dr. Elliot has left us an excellent description of what was probably a venous occlusion. The patient was an otherwise healthy male in his mid-forties who was operated upon early and made an uneventful recovery in the absence of any of our modern supportive therapy.

Since the turn of this century, numerous articles have appeared. In 1904 Jackson, Porter, and Quimby[6] collected 214 cases of arterial, venous and mixed thrombosis, 26 of which were new. The ages of the patients varied from *one month to 90 years.* In 1909 Welch wrote on mesenteric thrombosis in Allbutt and Rolleston's Medicine.[7] In 1913 Trotter[8] surveyed 360 cases with an age range between 30 and 70. The correct diagnosis was made preoperatively in 3.6 per cent and the operative mortality was 63.8 per cent; the thrombosis was described as venous in 41 per cent. In 1935 Donaldson and Stout[9] discussed venous mesenteric thrombosis as an entity separate from

* Read before the American Surgical Association, Colorado Springs, Colorado, April 19, 1950.

arterial thrombosis. They suggested that the venous form was "a slowly progressing condition" and in the early stages "most thoroughly amenable to surgery." Also in 1935, Warren and Eberhardt[10] presented 73 cases from the literature and two of their own of venous thrombosis. In discussing the etiology they listed four types:

1. Known infection, as thrombophlebitis, appendicitis, pelvic abscess, peritonitis, sepsis.

2. Hematogenous causation, as blood dyscrasias or changes known to predispose to thrombosis, such as splenic anemia and polycythemia vera.

3. Trauma of any sort to mesenteric veins.

4. Mechanical causes, such as portal stasis, pressure from tumors, adhesions and bands, volvulus.

In 1938 Whittaker and Pemberton[11] reported 60 cases of mesenteric thrombosis from the Mayo Clinic with 57 deaths. The youngest was 13 and the oldest 83 years of age; 27 per cent were venous.

Following the introduction of the anticoagulants the record has changed for the better, though progress has been slow. Murray,[12] in 1940, reported six cases of mesenteric thrombosis with two deaths. All were operated upon with resection of the involved area, 45 cm. to 7 meters, and all were treated with heparin postoperatively. D'Abreu and Humble[13] reported a similar case in 1946, and also described a rather ingenious heparin tolerance test which they employed.

Closely associated with the whole problem of mesenteric thrombosis is consideration of the blood circulation in the mesentery. This was brought to attention by Mayo-Robson in 1897,[14] and Wilms[15] in 1901, when they reported ligation of the superior mesenteric vein near the entrance of the right colic vein for wounds of the vein, with recovery of both patients. Twenty years before Solowieff[16] had shown that individual staged ligation of the superior mesenteric, splenic, and portal veins in dogs did not cause death. More recently Scott and Wangensteen[17]; Boyce and McFettridge[18]; and Noer and co-workers[19-21] have all studied this problem in its various phases; and Laufman,[22] working with heparin, found that in experimental occlusion of the superior mesenteric vein in dogs, or ligation of the vasa recti, there was a higher survival rate when heparin was used.

CASES

With this as a background we present 13 instances of agnogenic venous mesenteric thrombosis in 12 patients. Eleven of these cases are from the records of the Presbyterian Hospital, New York,* over the past 22 years. During this period 53 cases were classified as venous mesenteric thrombosis.

* The authors wish to thank Drs. W. B. Parsons, and G. C. Hennig and E. B. Self for permission to include private patients; Drs. J. H. Mulholland and V. Carabba of Bellevue Hospital, and the Commanding Officer of Gorgas Hospital, for permission to include these cases.

Of these only 11 are true agnogenic; ten patients comprise this group as one had two episodes with a free interval of 32 months between attacks. One other, who developed the disease while in terminal coma from a brain tumor, is not included. These 11 cases occurred in 54,000 surgical admissions in this period, an incidence of 0.02 per cent. In the other 42 cases the possible causes are given, as listed, in Tables I and II.

TABLE I.—*Listed Causes of Venous Mesenteric Thrombosis, Other Than Agnogenic Variety, in 42 Patients, Presbyterian Hospital.*

Mechanical Obstruction	Intra-Abd. Tumors	Intra-Abd. Suppuration	Trauma
Cirrhosis..... 4	CA pancreas..... 4	Appendicitis..... 7	Sup. mes. vein... 1
Cong. portal malform 1	Mesothelioma..... 1	Chr. ulc. colitis with	
Volvulus..... 2	CA colon..... 3	abscess..... 1	
Strang. hernia..... 1	CA liver..... 1	Pelvic abscess..... 1	
Adhesions..... 5	Carcinoid..... 1	Postop. sepsis..... 2	
Schistosomiasis..... 1	Lymphosarcoma..... 1	Perf. viscus..... 1	
	Leiomyoma bowel... 1	Pancreatitis..... 1	

It may be of interest to record here that in 1932 McIver[23] reported from the Massachusetts General Hospital that 3 per cent of 355 cases of intestinal obstruction were caused by vascular occlusions in the mesentery.

Case 12 is from the Third Surgical Division, Bellevue Hospital,* and Case 13 is a patient from Gorgas Hospital,* Panama, seen by the senior author.

Four of these patients survived, one from two episodes. In all, operation with resection of the involved area was performed and anticoagulant therapy

TABLE II.—*Agnogenic Venous Mesenteric Thrombosis; Time of Onset to Admission and Surgery; Outcome.*

Case	Age	Sex	Onset: To Admission	Onset: To Surgery	Outcome
1.....	40	M	4 D	8 D	R
1A.....	43	M	6 H	30 H	R
2.....	30	F	40 H	62 H	Dead
3.....	39	M	7 D	7 D, 17 H	Dead
4.....	74	F	24 H	25 H	Dead*
5.....	58	F	14 D	None	Dead*
6.....	36	M	8 D	8 D	Dead
7.....	73	F	7 D	7 D	R
8.....	73	M	7 D	None	Dead
9.....	43	M	14 D	21 D	Dead
10.....	52	F	15 D	23 D	R
11.....	40	M	11 H	15 H	R
12.....	50	M	4 D	None	Dead

* Thrombosis portal vein. D = Days. H = Hours.

was used following surgery in four of the five successful cases. Although the histories are given in detail and the salient points shown in Tables II to VI, two of the patients are of unusual interest: Patient B. H., Case I and IA (778189) had seven Presbyterian Hospital admissions for migrating thrombophlebitis of his pelvic, arm and leg veins from 1935 to 1938, and from 1939

* See footnote on page 451.

to 1945 he was followed in the Clinic. After his eighth admission, his first attack of mesenteric thrombosis, he remained perfectly well for 32 months. On his ninth hospital admission, the second episode of mesenteric thrombosis, his condition was still sufficiently obscure that operation was delayed 24 hours. Anticoagulants were given during this second postoperative period and for the past two and a half years he has been kept on a maintenance dose of Dicumarol without further symptoms.

Patient A. R., Case 11 (BH 53967-48), had had three hospital admissions during the preceding 14 years for thrombophlebitis of the lower extremities, and home treatment for several minor attacks. Also, during his first hospital admission he had suffered a pulmonary infarction. His family history revealed that he had three brothers, and all of them had had repeated attacks of thrombophlebitis. Furthermore, two of his brothers had been operated upon for venous mesenteric thrombosis, one of whom recovered. The other, who also gave a history of a pulmonary infarction, made his own diagnosis, but, in spite of this, operation was delayed for 48 hours, no anticoagulant therapy was given, and he died on the second postoperative day. In view of this extraordinary family history, the patient thought that he too had a mesenteric thrombosis, which was proved at operation four hours after admission.

Case 1 and 1A.—B.H., 778189 was a male, age 43. During a 3-year period from 1935 to 1938 a post-office clerk afflicted with migrating thrombophlebitis was admitted to the Presbyterian Hospital 7 times with an average stay each time of 14 days. His exacerbations were treated with bed rest, elevation, fever therapy, and ligation of the right internal saphenous vein. Other veins involved were the short saphenous, femoral, common iliac, median, basilic, and ulnar. In the interval between admissions the patient continued to have swelling and discomfort in his legs and was thereby prevented from pursuing regularly his duties as clerk. He wore elastic stockings at all times. For 8 weeks at one time he remained in bed under the care of his personal physician for "swelling of the right leg."

From 1939 to 1945 the patient was followed closely in the clinic where he received multiple injections to the veins of the lower extremities.

In July 1945, 2 months after his last clinic visit, he was admitted for the eighth time. He complained of crampy, intermittent epigastric pain which had its onset 4 days prior to admission. Gradually the pain became steady and involved the entire abdomen, being, however, slightly more severe on the right than on the left. Anorexia and nausea were present early but vomiting occurred only on the day preceding admission. Bowels had moved regularly until the onset of pain. Enemata on each of the 4 days before admission had produced light tan stools with no gross blood. There had been no previous gastro-intestinal, genito-urinary, or cardiorespiratory symptom.

Physical examination revealed general abdominal tenderness, worst in the left lower quadrant. A slight resistance to palpation was present over the entire abdomen. A mass, thought to be the descending colon, was felt in the left abdomen. Peristalsis was diminished. Temperature was 100, WBC 13,000 (75 per cent neutrophiles), urinalysis negative. Roentgenograms of the abdomen showed some "gas filled, but not distended, loops of intestine on both sides of the abdomen . . . no more than usually seen." Barium enema one day later yielded no abnormal findings. Forty-eight hours after admission there was a slight distension with spasm and acute tenderness, direct and rebound, localized in the left lower quadrant, where a tender mass could be felt. Diverticular abscess was considered the most likely diagnosis.

On the morning of the fourth hospital day signs of shock appeared and there was blood in the fluids obtained from the stomach by constant suction. The WBC was 29,400 with 86 per cent neutrophiles. Roentgenograms of the abdomen showed increased density but no fluid levels and no free air. Preoperative diagnosis was peritonitis with possible left lower quadrant abscess from a bowel perforation. One observer felt that mesenteric thrombosis was present.

Operation. At celiotomy, when the peritoneal cavity was opened, sanguineous fluid gushed out as tension was relieved. A dark purple loop of jejunum presented in the wound. This loop measured 5 cm. in diameter and shaded from dark purple to normal pink both cephalad and caudad. No internal hernial ring could be found. The process was considered a mesenteric thrombosis. From a point 22 cm. beyond the ligament of Treitz 184 cm. of jejunum was resected and end-to-end anastomosis performed.

Pathology. The specimen consisted of 184 cm. of dark small intestine with an average diameter of 4 cm. It was odorless, without luster, and edematous. Ten centimeters at each end were cyanotic and the central segment was black. The mesentery was edematous and exhibited thrombosis of vessels. Thickness of the intestinal wall averaged 4 mm. in the cyanotic portions and 6 mm. in the black segments. There was a sharp line of demarcation between cyanotic and black areas. Numerous irregular ulcerations were evident in the black section. The lumen contained thick, dark, hemorrhagic material.

Microscopic study of the mesentery showed the veins to be filled with recent thrombi. There was no evidence of perivascular inflammatory infiltration, but there was evidence of recent fibroblastic proliferation. Numerous hemorrhagic areas were seen in the mesenteric fat.

Section of the black zone of the intestine showed gangrene. There was degeneration of the cells in all layers. The mucosal remnants were covered by a thick blanket of amorphous eosinophilic material, blood, inflammatory cells and blood pigment. All tissues showed edema, hemorrhage and recent thrombi in all veins.

Sections from both ends of the specimen showed edema and engorgement of the blood vessels, but nothing else of note. Diagnosis of venous mesenteric thrombosis was made.

Course. The postoperative period was marked by severe abdominal distension for 10 days and a sustained temperature of 102 to 104 for 4 days with a single sharp rise to 105. Two weeks after operation the patient's course became smoother and on the twenty-sixth day after operation he was discharged.

During the next 2 years the patient was followed carefully in the clinic, and one roentgen ray examination showed ". . . no evidence of filling defect, delay or obstruction at the site of the recent jejunal resection." He remained in good health until 1948, 3 years later.

Re-admission. He was re-admitted on March 22, 1948, at 8:00 A.M. with a history of mid-epigastric crampy pain one week earlier and of 3 days' duration with spontaneous remission. While at work as post office clerk during the night, 6 hours before admission, the patient noticed the onset of intermittent crampy pain most severe at a point to the right of the umbilicus. He had no nausea or vomiting but the pain was severe enough to cause him to "double over." He had a "normal bowel movement" 8 hours and a brown fluid stool 4 hours before admission.

At the time he was first seen examination revealed tenderness in the right upper quadrant with minimal rebound tenderness. There was no spasm. Peristalsis was diminished. No mass was outlined . . . WBC was 12,500 with 82 per cent neutrophiles. Four-position films of the abdomen were not contributory.

to 12,500 with 82 per cent neutrophiles. Decision to operate came with the diagnosis
to 12,500 with 82 per cent neutrophiles. Decision to operate came with the diagnosis of either acute appendicitis or mesenteric thrombosis.

Operation. Thirty hours after admission celiotomy was performed under ether-gas-oxygen-cyclopropane anesthesia with morphine and scopolamine premedication and curare to aid in muscle relaxation. The abdomen was entered through a right mid-rectus incision. Approximately 500 cc. of blood-tinged fluid were aspirated from the peritoneal cavity. This fluid appeared to have been under pressure. Inspection of the small bowel revealed a dark red thickened loop of ileum which showed several small areas of early gangrene in its wall on the mesenteric border. This loop measured 20 cm. in length and lay about 40 cm. from the ileocecal junction. Further examination revealed dark thrombotic areas in the mesentery of this loop. The entire length of small bowel was inspected, but no other disease of the bowel was found. There was nothing remarkable about the previous site of resection. Sixty centimeters of ileum were resected and end-to-end anastomosis accomplished.

Pathology. The surgical specimen consisted of a loop of ileum 60 cm. long with a fringe of mesentery which varied from 1.5 to 2.5 cm. in width. The bowel wall was mottled grey-green to a very dark red, with only small spots of nearly normal color remaining. Microscopic sections of the part of the bowel which appeared involved by the process showed mucosa almost completely destroyed, with marked infiltration by polymorphonuclear leukocytes into the lamina propria. In the more severely damaged portion, the surface was made up of a mass of necrotic cells. There had been much hemorrhage into the submucosa and into the muscularis with infiltration by leukocytes. All blood vessels throughout the bowel wall and mesentery were engorged, the veins showing recent thrombus formation. A section through the bowel immediately proximal to the distal line of resection showed slight engorgement of blood vessels in the submucosa, one vein exhibiting early thrombus formation. The bowel wall was not otherwise unusual. Sections through the normal appearing proximal portion were not unusual.

Diagnosis. Phlebothrombosis, multiple, mesenteric. Gangrene, ileum.

Course. The postoperative course was uneventful. On the first postoperative day the patient was started on Dicumarol medication which was controlled with prothrombin levels. He was discharged on the twenty-ninth postoperative day.

For 29 months he has been on continued Dicumarol medication controlled by prothrombin time determination done twice each week. He is working and asymptomatic.

Case 2.—L. W., 549034, was a female, age 30. Forty hours prior to admission the patient was awakened by severe epigastric colic. All food taken was vomited. On the day before admission she took a "vegetable laxative" and castor oil. She had 20 fluid bowel movements which, she stated, contained no blood. In the months preceding hospitalization she had received arsphenamine and bismuth for secondary lues. A bismuth series was being administered at the time of onset of her abdominal pain, but this was thought to be entirely coincidental.

On admission her temperature was 100.2, pulse regular, and blood pressure 108/78. She displayed a dermatitis resembling pityriasis rosea. Her abdomen was slightly distended, but presented no mass, spasm, or costovertebral tenderness. Peristalsis was present but diminished. WBC was 11,000 with 81 per cent neutrophiles. Urinalysis was unremarkable. Gynecologic pathology was considered improbable by the consultant. An impression of gastro-enteritis was entertained. Three-position roentgen ray films of the abdomen showed only a small amount of gas over fluid levels in the small intestine. Twenty-four hours after admission she suddenly developed shock.

Operation. Transfusion, infusions, and adrenal cortical extracts were given, and under ether anesthesia celiotomy was performed. The peritoneal cavity contained a large amount of blood-stained fluid. Nearly all of the small intestine was purplish-black, had lost its luster, and had no peristalsis. The intestine contained much fluid, later found to be blood, and edema of the mesentery was severe. Fifteen feet of intestine were resected to include all the involved portion. Wherever the mesentery was divided the arteries were patent, but the veins were filled with thrombi which could be extruded

in vermiform masses from small and large vessels alike. It was not possible to resect proximal to the thrombosis at the root of the mesentery. No cause for the thrombosis was found. Anastomosis was accomplished over a Murphy button and the abdomen closed over a drain to the peritoneal cavity.

Pathology. Microscopic study of the specimen showed edema, hemorrhage, necrosis, debris, fibrin, and hemosiderin pigment with polymorphonuclear leukocytes everywhere in the gangrenous areas. Thrombi in the veins of intestine and mesentery were striking.

Course. The surgery, with repeated transfusions, infusions, and other supportive measures, failed to forestall death, which came on the day following operation. No postmortem examination could be done.

Case 3.—W. H., 339700, was a male, age 39. He was admitted complaining of left lower abdominal colic which he had endured for one week. Past and family histories were not contributory. Two days prior to admission the patient took a laxative and had 5 copious passages. On the day prior to admission an enema gave return of brownish fluid thought by the patient to contain blood. Otherwise the patient had passed nothing but flatus for one week. Vomiting had been frequent in the 2 days before admission.

Upon admission temperature was 100.4, pulse 86, respirations 20, and blood pressure 170/95. The undernourished young man was more comfortable in the sitting position and appeared quite ill. The abdomen was distended. Peristalsis was absent. No masses were felt. Tenderness was generalized. Rebound tenderness was present and more marked on the left. Acute appendicitis or diverticulitis or carcinoma of the descending colon with peritonitis were considered.

Proctoscopy revealed nothing, but with the passage of much flatus the patient was relieved of symptoms and distension. WBC was 25,000 with 90 per cent neutrophiles. RBC was 4.8 million and hemoglobin was 12 Gm. Urinalysis showed glucose + + +. Stools and vomitus were guaiaced positive.

Operation. Sixteen hours after admission signs of acute abdominal process continued, and celiotomy was performed under spinal anesthesia. Clear amber fluid was found in the peritoneal cavity. Ninety centimeters of mid-ileum were gangrenous. Resection of 123 cm. was completed and end-to-end anastomosis done. Jejunostomy was performed through a separate incision.

Pathology. The surgical specimen consisted of 123 cm. of small intestine with attached mesentery. At each end of the specimen there was gradual transition from dark brown to more normal color. Everywhere edema was marked; the mesentery measured 0.5 to 1.5 cm. in thickness. The infarcted intestine wall was thinned to 0.3 cm., while the more normal, but edematous, wall measured 0.7 cm. No perforation was present. Microscopic examination showed much of the mucosa to be absent, and in areas where it remained the cell outlines were indistinct. The connective tissue was edematous and gave evidence of erythrocyte diapedesis. Small thrombi were present in venules. Polymorphonuclear infiltration was scattered but prominent. Arterioles and arteries were uninvolved.

Course. The patient developed irreversible shock at operation and died 36 hours later. Postmortem examination revealed the entire superior mesenteric vein and its tributaries to be occluded by a friable and slightly adherent thrombus. Edema of the small intestine nearly occluded the lumen at the site of anastomosis. An older, organized thrombus only partially occluded the inferior vena cava. The deeper portions of this thrombus contained calcium.

Case 4.—R. L., 660903, was a female, age 74. For the 24 hours preceding admission the patient had suffered general abdominal pain and marked abdominal distension associated with passage of gross blood by rectum. "Phlebitis of the legs" had been troublesome "for some time," and 7 years before admission she had had a cerebral accident.

WBC done by her personal physician prior to admission was 18,000 cells with 90 per cent neutrophiles. Significant positive findings on admission included a temperature

of 100, pulse 120, abdominal distension, lower abdominal tenderness, and blood sugar values of 188 and 160 mg. per 100 cc. Hematocrit was 47.7; plasma proteins 7.2; plasma specific gravity 1.028; urine positive for albumin and glucose. Roentgenogram of the abdomen showed gas-distended loops of the small bowel. A diagnosis of gangrene of the small intestine, possibly vascular in etiology, was made. A Miller-Abbott tube was passed into the stomach and operation undertaken immediately.

Operation. With local anesthesia and nitrous oxide supplement the peritoneal cavity was opened in the midline of the lower abdomen to reveal a moderate amount of free sanguineous fluid and 112 cm. of infarcted lower ileum. The mesentery was dark, friable, edematous, and contained thromboses. Resection of 174 cm. was accomplished. Sutures would not hold in the friable intestine at the line of resection. The patient's condition was precarious; therefore a Rankin clamp was applied, a catheter inserted into the proximal bowel, and the abdomen closed, leaving the resected ends of the bowel exteriorized.

Course. The patient's temperature rose to 105° and she died on the third day following operation despite a well maintained blood pressure. Permission for a postmortem examination was not granted.

Pathology. There were 25 cm. and 34 cm. normal margins of intestine at either end of the 112 cm. of infarcted length. Gross blood was present in the intestine. Microscopic examination revealed absence of mucosa and extensive necrosis of all layers, especially of submucosa and muscularis where not even the nuclei of the neurolemma were seen. The hemorrhagic and normal sections both were edematous. Everywhere the vessels were enlarged and the veins in the mesentery of the gangrenous and hemorrhagic region were filled with fresh and some organized thrombi. Arteries were normal.

Case 5.—A. T., 62357, was a female, age 58, who sought medical relief for palpitation, dyspnea, and precordial pain of 2 weeks' duration. She had had slight ankle edema for 3 months. There was no history of previous cardiac difficulties or of rheumatic fever. Nausea was present, but vomiting had never occurred. The precordial pain radiated to the epigastrium and through to the back. At the time ankle edema appeared the patient's personal physician had prescribed digitalis, which had been taken intermittently. During the 2 weeks immediately preceding her admission, the patient had received one or two injections of morphia from her physician for relief of the pain she experienced.

Physical examination showed temperature 101.2, pulse 120, respirations 28, blood pressure 135/55. The patient was well nourished, well developed, had flushed cheeks, and exhibited cyanosis of her nailbeds with clubbing of her fingertips. Her heart was enlarged; its sounds were totally irregular; its impulse was diffuse; a blowing systolic murmur was present at the mitral area. Pretibial and sacral edema were moderate. The isthmus and lower right lobe of the thyroid were enlarged, soft, and possessed a bruit. There was slight dullness at the right posterior lung base.

Laboratory findings were RBC 5.1 million; hemoglobin 12 Gm.; WBC 11,700 with 66 per cent neutrophiles; a stool specimen was negative for blood; urinalysis was not remarkable.

The patient was in the hospital 2 days, during which time she became rapidly worse. The abdominal pain became more severe and was only temporarily relieved by morphine. She was given a soap-suds enema without result. Her pulse remained totally irregular but was of fairly good quality. She died suddenly on the morning of the third day. The clinical diagnosis was cardiac failure with auricular fibrillation.

Necropsy revealed 250 cc. of dark, bloody fluid in the peritoneal cavity. About 2 meters of mid-ileum was a deep red-purple. The transition between normal and abnormal intestine was gradual at the proximal portion but abrupt at the distal. The lumen of the involved intestine contained blood without exudate. Above the involved portion the intestine was slightly dilated and filled with fecal material. The area of discoloration

extended to the base of the mesentery. The trunk and branches of the superior mesenteric artery supplying the involved and uninvolved areas were patent and exhibited no pathologic changes. The mesenteric vein tributaries contained clotted blood. As the portal vein was approached, the clot became more dense. Beneath the pancreas the thrombus was adherent to the intima. The entrance of the splenic vein was occluded, and beyond this point the thrombus tapered in diameter to enter the liver by the right branch of the portal vein. The pancreas was normal. Outline of the involved ileum was retained, but erythrocytes replaced the normal cellular structure.

In summary, there was thrombosis of the superior mesenteric vein with infarction of small intestine. The thrombus appeared to be of some duration—possibly 2 weeks. Platelet thrombi in the pulmonary artery were covered by endothelium. It was impossible to tell whether these arose in situ or were transplanted from the liver via hepatic veins.

A final diagnosis was made of chronic myocarditis, cardiac insufficiency, cardiac arrhythmia, auricular fibrillation, ascites, thrombosis of the superior mesenteric vein, infarction of small intestine, and non-toxic nodular goiter.

Case 6.—S. B., 287914, was a male, age 36, with rheumatic heart disease, auricular fibrillation, and mitral stenosis. He had attacks of severe abdominal pains twice in the 2 months preceding admission. One was accompanied by vomiting, but both receded within one week under conservative sedation and bed rest in other hospitals. Eight days prior to admission he suffered onset of a third episode of similar generalized abdominal pain and vomiting.

Upon admission his temperature was 101.4, pulse 76, respirations 20, and blood pressure 150/90. He squirmed in pain and begged for relief. In addition to a mitral rumble on cardiac auscultation he revealed direct tenderness and voluntary spasm over the lower mid-abdomen without distension or masses. WBC was 24,100 with 91 per cent neutrophiles, hemoglobin was 16 Gm., RBC was 7.5 million, urinalysis normal. Roentgenogram of abdomen revealed no pathologic condition. A diagnosis of embolism of the mesenteric artery was made and exploration of the abdomen undertaken with spinal anesthesia supplemented by nitrous oxide.

Operation. A moderate amount of thin, apparently non-infected, serosanguineous fluid was present in the peritoneal cavity. A 20 cm. loop of small intestine in the left lower quadrant was dark red, edematous, and rigid. The mesentery of the involved loop was edematous, injected, and contained several blood clots. Fifty-five centimeters of small intestine were resected with a wedge of mesentery and end-to-end anastomosis done. A catheter enterostomy was placed above the anastomosis.

Pathology. Microscopic examination showed degeneration of the superficial mucosa, infiltration by leukocytes of all bowel layers, and hemorrhage everywhere. Sections through the mesentery showed thrombosis of veins with beginning organization. Careful search uncovered no thrombosis of any artery.

Course. The patient's condition rapidly deteriorated and he died a few hours after operation. Necropsy was not permitted.

Case 7.—J. D., 934607, was a female, age 73. Previously always well and active, the patient had had a complete physical examination by her personal physician 2 weeks prior to her hospital admission. Three pregnancies and deliveries in earlier years had been uncomplicated.

About a week before admission she began to have a heavy feeling in the lower chest when eating and vague abdominal discomfort with flatus and looseness of bowels. This continued until the morning of admission, when she felt generally upset and called her physician. He found normal temperature and pulse and a blood pressure of 150/90. In the afternoon generalized abdominal cramps, nausea, and vomiting began. In the early evening she stated that the pain was severe and localizing in the right lower quadrant.

Upon her admission temperature was 98.2, pulse 86, and blood pressure 150/90, and she was somewhat dehydrated. Her abdomen was soft, flat, tender in both lower quadrants with rebound tenderness in the left lower quadrant. Costovertebral angles were negative. In 3 hours the tenderness localized at the outer border of the rectus on the right side just below the umbilicus, where there was spasm. Hemoglobin was 15.8 Gm., RBC 5.2 million, WBC 13,400 with 85 per cent neutrophiles. Urinalysis showed a slight albuminuria and glycosuria. An impression of acute appendicitis was held and exploratory laparotomy undertaken immediately with Pentothal, cyclopropane anesthesia with curare for added relaxation. One thousand cubic centimeters of 5 per cent dextrose in saline and 1000 cc. of 5 per cent dextrose in distilled water were given.

Operation. The abdomen contained a moderate amount of clear blood stained fluid. The appendix was normal. In the upper portion of the ileum a segment 23 cm. in length was edematous and deep violet-red in color. The mesentery of this loop was thick, edematous, and filled with well-formed thrombi. There was no bleeding from the arteries in the mesentery immediately underlying the lesion, but there was free bleeding from the arteries in the more outlying areas where veins contained thrombi. It was presumed, therefore, that this was a venous thrombosis. The appendix was normal but was removed. Forty centimeters of ileum were resected so as to leave a wide margin of good intestine on either side of the damaged area. When the resection was completed there was free bleeding of bright red blood from all the cut surfaces. Anastomosis was made in a double layer, and the wound closed with difficulty because the tissues were friable. A drain was left in the subcutaneous tissues.

Pathology. Microscopy showed the large veins of the mesentery to be densely packed with erythrocytes, among which ran many strands and sheets of fibrin containing many polymorphonuclear cells and platelets. An artery was distended with blood but contained no thrombus. Edema and fibrin network were present in all the layers of the intestine. There was superficial denudation of some areas of mucosa.

Course. Twelve hours after the operation the venous clotting time was 17 minutes. Twenty hours after operation heparinization was begun. The clotting time as taken just before the three hourly dose of heparin was maintained at an average time of 17 minutes for 11 days. Recovery was without event except for a slight serosanguineous drainage from the wound which suggested deep-layer disruption. The patient was discharged from the hospital on the seventeenth day after operation. Ten months later she was well and active with an asymptomatic small incisional hernia which required no treatment. Her prothrombin time was 12.5 seconds (normal value 14 seconds with plus or minus 2 deviation), and her clotting time was 5 minutes.

Case 8.—D. S., 804329, was a male, age 73. His history follows:

1935. Intermittent, undiagnosed abdominal pain. Acute pyelitis after diagnostic cystoscopy.

1937. Right upper quadrant pain. Toxic nodular goiter. Operation was delayed 2 months while investigation of possible bronchiectasis was concluded.

1938. Partial thyroidectomy.

1945. October to November—Arteriosclerotic heart disease with bilateral pleural effusion, early congestive failure, and pulmonary infarcts, cause unknown.

One month after going to a convalescent home the patient was re-admitted. He complained of epigastric cramps associated with dyspnea, orthopnea, and vomiting. Fever of low degree had persisted for two days.

On admission his temperature was 102.6, pulse 100, respirations 32, and blood pressure 128/65. Hemoglobin was 13 Gm., RBC 5.2 million, WBC 10,600 with 82 per cent neutrophiles. Urinalysis showed a moderate amount of albumin and rare formed elements. The WBC climbed to 14,700, and the abdomen became distended and generally tender but never evinced spasm or mass. Stools were guaiac positive; vomitus

was negative. Death came on the fourth hospital day despite penicillin therapy for right lower lobe pneumonia.

Postmortem examination showed generalized arteriosclerosis including the arteries of the mesentery. Healed cardiac infarcts were evident. Calcific stenosis of the aortic valves was present. Superior mesenteric vein thrombosis with focal infarction of the small intestine, right colon, and spleen was an unsuspected finding. Microscopy displayed the arterial intima and media to be moderately thickened and the lumen to be partially obliterated by connective tissue. The veins contained large masses of recent thrombus completely occluding the vessels. Autolysis did not obscure the usual architecture of focally infarcted intestine.

Case 9.—R. H., 361340, was a male, age 43. Two weeks of severe epigastric "cramps," constipation, and a low grade fever brought him to the hospital. He had had 8 episodes of epigastric "cramps" in the preceding 2 years, but they had all been relieved by enemata. Past history was otherwise not contributory. He had never had an operation.

The pains leading to his hospitalization were preceded by a half-day of headache, drowsiness, and inability to concentrate. For his cramps the patient ingested Seidlitz powders without relief. An enema gave some comfort but the cramps continued. After a night with fever of 102° and delirium he called his personal physician, who gave him codeine. The cramps subsided, leaving a dull steady pain in the lower abdomen and in the right upper quadrant. Much flatus was passed. Fever continued unabated. There was no nausea or vomiting though anorexia increased.

Upon admission he was found to have a temperature of 103.6 and a pulse of 96. WBC was 26,800 with 90 per cent neutrophiles. Blood culture proved negative. Stools revealed no parasites or occult blood. Cystoscopy was not remarkable, although urine was seen to contain bile. Roentgenograms of chest, abdomen, and liver area gave no aid. Liver abscess was suspected. Icterus index was 12.5, but plasma bilirubin was 2 mg. per 100 cc. Agglutination for brucellosis was negative.

On the sixth day after admission he had profuse watery diarrhea and recurrence of severe epigastric cramps. The seventh day saw the onset of tenderness, direct and rebound, in both lower quadrants. Liver percussion elicited no pain. Diagnosis of an acute abdominal situation led to exploratory celiotomy with ether anesthesia.

Operation. An unsuspected extensive thrombosis of the superior mesenteric vein and portal vein was discovered. The thrombosis was firm and not suppurative. Ligation of the portal vein was thought to be a hopeless procedure. No evidence for liver abscess was made out. The appendix appeared normal, but appendicectomy was done with a terminal ileostomy.

Pathology. The appendix was a small, white, non-injected, shriveled organ measuring 2.2 by 0.7 cm. The wall was fibrous. Microscopy showed some necrotic material in a tiny lumen at the proximal portion. Tissues were well preserved with a diffuse scattering of polymorphonuclear leukocytes. Lymphatics and blood vessels were dilated, and one venule appeared thrombosed. The pathologist felt that the histology probably represented an inflammatory process in the whole of the intestinal tract involved by the mesenteric occlusion.

Course. On the second day after the operation the patient died; necropsy was not performed.

Case 10.—C. E., 967794, was a female, age 52. Fifteen days prior to admission, after 2 or 3 months of poor appetite with watery eructations and a weight loss of 10 to 20 pounds, the patient suffered onset of a low grade fever, distension, and diffuse pain in the abdomen—worse in the left lower quadrant. During the 4 days immediately preceding admission she had, in addition, severe crampy pain in the entire right side and mid-back. Bowels had always moved irregularly. There had been no evident gastrointestinal bleeding. Though anorexia was prominent vomiting had not occurred.

Five years ago the patient had diarrhea and parasites in the stools for which she received treatment. One year before the present admission stool examinations revealed no parasites or ova. Three months ago, shortly before onset of the present illness, she experienced an acute episode of malaria proved in blood films and treated successfully with Atabrine and quinine. Cystitis had been an occasional mild irritation for several years. Menses continued normally, and the most recent had been completed just before the present hospitalization.

Physical examination demonstrated the significant findings of diffuse abdominal tenderness more severe in the left lower quadrant. No spasm was present. Some rebound tenderness could be elicited. The costovertebral angle was only slightly tender on the left. Temperature was 98.8, pulse 86, respirations 20, and blood pressure 110/50.

Hemoglobin was 8.0 Gm., RBC 3.4 million, WBC 8400 with 70 per cent neutrophiles. Urinalysis revealed nothing unusual. Serum amylase was 32 Myers and Killian units—within the normal range. A roentgenogram of the abdomen demonstrated no gas or pathology.

The patient complained that her abdomen felt as though it were distending and she was restless and perspired a great deal. Demerol and barbiturates failed to give complete surcease from her abdominal pain. Erythrocyte sedimentation was elevated to 62 mm./hr. Serum bilirubin was 0.5 mg. per 100 cc. The first stool specimen was negative for occult blood, parasites, and ova; the second gave a positive guaiac test. Sigmoidoscopy gave no added information. Priodax given for gallbladder examination remained in the stomach 18 hours. Barium enema suggested possible diverticulitis. WBC rose to 17,500 with 86 per cent neutrophiles. Hemoglobin dropped to 6.5 Gm. with parenteral fluid infusion. Temperature rose to 100.2. Sulfadiazine and penicillin therapy were instituted. Sulfadiazine was soon discontinued when urinary output began to fall, although there was no hematuria or other evidence of nephritis. Dehydration was combated with increased amounts of parenteral fluid. Morphine replaced Demerol, but still not all pain was relieved. Symptoms vacillated in severity. Streptomycin therapy was begun.

Gross blood was passed per rectum and vomiting began. The vomitus was of fecal odor and without blood, and measured 2000 cc. in two days. A Miller-Abbott tube would not pass through the stomach. The surgical consultant observed the patient to be dehydrated and with a rotund, distended, tender abdomen; there was no spasm, scar, or mass, and direct and rebound tenderness was referred to the left lower quadrant where there appeared a soft mass hours later. Audible peristalsis was very occasionally present. Slight rectal tenderness was without localization and there was no fullness of the Pouch of Douglas.

NPN was 33. CO_2 was 53 vol. per 100 (28 meq/1) and serum chlorides 519 mg. per 100 cc. (89 meq/1). Repeat roentgenograms of the abdomen revealed nothing unusual; her GI series suggested a partial obstruction of small intestine. It was decided that signs of peritoneal irritation were clear and the most likely possibility seemed to be some complication of diverticulitis.

Operation. Therefore, 8 days after admission celiotomy was performed under ether-cyclopropane anesthesia. One liter of clear amber fluid was in the peritoneal cavity. In the left lower quadrant was a purple-red loop of jejunum with thickened wall and 4 cm. diameter; there was very little fibrinous exudate and the serosal surface glistened. The loop was adherent to adjacent omentum and to descending colon. When these adhesions were divided, blood oozed freely. Two neighboring segments of jejunum about 12 cm. in length were involved with 15 cm. of more normal appearing bowel between. The mesentery was 1.5 cm. thick, hard, and inflexible. When cut, the vessels of the mesentery permitted extrusion of stringy, gelatinous casts from small vessels. Resection was accomplished with end-to-end anastomosis about 4 feet distal to the ligament of Treitz.

Pathology. The resected jejunum measured 51 cm. in total length. The mucosa was thickened and hemorrhagic. Microscopic sections showed mucosal ulceration and the submucosa was infiltrated diffusely with lymphocytes and neutrophiles. Eosinophiles were not prominent. Many thrombosed veins showed early fibroplastic organization with some recanalization. Recent thrombi were also present in the veins. Sections through the mesentery revealed the arteries to be everywhere patent and normal, while veins were thrombosed and undergoing organization. The lines of resection were free of disease.

Course. 3000 cc. of whole blood were given in the days before, during, and after the operation. Hemoglobin rose to 11.6 Gm. and RBC to 4 million with a hematocrit of 34.6. Temperature rose to 101.6, pulse to 100. Dyspnea with cyanosis occurred suddenly on the sixth postoperative day. Roentgen ray evidence suggested infarct of bronchopneumonia. There was no evidence for extra-abdominal sites of thrombosis. Heparinization was accomplished. A pleural friction rub appeared and the patient was placed in an oxygen tent. The WBC was 20,300 with 87 per cent neutrophiles. Gradually the WBC dropped and the patient improved. Cephalin flocculation, thymol turbidity, alkaline phosphatase determinations were within normal range. Studies for parasites in the stool were repeatedly negative.

On the fiftieth hospital day, 42 days after operation, the patient left the hospital with no disability. Clotting time was 8 minutes. Platelet count showed 270,000 platelets. Prothrombin time was 20.2 seconds (normal 16 ± 2 seconds). Total plasma proteins were 7.21 Gm. per cent. Protamine titration was within normal range.

Case 11.—A. R., 53967-48 (BH), was a male, age 40. The patient was admitted to Bellevue Hospital with a history of severe, colicky, generalized abdominal pain of 11 hours' duration. This pain had been preceded by 5 days of intermittent, vague, mild abdominal cramps with no accompanying difficulty. Diarrhea and vomiting had not occurred. Physical examination demonstrated direct and rebound tenderness referred to the entire abdomen but more severe in the right lower quadrant.

Previous illnesses had included appendicitis with appendicectomy at the age of 5 years. Viral parotitis occurred when the patient was 35 years of age. During the period of 14 years preceding this admission, there were 3 hospital admissions for thrombophlebitis of the lower extremities and home treatment of several minor thrombotic episodes in the leg veins. Evidence of pulmonary infarction was prominent during the first hospital admission. There was no history of any other disease, operation, or injury.

Family history as corroborated by records from other hospitals revealed the patient to have been one of four brothers, two of whom had had intestinal resection for venous mesenteric thrombosis.

One brother, at the age of 36 years, underwent appendicectomy in January, 1934, at a New York hospital. The postoperative course was complicated by pneumonia and bilateral thrombophlebitis of the lower extremities. He was convalescing—still in bed—2 months later in March when he began to experience indigestion, anorexia, nausea, vomiting, and pain in the lower abdomen. Physical examination revealed the abdomen to be distended. Periumbilical pain and tenderness were striking. There was no rigidity, and no masses were felt. Hemoglobin was 64 per 100 cc., RBC 3.8, and WBC 12,800. At operation in April, 1934, two and one-half months after the appendicectomy, venous mesenteric thrombosis with gangrene of the ileum were found. Resection of two and a half feet of ileum with end-to-end anastomosis of small intestine was performed. Histologic examination was interpreted as showing thrombi in veins, edema and hemorrhage into the wall of the ileum, and no arterial lesion. Following surgery there was some distension, but this gradually subsided, and at the time of discharge on the thirty-sixth postoperative day the intestinal tract was functioning normally. Fear of recurrence has induced this patient to ingest Dicumarol without medical supervision. He has had three large gastrointestinal hemorrhages treated in three hospitals in various parts of the United States.

The second brother, an M.D., was admitted in 1939 to another New York hospital with acute colicky abdominal pain. This brother told the hospital physicians that he believed the diagnosis to be venous mesenteric thrombosis since he had had venous thrombi in his leg a short time before and because his 3 brothers were subject to intravascular thrombosis or thrombophlebitis. Some time before this admission he had been hospitalized with spontaneous left leg phlebitis complicated by pulmonary infarction. At this admission for abdominal pain he looked very ill, was pallid, and had cyanotic lips. His pulse was of poor quality. His abdomen was uniformly distended and tense with slight tympany on the right side. Peristalsis was absent. Intraperitoneal fluid could not be detected. Tenderness was marked over the left upper quadrant. Hemoglobin was 108 per cent, RBC 5.6 million, WBC 24,100 with 85 per cent neutrophiles. Wassermann was negative. Urine contained albumin and reduced Benedict's reagent. Blood urea nitrogen was 20, and blood sugar was 266. Roentgen ray examination of the abdomen showed gaseous distension of stomach, distal small intestine, and right half of the colon. Barium enema examination gave no significant positive information. It was decided that operation could not be undertaken with the patient in so poor a condition. A Miller-Abbott tube was inserted but did not pass beyond the duodenum. Two days after admission he passed gross blood per rectum and vomited blood containing material. Operative exploration of the abdomen was done through a left rectus incision. A large quantity of brownish, non-odorous fluid was found free in the peritoneal cavity. Cultures were taken and the fluid was removed by suction. The presenting small intestine except for the terminal ileum was purple-red but the overlying peritoneum was glistening. The entire small intestine except for the terminal ileum was edematous, discolored, and hemorrhagic together with its mesentery. Colon, stomach, liver appeared normal. Because of the extent of disease and the poor condition of the patient no resection was attempted. The abdomen was closed in layers without drainage. Transfusion and other supportive therapy were of no avail and death came on the fourth hospital day. Necropsy revealed the edematous, discolored small intestine. The thickened, congested, hemorrhagic, edematous mesentery contained the tributaries of the superior mesenteric vein which were filled with firm, gray-red, adherent thrombi extending into the portal vein. All the arteries were free of thrombus. One large venous tributary draining a scarred area of renal cortex contained an organized thrombus.

In the face of this family history, the patient, A.R., felt that he, too, had venous mesenteric thrombosis. His temperature was 100; WBC 17,000, clotting time (Lee-White) 2.5 minutes. Physical examination showed a moderately obese male with a well-healed right lower quadrant abdominal scar. There was no abdominal distension, but tenderness was acute and accompanied by rebound phenomena over the entire abdomen and worse in the right lower quadrant. Audible bowel sounds were absent. No masses were palpable. No hernia or costovertebral tenderness was identified. Blood was cross-matched, and 4 hours after admission celiotomy was performed.

Operation. Under spinal and general anesthesia, through a lower right rectus incision about 70 cm. of very dark ileum was identified. Its distal portion was 25 cm. from the ileoceal valve. With the Furness clamp technic the ileum was resected through normal appearing areas and an end-to-end anastomosis was accomplished. Careful examination revealed no other pathologic condition of the intestine.

Pathology. Microscopic examination of the resected intestinal segment revealed an intact mucosa. Moderate edema was present in the entire thickness of the wall. Congestion of subserosal and intramural blood vessels was prominent. Sections through the mesentery exhibited many thrombosed veins. No arterial thrombosis was demonstrated. The walls of the veins showed no inflammatory reaction.

Course. The patient was given 1500 cc. of whole blood during and after the operation. Dicumarol was administered postoperatively. Fifteen days after operation he felt well and was discharged to his home. Eleven months later he was asymptomatic and in good

health with only a weakness in abdominal musculature under the operative scar. At this time he was taking no anticoagulants. Prothrombin time was 16.1 seconds (normal 18 ± 2 seconds); platelet count 220,000; clotting time was ten minutes by the Lee-White method. Protamine titration for heparin sensitivity or circulating heparin-like substance was within normal limits. Total plasma protein was 8 Gm.

Case 12.—D. F., 629258 (P.C.), was a male, age 50. The patient presented himself stating that he had awakened 4 days earlier with a periumbilical pain, dull and intermittent in quality. The pain continued, becoming more severe as time passed. On the third day of his pain he induced vomiting without relief. On the morning of his admission he began to vomit spontaneously and profusely. He vomited a greenish-yellow material 6 or 10 times without relation to or relief of the pain. He had noted no bowel changes, nocturia, or frequency. He was pale, perspiring profusely, and walking about while stating that he was in acute pain. His blood pressure was 110/60. The skin was cold and moist. Examination revealed nothing focally significant. His abdomen was soft, obese, but diffusely tender. A perforated ulcer was suspected. Roentgen ray film of the abdomen showed nothing unusual. He was admitted to the ward. His temperature was 101.2. One-quarter of a grain of morphine failed to relieve the pain, and the patient paced up and down complaining all the while of severe abdominal pain.

Hemoglobin was 14 Gm.; RBC 4.95 million; WBC 18,200 with 76 per cent neutrophiles; plasma proteins 6.6 Gm.; urinalysis 1+ reducing and 1+ protein. Blood sugar was 50 mg. per 100 cc.

The patient was given intravenous fluids, antibiotics, Levin tube with continuous suction and nothing by mouth. On the second hospital day he passed blood in a liquid stool. That evening he passed more blood by rectum. He complained of severe cramps in the right lower quadrant. Blood pressure was 128/84 and pulse was good. Later in the evening he felt better. By the next morning the patient was in shock with thready pulse and blood pressure 60/40.

A consultant felt that the most likely diagnosis was that of bleeding ulcer with perforation. The Levin tube drainage was bloody, and more blood was passed by rectum. With treatment the patient seemed to improve, then became irrational, cyanotic, anuric, and expired on the fourth hospital day without recovering from the shock state.

Necropsy showed a thickened, dark-red, and in some areas gangrenous small intestine from a point 15 cm. distal to the duodenum to a point 7 cm. proximal to the ileocecal valve. The peritoneal cavity and the bowel lumen contained bloody fluid. The superior mesenteric artery was patent throughout its length, but all the tributaries of the superior mesenteric vein were thrombosed. The mesentery was thickened and contained large areas of ecchymosis.

DISCUSSION

Discussion of this material quite naturally follows two pathways. First, there is the consideration of agnogenic venous mesenteric thrombosis and a study of the material presented. Second, the somewhat confused problem of coagulation of the blood will be considered to see if, by study of these factors, we have any means at present which might aid in earlier diagnosis and more effective treatment of this condition.

Agnogenic venous mesenteric thrombosis lacks definite etiology because there is no scientific evidence that any factors, alone or in combination, are responsible for initiation of the process. Four lines of inquiry present themselves:

(a) There may be temporary kinking, volvulus, intussuception, hernia or other temporary obstruction to venous blood flow. Operative findings on

some pure venous mesenteric thromboses have been associated with these obstructions to circulation in the mesentery.

(b) Infection and sepsis may be the underlying cause as with septic pylephlebitis complicating suppurative conditions within the abdomen.

(c) The etiology may be attributed to Banti's disease, cirrhosis of the liver, portal hypertension, or tumors. There is no evidence of any of the above, however, in the true idiopathic variety of mesenteric thrombosis.

(d) In the group of cases we are reporting as agnogenic venous thrombosis it seems most likely that some change in balance of the hematologic elements concerned in coagulation probably plays the major role in producing thrombosis of the mesenteric veins. This dyscrasia is indeed necessary for thrombosis and may be induced by some local damage to the intima and stagnation of the circulation or by other known or unknown factors. Such a temporary imbalance might follow over-transfusion, perhaps, or severe enteritis with fluid loss and resultant hemoconcentration and temporary thrombophilic state. General factors, too, probably have a role, as suggested by the cases reported.

With the increasing use of antibiotics the question has arisen as to whether or not there may be a resultant increase in blood coagulability.[24, 25] At present the evidence is insufficient and unsubstantiated. Certain drugs also, such as the digitalis[26-28] group have thromboplastic properties, and the mercurial diuretics have also been implicated.[29, 30] In addition, the frequency of migratory phlebitis in patients with carcinoma,[31] notably of the pancreas, suggests a change in the clotting mechanism in these conditions. This, perhaps, may be in whole or in part attributed to the anemia that usually accompanies malignant disease.

SYMPTOMS AND SIGNS FOR DIAGNOSIS

Clinical descriptions of venous mesenteric thrombosis have been modified by inclusion of arterial and mixed venous-arterial thromboses, but most of all by addition of the symptoms and signs of those diseases commonly associated with the venous thromboses. Thus appendicitis, hepatic cirrhosis, abdominal neoplasia, adhesions, volvulus, strangulated hernia, salpingitis, and diverticulitis have contributed confusing symptoms and signs to mislead the clinician.

Prodrome. Agnogenic venous mesenteric thrombosis often displays a prodromal period. This may be represented by a past history of "migrating thrombophlebitis," lower extremity "thrombophlebitis," pulmonary infarcts, or vague abdominal discomfort of episodic character. In addition, the prodrome may be characterized by diffuse, intermittent, abdominal pain which is often colicky and may last days or even several weeks.

Acute Symptoms. The more acute symptoms are those of intestinal obstruction or, less commonly and later in the course of the disease, symptoms of peritonitis. In our series all patients complained of abdominal pain (Table III). The pain was intense, often intermittent and colicky, and was general-

ized or with exaggeration in any region of the abdomen. Peculiarly, it possessed an intensity not easily controlled by opiates. Vomiting occurred in more than half of the patients. Hematemesis, a very suggestive though not diagnostic symptom, was rare, occurring in only one case. Blood in the stomach might be expected as a late sign since infarction of the intestine was

TABLE III.—*Presenting Symptoms, Temperature and Pulse.*

Case	History and Presenting Complaint	Temp.	Pulse
1	7 attacks of phlebitis—epigastric pain—colic—vomiting	100	90
1A	Mesenteric thrombosis—epigastric pain—colic—vomiting	99.8	88
2	Epigastric colic—vomiting	100.2	..
3	Abdominal cramps—vomiting	100.4	86
4	Severe abdominal pain—distension	100	120
5	Severe abdominal pain—constipation	101.2	120
6	Abdominal pain—vomiting	101.4	76
7	Abdominal discomfort, then severe pain	98.2	86
8	Abdominal pain	102.6	100
9	Abdominal cramps—constipation	103.6	96
10	Abdominal pain—anorexia	98.8	86
11	Severe abdominal colic	100	..
12	Severe abdominal pain—vomiting	101.2	..

always some distance beyond the ligament of Treitz. Though diarrhea and constipation are described as common findings in series of mesenteric vein occlusion from mixed causes, agnogenic venous thrombosis is not often heralded by bowel irregularities. When the prodromal period was several days in length, constipation was more common.

TABLE IV.—*Presenting Physical Signs.*

Case	Physical Examination					
	Distension	Spasm	Tenderness	Rebound	Mass	Peristalsis
1	+	0	+	0	+	Decrease
1A	0	0	+	+	0	Decrease
2	+	0	+	0	0	0
3	+	+	+	+	0	0
4	+	+	+	0	0	
5	+	0	0	0	0	0
6	0	+	+	+	0	
7	0	+	+	+	0	
8	+	0	+	0	0	0
9	+	0	+	+	0	
10	+	0	+	+	+	Decrease
11	0	+	+	+	0	0
12	0	0	+	+	0	

Physical Signs. In series of mesenteric vein thrombosis with mixed etiology abdominal signs are often confused with those of acute appendicitis or other emergencies (Table IV). Upon admission agnogenic thrombosis presents as a frequent finding a striking disproportion of abdominal rigidity to the probable duration of symptoms and to palpation tenderness in the abdomen. Rigidity is often very slight or entirely absent, although tenderness is acute. Rebound tenderness, usually considered to represent peritoneal inflammation, is not seen in the first days of symptoms. Distension occurs

quickly in most cases but frequently lacks tympanitic qualities because the distended loops of intestine are filled with fluid and blood. When these loops are so filled, roentgenograms fail to show gas-distended intestinal shadows; gas shadows, however, appear in about half the cases and may have a peculiar distribution. According to Harrington[32] a film that shows gas in the proximal half of the colon, stopping abruptly in the mid-transverse colon, is a helpful finding. Free fluid in the peritoneum is always present in amounts usually measuring from one-half to one liter. All observers agree that distension and fluid loss into the peritoneal cavity and intestine are greater in venous mesenteric occlusion than in the arterial form. A palpable loop of intestine is rarely felt because it lies behind a stretched abdominal wall and because palpation elicits tenderness and voluntary guarding sufficient to hide the soft mass of intestine, which with a structurally open lumen everywhere, permits the ac-

TABLE V.—*Laboratory Data.*

Case	HGB (Gm.)	RBC	WBC	Neutrophiles Per cent	Guaiac	Other
1	....	.....	13,000	75	.....	
1A	16.2	.....	12,500	82	F +	
2	9.7	4.1 million	11,000	81	.....	
3	12.8	4.8 million	25,000	90	V 4+ F 4+	
4	11.9	4.2 million	18,000	90	V 3+ F Gross	
5	12.0	5.1 million	11,700	66	F 0	
6	16.0	7.5 million	24,100	91	.....	
7	15.8	5.2 million	13,400	85	Enema 0	
8	13.0	5.2 million	10,600	82	V 0 F 4+	
9	....	3.9 million	26,800	90	F 0	
10	8.0	3.4 million	8,400	70	F 2+	
11	....	.....	17,000	..	.....	Clotting time 2.5 min.
12	14.0	4.95 million	18,200	76	F Gross	

V = vomitus. F = feces.

cumulated fluid in the paralyzed segment to be easily displaced by pressure of the examiner's hand.

Melena, gross or occult, occurs less frequently than one might expect from the rather consistent finding of blood in the involved intestine, inasmuch as blood in the small intestine with associated paralytic ileus may not find its way to the large bowel to be identified in stool, gloved-finger specimen, or enema return. About one-third of the patients in this series displayed melena. Increased attempts to demonstrate melena by use of the "diagnostic enema" and guaiac test may increase somewhat the positive findings; when positive, this test is a valuable aid in diagnosis.

Borborygmi may be marked when the intestine demonstrates increased peristalsis, later, as paralytic ileus develops, audible peristalsis is diminished or absent. Vomiting is common as in any intestinal obstruction and guaiac tests on vomitus may be positive for blood.

Shock is rare and is a late and grave sign of venous mesenteric thrombosis. In Whittaker and Pemberton's[11] series, 47 per cent of arterial occlusion and only 7 per cent of venous occlusion demonstrated shock.

Temperature in most early cases is not elevated. After several days of severe symptoms the temperature may rise to between 101 and 103. The pulse varies but rises as time passes. Leukocytosis averages about 20,000, somewhat lower than the 27,000 of arterial occlusion. The average admission WBC for this series was 18,000 with 83 per cent neutrophilic leukocytes (Table V).

At operation the finding of sanguineous fluid in the peritoneal cavity should immediately suggest the possibility of venous mesenteric occlusion. Early the fluid is odorless, but after invasion by organisms penetrating infarcted intestinal wall it develops a foul odor.

Unless the disease is kept in mind for all patients with a suggestive history and physical examination the diagnosis will not be made. Even the

TABLE VI.—*Preoperative Diagnoses in Series Reported.*

Case	Preoperative Diagnoses	Cases	Preoperative Diagnoses
1	Peritonitis	7	Acute appendicitis
1A	Appendicitis, ? mesenteric thrombosis	8*	Lower lobe pneumonia
2	Acute abdomen	9	Acute abdomen, ? liver abscess
3	Acute appendicitis, lesion large bowel, peritonitis	10	Diverticulitis, ? perforation
4	Gangrene small intestine, ? vascular	11	Venous mesenteric thrombosis (diagnosis made by patient)
5*	Cardiac failure, auricular fibrillation	12	Bleeding peptic ulcer, perforation
6	Embolism of mesenteric artery		

* No operation. Necropsy only.

diagnosis, however, is not as important as the recognition by the surgeon of the fact that he is dealing with an acute abdominal emergency which requires immediate intervention. On no account should operation be delayed in order to attempt an academic diagnosis (Table VI).

Only 5 per cent of Trotter's[8] and 15 per cent of Cokkinis' series were correctly diagnosed before operation. That the diagnosis is frequently in error is not surprising in view of the lack of distinguishing findings. Non-specific enteritis, typhoid, cholecystitis, appendicitis, peptic ulcer, volvulus, internal hernia, adhesive bands with obstruction, intussuception, lead poisoning, acute pancreatitis, in fact most acute abdominal emergencies, can be simulated during some stage of the disease. It is important that, despite the frequent lack of spasm and rebound tenderness early in venous mesenteric thrombosis, the condition be recognized as an acute abdominal emergency.

Pathology. Complete occlusion of the superior mesenteric vein or a portion of its tributaries while all arterial branches remain patent constitutes the dominant feature of agnogenic venous mesenteric thrombosis. Associated with the venous thromboses in those cases that come to surgery or postmortem examination are severe structural changes in intestine and mesentery. With etiology yet to be determined it is impossible to ascribe initiation of the patho-

logic process to any portion of the structural pattern. It seems reasonable, however, that whatever the cause of preceding events, thrombosis of the venous channels represents a stage in pathogenesis to which the other observed functional and structural pathology can be attributed. The patterns of the lesions vary with the degree of vascular occlusion and with the age of the lesions.

An uninfected thrombus recently formed in a vein is dark-red, gelatinous, easily withdrawn from the lumen, and unattached to intima. With the passing days the thrombus becomes grey, firm, and adherent to the intima as fibroblasts invade to organize the mass. Various stages of this process present simultaneously, thereby suggesting that thrombosis has occurred intermittently or progressively and may have blocked anastomosing channels until collateral circulation is impossible. One-fourth of the cases with surgical resection exhibited organized as well as more recently formed thrombi. The extent of thrombosis varies within wide limits and may even include the portal, splenic, and tributaries of the superior mesenteric vein, even to the intramural vessels. Whether thrombosis begins in the finer tributaries or in the larger collecting veins cannot be determined from the limited amount of material so far available. If the segments of diseased intestine in this small series could be considered a reasonable indication, it would appear that thrombosis of the ileal veins is about twice as frequent as thrombosis of jejunal veins.

Edema and extravasation of blood into the mesentery produce a thickening which often measures 2 to 5 cm.; this often obscures all pulsations and architecture in the mesentery. Various lengths of small intestine, in this series from 18 to 250 cm., present as dark-red, purple, or blue-black loops. Gross perforation was not present in this group but may conceivably be a late complication. The walls of the intestine are usually much thickened by infiltrations of blood and plasma but the serous coat retains a gloss that is only infrequently broken by flecks of fibrin. Especially in cases with long-existing symptoms there may be adhesions with omentum or other loops of intestine. These adhesions carry patent blood vessels and probably act as collateral channels. In a case of acute pancreatitis with associated venous mesenteric thrombosis, but not included in the present series, anastomoses of ileal veins with the right ovarian vein were found patent and measuring 0.5 to 1.0 mm. in diameter. Also, in Case 10, adhesions of the involved small intestine to omentum and descending colon exhibited free bleeding when divided.

TREATMENT

The treatment of this abdominal catastrophe is *operative*. As with acute intestinal obstruction, the time for surgery is before one's hand is forced. The presence of an acute abdominal emergency should be recognized and the temptation to delay until the perfect diagnosis can be established must be

eschewed. In studying our series of cases one cannot but be somewhat appalled at the long delays between admission to the hospital and decision to operate. Today, exploratory celiotomy, even in the aged, carries little risk—one far lower than when operation is too long delayed in intestinal obstruction, whatever its cause. And when there is the added risk of a progressing thrombosis, the urgency of surgery is still more clearly indicated.

Prior to the advent of the anticoagulants the operative mortality was so high that some advocated expectant treatment. A fallacy in this advice is the very great question of accurate diagnosis in the non-operative group. In the group reported, for example, only two correct diagnoses were made, in one instance by the patient. There can be little sound argument, therefore, for expectant treatment; in fact it seems likely that with this form of therapy the mortality will be over 70 per cent.[9, 33] The surgical mortality figures for the series reported in the past are likewise high but no differentiation has been made between arterial and venous thrombosis. In our own small group of 13 cases of the agnogenic venous variety there were eight deaths. After reviewing some of the literature and studying our own series it is probable that the mortality might well have been lowered by earlier operation.

As has been stated already there were two deaths in Murray's[12] group of six cases treated with resection and heparin. One was from bronchopneumonia and one from peritonitis. Necropsy showed no extension of the thrombosis in either instance. An increasing number of cases treated successfully with heparin has been reported during the past decade, and in our series all but one of the patients who recovered were so treated.

In essence, then, a successful outcome depends upon early operation with resection of the involved area and prompt institution of anticoagulant therapy postoperatively. Furthermore it is our belief that heparin rather than Dicumarol is safer and more effective in the early postoperative period.

EARLY DIAGNOSIS AND THE LABORATORY

Up to the present time our chief reliance must still be placed upon a careful history and physical examination in order to suspect the diagnosis and institute prompt treatment. Age does not help one way or the other, as cases from one month to 90 years have been reported. In our group ten of the 12 patients were under 60 years of age. The salient points in the history and physical examination are:

(a) Previous attacks of phlebitis or thrombotic episodes.

(b) A family history of the above.

(c) A prodromal period of vague abdominal discomfort with constipation or diarrhea.

(d) Severe abdominal pain, often colicky, out of all proportion to the physical findings, and difficult to relieve with the usual doses of opiates.

(e) Marked abdominal tenderness with comparatively little spasm.

(f) Only slight temperature rise.

(g) Blood on rectal examination.

Suspicious laboratory findings are:

(a) Leukocytosis of 15,000 to 25,000 with neutrophiles 80 to 90 per cent.

(b) Polycythemia, real or due to dehydration.

(c) Positive guaiac test in stool or vomitus.

(d) Anemia.

(e) High hematocrit.

It would be most helpful were some comparatively simple test available to aid us in the early diagnosis of this obscure manifestation of intravascular

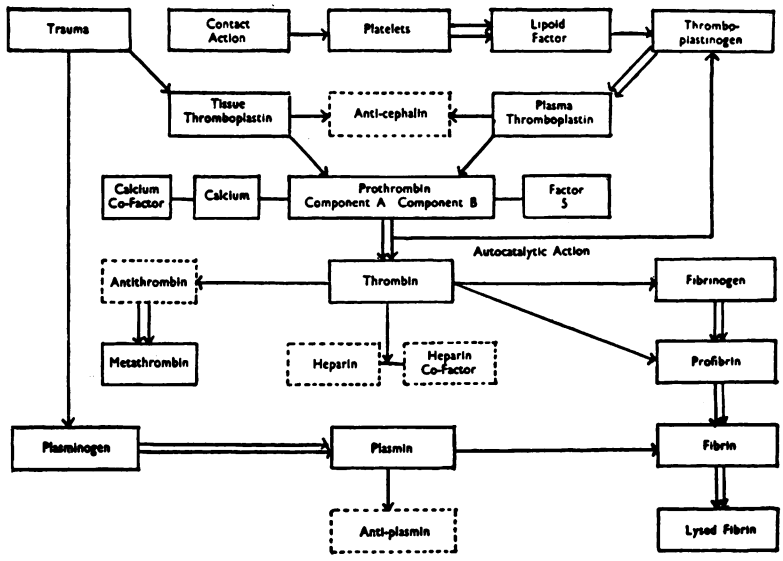

FIG. 1.—A diagrammatic synthesis of the factors probably concerned in coagulation, and their interrelationship. A single arrow signifies "reacts with." A double arrow signifies "produces." A line joining two factors signifies "in conjunction with," more precise information in this case being not available. Anticoagulant factors are outlined with a dotted line. (Macfarlane, R. G.: Normal and Abnormal Blood Coagulation. J. Clin. Path., 1: 113 (May) 1948.)

coagulation. According to Macfarlane,[34] "this mysterious and unpredictable occurrence apparently is not primarily due to an abnormality of the blood-clotting mechanism, but to the combination of tissue damage and circulatory stasis that may displace the clotting-anticlotting equilibrium in favour of coagulation."

Quick,[35] in a recent letter says: "One must not overlook the fact that the coagulation time is entirely empyric and totally unphysiologic. While a prolonged coagulation time denotes an abnormality in the coagulation reaction, a normal value gives no assurance that the coagulation mechanism is normal or that hemostasis is adequate. . . . With a test that is as poorly controlled

as the coagulation time, it is difficult to determine how much shortening must occur before a state of hypercoagulability exists."

A vast amount of work has been done on intravascular clotting over the past quarter century, yet the problem is still complicated and there is tremendous disparity between *in vitro* and *in vivo*. The classical conception of the clotting of blood was stated by Morawitz almost 50 years ago.[34]

1. Prothrombin + Ca + Thromboplastin = Thrombin
2. Fibrinogen + Thrombin = Fibrin

Our present conception, however, is completely different, as may be seen in the diagram reproduced with the kind permission of Dr. R. G. Macfarlane, and the *Journal of Clinical Pathology,* from his article on "Normal and Abnormal Blood Coagulation," in the May, 1948, issue (Figure 1).

TABLE VII.—*Follow-up Studies and Survivors.*

Case	Time	Status	Platelets	Coagulation Tests
1	5 years	Well	Normal	Protamine titration...Normal Clotting time.....8–10 minutes
1A	2 years	Well on Dicumarol	Normal	Prothrombin time....17.8–52.9 seconds (normal 14±1)
7	1 year	Well	Normal	Clotting time.....5 minutes Prothrombin time....12.2 seconds (normal 14±2)
10	6 months	Well	Normal	Protamine titration...Normal Clotting time.....8 minutes Prothrombin time....20.2 seconds (normal 16±2)
11	2 years	Well	Normal	Protamine titration...Normal Clotting time.....10 minutes Prothrombin time....16.1 seconds (normal 08±2)

In spite of the pitfalls of inaccuracy, some of the simpler laboratory studies might well be of benefit in establishing a diagnosis and in follow-up studies (Table VII). The most familiar of these are:

1. Coagulation time.
2. Prothrombin level.
3. Platelet count.[34, 36]
4. Clot retraction time.[37, 38]
5. Hematocrit.

Quick[36] believes that his prothrombin consumption determination is of considerably more value than the simple prothrombin time. This, and other determinations such as protamine titration, and the studies on alpha tocopherol phosphate by Ochsner and his group, may prove to be of benefit in the follow-up of these patients.

SUMMARY AND CONCLUSIONS

1. A review of agnogenic venous mesenteric thrombosis has been given.

2. Thirteen examples in 12 patients have been described and their case histories presented.

3. There were five recoveries; one patient survived two attacks.

4. All the successful cases were operated upon, and in four anticoagulants were administered postoperatively.

5. The difficulties of correct diagnosis are recognized; in only two instances in our series was a correct diagnosis made.

6. Suggestions concerning laboratory aids in diagnosis and in follow-up studies have been made.

7. In order to lower the mortality a strong plea has been made for the early recognition of an acute abdominal emergency, early operation, and immediate institution of anticoagulant therapy with heparin postoperatively.

BIBLIOGRAPHY

[1] Albutt, Clifford: The Historical Relations of Medicine and Surgery. London, MacMillan & Co., Ltd., 1905.

[2] Hodgson, Joseph: A Treatise on the Diseases of Arteries and Veins, Containing the Pathology and Treatment of Aneurisms and Wounded Arteries. London, T. Underwood, 1815.

[3] Tiedman, F.: Von der Verengerung and Schliessung der Pulsadern in Krankheiten. Leipzig, K. Gross, 1843.

[4] Moore, T.: Mesenteric Vascular Occlusion. Brit. J. Surg., **28**: 347, 1941.

[5] Elliot, J. W.: The Operative Relief of Gangrene of Intestine Due to Occlusion of the Mesenteric Vessels. Ann. Surg., **21**: 9, 1895.

[6] Jackson, J. M., C. A. Allen and W. C. Quimby: Mesenteric Embolism and Thrombosis. J. A. M. A., **42**: 1469, 1904; **43**: 25, 1904; **43**: 110, 1904; **43**: 183, 1904.

[7] Allbutt, C., and H. D. Rolleston: System of Medicine. London, 1909 (Welch, W. H.).

[8] Trotter, L. B. C.: Embolism and Thrombosis of Mesenteric Vessels. London, Cambridge U. Press, 1913.

[9] Donaldson, J. K., and B. F. Stout: Mesenteric Thrombosis. Am. J. Surg., **29**: 208, 1935.

[10] Warren, S., and T. P. Eberhard: Mesenteric Vascular Thrombosis. Surg., Gynec. & Obst., **61**: 102, 1935.

[11] Whittaker, L. D., and deJ. Pemberton: Mesenteric Vascular Occlusion. J. A. M. A., **111**: 21, 1938.

[12] Murray, G.: Heparin in Surgical Treatment of Blood Vessels. Arch. Surg., **40**: 307, 1940.

[13] d'Abreu, F., and J. G. Humble: Mesenteric Venous Thrombosis: Recovery After Resection With Heparin. Lancet, **I**: 534, 1946.

[14] Robson, A. W. M.: Ligature of Superior Mesenteric Vein With Recovery. Brit. M. J., **2**: 77, 1897.

[15] Wilms: Zur Frage der Gefässverletzungen der Radix mesenterii (Problem of injuries to the vessels of the root of the mesentery). Münch. med. Wchnschr., **48**: 1277, 1901.

[16] Solowieff, A.: Veränderungen in der Leber unter dem Einflusse künstlicher Verstopfung der Pfortader (Changes in the liver due to artificial obstruction of the portal vein), Virchow's Arch. f. path. Anat., **62**: 195, 1875.

[17] Scott, H. G., and O. H. Wangensteen: Length of Life Following Various Types of Strangulation Obstruction in Dogs. Proc. Soc. Exper. Biol. & Med., **29**: 424, 428, 559, 748, 1932.

[18] Boyce, F. F., and E. M. McFettridge: Mesenteric Vascular Occlusion. Int. Surg. Dig., **20**: 67, 1935.

[19] Noer, R. J.: The Blood Vessels of the Jejunum and Ileum: A Comparative Study of Man and Certain Lab. Animals. Am. J. Anat., **73**: 293, 1943.

[20] Noer, R. J., and J. W. Derr: Revascularization Following Experimental Mesenteric Occlusion. Arch. Surg., **58**: 576, 1949.
[21] Derr, J. W., and R. J. Noer: Experimental Vascular Occlusion. Surg., Gynec. & Obst., **89**: 393, 1949.
[22] Laufman, H.: The Effect of Heparin on the Behavior of Infarction of the Intestine. Surg., Gynec. & Obst., **74**: 479, 1942.
[23] McIver, Monroe A.: Acute Intestinal Obstruction. New York, P. B. Hoeber, 1934.
[24] Macht, D. I.: Thromboplastic Properties of Penicillin, Streptomycin—. Southern M. J., **41**: 720, 1948.
[25] Fleming, A., and E. W. Fish: Influence of Penicillin on the Coagulability of Blood. Brit. M. J., **2**: 242, 1947.
[26] Macht, D. I.: Digitalis and Coagulation of the Blood. Med. Rec., 1945.
[27] Macht, D. I., E. C. Spencer and L. Liston: Thromboplastic Properties of Some Digitaloid Drugs. Fed. Proc., **1**: 1942.
[28] deTakats, G., R. A. Trump and N. C. Gilbert: Effects of Digitalis on the Clotting Mechanism. J. A. M. A., **125**: 840, 1944.
[29] Macht, D. I.: Thromboplastic Properties of Some Mercurial Diuretics. Am. Heart J., **31**: 460, 1946.
[30] ————: Thromboplastic Properties of Digitaloids and Mercurials Employed in Cardiology. Arch. Int. Pharmacodyn. et de Ther., **72**: 297, 1946.
[31] Edwards, Edward A.: Migrating Thrombophlebitis in Carcinoma. New England J. Med., **240**: 1037, 1949.
[32] Harrington, L. A.: Mesenteric Thrombosis. Am. J. Roent., **58**: 637, 1947.
[33] Laufman, H., and S. Scheinberg: Arterial and Venous Mesenteric Occlusion. Am. J. Surg., **58**: 84, 1942.
[34] Macfarlane, R. G.: Normal and Abnormal Blood Coagulation. J. Clin. Path., **I**: 113, 1948.
[35] Quick, A. J.: Antibiotics and Blood Coagulation. J. A. M. A., **142**: 505, 1950.
[36] Quick, A. J.: Hemostatic Dysfunction of Hemophilia. Am. J. Med. Sci., **214**: 272, 1947.
[37] Hirschboeck, J. S., and W. L. Coffey, Jr.: Method for Measuring Clot Retraction Time. Arch. Path., **33**: 380, 1942.
[38] Hirschboeck, J. S., and W. L. Coffey, Jr.: Clot Retraction Time. Am. J. Med. Sci., **205**: 727, 1943.

AWARD FOR OUTSTANDING RESEARCH IN THE FIELD OF INFERTILITY

The American Society for the Study of Sterility offers an annual award of $1000 known as the Ortho Award, for an outstanding contribution to the subject of infertility and sterility. Competition is open to those in clinical practice as well as individuals whose work is restricted to research in the basic sciences. Essays submitted for the 1951 contest must be received not later than March 1, 1951. The Prize Essay will appear on the program of the 1951 meeting of the Society. For full particulars, address The American Society for the Study of Sterility, 20 Magnolia Terrace, Springfield, Mass.