Mesenteric Vascular Occlusion: Report of an Instance with Acute Venous Thrombosis Following Splenic Artery Embolism and Infarction*

By

ELMER MILCH, M.D.

and

GEORGE MASOTTI, M.D.

BUFFALO, NEW YORK

FEW disease entities in medicine make their appearance so dramatically, present so obscure a picture, and run so rapidly a fatal course in a large percentage of instances, as do the cases of mesenteric, vascular occlusion.

The term "mesenteric vascular occlusion" is to be preferred to "thrombosis" or "embolism," as it includes both of these conditions, and, therefore, it is less confusing unless one refers specifically to either a thrombosis or an embolism.

HISTORICAL DATA

The first case was reported by Tiedeman in 1843. Virchow, in 1847, was the first who described the pathology. In 1863, Kussmaul and Gerhardt made the first attempt to establish a definite clinical syndrome. From then until 1904 there is a paucity of literature concerning mesenteric occlusion, at which time Jackson, Porter and Quimby collected and carefully analyzed 214 cases from the literature and their own personal experience. In 1913, Trotter published his Cambridge monograph on "Embolism and Thrombosis of the Mesenteric Vessels" in which he summarized all the work done on the subject to that date. Since then the literature has become replete with summaries and case reports, perhaps the most comprehensive of which is that of Warren and Eberhard.

It is the purpose of the present contribution to review a few of the more salient features of venous and arterial mesenteric occlusion, and to report an instance of mesenteric, venous occlusion due to a comparatively rare combination of etiologic factors.

PATHOGENESIS

The pathologic changes produced by an occlusion of either the *arterial* or the *venous* mesenteric circulation are quite constant. The end result comprises a hemorrhagic infarction of the affected bowel. When the artery is occluded by either a thrombus or an embolus, the first change noted is a distinct edema associated with a leukocytic infiltration composed chiefly of mononuclear and polymorphonuclear leukocytes. As a result, the tissues become markedly swollen. Discrete capillary hemorrhages appear and the capillaries and venules distend with blood. Villi degenerate. Necrosis and gangrene constitute the terminal pathology.

The end result of *venous* mesenteric occlusion is essentially the same, only it is brought about in a different fashion. When the collateral venous circulation is not sufficient to cope with the occlusion, the blood remains in the venous capillaries. New blood is constantly being fed to these structures by the arteries, so that eventually the veins distend and become paralyzed. This leads to an extravasation of serum and blood between the intestinal coats and the production of a hemorrhagic infarct, accompanied by gangrene.

ANATOMICAL CONSIDERATIONS

The *superior mesenteric* artery arises from the anterior surface of the aorta about 1.25 cm. below the celiac artery; it supplies the entire small intestine from the duodenal-jejunal flexure to the ileo-cecal valve, cecum, ascending colon, and one-half of the transverse colon. It has numerous branches, each of which anastomoses with the other to form 3 or 4 tiers of "arcades." Where the most distal of these twigs enters the intestine a final anastomosis takes place. Likewise, the *inferior mesenteric* artery, which supplies the remainder of the large bowel to the pelvic colon, has many anastomoses. In addition, the *inferior phrenic artery* is linked with the upper jejunal, to the hepatic, gastro-duodenal, superior and inferior pancreatico-duodenal vessels. The *internal iliac* and inferior mesenteric arteries are linked through the internal pudic, inferior and middle hemorrhoidal arteries.

The *mesenteric venous circulation* has an even more pronounced and abundant collateral circulation. The chief vessels and their branches, which correspond to the arteries, practically have similar anastomoses. In addition, there exist numerous anastomoses between the portal and systemic circulation by means of small systems of tributary veins too numerous to detail.

EXPERIMENTAL CONSIDERATIONS

Since such a rich network of arterial and venous anastomoses is present, one naturally wonders why an occlusion should produce infarction in such a great number of instances. Numerous investigators have attempted to solve this problem. Among the outstanding of these workers are Conheim, Litten, Cohn, Bolognesi, and Reich. Their results do not agree in their entirety, but they do so on certain essential points.

If the *superior mesenteric artery* is ligated at its trunk, the affected portion of the intestine is immediately thrown into violent paroxysms or spasm, lasting 2 to 3 hours; such automatically increase the peripheral resistance, and prevent a dilatation of the capillaries, upon which the establishment of a collateral circulation is entirely dependent; an infarct follows. Very few cases do not react in the above fashion, and the collateral circulation may handle the situation, but

*From The Pathological Laboratory, Buffalo General Hospital (K. Terplan, M.D., Director) and the First Medical Service (N. G. Russell, M.D., and A. H. Aaron, M.D., Attending Physicians).

Submitted May 14, 1936.

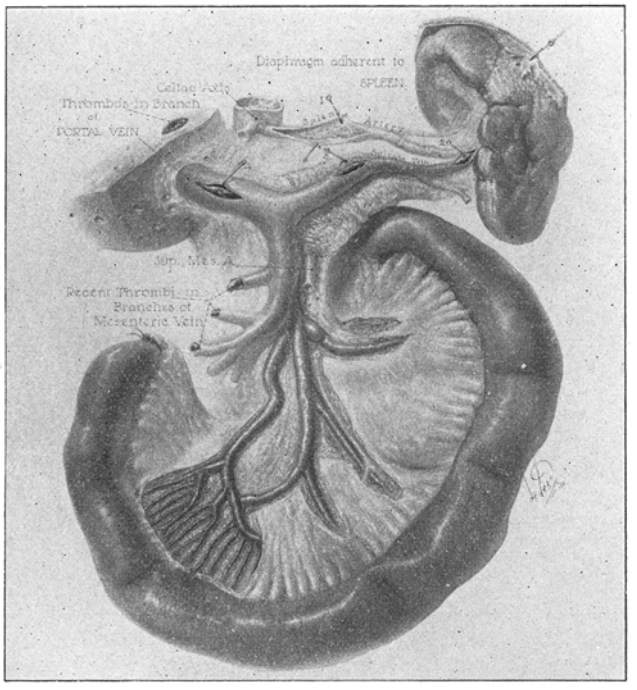

Fig. 1. Gross appearance of embolus in the splenic artery: infarction of the spleen, venous thrombosis, and hemorrhagic infarction of the intestines.

even that breaks down later in the patient's life when the original and primary etiologic factors are aggravated. A third possibility is that mesenteric occlusion may interfere with the circulation of the intestine only to the extent of destroying its function, but not doing so sufficiently to cause gangrene; in this fashion, a "functional" obstruction is produced.

If the occlusion is in a branch of the inferior mesenteric artery, whether or not an infarction will follow, is dependent entirely upon the size of the vessel and the amount of bowel which it nourishes.

In animals, ligation of the *superior mesenteric vein* is always associated with hemorrhagic infarction. However, in man, mesenteric venous occlusion definitely is a slower process. A great portion of the mesenteric venous circulation may be occluded before infarction results. Reich, after a careful analysis, concludes that infarction ensues only when the thrombus in the mesenteric vein extends so far into the smaller tributaries that it has reached the intestinal wall. In this manner, the clot extends into the mural "arcades," and, in so doing, prevents them from anastomosing with arcades of the adjacent free vessels, thence from emptying into the main veins above or below the superior level of the thrombosis.

INCIDENCE

The frequency with which the arterial system is involved as compared with the venous system varies according to the experiments of different investigators; both extremes are encountered. Most writers agree, however, that the incidence of arterial occlusion is greater than that of venous, in the ratio of 3:2.

The superior mesenteric artery is involved approximately 40 times more often than the inferior mesenteric artery. Three reasons have been advanced in an attempt to explain this preponderance: (1) the superior mesenteric artery has a diameter 3 times as great as that of the inferior mesenteric artery; (2) the superior mesenteric artery lies almost parallel with the aorta, whereas, the inferior mesenteric artery leaves the aorta at an angle of 45°; (3) because of its origin, the superior mesenteric artery has the first opportunity to intercept an embolus.

Primary occlusion of the superior mesenteric vein *alone* comparatively is an uncommon lesion, although there have been a few isolated instances recorded. Usually, the vein is involved terminally in a process descending from the portal vein or one of its tributaries. Thrombosis of the inferior mesenteric vein, *per se,* is of rare occurrence, and when present only occasionally results in infarction because of the elaborate collateral circulation for the relatively small area drained.

ETIOLOGY

The etiologic factors concerned in mesenteric occlusion vary. Infarction, as a result of closure of the arteries, may be due either to a thrombosis or to an embolus. Factors which predispose to thrombosis are arteriosclerosis and arteritis. Those which predispose to embolism are: (1) endocarditis, (2) cardiac parietal thrombi, (3) and possibly ulcerated atheromatous plaques (?) etc.

Mesenteric venous occlusion practically is always due to thrombosis. One case (Moloschin's) due to a retrograde embolism, has been reported. The occurrence of venous occlusion by embolism is so rare as to make the condition almost negligible. Here, again, constitutional diseases which predispose a patient to thrombosis may cause either primary closure of the mesenteric vein or terminal involvement in a descending thrombotic process. The causative agents of mesenteric venous occlusion are generally divided into four main groups:

A—Infectious: This group includes all cases in which there are infections in the region drained by the mesenteric veins; such permit penetration of the vein walls by bacteria, and the setting up of a local phlebitis, *e.g.*: appendicitis, pelvic abscess, severe enteritides, peritonitis, subdiaphragmatic abscess, perforated peptic ulcer.

B—Hematogenous: This group consists of the blood dyscrasias which so alter the constitution of the blood

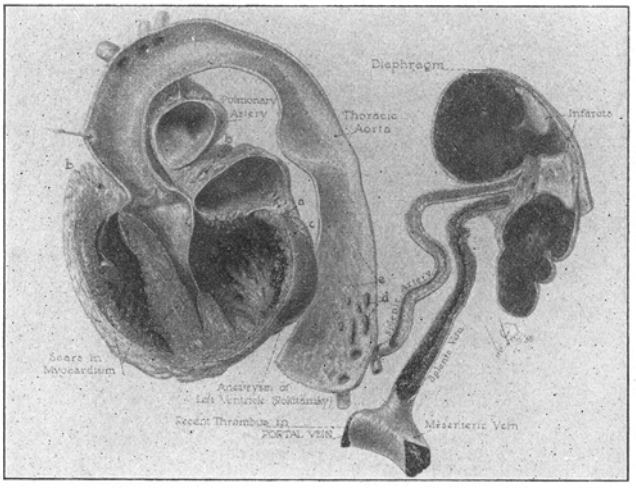

Fig. 2. Diagrammatic representation of coronary occlusion (a, b), parietal thrombi (c), thrombi in aorta (d), splenic artery embolus, infarction of spleen, and venous thrombosis.

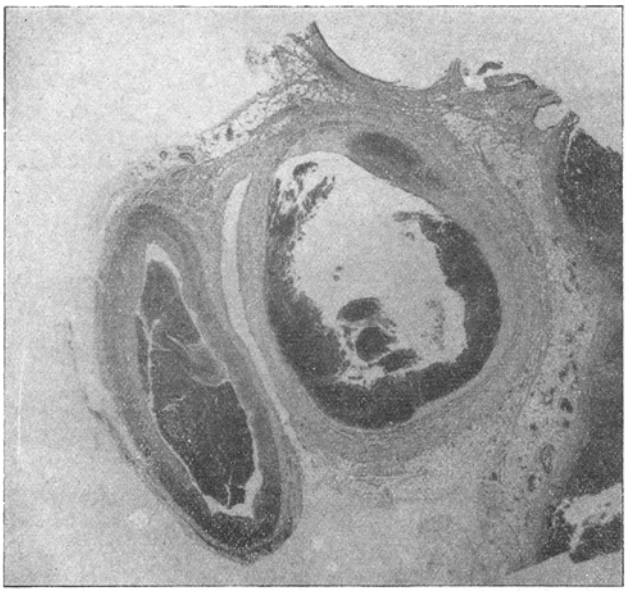

Fig. 3. Cross-section of splenic artery and vein showing embolus and thrombus in each respectively.

that there is a definite tendency to thrombus formation, *e.g.:* splenic anemias, polycythemia *vera.*

C—Traumatic: This group is comprised of those cases in which the thrombosis is the end-result of injury, *e.g.:* abdominal surgical procedures, tearing of the mesentery, rupture of a viscus.

D—Mechanical: This group, perhaps the largest, includes those cases which are due to occlusion of the veins by (1) regional neoplastic processes, (2) portal stasis caused by such entities as cirrhosis of liver, hepatitis, syphilis, cavernomatous transformation of the portal vein; (3) adhesions, (4) volvulus, (5) strangulated herniae.

PERSONAL EXPERIENCE

The Buffalo General Hospital is an institution serving both a private and ward clientele. It cares for medical and surgical cases and averages approximately 9,000 admissions per year not including those received in the Out-patient Department. Of these admissions about 58% are surgical cases.

During the years 1927-34, there were 72,409 admissions of which 44,502 were surgical patients. Mesenteric vascular occlusion was found in 17 cases. The incidence of mesenteric occlusion, proven either by necropsy or by operation among the general admissions was .015%, and among the surgical admissions .025%. In the same time-period, there were 1395 autopsies; mesenteric occlusion comprised 0.6% of the necropsies. Of these, 40% were instances of arterial occlusion and 60% were those of venous occlusion.

The average age incidence of these cases was 44 years, the youngest was 20 years, and the oldest 66 years. Peculiarly, in our series, males predominated in the ratio of 11-6; only in this respect did our statistical analysis exhibit a marked difference from instances recorded by other observers.

We were fortunate either in making the definite diagnosis of or in suspecting mesenteric vascular occlusion in 25% of the patients, but unfortunate in experiencing a mortality rate of 100%, whether or not the subjects came to surgery. We were unfortunate again in having no instances of spontaneous recovery such as has been reported repeatedly in the literature.

The average time duration from the onset of symptoms to hospital admission was slightly more than 54 hours. Of course, we had no way of determining how long the occlusion had been present before signs and symptoms developed.

Post-mortem observations: Of the 17 cases, 10 came to necropsy. The following is a list of the *causes of the mesenteric vascular occlusion:* arterial occlusion was caused twice by emboli originating in an aortic and mitral endocarditis; twice by emboli from mural thrombi in a fibrillating heart; and once by thrombosis associated with marked atherosclerotic changes in the wall of the superior mesenteric artery; venous occlusion was caused three times by thrombophlebitis associated with appendicitis; once subsequent to splenectomy, and once following splenic infarction, brought about by emboli carried into the splenic artery from cardiac mural thrombi. (This last case will be described in detail later).

CLINICAL PICTURE

The clinical picture essentially is alike for both arterial and venous occlusion. There are two accepted syndromes: one, *acute;* and two, *chronic* or "phlegmatic." The latter form rarely is diagnosed clinically, exhibits very vague and obscure gastro-intestinal symptoms, which to the clinician often are meaningless. It is usually associated with venous occlusion and is only recognized *in vivo,* as a rule, when, violently and dramatically, it assumes the characteristics of the acute group.

Pain is the outstanding symptom. Generally it comes on suddenly and, more often than not, without any premonitory symptoms. It is severe, lancinating, and colicky in nature at the start. It may be generalized throughout the abdomen, but frequently is localized in one area. The patient verges on complete collapse. The pulse is rapid, thready and weak. The lips are cyanotic and the extremities cold and clammy. Initially, temperature is subnormal. The patient is restless and apprehensive; he seems to realize as if by a sixth sense, that he is desperately ill. The pain may disappear only to return repeatedly in the same form; the time interval between attacks becomes less and less.

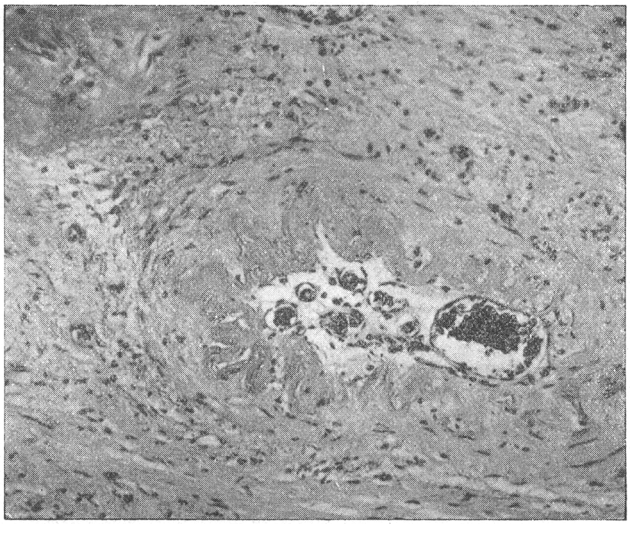

Fig. 4. Splenic artery with recanalization.

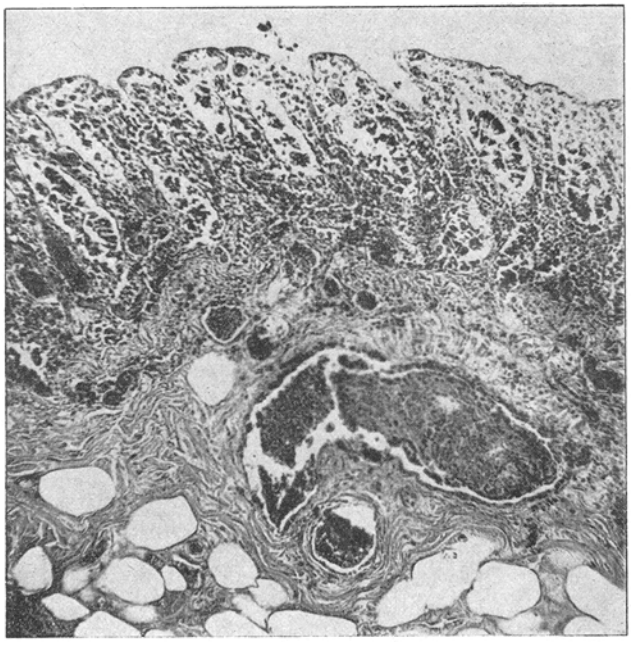

Fig. 5. Jejunum showing hemorrhagic infarction with recent thrombi in the submucosal veins.

Emesis is a quite constant sign, and at this stage is reflex. *Constipation* or *diarrhea,* or both, may occur. *Melena,* when present, indicates that some mechanism is causing serious interference with the intestinal blood supply.

At this stage, there are few *physical findings.* Generalized or localized tenderness may exist; as yet there has occurred no irritation of the parietal peritoneum and consequently there is no muscle spasm.

Very early in the clinical episode, however, a marked leucocytosis customarily is found, associated with a distinct increase in the percentage of polymorphonuclear leukocytes.

If the patient survives the initial shock, and mesenteric occlusion is neither diagnosed nor suspected, the picture rapidly progresses to one of intestinal obstruction. The pain loses its rhythmic character and becomes a constant, persistant, dull ache of peritonitis. The emesis is no longer reflex but obstructive. If bloody, it indicates a high circulatory interference involving the jejunum; it is a grave prognostic omen. At this stage, the course rapidly assumes the terminal features of intestinal obstruction and peritonitis.

Kussmaul and Gerhardt, in 1863, advanced certain postulates to aid the clinician in suspecting or actually making the pre-operative or ante-mortem diagnosis of mesenteric occlusion. These postulates are still held good:

(1)—The source for an embolus or thrombus, (2)—The presence of embolic phenomena elsewhere in the body, (3)—Melena, not to be accounted for by a primary intestinal lesion, (4)—Acute, severe, lancinating, colicky, abdominal pain, (5)—Subnormal temperature at the onset.

The *differential diagnosis* must consider the possible presence of any acute, abdominal surgical lesion; reference well may be made to the statement of Ross, in which he claims that in the majority of cases mesenteric occlusion is not a question of wrong diagnosis, but one of no diagnosis.

TREATMENT

If mesenteric vascular occlusion is to be treated intelligently it has to be diagnosed or suspected very soon after the onset of symptoms. The treatment is the same as that for any form of intestinal obstruction, *i.e.* early surgery. One point need be emphasized. No matter how critical the patient's condition appears unless the infarcted portion of bowel is removed it will terminate fatally in almost 100% of cases.

CASE REPORT

First admission 1/8/35. Service of Doctors Wright and Regan. The patient was a white male, aged 53 years, whose occupation was that of a waiter.

For the past eight months he had noticed a bluish discoloration of both feet, and that they had become progressively colder to touch. Two months before the patient inadvertently dropped a dresser drawer across the metatarsals of the left foot, and, subsequently, he was troubled with severe pain in the left foot, most marked in the fourth toe. The toe gradually assumed a darker hue and the pain became more severe. The patient consulted his personal physician, who administered a course of foreign protein therapy (typhoid vaccine); this aggravated the symptoms. On admission to our hospital the patient was unable to walk, and the foot had to be held below the level of the bed for the greatest degree of comfort.

The past history revealed a gastric hemorrhage four years ago, the etiology of which could not be ascertained and a bilateral thrombophlebitis of both lower extremities subsequent to a motor accident two years ago.

Examination: The temperature, pulse and respirations were normal. The heart was enlarged definitely to the left, and no murmurs were present. Both feet were cold and cyanotic. The fourth toe of the left foot exhibited dry gangrene. The dorsalis pedis and posterior tibial arteries were not palpable on the left leg and were barely palpable on the right.

The urine had a specific gravity of 1018, its analysis negative. The r. b. c. was 4,000,000; Hg. 80(S); color index 1. The w. b. c. was 12,500; the differential count was normal. The blood sugar was 115 mgms. and blood urea N. 11 mgms. The Kahn and Wassermann tests were negative with all antigens. Radiographic examination of the lower extremities did not reveal any evidence of calcification in the arteries.

On 1/14/35 Doctor Regan crushed the posterior tibial and superficial peroneal nerves for the sole purpose of relieving the excruciating pain. On 1/24/35 he amputated the gangrenous toe, and shortly thereafter Buerger's exercises were inaugurated. On 1/30/35 hyperemia and slight edema developed along the course of the right saphenous vein. This responded nicely to conservative treatment. On 3/3/35 the patient was discharged to the care of his private physician. All of the operative wounds had healed nicely, and there had been no pain since the nerves were crushed.

Second admission, 9/18/35—service of Doctor N. G. Russell. Since his discharge the patient had been in excellent health until approximately 4 weeks prior to readmission; at this time he began to experience constant, persistent, dull, gnawing pain, just to the left of the epigastrium; this pain was not relieved by food or alkali. On 9/7/35, about one hour after eating his evening meal, he experienced a sudden, severe, excruciating and lancinating pain in the abdomen and he collapsed. About 2 a.m. he vomited what was described as coffee-ground material. After vomiting he drank some water, but immediately regurgiated the liquid plus some blood clots. About this time he developed a bloody diarrhea. The patient required repeated ½ grain

doses of morphine for relief, and the morning of 9/8/35 was admitted to the hospital; this was approximately 15 hours after the onset of symptoms.

Temperature 100(R), pulse 140, Respirations 12.

Physical examination revealed a desperately ill patient, apprehensive, cold, clammy, and with a peculiar ashen gray cyanosis about the face. There were a few crackling rales at the bases of both lungs. The heart was very rapid, tones distant, regular; there were no murmurs. Blood pressure 104/86, (pulse pressure 18!) The abdomen was not distended, but there was marked tenderness in the epigastrium and in the left flank. At no time could muscle spasm or a mass be demonstrated. Rectal examination revealed no abnormalities.

The urine had a specific gravity of 1020; albumen and glucose were 1-plus, and the sediment revealed many w. b. cells and an occasional r. b. cell. The r. b. cell count was 5,000,000, Hg. 100% (T); the w.b.c. was 35,000, polys 93%. The blood sugar was 248 mgms.. and urea N. 41 mgms. per 100 c.c. The stool exhibited 4-plus occult blood, and was watery and grossly bloody.

The electrocardiogram was interpreted as showing no change significant of recent coronary occlusion, but definite changes referable to an old infarction.

The patient failed rapidly in spite of all the supportive therapeutic measures instituted. Death occurred 26 hours subsequent to hospital admission.

The clinical diagnosis rested between a perforating and penetrating ulcer involving the pancreas and a mesenteric thrombosis.

Necropsy findings: The autopsy was performed 30 minutes after death. The pertinent anatomical features were — total occlusion of the circumflexing branch of the left coronary artery by a completely obliterative thrombosis; marked narrowing of the oblique descending branch in the anterior wall of the left ventricle; moderate atherosclerosis of the descending anterior branch of the left coronary artery without complete obstruction; very extensive fibrous myomalacia of the left ventricle, most marked in the posterior wall, with several polypoid vegetations attached to the fibrous endocardium; distinct diffuse fibrosis of the anterior wall decreasing in severity towards the septum; so-called "diffuse wall aneurysm" of the left ventricle, especially at the anterior and posterior walls from fibrous organization of myomalacious infarcts. (Rokitansky aneurysm); distinctly dilated left ventricle; marked atherosclerosis of the lower thoracic and entire abdominal aorta; localized recent parietal thrombi at the lower end of the thoracic aorta; multiple old infarctions of the spleen, with extensive adhesions to the diaphragm; considerable atherosclerosis of the splenic artery (aneurysm serpentinum).

There were *complete occlusion of the distal portion of the splenic artery by thromb-embolus;* firm adhesions between splenic artery and splenic vein near and at the hilus; *obliteration of the distal portion of the splenic vein by an organized thrombus; more recent ascending thrombosis in the proximal part of the splenic vein; entirely recent massive thrombosis of the mesenteric vein; portal vein, and colic vein, with recent hemorrhagic infarction of the upper jejunum, and hemorrhagic necrosis of its entire wall;* very severe enterorrhagia; no hemorrhagic necrosis in lower jejunum and ileum; approximately 1,000 c.c. of thin blood tinged fluid in the peritoneal cavity.

The involved portion of the intestine measured 65 cm. and was markedly distended. The serosa presented a dusky bluish red hue, and was covered with flakes of fibrin. The bowel wall felt soggy, edematous, and was studded with many petechial hemorrhages. The normal sheen and lustre of the peritoneal coat had entirely disappeared. There were a few focal areas of necrosis, varying in size from pinhead to split pea. The arterial mesenteric system exhibited no gross involvement. The thrombosis of the portal and mesenteric veins was very recent, dark red in color and only slightly adherent to the intima. It extended into the smallest of the mural arcades on the intestinal wall. The thrombosis of the splenic vein felt firm, was grayish red in color, completely adherent to the intima, and extended directly into a large infarcted area located in the hilus of the spleen.

On serial sagittal section of the spleen, an old, firm, wedge shaped, infarct was found measuring 3 x 2.5 x 0.5 cm. beginning in the hilus of the spleen, and extending through the entire splenic structure, to the serosa on the opposite side. The apex of the wedge was situated in the hilus, and the fan shaped portion at the periphery. The splenic artery and vein, together with their associated thrombi could be traced directly into the apex of the infarcted portion of the spleen.

Splenic artery: Histologically, the intima for the most part was of average thickness. In certain localized areas, however, it was markedly thickened, apparently due to fibrous tissue. The internal elastic membrane had undergone reduplication. The tunica media was of normal width. The adventitia was composed of fibrous tissue, and in sections examined was not adherent to the vein. It contained a few scattered lymphocytes. The lumen was practically entirely filled with thromb-embolus composed chiefly of fibrin, red blood cells, and a very few leukocytes. In one area it was adherent to the intima, and here the endothelium was deficient. The thromb-embolus exhibited a focal area of organization. No evidence of a tuberculous or leutic arteritis could be demonstrated.

Spleen: Typical anemic infarction with beginning organization and reactive inflammation.

Splenic vein: The vein was completely occluded by an adherent thrombus made up of fibrin, red blood cells, and leukocytes. The wall appeared not remarkable. There was no evidence of a phlebitis.

Intestine: Practically complete necrosis of the mucosa and submucosa was present with small isolated areas of desquamation. The mucosal and submucosal vessels were markedly injected. Distinct recent hemorrhages were visible in the mucosa and submucosa. Submucosal veins showed recent thrombi, composed of fibrin, red cells, and leukocytes. Surrounding the veins was a distinct leukocytic infiltration. The entire picture was that of hemorrhagic necrosis with recent venous thrombosis.

SUMMARY

A case of mesenteric venous occlusion subsequent to infarction of the spleen is reported.

This case seems worthy of recording, not alone because of the symptomatology, but because of the sequence of etiologic factors concerned in the production of the pathologic lesions which were demonstrated post-mortem. Two sources manifest themselves as a possible origin of the thromb-embolus demonstrated in the splenic artery with the production of an anemic infarct located at the hilus of the spleen. (1), the polypoid vegetations found at autopsy clinging to the fibrous endocardium, and (2), the parietal thrombi situated in the lower third of the thoracic aorta. We feel that based merely on the incidence of occurrence, the most likely site of the two was in the heart. Since it is a proven fact that infarction of any tissue will produce thrombosis in the veins and the splenic vein was proved both grossly and histologically, to have its origin in the infarcted area, it is proper to assume that the original embolus causing the splenic infarct also was indirectly the cause of the thrombosis in the splenic vein. Also we feel that the terminal, mesenteric, venous occlusion definitely was a descending thrombotic process of some duration, as evidenced by

the gross and histologic appearance of the thrombus in different areas of the vein.

Bacterial stains (Gram and methylene blue), did not reveal the presence of any organisms in either the splenic artery or vein. Careful macroscopic and microscopic studies for a specific arteritis or phlebitis (tuberculous or syphilitic) as the causative agents in the production of the thrombosis were negative. As far as we are able to determine the splenic vein thrombosis was not due to adhesions between the artery and vein which may have formed after the throm-embolus occurred in the splenic artery.

A careful search of the literature revealed many cases of mesenteric, vascular occlusion, with incidental findings of infarctions in the spleen, or splenic vein thrombosis with a subsequent descending thrombosis of the mesenteric vein. However, the only case which we discovered in which mesenteric occlusion is a direct result of a splenic infarction, was one reported by L. T. Webster in 1921. This was a 45 year old man, who had a penetrating ulcer of the stomach with perforation into the splenic artery with a resultant thrombosis of this artery followed by massive infarction of the spleen, and terminally, a complete descending thrombosis of the portal system initiated in the splenic vein. We were unable to find record of any proved report in which the thrombosis of the splenic vein was due to a splenic infarction having as its source a thromboembolus originating in the heart, and lodging in the splenic artery.

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SECTION II—*Experimental Physiology*

An Investigation into the Production of a Proteolytic Ferment in the Duodenum which will Increase the Anti-anemic Efficacy of Liver; Its Relationship to the Cause of Pernicious Anemia*

By

GARNETT CHENEY, M.D.

SAN FRANCISCO, CALIFORNIA

THE theory that pernicious anemia is due to the absence in the stomach of an intrinsic gastric factor, probably a proteolytic ferment, has received wide acceptance, but has seemed inadequate to the minds of a number of investigators (1, 2, 3, 4). The experiments herein described by the author apparently demonstrate the presence of this factor or ferment in the duodenal mucosa in a concentration equal to or greater than in the gastric mucosa. Proof of its presence in the small intestine would greatly alter the present concept of the etiological factors contributing to the cause of macrocytic hyperchromic anemias.

A vast amount of recent experimental work has led to the following explanation for the development of pernicious anemia, which has been widely accepted despite the recent report of Greenspon (5) to the contrary. Briefly, certain elements of the diet, notably muscle and organ tissue, supply a source of material which can normally be digested in the stomach to produce a substance necessary for the maturation of red blood corpuscles. Castle has called this part of the diet the extrinsic factor. He has named the digesting agent or unknown proteolytic ferment the intrinsic gastric factor. The substance produced by the interaction of these two factors may be termed an anti-anemic substance or maturation substance. The extrinsic factor is contained in most meats which are injested, particularly beef muscle, and in yeast preparations. Liver is an extremely rich source of this factor. The intrinsic factor has heretofore only been demonstrated in the gastric juice and the gastric mucosa. It is characteristically absent in pernicious anemia, or greatly diminished in amount (6). Consequently the necessary maturation substance is not formed and anemia results. However, this maturation substance

*From the Department of Medicine, Stanford University Medical School.