Acute Hemorrhage and Necrosis of the Intestines
Associated with Digitalization

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ENTEROCOLITIS is a rather common entity seen often in a variety of forms by the clinician and the pathologist. There have been four reports of special types of gastrointestinal lesions in the patient with cardiovascular disease. Kleckner et al. reported two cases of cardiac disease with acute pseudomembranous enterocolitis. Wilson and Qualheim described a form of acute hemorrhagic enterocolitis afflicting chronically ill individuals. They considered this to be unlike acute pseudomembranous colitis. Seventeen of their 20 cases had chronic cardiovascular disease. Ende described infarction of the bowel in cardiac failure in six cases. Recently, Katz described a hemorrhagic duodenitis in myocardial infarction.

During the past 10 years we have observed, clinically and at autopsy, 10 cases of acute hemorrhage and necrosis of the bowel in patients with cardiac disease. In one additional case no autopsy was obtained but similar pathologic lesions were seen at laparotomy. Although the etiology is not apparent, it is of interest that all these patients had received large amounts of digitalis and several were in digitalis toxicity. Digitalization is considered as the main associated factor in these cases, especially since there was no mesenteric arterial involvement and only venous engorgement.

Case Reports

Case 1

A 72-year-old white man was admitted to the hospital because of syphilitic heart disease with congestive heart failure and atrial fibrillation.

About 1 year earlier he began having dyspnea and took tincture of digitalis until one month before admission. In the hospital 0.3 Gm. of digitalis leaf was given daily for 13 days, a total of 3.9 Gm., in order to reduce the ventricular rate to 80. Subsequently, maintenance dosage was 0.2 Gm. daily. He had seven subsequent admissions in the next 11/2 years for congestive heart failure and during the fourth admission was given an extra 0.5 mg. of digi- toxicin in addition to maintenance digitalis dosage. For 1 month prior to his last admission the patient had been taking 0.3 to 0.4 Gm. of digitalis leaf per day as he thought necessary for dyspnea. The day before admission he began to have some nausea and vomiting. The vomiting continued and 3 days later his abdomen became extremely tender with muscle guarding. An exploratory laparotomy was done because of the possibility of a mesenteric embolism or thrombosis. The entire small bowel beginning at the ligament of Trietz, cecum, and colon were dark and appeared nonviable. Sixteen hours later the patient died.

Case 2

A 58-year-old Negro was admitted to the hospital because of syphilitic heart disease with congestive failure. He was taking digitoxin, 0.2 mg. twice per day, for an unknown length of time. On the second day after admission 0.3 Gm. of digitalis leaf was begun daily and was continued until death. An electrocardiogram revealed second-degree atrioventricular block. On the fourth hospital day the patient complained of epigastric pain and passed a tarry stool. At this time his blood pressure was 188/70 and the hemoglobin was 9 Gm. per cent. Tarry stools continued until death 4 days later.

Case 3

A 66-year-old Negro woman was admitted to the hospital because of hypertensive cardiovascular disease with congestive failure. She was digitalized with a total of 2 Gm. of digitalis leaf and maintained on 0.1 Gm. daily. The patient was readmitted 11 months later because of congestive failure. During the first 24 hours of this period she was given 1.2 Gm. of digitalis leaf and subsequently 0.2 Gm. daily along with mercurial diuretics. About 2 weeks later, premature beats were noted and 3 days later an electrocardiogram re-
revealed premature ventricular beats as trigeminy and first-degree atrioventricular block. Nausea developed, and the digitalis was stopped. Five days later she was compensated but began to have abdominal pain with marked tenderness. Abdominal tenderness was still present 24 hours later and the blood pressure was stable at 120/80. A few hours later she vomited blood and died.

Case 4

A 62-year-old white man was admitted to the hospital because of hypertensive cardiovascular disease with congestive failure. He had intermittent episodes of congestive failure for 4 years and was taking 0.1 Gm. of digitalis daily. On this admission 0.5 Gm. of digitalis leaf was given and then 0.2 Gm. daily. The patient was readmitted 11 months later because of congestive failure and received 0.3 Gm. of digitalis leaf daily for 11 days when it was increased to 0.3 Gm. per day. Also, at this time 4 ml. of digalen were given intramuscularly because of rapid atrial fibrillation. Two days later digitoxin 0.3 mg. was given and continued daily until death. He became compensated and his ventricular rate slowed to 86 beats per minute. Six weeks later, however, he had a profuse liquid black stool and complained of lower abdominal pain. The blood pressure remained at a level of 220/110 and the hemoglobin was 14 Gm. per cent. A week later the patient began to vomit and complained of epigastric pain. Nausea and vomiting continued for 3 days until he died after a hematemesis.

Case 5

A 71-year-old Negro man was admitted to the hospital in congestive heart failure with a diagnosis of hypertensive cardiovascular disease. He received 1.6 Gm. of digitalis leaf and was maintained with 0.1 Gm. daily. The patient was readmitted to the hospital 20 months later and the digitalis was increased to 0.2 Gm. per day. Subsequently digoxin, 0.25 mg. twice per day, was given instead of digitalis leaf. He was readmitted 2½ years later because of an injury to his right leg of 1 month's duration. He appeared to be compensated and was maintained on 0.2 Gm. of digitalis leaf per day. After 2 weeks he developed extreme generalized abdominal tenderness and voluntary rigidity with active peristalsis and died several hours later.

Case 6

An 81-year-old white woman was admitted to the hospital because of arteriosclerotic heart disease with congestive heart failure. She had been digitalized previously and was on maintenance dosage and metacaptoperin (Thiomerin) 2 ml. intramuscularly per week. Two days prior to admission she began to have nausea and vomiting. The electrocardiogram revealed left ventricular hypertrophy, ST-T changes of digitalis, and ventricular bigeminy. The vomiting continued over a 24-hour period with vague generalized abdominal pain and tenderness and slight distention. Digitalis was discontinued, and a Levine tube was passed. Forty-eight hours after admission she suddenly became unconscious, developed a very irregular rhythm, and died.

Case 7

A 55-year-old Negro woman was admitted to the hospital with a cerebral vascular accident and rapid atrial fibrillation. She received a total of 2 mg. of lanatoside C (Cedilanid) intravenously over an 8-hour period with a slowing of the ventricular rate from 180 to 120. In spite of supportive therapy she weakened rapidly and died 10 hours after admission.

Case 8

A 72-year-old white man was admitted to the hospital because of arteriosclerotic heart disease with congestive heart failure. For 2 years prior to admission he had intermittent episodes of congestive failure requiring increases in his maintenance digitalis and diuretics. The day prior to admission an additional 1 mg. of digoxin was given and maintenance was started of digitalis leaf, 0.2 Gm. daily. While in the hospital the patient received diuretics, 2 ml., and potassium solution three times per day. Episodes of sudden dyspnea and cough occurred and anticoagulation was started because of the possibility of pulmonary emboli. After 1 week he began to have epigastric pain, which gradually increased with generalized abdominal tenderness. He progressively weakened and died 2 days later.

Case 9

A 68-year-old Negro woman was admitted to the hospital because of hypertensive arteriosclerotic heart disease with congestive heart failure. Three days prior to admission she was given gitalin 2.5 mg. followed with 0.75 mg. every 6 hours for six doses, with a maintenance of 0.5 mg. daily. She also was receiving chlorothiazide, 500 mg. daily. The first day in the hospital 1 mg. of gitalin was given and subsequently 0.1 Gm. of digitalis leaf daily. On admission the patient complained of mild nausea and anorexia. An electrocardiogram revealed first-degree atrioventricular block with periods of complete block. The following day the nausea and anorexia became worse and she had vague abdominal pain. At this time the electrocardiogram revealed atrioventricular dissociation with interference beats. She passed several bloody stools and had some drop in blood pressure but did not develop shock. The abdominal pain increased and bright red blood was passed through
a gastric tube. The blood pressure gradually fell and she died 3 days later.

**Case 10**

A 75-year-old white woman weighing about 70 pounds was admitted to the hospital with arteriosclerotic heart disease and digitalis toxicity. She had dyspnea for about 6 months prior to admission. Each attempt at digitalization produced nausea. Two weeks prior to death she was given digitoxin, 0.2 mg. twice per day, for 1 week then 0.2 mg. daily. She also took Trilafon, which prevented nausea, and 500 mg. of chlorothiazide daily. A few days prior to admission an electrocardiogram showed first-degree atrioventricular block and there was no evidence of heart failure. Admission was necessary because of nausea, vomiting, rapid heart beat, and lower left abdominal pain. The patient was found to be compensated with a blood pressure of 150/90, and there was some tenderness over the left lower quadrant. An electrocardiogram revealed long runs of ventricular tachycardia. She was given 40 mEq. of potassium chloride and 500 ml. of glucose in water with clearing of the ventricular tachycardia and appearance of atrial fibrillation. Over 24 hours the abdominal pain became worse and the blood pressure gradually dropped. She became distended and had marked tenderness in the left lower abdominal quadrant and absent peristalsis. Laparotomy was performed because of the possibility of a mesenteric embolism. The small bowel and entire colon were discolored and appeared to be in varying stages of gangrene. The ileocecal area was involved most. The stomach was normal and the mesenteric arteries appeared patent. The mesenteric veins were congested and thrombosed at the junction of the venules to the bowel. A few hours after surgery the patient died. No autopsy was obtained.

**Case 11**

A 60-year-old Negro woman was admitted to the hospital because of arteriosclerotic heart disease and digitalis toxicity. She was digitalized about 5 years prior to admission and subsequently took 0.1 Gm. of digitalis leaf a day. During the past few months she increased this to twice a day and began to have nausea and vomiting 1 week prior to admission. On admission an electrocardiogram revealed first-degree atrioventricular block and periods of atrioventricular dissociation. The patient appeared compensated and was given intravenous fluids and oral potassium salts. Epigastric pain was noted on the day of admission. Digitalis was resumed at a dose of 0.1 Gm. daily, 3 days after admission. Two days later the abdominal pain became more severe and she gradually became distended with generalized tenderness, bound tenderness, and hypoactive peristalsis. Mesenteric thrombosis was considered, and laparotomy was performed. During this procedure her blood pressure dropped and she required l-arterenol. At surgery, the entire large bowel was discolored greenish black, it contained hemorrhagic material, and its walls were friable. The entire jejunum, colon, and ileum, except for a central five feet, were similarly discolored. All of the bowel was edematous. There was no evidence of mesenteric thrombosis. Extensive resection of involved areas was performed, but the patient died 2 hours later.

**Comment**

The common denominator in these cases was digitalization with definite digitalis toxicity in seven. All these cases were autopsied except case 10, in which the abdomen was explored. The intestinal lesions resembled those described by Wilson and Qualheim and by Ende.

Grossly the intestine is described characteristically as showing marked venous engorgement with hemorrhage and edema of the wall. In the most heavily implicated areas it is purplish or reddish black. These changes are likely to be described as gangrenous by the surgeon or by the pathologist. In the strict sense it is not gangrene, since there is usually very little inflammatory reaction and no massive infarction. There is epithelial devitalization, and in cases that live for a sufficient length of time mucosal necrosis, ulceration, and secondary infection will supervene. The darkening of the intestine is due to the profound venous engorgement (fig. 1), which may be further intensified by blood in the lumen and mucosa. In eight cases there was blood in the lumen of the bowel. The intestinal wall is commonly friable.

Careful dissection of the mesenteric arterial system revealed no instance of thrombosis. In only one instance was there a significant degree of mesenteric arteriosclerosis, and this did not severely compromise the lumen. Venous thrombi were occasionally observed. In two cases thrombi were present at the mesenteric-enteric junction, but were obviously very recent and secondary to the venous stasis. Thrombi occurred in a few other instances but were related to inflammation and ulceration.
Microscopically the most conspicuous feature is the profound degree of venous engorgement, which is most evident in the submucoa, (fig. 2). Hemorrhage into the mucosa and edema of the submucose are constant findings.

The gastrointestinal tract in this condition is not uniformly involved and most commonly shows a segmental or patchy distribution. The stomach was involved in only three instances and seldom to the degree observed in the intestine. Gastric ulcers were present in two others. Some portion of the small intestine was implicated in all instances and the degree of involvement was usually extensive. In four cases the entire small intestine showed conspicuous edema, congestion, and hemorrhage. In two, the ileum was the only portion of the small intestine affected. In one case the vascular engorgement was limited to the jejunum, and in three others various combinations of involvement of the duode-num, jejunum, and ileum were observed. It was remarkable that an uninvolved segment of intestine could occur with massive changes in the contiguous bowel. In four patients the entire colon showed congestive and hemorrhagic phenomena. In one there was no change in the large bowel. Patchy involvement of the colon occurred in the other five cases and in two of these the process did not extend beyond the cecum.

Six of the cases were judged pathologically to be in congestive failure. The presence of failure was based on peripheral edema, excess fluid in the serous cavities, pulmonary edema, and chronic passive congestion of the liver. The liver revealed chronic passive congestion in three cases, sinusoidal congestion in four cases, and no abnormality in four. Those with chronic passive congestion had definite digitalis toxicity.

Discussion
Kleckner et al.1 considered their cardiac cases to have acute pseudomembranous enterocolitis. This form of enterocolitis has been reported in a variety of other situations, such as after surgery, during antibiotic therapy, with shock, and with staphylocoecal infec-

tions. Wilson and Qualheim2 described in 17 cases of chronic cardiovascular disease a form of acute hemorrhagic enterocolitis that they considered to be unlike the acute pseudo-membranous type. Their cases were very similar pathologically to those described in this paper. The only common denominator noted by the authors was cardiovascular disease with congestive failure. They mentioned that "the temporal relationship to vigorous therapy for heart failure with digitalis or digi-toxin and with mercurial diuretic agents is striking in many instances, and it is tempting to ascribe causal relationship to any one of these agents." Ende3 was of the opinion that infarction of the bowel can occur with severe cardiac failure in the presence of insignificant vascular disease of the mesenteric vessels. He encountered this in six cases and described in detail the three most severe ones. In the milder cases, various segments of small bowel were hemorrhagic and the lumen contained frank blood. He believed that these changes represented mild pathologic changes associated with severe cardiac failure by contrast with the much more serious lesion of infarc-tion of the bowel. It was postulated that severe cardiac failure, perhaps aided by vascular spasm, can produce ischemia severe enough to lead to infarction.

Wilson and Qualheim2 mentioned that the liver was chronically congested in one case but did not mention the hepatic status in the others. They did not mention whether or not mesenteric vein congestion was present nor did they note the digitalization status.
of the patients. Ende's mentioned liver congestion in only one of his patients and in another that the blood vessels of the mesentery of the bowel had evidence of congestion but no thrombi. The first of his cases was given digitalis and mercurials but the amounts were not mentioned. A run of ventricular tachycardia occurred in this case. The second case had atrial fibrillation and ventricular bigeminy and was given diuretics and potassium chloride but the amount of digitalis was not stated. The third case had first-degree heart block and was on digitoxin, 0.2 mg. daily.

Portal Congestion Associated with Digitalization in Experimental Conditions

In view of the considerable experimentation and discussion related to the effects of digitalis glycosides on the liver and portal system, it is possible an extracardiac action of digitalis, especially in overdosage, produces pooling of blood in the splanchic venous system.

In 1932 Bauer et al. 6 concluded from work on isolated perfused livers that there was a "sluice or sphincter mechanism" in the livers of dogs. The sphincter mechanism was located near the caval orifices of the main hepatic veins. Epinephrine opened and histamine closed the sluice while both drugs appeared to exert a weak constrictive action on the deeper veins. Specific localization of hepatic sphincters and their dynamic role in circulatory adjustments have been reviewed at length by Knisely and associates. 8 7 Dock and Tainter 8 9 particularly formulated the interpretation that digitalis, in addition to its cardiac effect, acts to reduce active circulating blood volume by pooling blood in the splanchic area through constrictive effects in the hepatic veins. Their experimental observations were supported by those of Katz and associates 10 and, to some degree, by those of Nadler and associates 11 although the latter were led to question the significance of this extracardiac action of digitalis. McMichael and Sharpey-Schafer 12 considered that digitalis may produce its immediate beneficial effect by lowering of the venous pressure, which could be on a basis of constriction of the portal venules in the liver. Thomas and Essex 13 demonstrated that spasm of the hepatic vein could be produced by anaphylactic shock, histamine, digitoxin, hydatid cyst fluid, and anoxia. Eddleman et al. 14 studied the effect of oral digitoxin in 12 normal subjects with the use of the electrokymograph and concluded that it acts to decrease the volume of blood returned to the heart and to increase force of cardiac contraction. More recently, Cotten and associates have used current methods to measure the effects of cardiac glycosides in reducing venous return and cardiac output 15 in the absence of important changes in total plasma volume or extracellular water. 16 These various hemodynamic studies offer indirect but highly suggestive evidence that digitalis exerts constrictive effects in the liver or hepatic vein structures. Such effects presumably can occur to a marked degree with excessive digitalization. Hueper and Ichiniowski 17 found marked congestion and engorgement of the liver with areas of necrosis, hyalinization, and edema in animals poisoned with digitalis leaf.

Clinical Considerations

Congestive failure, especially when chronic in nature, can be an additive factor with overdigitalization. At autopsy, however, four of our cases did not manifest congestive failure and many were clinically compensated.

Figure 2

Distended veins in the edematous submucosa of the intestine. Mucosal hemorrhage is apparent in the upper left. Note the absence of inflammatory reaction.
DIGITALIS AND INTESTINAL NECROSIS

when they developed abdominal symptoms. If congestive failure were the sole cause, then we would expect to see this bowel syndrome more often. Only one of our patients, case 8, had received an anticoagulant, and the prothrombin times in this case were in a satisfactory range. Friedman et al.\textsuperscript{18} demonstrated in dogs that during hemorrhagic shock or administration of epinephrine, constriction of the portal and hepatic veins occurred. Because of the sustained intrahepatic resistance, intestinal hemorrhage and even hemoperitoneum eventually occurred. In our cases there was no evidence of shock prior to or during this syndrome. Five patients had received a mercurial diuretic but this has been discounted as a factor.

This syndrome can be suspected when a patient develops abdominal pain while receiving large amounts of digitalis; unnecessary surgery thus may be avoided. Frequently a diagnosis of mesenteric thrombosis or embolism is suggested. Abdominal examination and flat plates do not reveal any characteristic diagnostic feature. It is well to stress again, especially with the advent of so many new preparations, that patients should be digitized with caution. The antiemetic tranquilizer drugs are often given during digitalization, and so the early nausea of digitalis toxicity may be masked, as occurred in case 10. Also, maintenance digitalis alone can produce toxicity in the presence of potassium loss, such as occurs with diuretics and steroids.

Summary

Eleven cases with acute hemorrhage and necrosis of the bowel are described. In all cases there was high dosage of digitalis and definite toxicity in seven. Digitalis was considered as the main associated factor, especially since there was no mesenteric arterial involvement and, in four cases, there was no congestive failure at autopsy. Hepatic vein or sinusoidal sphincter constriction with resulting portal splanchnic venous congestion was considered as possible mechanisms by which digitalization produced this syndrome.

Acknowledgment

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References


I made a bladder very supple by wetting of it, and then cut off so much of the neck as would make a hole wide enough for the biggest end of the largest fosset to enter, to which the bladder was bound fast. The bladder and fosset contained 74 cubic inches. Having blown up the bladder, I put the small end of the fosset into my mouth: and at the same time pinched my nostrils close, that no air might pass that way, so that I could only breathe to and fro the air contained in the bladder. In less than half a minute I found a considerable difficulty in breathing, and was forced after that to fetch my breath very fast; and at the end of the minute, the suffocating uneasiness was so great, that I was forced to take away the bladder from my mouth. Towards the end of the minute the bladder was become so flaccid, that I could now blow it above half full with the greatest expiration that I could make.—Stephen Hales, B.D., F.R.S. Vegetable Statics, 1727.
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