

EXPERIMENTAL PRODUCTION OF DIGESTIVE TRACT ULCERATIONS

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PLATES 35 AND 36

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In reviewing a series of cases which came to autopsy and showed an unusual type of ulcerative process occurring in the digestive tract, we concluded that the lesions were the result of the compensatory vasomotor phenomena which are known to occur in shock. The vasoconstriction which is the primary reaction in shock, may, if prolonged, lead to pronounced tissue anoxemia, a drop in pressure gradient in the capillaries, increased capillary permeability resulting in edema, diapedesis and finally tissue necrosis with its sequellae. The details of this process have been reviewed elsewhere and need not be repeated here (1, 2).

In order to reproduce the lesions which were observed in our human material we decided to cause a prolonged sympathetic stimulation of the visceral vascular bed. While clinically this may result through reflex neural pathways through the cord as well as *via* the hypothalamus, there is also a hormonal mechanism involving a discharge of adrenalin from the suprarenal glands. In order to simplify the experimental conditions and avoid operative trauma, we determined to use the intraperitoneal injection of sterile adrenalin solution as most closely simulating the prolonged discharge of adrenalin known to occur in shock (3).

Methods

While our original intention had been to limit our experiments to the dog, since this is the animal most commonly employed in shock experiments, our results soon led us to use the cat, rabbit and guinea pig as well.

The intravenous injection of effective doses of adrenalin produces effects which reach their maximum very rapidly, and then disappear within a few minutes. In our hands this yielded only insignificant anatomical changes, in a single injection. We therefore, as noted above, decided to inject the adrenalin intraperitoneally, since it is known that its absorption from this area is relatively slow and that this mode of injection results in a rise of blood sugar which may persist as long as 6 hours (3). We are thus assured of its prolonged absorption and systemic action. In none of our animals did we note

the development of a peritonitis which could be directly attributed to the presence of the drug in the peritoneal cavity.

The site of injection was uniformly the left lower quadrant of the abdomen, as close to the flank and inguinal ligament as was feasible. This site was chosen in order to avoid the possibility of directly traumatizing any fixed, immovable viscus.

The injections were made daily for from 5 to 10 days for the dogs; 5 to 6 days for the cats; 3 to 8 days for the guinea pigs; and 4 to 8 days for the rabbits. Sterile adrenalin hydrochloride solution, 1:1000 was used.

The doses used varied from animal to animal and from day to day. The maximum dose varied between 0.3 and 0.5 mg. per kg. in the case of the dogs; from 1.2 to 4.2 mg. per kg. in the case of the rabbits; and from 0.4 to 1.3 mg. per kg. in the case of the guinea pigs. Inasmuch as the hyperglycemic reaction of adrenalin is much more sensitive than the vasomotor, we feel justified in conservatively estimating the duration of the latter effect in our dogs and cats as about 2 hours. This would indicate a maximum dose varying from about 0.003 to 0.004 mg./kg./min. in the case of the dogs. The corresponding doses for the cats was 0.007 to 0.01 mg./kg./min. According to Trendelenberg (4), the intravenous threshold value for the vasomotor reaction just causing a rise in blood pressure is 0.0005 mg./kg./min., while 0.002 mg./kg./min. causes the maximal rise in blood pressure.

During the course of the experiments the animals were fed their regular diets, and their daily régime was altered in no way from its previous routine except that after the injections, the dogs were placed in their cages because of the occasional occurrence of a rage reaction in which the animal became violently aggressive. In animals which did not react so violently we nevertheless noted the presence of a marked tachycardia, restlessness, panting and cyanosis and occasionally sialorrhea, epiphora, fine tremor and weakness. More rarely, vomiting occurred and occasionally diarrhea, which in the case of some of the cats, was tarry.

The dog experiments were terminated by killing the animals with an intravenous injection of chloroform. In the case of the rabbits, air was injected into the marginal ear vein. The cats and guinea pigs were chloroformed under a cone. One of the cats died as a result of a severe diarrhea leading to a terminal cachexia, and was autopsied, directly it ceased to breathe. One guinea pig succumbed to a perforated gastric ulcer.

The details of the dosage and the locations of lesions are indicated in Table I.

RESULTS

Dogs.—As can be noted from Table I, the major site of localization of the lesions in the dog was the terminal portion of the ileum. The lower limit of the involved intestine was always separated from the ileocecal valve by at least 6 cm. of intestine which appeared normal in the gross.

In the stomach, aside from the mucosal petechiae noted in two instances, there was observed only a marked congestion, limited to the fundus and body of the stomach. In contrast, the antral portion appeared pale.

The duodenum showed an irregularly mottled congestion which increased distally. In one dog there was noted a superficial mucosal erosion near the papilla of Vater.

The focal areas of congestion increased in number distally in the jejunum and fused to form a reddish velvety surface in which pale areas were interspersed. In the lower jejunum small hemorrhagic areas were seen and the bowel contents were frequently blood stained. Small focal ulcerations

TABLE I

Animal No.	Sex	Body weight lost	Number of injections received	Total adrenalin HCl received	Maximum dose	Location and nature of digestive tract lesion				Comment
						Stomach	Small intestine	Cecum	Colon	
		per cent		mg.	mg. per kg.					
Dog 1-45	F	14	5	17.5	0.3		Ulc. ileum			
" 1-46	F	0	10	39.5	0.4		" "		Ulc.	
" 1-49	F	10	6	26	0.4	Petechiae	" "			
" 1-57	F	10	6	18	0.5		" "		Ulc.	
" 1-72	M	13	5	21.5	0.3	Petechiae	" "		"	
" 1-73	M	10	8	34	0.4		" "			
Cat 2-35	F	23	6	13	1.1				Nec.	
" 2-38	F	12	5	10	0.9				"	Died
" 2-55	M	24	6	13	1.9				"	
" 2-87	M	19	6	13	1.2				"	
" 2-76	M	11	6	13	0.9		Mic. nec.		"	
" 4-89	F	5	5	10	1.0	Ulc.	Petechiae		"	
Guinea pig 2-92	M	6	3	1.2	1.2	Perf. ulc.				Died
" " 2-07	M	26	7	2.9	2.2			Ulc. (perf.)		
" " 2-01	M	1	8	4.1	3.2			Hemorrhage		
" " 2-11	F	15	8	7.1	4.2	Ulc.		Ulc.		
Rabbit 2-46	M	12	4	4.0	0.4					Died
" 2-89	M	14	4	4.0	0.56	Ulc.	Nec.	Petechiae	Nec.	"
" 2-66	M	15	7	7.0	0.45				Ulc.	
" 2-65	M	21	8	9.0	1.1		Edema			
" 2-36	M	16	8	9.5	0.95			Ulc.		
" 2-63	M	20	8	12.3	1.3		Mic. nec.	"	Petechiae	

Ulc. = ulceration. Nec. = necrosis. Mic. = microscopic.

could be made out. These increased in number distally and were seen to fuse so that larger ulcerated areas were formed. The smaller ulcerations were limited to the mucosa. The larger ones extended into the submucosa. The bases of these ulcers were hemorrhagic and not infrequently covered with a greenish, diphtheritic pseudomembrane (Figs. 1, 2, and 3).

The ulcerations were generally located on the antimesenteric border of the bowel but where extensive, almost completely encircled it. Even in

the latter instances the mucosa along the mesenteric border was usually well preserved.

The length of the involved intestine varied from 9 cm. to 50 cm. In the instances where the lesion was very extensive, uninvolved areas of varying extent were interspersed in the ulcerated loops. Peyer's patches were frequently seen uninvolved, adjacent to areas of ulcerated mucosa.

In no instance was a peritonitis observed, but in areas in which the ulceration was most severe the hemorrhagic discoloration of the mucosal lesion was reflected through the serosa. There was no thickening of the intestinal wall.

In three instances a lesion was observed, located in the lower sigmoid and rectosigmoid portions of the colon. These lesions showed a small diphtheritic pseudomembrane on the mucosal surface, and were arranged with their long axes perpendicular to the long axis of the bowel.

Microscopically the gastric petechiae showed a focal hemorrhage situated in the stroma between the pits of the glands. The involved areas were intensely congested. The cells of the mucosa in this area showed pyknotic nuclei and the stroma was edematous. Other areas showed focal congestion and edema of the stroma near the free border of the glands.

In the small intestine the earliest changes were noted to occur in the mucosa near the tips of the villi. These consisted of foci of congestion which in individual villi were associated with varying degrees of edema of the villar stroma (Fig. 4). This occasionally was severe enough to elevate the mucosal cells from the core of stroma of the villus and was usually seen at the tip of the villus. At times intact villi adjacent to ulcerated areas were actually bulbous with edema. Such villi showed extravasation of red blood cells to a varying degree. Occasionally we observed individual villi in which the process had advanced to the stage of necrosis. Such villi were not infrequently directly adjacent to villi which appeared entirely normal. In such cases the lesions were found to be restricted to the mucosa, and the submucosa was observed to be uninvolved (Fig. 5).

The more advanced lesions consisted of distinct erosions and ulcerations varying in size from several millimeters to several centimeters. The erosions consisted of necrotic groups of villi in which the poorly stained, degenerated epithelial cells were enmeshed in a fibrin network in which were also seen red blood cells, white blood cells and at times bacteria. The more advanced lesions showed a progression both in areas involved and in depth of involvement (Fig. 6). The line of demarcation between involved and uninvolved mucosa was quite sharp. In the colon we observed

several foci in which the process extended through the muscularis mucosa into the submucosa. However, where the necrotic process had extended deeply into the mucosa even without involving the muscularis mucosa directly, we have observed congestion in the adjacent submucosa with increase in the number of leucocytes and with edema.

DISCUSSION

A comparison of the various stages of development of the intestinal lesions in our human material with those observed in our dogs revealed that we were dealing with a process which took its origin in different layers of the intestinal wall in the two species. In our human material it was found that the earliest changes were located in the submucosa and that with progression of the process, extension to the mucosa occurred. Our observations in the dog indicate that the process, while identical in the nature of the changes which occur, originates in the mucosa and spreads thence to the submucosa.

Such a striking difference in the location of the primary lesion could only be due to some basic anatomical dissimilarity. This was found to exist in the different anatomical distributions of the blood supply to the intestinal wall in the two species. The work of Spanner (5) has demonstrated fundamental and physiologically significant differences in the circulatory pathways in the intestine of various animal species.

Thus in man, the rabbit, rat, mouse and bat he observed that the main arteriole which supplies a given villus passes up the villus without branching until it reaches the villar tip, where it divides into two branches. One of these enters into and supplies the capillary network of the villus. The other branch is larger in caliber than the capillaries and passes without further connections directly into the major venous channel of the villus, *i.e.* forms an arteriovenous shunt. During digestion the villi are filled with blood and the flow through the arteriovenous shunt is diminished in favor of the functionally necessary flow through the capillaries. In starvation, the capillary network is short circuited by the arteriovenous shunt and the villi are pale and relatively anemic. The blood flow through the villi is thus rapidly adapted to varying functional needs.

In the dog, cat, pig and horse the arteriovenous shunt is strikingly different in type and location. In these species the anastomosis is found in the submucosa in large numbers. The arteries which participate in the anastomoses with the submucosal venous nets, differ both in location and in wall structure from the arteries which go to the mucosa. They arise proximal to the origin of the mucosal vessels out of the larger sub-

mucosal arterioles, *i.e.* are intercalated proximal to the mucosal vessels. These vessels at their origin show a sharp constriction with a bulbous dilatation beyond this point. In these animals the flow of blood can pass directly into the veins with short circuiting of the villar blood supply since these anastomoses are intercalated before the vessels of the villi.

These arteriovenous shunts are obviously of importance in the circulatory adjustments which occur in shock (6). They form a path through which blood may be returned to the heart most rapidly. They permit the rapid redistribution of blood to the periphery in response to physical work. Similarly they function to adjust the changes in blood supply which occur in response to digestion and serve to short circuit the blood during the interdigestive phase and thus reduce the burden on the heart.

The ability to short circuit the blood flow if prolonged and rendered fairly complete, may become of importance in the pathogenesis and localization of intestinal lesions. Our anatomical observations indicate that in addition to the deviation of blood flow through the arteriovenous shunt there is also a vasoconstriction which uniformly involves the arteriolar vessels which form the other terminal branches of the main submucosal artery. Thus in the dog, the shunting of blood flow through the submucosa associated with vasoconstriction of the mucosal arteriole located beyond the shunting point, and which forms the other terminal branch of the main submucosal artery results in a cessation of blood flow to the area of mucosa involved. In this way is initiated the sequence of events which results in the localization of a necrotic lesion in the mucosa, as it occurs in the dog.

In man, however, the identical physiological process (*i.e.* short circuit of blood flow through the arteriovenous anastomosis with an associated vasoconstriction in the arterioles which form the other terminal branches of the large submucosal arteriole) leads to a cessation of blood flow through the affected area of submucosa. Here, the sequence of events leads to an anatomical lesion which begins in the submucosa and progresses towards the mucosa. This sequence of events is clearly indicated in a study of our human material.

In order to check the validity of the physiological inferences drawn from the application of our pathogenetic observations to the distribution of the arteriovenous shunts, we determined to include other animal species in our study. We therefore employed the cat, rabbit and guinea pig.

In order to avoid unnecessary repetition we may merely note that our observations in the cat indicate that the process is mucosal in origin and that progression leads to later involvement of the deeper layers of the intestinal wall. In other words, the sequence of events is identical with

that in the dog. It will be noted, however, from Table I that the lesions have a tendency to localize in the colon.

In contrast to the observations in the cat and dog the pathologic process in the case of the rabbit and guinea pig shows a primary localization in the submucosa (Fig. 7). It is only with progression of the lesion that the mucosa becomes involved. The histogenesis and course of the lesions in these animals resembles that which we have observed and reported in man. We feel that the presence of arteriovenous anastomoses and their varying locations in the bowel wall constitutes the anatomical substratum of the localizing mechanism in the histogenesis of the adrenalin and shock lesions.

In addition to the gastrointestinal changes produced in the manner indicated we also observed renal lesions which in the gross and microscopically bear a close resemblance to those observed in human cases of bilateral cortical necrosis of the kidneys. Such lesions have been observed in dysentery (7), in experimental renal necroses produced by mercury poisoning (8), in diphtheria (9), following lithium carmine injection (10) as well as in the production of a renal lesion with the Shwartzman phenomenon (11). We feel that these lesions have as their common mechanism, the process which we have outlined above: namely, a vasoconstriction resulting from sympathetic stimulation, affecting the renal arterioles. This we feel is part of the systemic reaction brought about by various so called toxins, organic or inorganic. The resulting necrosis in the kidney represents merely another localization of the vasospastic anemic infarct. This and changes observed in other viscera, will be detailed in another communication.

SUMMARY

We have attempted to reproduce in animal experiments a group of pathological findings which we have observed to be associated with shock. In order to simulate the compensatory vasomotor reactions occurring in shock, we have utilized the intraperitoneal injection of adrenalin hydrochloride in dogs, cats, rabbits and guinea pigs. That the effect of adrenalin hydrochloride when injected by this route is of long duration has been shown by the prolonged hyperglycemia which it produces.

Our experiments have resulted in the production of a lesion in the digestive tract which is identical in the gross with those which we observed in our human material. The histological changes, however, have been found to differ from those encountered in the latter. These differences have been noted to occur only in the dog and cat, where the initial changes

take place in the mucosa, and the alterations in the submucosa appear secondary to these. In the rabbit and guinea pig the histogenesis of the lesions is identical with that observed in man, the lesions first manifesting themselves in changes in the submucosa, congestion, edema and hemorrhage. Only later are similar changes seen in the mucosa, progressing finally to necrosis and ulceration.

The cause of the histological differences has been found in the presence of arteriovenous anastomoses which occur in the submucosa in the case of the dog and cat and in the mucosa in the case of the rabbit, guinea pig and man.

We have pointed out that variations in blood flow through the intestinal wall may result from the short circuiting of the blood through the arteriovenous anastomoses. This, associated with the vasoconstriction known to occur in shock, may if severe and prolonged, result in necrosis of the intestinal wall. We have experimentally reproduced the same lesion by the injection of adrenalin, which acts in a similar way.

The experimentally produced anatomical changes offer additional evidence in support of the clinical occurrence of a vasospasm which is of sufficient severity and duration to cause tissue necrosis.

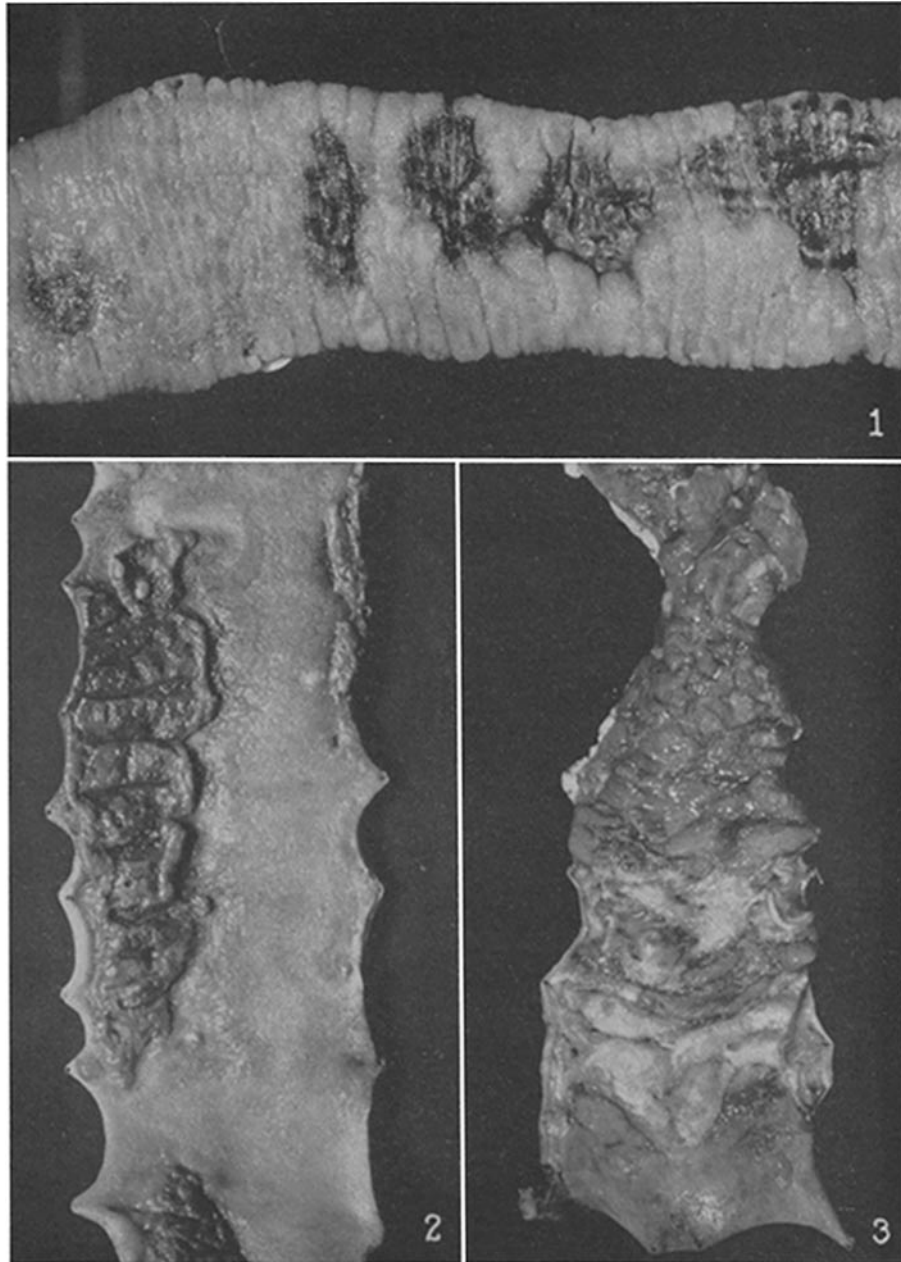
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EXPLANATION OF PLATES

PLATE 35

- FIG. 1. Dog 1-45. Gross appearance of ulcerations in ileum. Natural size.
- FIG. 2. Dog 1-57. Gross appearance of diphtheritic pseudomembranous ulceration in ileum. Natural size.
- FIG. 3. Cat 2-76. Gross appearance of pseudomembranous ulceration in colon. 2/3 natural size.



(Penner and Bernheim: Production of digestive tract ulcerations)

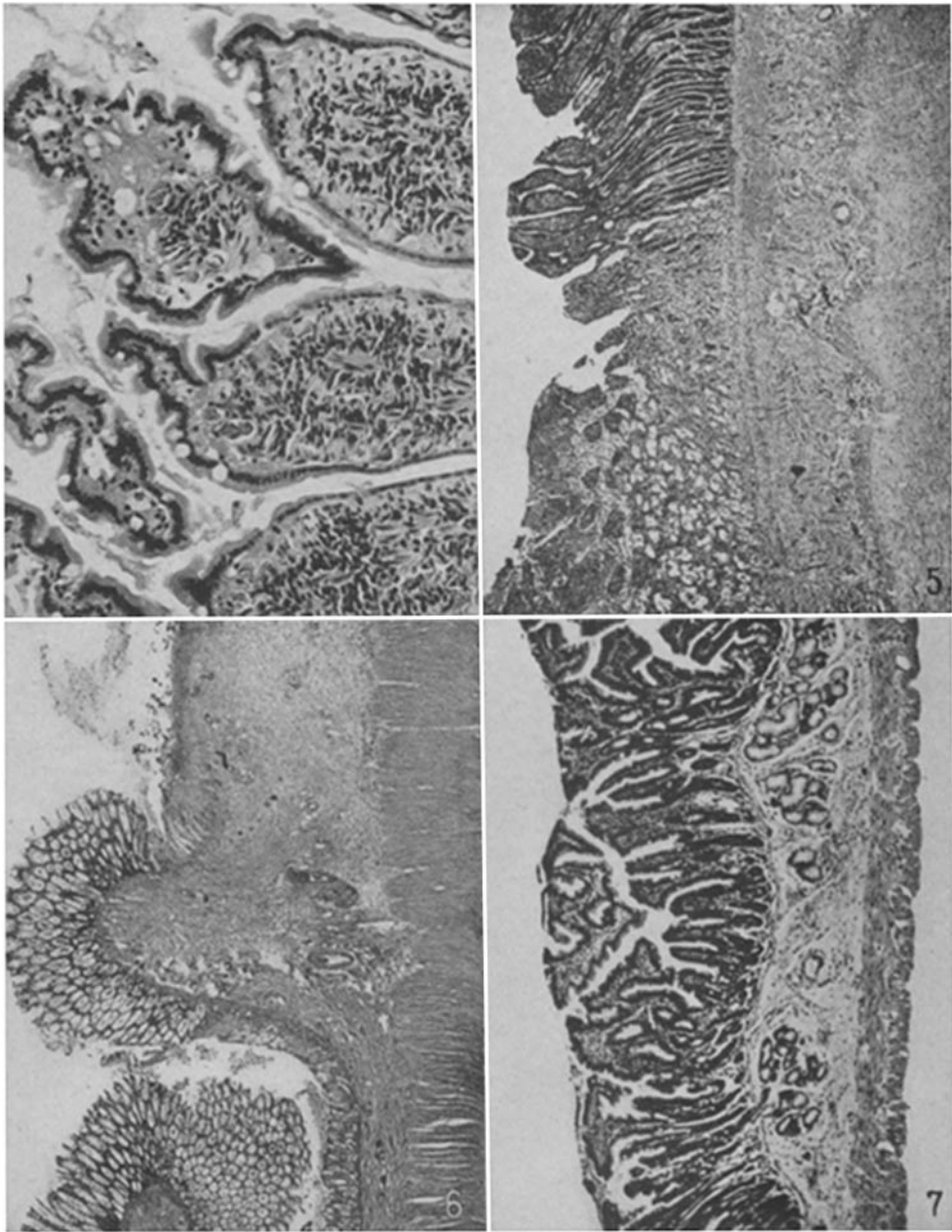
PLATE 36

FIG. 4. Dog 1-45. High power field of small intestine showing early lesion. Intact villus with congestion and edema of tip. Hematoxylin and eosin. $\times 172$.

FIG. 5. Dog 1-57. Low power field of small intestine. Taken at edge of mucosal ulcer, showing severe mucosal lesion without involvement of the submucosa. Hematoxylin and eosin. $\times 33$.

FIG. 6. Cat 2-76. Colon showing two ulcers separated by well preserved mucosa. The more advanced lesion shows involvement of muscularis mucosa and submucosa in addition to the mucosa. The earlier lesion is confined to the mucosa. Hematoxylin and eosin. $\times 17$.

FIG. 7. Rabbit 2-63. Early lesion in the small intestine showing submucosal edema and focal extravasation of red blood cells in the presence of an intact mucosa and uninvolved Brunners' glands. Hematoxylin and eosin. $\times 58$.



(Penner and Bernheim: Production of digestive tract ulcerations)