dence of a dominant left ventricular depression seemed to be present in 3 of these experiments and signs of right ventricular depression in one of them.

Summary and Conclusions. 1. Simultaneous changes in right and left atrial pressures together with aortic pressure pulses were successfully recorded through the experiments in 6 out of 16 dogs which were submitted to standardized procedures of bleeding and reinfusion developed in this laboratory. 2. An analysis of the results supports previous observations from this laboratory that myocardial depression can supervene during the circulatory failure which develops after prolonged hemorrhagic hypotension and subsequent reinfusion of the withdrawn blood. It extends these observations in showing that such myocardial failure may affect either the left or right ventricle dominantly.

Received December 12, 1950. P.S.E.B.M., 1951, v76.

Lysozyme Production in Response to Injury of Gastrointestinal Tract in Dogs. (18422)

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(Introduced by Walter L. Palmer.)
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The recent investigation of Meyer and his co-workers suggesting a relationship between lysozyme(1) and certain ulcerative diseases of the alimentary tract has aroused widespread interest(2,3). The evidence suggested that lysozyme locally initiated the lesions of chronic ulcerative colitis by removal of the surface mucus, with dissolution of the mucous cells; necrosis of the denuded tissue by proteolytic enzymes, presumably furnished by micro-organisms, subsequently ensued. Wang, Grossman, *et al.*(4) showed that lysozyme produced erosions and hemorrhages in the gastric and colonic mucosa of rats, and increased the digestive effect of hydrochloric acid and pepsin *in vivo*. Lysozyme was considered capable of damaging mucous membranes, but no evidence was adduced that it removes surface mucus from the mucosa.

The hypothesis that the polysaccharolytic activity of lysozyme leads to gastrointestinal ulceration has not been substantiated, as yet, by the demonstration of a lysozyme substrate in the gastrointestinal wall or lumen(5,6). High lysozyme titers have been demonstrated in healing skin incisions, callus of healing rabbit fractures, and in inflammatory exudates(7, 8,9). The possibility exists, therefore, that lysozyme is a result rather than a cause of the inflammatory reaction in chronic ulcerative colitis. To evaluate this possibility, the concentrations of lysozyme were measured before and during experimentally induced injury to the bowel in dogs.

Methods of Study. Lysozyme titers were

* Public Health Service Research Fellow of the National Institutes of Health.

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2. Meyer, K., Prudden, J. F., Lehman, W. L., and Steinberg, A., PROC. SOC. EXP. BIOL. AND MED., 1947, v65, 220; *Am. J. Med.,* 1948, v5, 482.

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8. Hudack, S. S., Blunt, J. W., Jr., Higbee, P., and Kearin, G. M., PROC. SOC. EXP. BIOL. AND MED., 1949, v72, 526.

9. Prudden, J. F., Lane, N., and Levinson, J., PROC. SOC. EXP. BIOL. AND MED., 1949, v72, 220.

determined by a modification of Fleming's turbidimetric method(10). Repeated determinations of crystallized egg white lysozyme indicated an end point at 0.001 mg lysozyme per cc of material. The test is gross and does not detect small amounts of lysozyme or minor changes in concentration; it has the advantages of simplicity and rapidity, facilitating the simultaneous examination of a large number of specimens.

In a long-term study of the effect of prolonged hypermotility upon the gastrointestinal tract(11), in progress in our laboratory since 1948, adult mongrel dogs with a normal rectal mucosa, as seen at proctoscopy, received daily intramuscular injections of Mecholyl chloride† suspended in a beeswax-peanut oil mixture. Fecal specimens from some of these animals were tested for lysozyme before and after the administration of the Mecholyl mixture. Lysozyme is not demonstrable in the feces of normal dogs by the method used. Mecholyl in doses of 2 mg/kilo/24 hours produced bloody diarrhea with variable side effects, consisting chiefly of lacrimation, salivation, and occasionally vomiting. Proctoscopy revealed an edematous, friable, hyperemic, bleeding mucosa; this state could be made to persist for many months by continued injections. Autopsy revealed intense hyperemia and superficial erosions of the mucosa in the stomach, small intestine, and colon. Microscopic examination demonstrated epithelial necrosis, distention of mucosal capillaries, extensive intramucosal hemorrhage, and edema of the submucosa. Similar changes have been described by Wener and Hoff(12). Irregular elevations of the lysozyme titers in the feces of these animals were demonstrable after the administration of Mecholyl.

To quantitate and better interpret results,

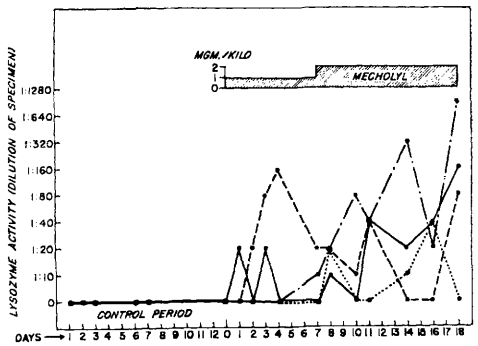

FIG. 1.
Output of lysozyme in colonic pouches of dogs before and during administration of mecholyl.

blind ileocolic pouches were established surgically in 6 normal dogs. One month after surgery the pouch contents were tested for lysozyme before and after stimulation with Mecholyl (Fig. 1). Thirty determinations on a 1:1 dilution of secretions from blind pouches before treatment revealed no lysozyme activity. In contrast, more than 40 determinations on the pouch secretions in the same animals at intervals of 1 to 20 days of daily Mecholyl administration revealed lysozyme activity ranging up to dilutions of 1:1000.

Six dogs under intravenous nembutal anesthesia were subjected to cauterization of the rectum by an electrocautery introduced through the proctoscope. Washings of the cauterized bowel were tested for lysozyme at varying intervals thereafter. Uniformly high concentrations of lysozyme were found in more than 30 determinations. At times, 20 cc of washing material from the 15 cm section of bowel contained appreciable lysozyme activity when diluted 1:5000 with saline. These concentrations are higher than those usually encountered in the feces or colonic mucus from patients with active, severe chronic ulcerative colitis (Fig. 2).

To determine whether or not the lysozyme is produced locally at the site of injury, 2 blind loops of colon were established. One of these loops was cauterized and the other served as a control. Lysozyme titers of saline washings of the 2 loops were compared at intervals for 24 hours. Lysozyme was found in both loops 2 hours after the operation. The lysozyme remained at a low level for the

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† Furnished through the generosity of Merck and Co., Rahway, N. J.

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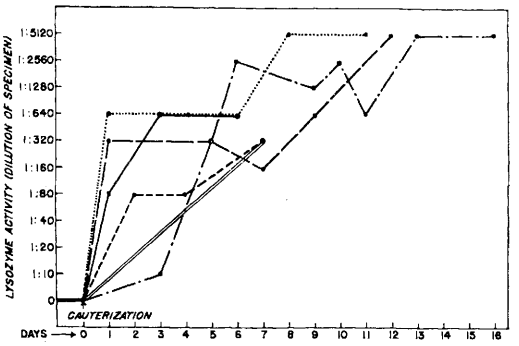

FIG. 2.

Output of lysozyme in rectum of dogs before and after cauterization.

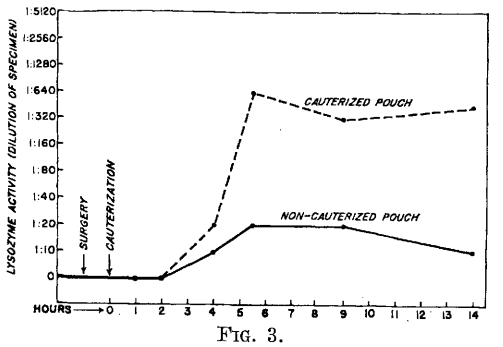

FIG. 3.

Early lysozyme activity of injured bowel.

duration of the experiment in the non-cauterized loop. Lysozyme activity of the washing from the cauterized loop continued to rise and reached a peak within 5½ hours after surgery and cautery (Fig. 3). Tissue lysozyme was detected at 1:20 dilution in a saline homogenate of the non-cauterized loop and in a 1:640 dilution of the cauterized loop homogenate. Both specimens were taken 15 hours after surgery.

Comment. The marked rise in production of lysozyme by the canine gastrointestinal tract injured by Mecholyl stimulation or by electrocautery suggests that the observed increase in lysozyme in the feces and bowel of patients with chronic ulcerative colitis may be a result of the disease process. Lysozyme seems to be produced locally in injured bowel. The marked increase in lysozyme production occurring within 5½ hours after cautery suggests that its increase is part of an early inflammatory process. Its precise biological significance remains to be determined.

Summary. 1. Lysozyme is produced in moderately large amounts by the gastrointestinal tract of dogs subjected to chronic stimulation with Mecholyl. The increase in lysozyme is demonstrable in the bloody diarrheal stools of intact animals and in material aspirated from isolated pouches of colon. 2. Cautery of canine rectum stimulates the local production of large amounts of lysozyme within 5½ hours after injury. 3. The rapid production of lysozyme by injured bowel suggests that it is an early accompaniment of the inflammatory reaction and that its presence is a reflection rather than a cause of ulcerative alimentary disease.

Received December 13, 1950. P.S.E.B.M., 1951, v76.

Susceptibility to Estrogen of Breast, Vagina, and Endometrium of Various Strains of Mice.* (18423)

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Strain differences in the susceptibility to breast cancer have been attributed by Loeb to variations in the sensitivity of the mammary gland to estrogen(1,2). According to other investigators, ovaries of mice of different strains produce different amounts of estrogen, and the larger the output of estrogen, the more readily mammary cancer will develop. Studies of vaginal smears and of whole mounts of breasts have indicated that the responses of mammary gland and vagina do not run parallel within the same animal

* This investigation was supported by the National Cancer Institute, National Institutes of Health.

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