fect the serum disease lesions does not support this assumption since the doses used depress ground substance permeability as effectively as cortisone(9), but larger doses would have to be administered before the permeability factor could be evaluated. The permeability of different ground substance structures may be affected to different degrees by various steroids.

These studies seem to show that serum disease is an excellent experimental tool for evaluating the total actions of cortisone-like drugs in alleviating diseases of the ground substance. Permeability studies of the joints previously described are useful as preliminary screening, for it has been found that all effective anti-rheumatic drugs suppress permeability of the synovial membrane.

Conclusions. Cortisone in doses of 4 mg twice daily depressed the Arthus reaction in the skin and completely prevented arteritis and carditis in 8 of 9 rabbits treated with horse serum. Glomerular nephritis, on the other hand, was not prevented. The zona fasciculata of the adrenals was atrophied. The mortality rate was highest among the animals receiving cortisone. Hyaluronidase in doses of 6000 T.R.U. per kg depressed the Arthus reaction in the skin and diminished glomerular nephritis, but enhanced arteritis and carditis. These observations may be explained by the ability of hyaluronidase to weaken ground substance barriers, thereby diverting antigen and antibody from the kidneys to the general vascular bed. DCA and Artisone in the doses used had no remarkable effect on the histological manifestations of serum disease, but DCA caused a depression of the Arthus reaction in the skin possibly through its hyaluronidase-like effect upon the ground substance.

It appears that serum disease is an excellent experimental tool for comparing the total efficacy of cortisone-like drugs after preliminary screening for their anti-permeability action on ground substance.

8. Opsahl, J. C., *Yale J. Biol. and Med.*, 1949, v22, 115.

9. Seifter, J., Warter, P. J., and Fitch, D. R., PROC. SOC. EXP. BIOL. AND MED., 1950, v73, 131.

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Histological Manifestations of Feeding Polyoxyethylene Monostearates To Weanling Hamsters.*† (18192)

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It was reported recently(1) that the ingestion of 5 or 15% of polyoxyethylene monostearate preparations (Sta-soft and Myrj) by weanling hamsters caused an increased mortality rate, a decrease in food efficiency and rate of gain as compared to similar animals fed 5 or 15% lard, or 7½% lard plus 7½% celluflour in addition to the basal ration. The experimental animals suffered a high incidence of diarrhea and other gross pathological manifestations. Similar results were obtained when other surface active agents were fed to hamsters and rats(2,3). In the present report histological changes observed in the organs of the hamsters from the investigations described previously(1) are presented.

Experimental. One animal fed either 5

* We are indebted to Mrs. Marjorie Ismond for assistance in preparation of the slides.

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1. Schweigert, B. S., McBride, B. H., and Carlson, A. J., PROC. SOC. EXP. BIOL. AND MED., 1950, v73, 427.

2. Sherman, H., Harris, R. S., and Jetter, W. W., *Fed. Proc.*, 1950, v9, 370.

3. Harris, R. S., Sherman, H., and Jetter, W. W., *Ibid.*, 1950, v9, 361.

TABLE I. Summary of Histological Changes in Hamsters Fed Sta-soft, Myrj or Lard.* (0 = no effect; 1+, 2+, 3+ = slight, moderate, and severe effect, respectively.)

Duration, wk	Experimental groups: 5% Sta-soft	5% Myrj	15% Sta-soft	15% Myrj	Total	Control groups†: 5% Lard	15% Lard	Total
				Duodenum				
2	3+	lost	0	3+		0	0	
4	0	0	2+	2+		0	1+	
6	1+	1+	2+	3+		0	1+	
8	1+	1+	1+	1+		0	1+	
10	2+	0	0	0		0	0	
Frequency	4	2	3	4	13/19	0	3	3/10
Mean intensity	1.75+	1+	1.7+	2.25+	1.8+		1+	1.0+
				Ileum				
2	2+	3+	0	1+		0	0	
4	3+	3+	3+	3+		0	1+	
6	3+	3+	2+	1+		1+	1+	
8	3+	3+	3+	0		1+	0	
10	3+	3+	3+	2+		1+	1+	
Frequency	5	5	4	4	18/20	3	3	6/10
Mean intensity	2.8+	3+	2.75+	1.75+	2.6+	1+	1+	1.0+
				Liver				
2	0	1+	2+	0		0	1+	
4	1+	1+	0	1+		0	0	
6	1+	2+	3+	2+		0	1+	
8	3+	2+	2+	3+		0	1+	
10	2+	3+	3+	3+		0	0	
Frequency	4	5	4	4	17/20	0	3	3/10
Mean intensity	1.75+	1.8+	2.5+	2.25+	2+		1	1.0+

* See text for effect on other tissues.

† The duodenum, ileum and liver from animals fed either 5 or 15% lard with restricted food intake, or 7½% lard plus 7½% celluflour, revealed damages of frequency and intensity comparable to those of animals fed 5 and 15% lard (fed *ad libitum*). Also, no injury of any kind was found in the kidneys.

or 15% lard, Myrj or Sta-soft was sacrificed at 2 weeks and additional animals were sacrificed at 4, 6, 8, and 10 weeks [details of diets, etc. see(1)]. In addition, other control animals (5 or 15% lard—food restricted, and 7½% lard + 7½% celluflour) were sacrificed at 6 and 10 weeks. The animals used for histological study were selected on the basis of sex, general performance typical of the group, initial weight, etc. They were anesthetized with ether, decapitated, bled, and opened by an abdominal incision. Standardized sections of duodenum, ileum, rectum, liver, and one kidney (left) were removed. In addition to these organs, 5 testes (greatly reduced in size) from animals fed the test products were examined. A section containing the joined heads of the femur and tibia from animals studied in the 10-week period was also obtained. Tissues were fixed immediately in Zenker-formol for 8 hours, processed by the standard celloidin method, cut at 10 μ, and stained with Hematoxylin and eosin-azure II (Maximow). The organs from each animal were imbedded in one block. In the majority of cases 2 slides, each containing 3 consecutive sections, were made for the tissues from each animal. For the testes, serial sections of the entire organ were made.

Results. The results are summarized for the duodenum, ileum, and liver in Table I in order to show both the frequency and intensity of cases which definitely deviated from the normal. *General observations*: (A) Marked histological changes in the tissues were observed when 5 or 15% Myrj or Sta-soft was fed. (B) Deleterious effect of the test products used (Sta-soft and Myrj) was

similar. (C) No appreciable increase in the extent of damage was found for animals fed the diets from 2 to 10 weeks; some evidence for acclimatization occurred in certain cases. (D) Little evidence for proportionately greater damage due to ingestion of the higher level of the test compounds was apparent. (E) No difference in effect of these products due to sex of the animals was observed. (F) Significantly less damage, both in frequency and in extent, was observed for the animals fed lard.

A description of the specific injuries observed follows:

Duodenum and ileum. The histological damage in these 2 organs was of a similar nature, but varied in intensity in different cases (Table I). For both organs, the cases which showed no or slight effect were from animals fed lard, and those with moderate and severe injuries were from animals fed either Sta-soft or Myrj. The injury was principally a necrotic erosion of the mucosa, and in severe cases, half of the thickness of the entire layer of mucosa was sloughed off (Fig. 1 and 3). The erosion of the ileum usually was more intensified on one side, presumably that in contact with the intestinal contents (Fig. 2). Other injuries common to both duodenum and ileum were frequently congested villi with fully loaded capillaries and leukocytic infiltration. Such congestion might increase the amount of blood lost. Blood was detected in the intestinal contents of some of the animals fed the test products(1).

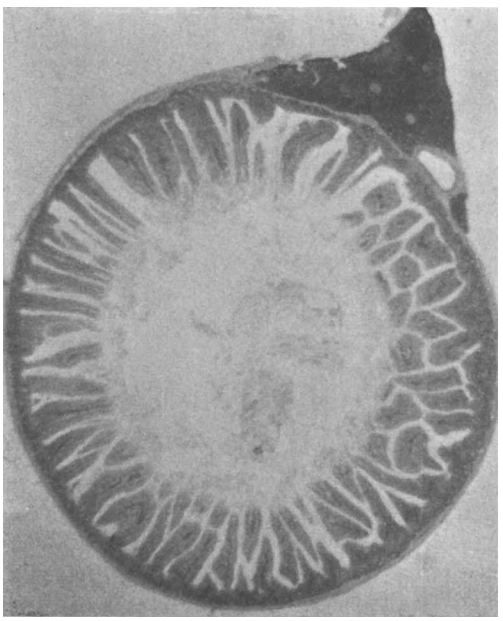

FIG. 1.
Duodenum; 5% Sta-soft, 2 wk; showing severe mucosa erosion reducing the normal thickness to half. ×24.

Liver. Injuries to the liver consisted of necrotic lesions of relatively small areas which occurred peripherally (hemorrhagic) but sometimes more deeply located. The necrotic hepatic cells were pyknotic, had a highly granular type of cytoplasm (Fig. 4) and some of the inclusions stained green with Azure II. The blood vessels and bile ducts appeared normal except for an apparent increase in blood volume, since the central veins were several times the diameter of the veins from animals fed lard. Sinusoidal congestion was observed particularly in the periphery (Fig. 5), which would likely lead to hemorrhage. As in the duodenum and ileum, leukocytic infiltration along congested sinusoids occurred frequently.

Other tissues. The rectum and myeloid tissue of bone marrow were found to be normal for all animals studied. Injury to the kidney was noted in 5 out of 20 hamsters fed either Sta-soft or Myrj. These included 2 cases evaluated as 1+, 2 cases as 2+ and 1 case as 3+. The main histological changes included deposition of an amorphous substance which stained a greenish blue inside the convoluted tubules. This substance presumably had filtered through the glomeruli of the renal capsules, but later was deposited in the uriniferous tubules (Fig. 6). Some of the renal capsules were both congested and disintegrated. This may be caused by a shrinkage of the cortex as indicated by the nodular appearance of the contour of this kidney (Fig. 6). Some of the tubules of Henle's loop were dilated and filled with a debris largely composed of the same amorphous substance and dead cells (erythrocytes and epithelial fragments). These changes are similar to those observed when large amounts of pteroylglutamic acid were injected

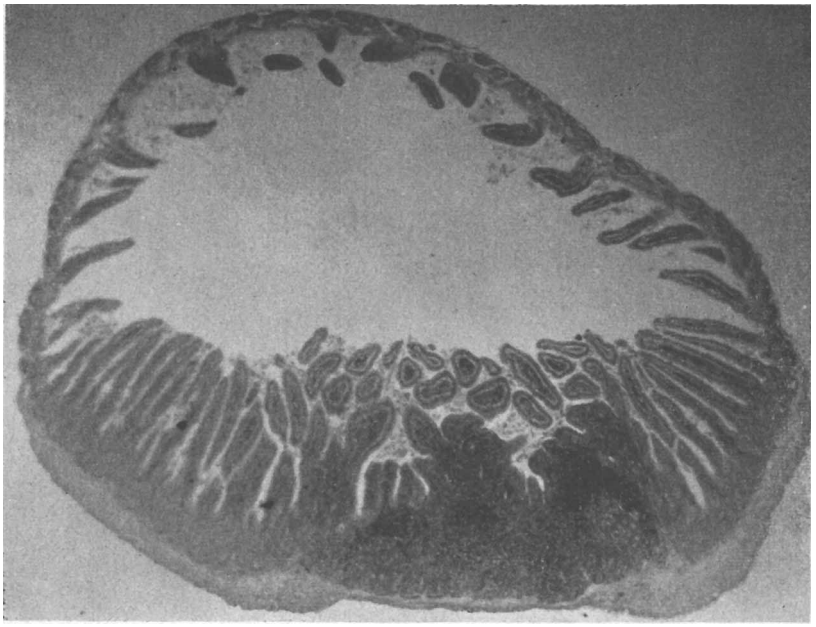

FIG. 2.
Ileum; 15% Myrj, 4 wk; showing severe injury to the mucosa of half the circumference. ×37.

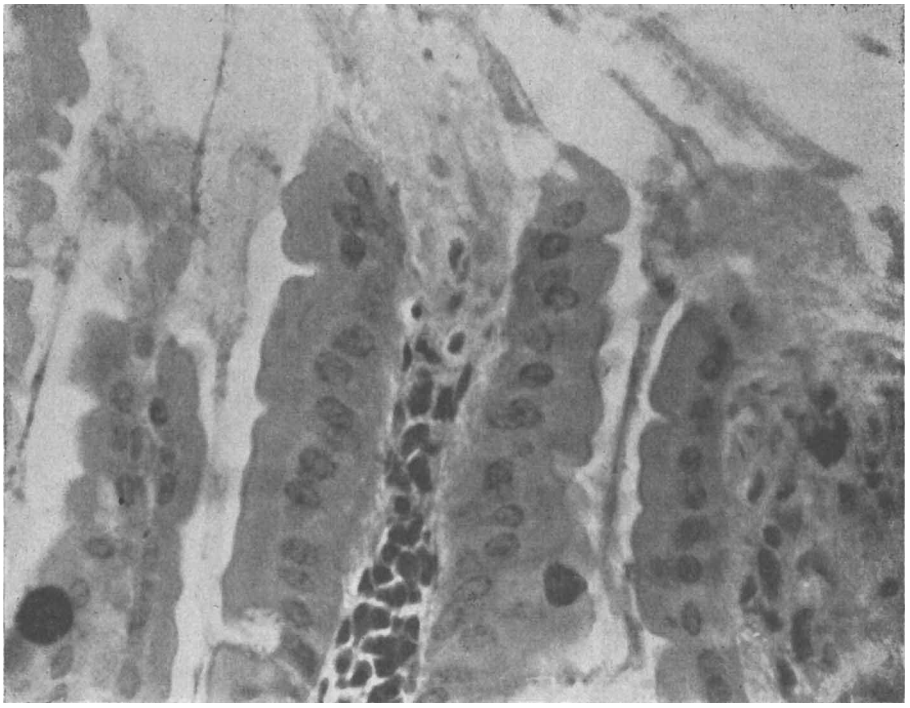

FIG. 3.
Duodenum; 5% Myrj, 8 wk; showing eroding tips of villi highly magnified (2 goblet cells as 2 dark spots). ×550.

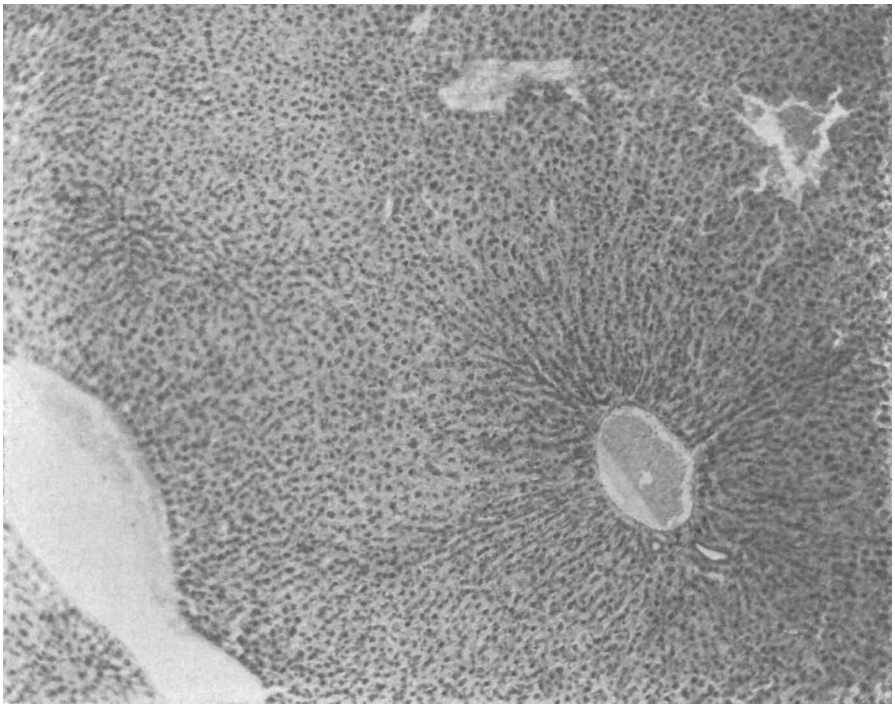

FIG. 4.
Liver; 15% Sta-soft, 10 wk; showing two intralobular necrotic lesions (upper right), one distended central vein of a lobule filled almost completely with blood cells, and one greatly distended interlobular vein (lower left). Cells of the lobule are granular and pyknotic. ×65.

into guinea pigs(4). No damage was observed in the kidneys of the animals fed lard (total of 16 animals examined).

The five testes (one each from animals fed 15% Myrj for 2, 4, and 10 weeks; 5% Myrj for 10 weeks, and 5% Sta-soft for 10 weeks) ranged in size from 1/5 to 1/3 of those from the control animals.‡ In 4 of the 5 cases, little or no spermatogenetic activity was observed in the seminiferous tubules. The lumen was either empty or contained material which resembled the remnants of spermatozoa. Normal spermatogonia and spermatocytes with occasional mitotic figures were present in these tubules. This condition suggested that spermatogenesis was abruptly halted at the level of secondary spermatocytes. Both the ductuli efferent and epididymis tubules were packed full of spermatocytes, but no spermatids or spermatozoa.

Discussion. Judging from the number of affected cases, the organs range in the order of ileum, duodenum, liver, and kidney in decreasing susceptibility to the effect of polyoxyethylene monostearates (Table I). This may mean that the greatest toxicity resulted from direct contact with the cells; and affords an explanation of why no damage was observed for the tissues of the rectum. The duodenum, which showed severe damage in animals sacrificed at 2 weeks, nevertheless, definitely showed a smaller amount of damage in the animals that were sacrificed later in the study. Both ileum and liver reached the height of damage for the animals sacrificed at 4 weeks and then remained at this level for the animals sacrificed at 6-10 weeks without noticeable acclimatization. The ef-

4. Dawson, J. R., Jr., Woodruff, C. W., and Darby, W. J., PROC. SOC. EXP. BIOL. AND MED., 1950, v73, 646.

‡ Autopsy findings showed that in 3 cases the testes were approximately 1/10 the size of those from animals fed lard.

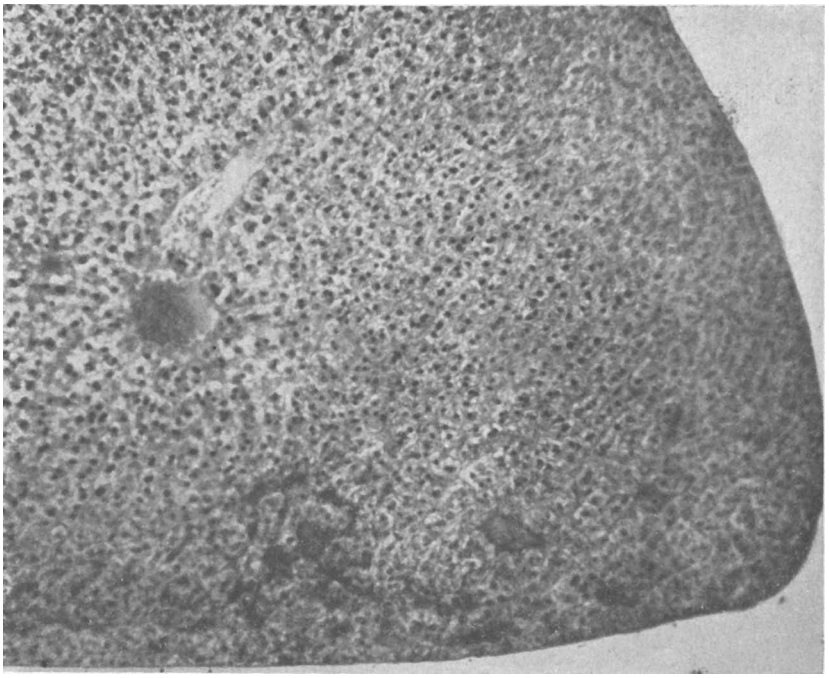

FIG. 5.
Liver; 5% Sta-soft, 10 wk; showing peripheral sinusoidal congestion. ×120.

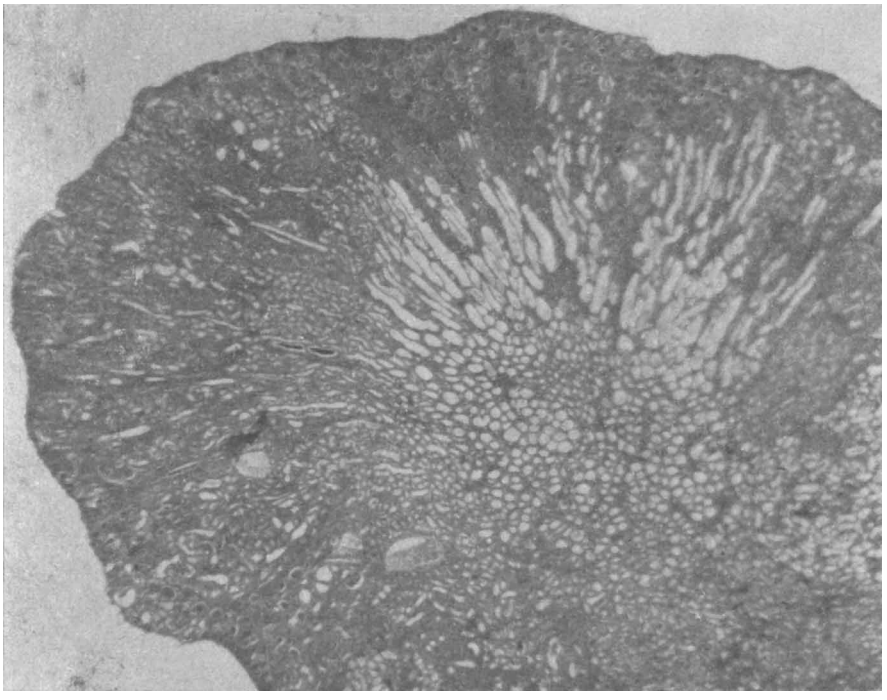

FIG. 6.
Kidney; 15% Myrj, 8 wk. Note the nodular surface and other pathological symptoms. ×20.

fects noted in the kidney were observed after the animals were on experiment for a longer time. Undoubtedly some of these trends may be attributable, in part, to the fact that the most susceptible animals died in the early phases of the study and consequently were not available for histological study.

Summary. A histological study of the duodenum, ileum, rectum, liver, kidney, testis and bone marrow of weanling hamsters fed on a basal diet containing 5 or 15% polyoxyethylene monostearates (Sta-soft or Myrj) or lard was conducted. Marked changes were observed in the duodenum, ileum, liver, kidney, and testis of hamsters fed Myrj or Sta-soft after 2-10 weeks on experiment. Histological changes observed in the small intestine, particularly the ileum, consisted of a severe erosion of the mucosa. Necrosis of the liver, decreased spermatogenetic activity of the testis, and tubular degeneration of the kidney were also observed.

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Studies on Urinary Histamine in Chronic Myelocytic Leukemia.*† (18193)

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It is now well established that there are increased amounts of histamine in the blood of patients with chronic myelocytic leukemia (1-5), and that the histamine resides mainly in the cells of the granulocytic series which are beyond the blast stage of development(5). Since blood histamine levels in chronic myelocytic leukemia as high as 25 μg/ml (250 times normal) are found, and since the turnover of white blood cells is probably rapid(6) an investigation of the fate of this potentially active material seemed of interest. It has been shown that considerable amounts of histamine are excreted in the urine(7). In man this is conjugated, probably in the form of acetyl histamine. It has also been shown that histamine base fed by mouth to dogs is excreted in the urine in the form of acetyl histamine(8). The present studies were initiated to determine whether or not the endogenous blood histamine was removed by this urinary route in patients with chronic myelocytic leukemia.

Methods. Blood histamine was estimated according to the method of Code(9) using the terminal ileum of the guinea pig as the assay object. Urine histamine was determined following the bioassay procedure of Anrep *et al.*(7) with the modifications that charcoal adsorption with subsequent elution was eliminated and the amount of alumina was increased from 2 g to 5 g for 5 ml of urine in

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1. Code, C. F., *J. Physiol.*, 1937, v90, 485.

2. Thiersch, J. B., *Australian J. Exp. Biol. and Med. Sc.*, 1947, v25, 73.

3. Valentine, W. N., and Lawrence, J. S., *Am. J. M. Sc.*, 1948, v216, 619.

4. Shimkin, M. B., Sapirstein, L., Goetzl, F. R., Wheeler, P. M. and Berlin, N. I., *J. Nat. Cancer Inst.*, 1949, v9, 379.

5. Valentine, W. N., Pearce, M. L., and Lawrence, J. S., *Blood*, 1950, v5, 623.

6. Lawrence, J. S., Erwin, D. E., and Wetrich, R. M., *Am. J. Physiol.*, 1945, v144, 284.

7. Anrep, G. V., Ayadi, M. S., Barsoum, G. S., Smith, J. R., and Talaat, M. M., *J. Physiol.*, 1944, v103, 155.

8. Urbach, K. F., PROC. SOC. EXP. BIOL. AND MED., 1949, v70, 146.

9. Code, C. F., *J. Physiol.*, 1937, v89, 257.