The Prophylactic Use of an "Elemental" Diet in Experimental Hemorrhagic Shock and Intestinal Ischemia

GUSTAVO BOUNOUS, M.D., N. GREGOR SUTHERLAND, M.D., A. HOPE MCARDLE, PH.D., FRASER N. GURD, M.D., F.R.C.S.(C)

From the McGill-Montreal General Hospital University Surgical Clinic, Montreal, P. Q., Canada

THE ROLE which conditions within the intestine may play in the course of human shock and severe illness has been brought into focus by a number of recent studies.[1-4, 8-17, 20, 21, 24, 25, 28] Intestinal necrosis associated with cardiac failure or shock has been reported frequently in the past few years, although the first description of such injury in the alimentary tract was provided by John Hunter over two centuries ago.[19] However, in view of the inherent difficulties of obtaining systematic data in the human, the most fruitful studies have been pursued under experimental conditions. We evolved a preparation in 1965 which eliminated acute death related to tryptic hemorrhagic enteritis in the dog, and since then we have sought to define the conditions which affect the anatomical and functional response of essential organs and tissues to controlled ischemic injury. This paper will report our findings on the use of a predigested or "elemental" diet used as a means of studying the consequences of radical alterations in the luminal content of the intestine upon the course of shock and upon the pathological sequelae.

A series of experiments performed in this laboratory has shown that when dogs fed normal food are submitted to either sublethal hemorrhagic shock or sublethal intestinal ischemia, a sequence of alterations in the histology and function of the intestine, heart, and other organs is observed. The common denominator is a non-hemorrhagic necrosis of the intestinal lining epithelium.

The pathological changes common to these two forms of injury will be described in a separate paper.[29] The characteristic initial lesions is early necrosis of the ileal and colonic epithelium with eventual loss of columnar cells, at first from the tips of villi, and then deeper towards the crypts. The normal epithelium is then replaced by flat cells which do not appear to produce mucin (Fig. 1). The heart shows areas of subendocardial hemorrhages early in both ventricles but particularly in the left chamber. From one to two days after injury, other anatomical lesions appear in the myocardium. Near the subendocardial aspect, particularly over the papillary muscles of the left ventricle, small focal infarcts can be seen (Fig. 2). Frequently large areas, especially of the right ventricle, show a yellowish pallor (Fig. 3) which under the microscope reveal cloudy swell-

Presented at the Annual Meeting of the American Surgical Association, May 11–13, 1967, Colorado Springs, Colorado.

Reprint address: Dr. Gustavo Bounous, University Surgical Clinic, The Montreal General Hospital, Montreal 25, Canada.

Supported by grants from the John A. Hartford Foundation, New York, and The Medical Research Council of Canada.

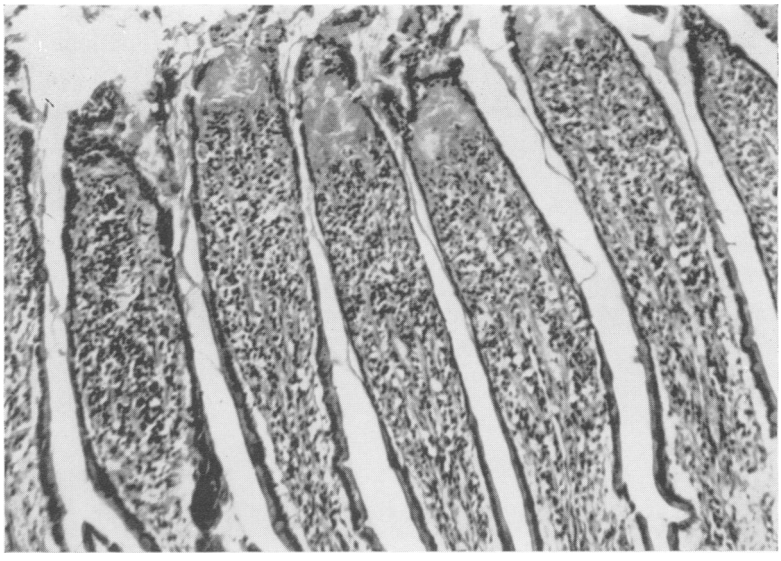

FIG. 1. Ileal mucosa (P.A.S.), flat epithelium.

ing and fatty infiltration. In the kidneys, medullary congestion or hemorrhage occurs very early as soon as blood is retransfused; 18 to 24 hours later, tubular necrosis develops accompanied often by glomerular tubular reflux (Fig. 4). The liver shows an early congestion that slowly recedes leaving a vacuolization of the pericentrolobular cells. In more severe cases, focal areas of hepatic necrosis can be seen. There are small hemorrhages in the central cerebrum and brainstem without apparent significant neuronal damage or cellular reaction. The walls of small arteries appear damaged and at least some of the hemorrhages are in relation to small arteries (Fig. 5, 6).

The time course of all these lesions follows a rather characteristic sequence or pattern. The earliest change to occur is

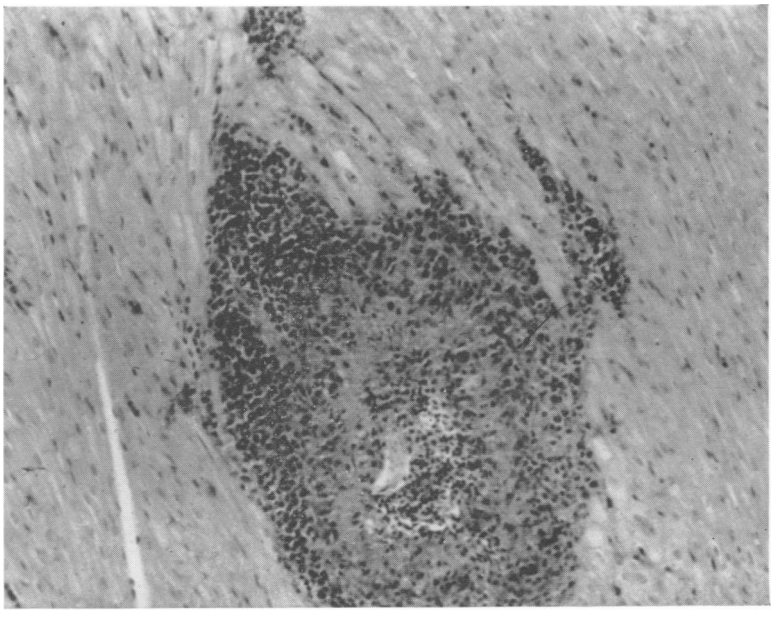

FIG. 2. Myocardium (H. E.), focal necrosis.

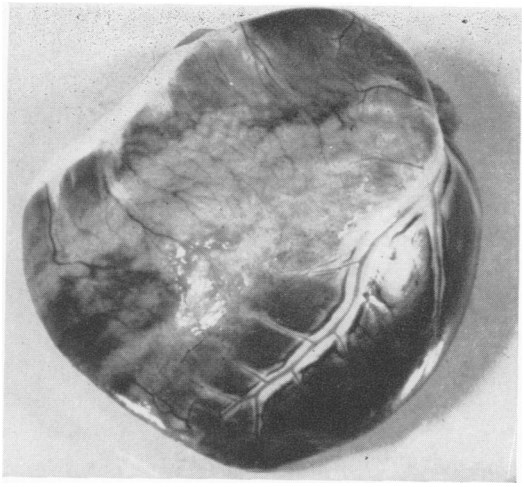

FIG. 3. Heart, fatty infiltration.

the necrosis of the small bowel epithelium, then the liver, the kidney, and finally, the heart and the brain. Two to three days after the injury, when most of the organic lesions are at the peak of visibility, the intestine is already healing and the mucosa covered throughout most of its surface with flat undifferentiated cells. If one examines the animal 2 months later, a total *restitutio ad integrum* is found to have occurred in that most anatomical alterations have been completely repaired. Although the functional manifestations of the syndrome are rather inconspicuous, a functional deficit is indeed present, but can be easily overshadowed by what we have been accustomed to interpret as the "normal" postoperative course following a major operative procedure. The heart works at suboptimal levels of efficiency; for a few days a 20 to 30% decrease in cardiac output may be seen with often a rise in left ventricular end-diastolic pressure responsive to digitalis. The blood urea nitrogen may be in the upper range of normal and by some indications the sensorium is depressed. As in the case of the anatomical changes, a return to normal usually occurs over a few weeks. The sequence of events in the experimental animal thus compares rather closely with what Mallory described in sublethal cases of shock during the Korean War.[23] His classic description of the pathology of sublethal human shock brings into focus the all-important role that the time factor plays in the development and healing of these lesions. It can be readily understood that, as in the clinical cases of Mallory, the animals which died within a few hours from the injury might not show

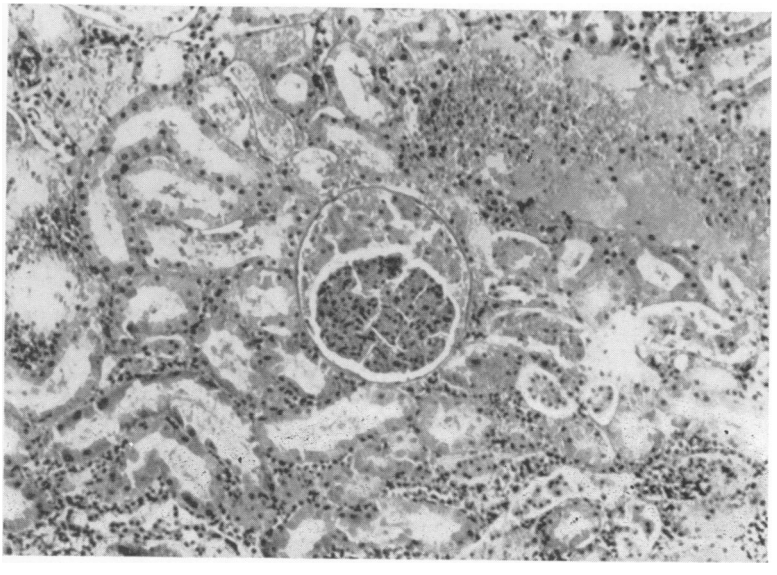

FIG. 4. Kidney (H. E.), tubular necrosis, glomerular tubular reflux.

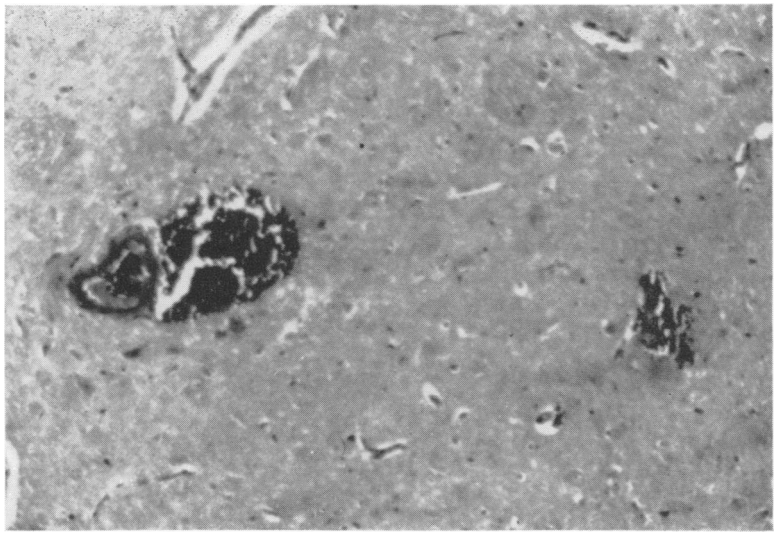

FIG.. 5. Thalamus (H.E.), focal perivascular hemorrhages.

any pathologic changes other than perhaps necrosis of the intestinal mucosa.

In terms of comparative pathology, necrosis of the intestinal epithelium is by far the most difficult element to assess. Biopsies in our experimental animals were taken *in vivo*; in humans this is rarely possible. It is well known how rapidly the epithelium of the ileum necrotizes and sloughs off postmortem. This fact explains why clinical pathologists do not pay too much attention to this area of the body in respect to this particular alteration. The denuded villi which we see when we fix *in vivo* a specimen of small bowel 18 to 24 hours after hemorrhagic shock or mesenteric arterial clamping would have no pathologic significance if the dog had been dead for 8 hours as is the case in most clinical postmortem studies. It is, nevertheless, possible that at a similar stage after injury a human ileum might present *in vivo* necrosis of a large number of epithelial cells followed by denudation of the tips of the villi.

The healing of intestinal lesions can be

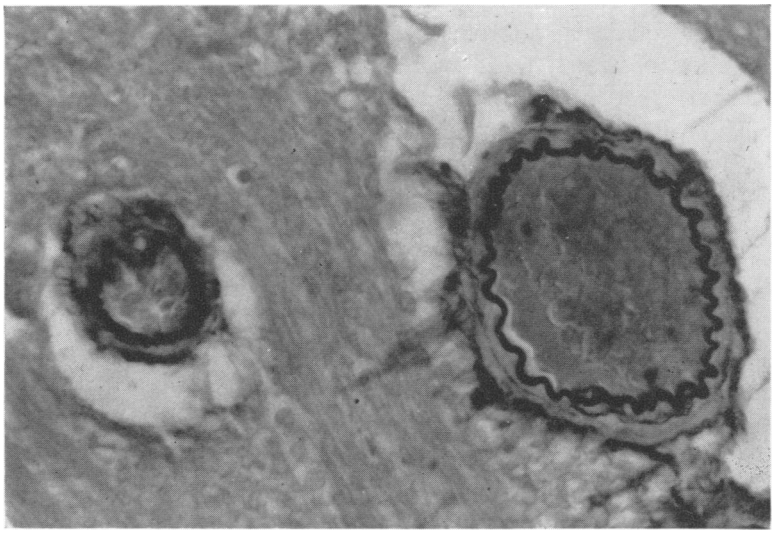

FIG. 6. Basal ganglia (Gomori), damaged elastica in small arteriole.

appreciated only in the 2 to 3 days after injury and up to a month afterwards, as the flat and cuboidal regenerating epithelium is gradually replaced by normal columnar cells. Therefore, these anatomic changes, whether intestinal or extra-intestinal, cannot be detected unless the dog is killed on the second or third day of its recovery, thereby providing a counterpart to Mallory's cases, where the patients died from a variety of causes in the "phase of recovery" during that limited time period in which the anatomic lesions were discernible.

The physiologic interpretation of these sublethal organic lesions is a matter of speculation. One can conceive that they represent the anatomical testimony of an insult incurred by these particular structures. Vital organs are involved, and it is conceivable that in the lethal cases death is the result of an overwhelming functional failure of these organs, in some cases before the time necessary for the development of visible anatomical lesions. If the animal dies spontaneously 2 to 3 days after injury, the previously described anatomic lesions are of far greater magnitude; myocardial infarcts are larger; liver damage may show necrosis. A post-shock syndrome is thus recognized in which the anatomic signs vary quantitatively in accordance with the clinical evolution, but the interpretation of which must take into proper account the element of time.

The role of the intestinal mucosa and of the content of the bowel both at the time of injury and afterwards, will be discussed in a separate paper to which the reader is referred for consultation of the vast literature on this all-important field.[29]

In two previous papers we illustrated the relationship between necrosis of the small bowel epithelium and the later occurrence of focal necrotic areas in the heart, liver, and kidneys.[5, 6] The presence of a sufficient quantity of necrotic tissue in one part of the body appears to influence the occurrence of necrosis in other areas which are not adjacent to the primary lesion. The similarity of the pathologic end-result, lysis of the cells, is striking and may warrant some thoughts in respect to the possible common pathogenetic factor. For example, the factors causing the rapid dissolution of the cells of the ileal epithelium, rendered necrotic by local ischemia, may have extended their hydrolytic effect via the blood to other distal cells without the predisposing stage of general ischemia. We have shown that the elimination of intermediate products of food digestion by the pre- and postoperative feeding of the "elemental" diet does indeed greatly reduce both sets of lesions in hemorrhagic shock.

We have previously studied the role of intraluminal trypsin in the pathogenesis of mucosal damage following ischemia.[7] We have found that pancreatic proteolytic enzymes play a definite part in the hemorrhagic digestion of the subepithelial structures of the villus once a depression of epithelial metabolism had developed, even though the epithelial necrosis and subsequent desquamation can occur during shock independently of the presence of intraluminal digestive enzymes. The pancreatic digestive enzymes appear to attack the devitalized area, and to extend the damage deeper into the villus structures, rapidly involving the dense capillary network. The presence of pancreatic proteolytic enzymes in the environment tends to transform a superficial necrosis of the epithelium into a major hemorrhagic infarction of the intestine. Pancreatic proteolytic enzymes constitute an aggravating part of the picture. Their role is not essential to the development of the epithelial necrosis nor of the extra-intestinal lesions of shock.

Repeated observations have left us with the strong impression that a certain relationship existed between the outcome of the shock experiment and the length of time between the dog's last meal and the shock procedure. The longer the period of

fasting, the better the animal appeared to fare under similar shocking procedures. For example, if the intestine was empty at the time of shock, things would go better. We have made numerous attempts in the past to prepare the intestine in such a way as to produce ideal conditions at the time of injury while avoiding starvation or dietary deficiency effects. The hypothesis was formulated that an intestinal lumen from which intermediate food products had been excluded for a few days might conceivably be free from many elements of toxicity.

This paper deals with experiments designed to test this hypothesis through observations on the effect of an "elemental" diet upon the course of dogs submitted to either hemorrhagic shock or intestinal ischemia.

Experimental Method

Dietary Management. The control diet used consisted of one 15-oz. can per day of a standard commercial dog food (Dr. Ballard's). The contents of the can were placed before the dogs each morning and consumed during the early part of the day. No food was given on the day of the experiment, but feeding was resumed the following morning.

The "elemental" ration was prepared to be precisely equivalent in composition and quantity to the control, not only in protein equivalent, fat and carbohydrate, but also in vitamins and minerals. The analysis of Dr. Ballard's Champion Dog Food showed the following:

	Per Cent
Moisture	72.19
Fat	4.09
Protein (N × 6.25)	8.58
Ash	1.80
Carbohydrates (by difference)	13.34
	100.00
Calcium (Ca)	0.185
Magnesium (Mg)	0.025
Sodium (Na)	0.235
Potassium (K)	0.239
Chloride (Cl)	0.008
Phosphorus (P)	0.089
Sulphur (S)	0.0004

The equivalent nutrients of the daily 15-oz. ration of Dr. Ballard's dog food were prepared in the following manner.

New Elemental Diet. The following ingredients were blended and the resultant liquid portion came to a little over 500 ml. This portion was equivalent to one can of the dog food and constituted a day's ration:

Aminosol:	500 mls.	Abbott
Sucrose:	20 Gm.	
Lipomul:	20 mls.	Upjohn
NaCl:	1.7 Gm.	
$KHCO_3$:	1.0 Gm.	
Vitamins:	5 Gm.	NBC Vit. fortification mixture
$CaCl_2\ 2H_2O$:	2 Gm.	

The above diet corresponds to the following values, expressed as Gm./day (500 ml.), with the source of each moiety shown in brackets:

Protein:	25	(Aminosol)
CHO:	25	(Aminosol)
CHO:	20	(Sucrose)
Fat:	13.7	(Lipomul)
Na+:	0.1	(Aminosol)
Na+:	0.674	(NaCl)
K+:	0.33	(Aminosol)
K+:	0.47	($KHCO_3$)
Cl−:	1.0	(NaCl)
Ca++:	0.6	($CaCl_2\ 2H_2O$)

The addition of the required amount of Ca and other minerals resulted in making the diet far more palatable to the dogs so that almost all animals showed eagerness to eat it. The daily nutritional requirements were fulfilled by a liquid volume of just over 500 ml. for an average 15 Kg. dog. This ration was divided into three fractions, each given at 7 a.m., 12 noon, and 4 p.m., respectively. The diet was given for 3 days prior to shock and during the following 3 days until sacrifice. The fractionation of the liquid non-residue diet into three daily meals made it possible to obtain a practical cessation of fecal transit into the lower ileum and in the colon without the inconvenience of a surgical colon bypass. The diet was prepared and stored in a cold room at 4° C. Under these conditions, cultures taken from the diet showed

no bacterial growth following cold room storage even for several days.

Experimental Procedures. A total of 120 healthy young dogs averaging 14.5 Kg. were used. Anesthesia was obtained using intravenous pentobarbital.

(a) *Hemorrhagic Shock Series (Groups I and II).* The animal was bled through a femoral catheter into a siliconized sterile bottle until a mean arterial pressure of 35–40 mm. Hg was reached. This level was maintained for 4½ hours. Blood in the reservoir was then reinfused over a period of 10 to 15 minutes.

The experiments were performed in pairs with the dog on the elemental diet on one table and the control dog on an adjacent table. The control dog was fed one 15-oz. can of Dr. Ballard's Champion Dog Food until the afternoon before the experiment at which time the food was withdrawn. The dogs on the elemental diet ate the third portion of their meal the afternoon of the day preceding the experiment at the time at which the normal food was withdrawn from the control dogs. Arterial blood samples were taken before hemorrhage and when about 20% of the blood in the bottle had been retransfused.

b) *Mesenteric Artery Occlusion Series (Groups III and IV).* The abdomen was entered under sterile conditions through a midline incision. Both superior and inferior mesenteric arteries were occluded with De Bakey vascular clamps for 90 minutes as described in another paper.[29] The mesenteric arteries were dissected free of their investing layer of sympathetic nerve fibers prior to clamping. After 90 minutes, the clamps were removed from the vessels and the laparotomy wound was closed. Arterial blood samples were drawn before clamping and 1 hour after declamping.

Blood Analyses. Arterial lactate and pyruvate were determined enzymatically with a Boehringer Test Kit. Blood pH, PO_2, and PCO_2 were measured on an Instrumentation Laboratories blood gas analyzer. Total proteins were measured with an Auto analyzer using the Biuret method. Serum glutamic oxalacetic acid transaminase (SGOT) and lactic dehydrogenase (LDH) were measured by a standard fluorometric method using an auto analyzer. SGOT is expressed in Karmen units and LDH in Wroblewski units. Plasma creatinine phosphokinase (CPK) was determined enzymatically with a Boehringer Test Kit. SGOT, LDH, and CPK estimations were done 24 hours postoperatively.

Bacteriological Studies. The specimens of intestinal content were collected as follows. Two non-crushing clamps were placed about 15 cm. apart across an area of the terminal ileum about 30 cm. from the ileocecal valve; another area of the midcolon was investigated in a similar fashion. Ten ml. of sterile saline were then injected between the clamps. After a few minutes for mixing, as much material as possible was aspirated. Each specimen was then plated separately on blood agar, McConkey and thioglycolate media. Plates were incubated at 37° C. for 18 hours. Direct smears were made and stained by the Gram method. Colony counts of the incubated media gave approximate concentrations of organisms per ml. Bacterial counts represented aerobic flora only. They were regarded as: 1) less than 10^3 col./ml., light; 2) between 10^3 and 10^5 col./ml., moderate; and 3) greater than 10^5 col./ml., heavy.

No isolation of anaerobic organisms was attempted. By examining the direct smear and the growth in the thioglycolate media, it was possible to determine the presence of clostridial species and other anaerobic organisms.

Pathological Examination. The specimens for histologic examination were fixed in 10% formalin immediately upon excision from the animal at the moment of killing. A thorough examination was made of the heart. The four chambers were opened and the endocardium examined. When both ventricles were open, the myocardium

was incised full-thickness in twenty sections for the left ventricles and several sections were also performed of the right ventricular wall. This investigation was done in order to ascertain the presence of focal infarcts in the myocardium. Sections for histologic examination were taken from any suspicious areas and from both major papillary muscles in the left ventricle and from the right ventricular wall. Two specimens of the ileum were taken about 10 cm. apart, approximately 30 cm. from the ileocecal valve.

Tissue Metabolism. (*a*) *Studies with Adenine-2,8-H.*[3] Twenty healthy young dogs were either subjected to pancreatic duct ligation 2 days prior to the experimental period, or were prepared with Trasylol administered intraluminally immediately prior to the experimental period, in order to protect them from tryptic hemorrhagic enteritis.

As shown in Table 8, Group I consisted of eight dogs which had been fed the normal laboratory ration up to 24 hours prior to the experimental procedure, whereas Group II (12 dogs) had been fed the "elemental" diet. Five dogs from each group served as controls. These animals were anesthetized with Nembutal and left on the table for at least 2 hours in order to minimize the effects of anesthesia. Three dogs from Group I (I-B) and seven dogs from Group II (II-B, II-C) were subjected to the hemorrhagic shock procedure described previously. Four dogs from Group II (II-C) were allowed to survive for 18 hours following the hemorrhagic shock, and were subsequently sacrificed.

Each animal was injected intravenously with Adenine-2,8-H^3 (Volk), 10 μc./Kg. In the case of the animals subjected to hemorrhagic shock, the isotope was administered one-half hour following retransfusion, and in the survivor dogs, 18 hours following retransfusion.

Samples of ileum, liver and blood were taken from all the animals at 30 minutes, 1, 2, and 4 hours after administration of radioactive adenine. The samples taken 2 hours following isotope administration, while the rates of incorporation are still increasing, are presented in this series of experiments (Table 8). At the final time interval, a sample of myocardium was also removed. The tissues were immediately placed in ice cold saline. They were then weighed and a 10% (w./v.) homogenate in saline was made using a Potter-Elvehien homogenizer. Three ml. of the homogenate was precipitated in the cold with an equal volume of 10% Trichloroacetic Acid (TCA). Blood samples were precipitated directly with 10% TCA. The cold material was then centrifuged and the supernatant (Acid-Soluble Fraction) was collected. For all tissues except blood and myocardium, the precipitate obtained above was washed twice with cold 5% TCA, then suspended in 5 ml. of 5% TCA and placed in a water bath at 90° C. for 20 minutes to hydrolyze the nucleic acids. The tubes were then cooled and centrifuged, and the supernatant was collected and designated the nucleic acid fraction.

Both the acid soluble and nucleic acid fractions were then neutralized by extracting three times with 10 volumes of ethyl ether to remove the TCA. The aqueous phase containing the nucleotides was then evaporated to dryness under air flow in a boiling water bath. 0.2 ml. of normal hydrochloric acid was added to the dried material, the tubes were stoppered, and placed in a boiling water bath for one hour to liberate the free purine bases from the nucleotides. Samples of the hydrolyzed material were applied to Whatman No. 1 paper and subjected to two-dimensional chromatography according to the method of Wyatt.[32]

After drying the chromatograms, the bases were located with an ultraviolet lamp and marked. The adenine spots were cut out and placed in 4 ml. of 0.1N HCl. The spots were eluted overnight, and the fol-

lowing day the eluates were estimated at 262.5 mμ in a Hitachi UV spectrophotometer to give a quantitative estimation of the base concentration in μM./ml. Aliquots of the analyzed solution were then placed in a scintillating medium (0.4% BBOT Packard, 80% Toluene, 30% Dioxane, 30% ethanol, with added naphthalene to give a final concentration of 18%) and radioactivity was counted in a Packard Series 4000 liquid scintillation spectrometer. All specific activities are expressed as disintegrations per minute per micromole of base (dpm./μM.).

In order to offset the limitations due to variations in the specific activity of the ATP of the blood among the groups of animals, the value for ATP in the tissue has also been expressed as a percentage of the ATP of the blood as follows:

$$\frac{\text{Specific Activity of ATP in Tissue}}{\text{Specific Activity of ATP Adenine in Blood}} \times 100$$

This factor reflects the capacity of the tissue to extract the circulating precursor.

A similar factor is used to express the percentage of tissue ATP which is utilized by the tissue for the synthesis of nucleic acids.

$$\frac{\text{Specific Activity of Tissue Nucleic Acid Adenine}}{\text{Specific Activity of Tissue Nucleic ATP Adenine}} \times 100$$

(*b*) *Glucose Metabolism.* A section of ileum was removed from the animal one hour following release of the mesenteric artery clamps. Slices of ileal mucosa, 0.5 mm. thick, were incubated in a Krebs Ringer phosphate medium in the presence of radioactive glucose labelled in the C-1 or C-6 position. Oxygen uptake was measured in a Gilson differential respirometer, and the carbon dioxide produced was absorbed by Hyamine-X placed in the center well of the Warburg vessel. The incubations were carried out for 30 minutes. At the end of the experiment, the Hyamine-X was placed directly into vials containing a scintillation medium, and the radioactivity was measured in a Packard Series 4000 liquid scintillation spectrometer. The incubation medium and the slice of mucosa were precipitated with perchloric acid, homogenized, and centrifuged. Charcoal, which had previously been treated with octanol to retard absorption of sugar phosphates, was added to the acid soluble fraction to absorb the nucleotides. After mixing, the charcoal was removed by centrifugation.

The charcoal precipitate was washed to remove latent radioactivity, and the nucleotides were removed with aqueous pyridine. Aliquots of the pyridine extracts were counted to determine their radioactivity.

For any given slice of mucosa, the radioactivity of the carbon dioxide produced by the C-6 labelled glucose, was divided by the radioactivity obtained from the C-1 labelled glucose, so that all results are expressed as a C-6/C-1. The oxygen uptake was expressed as Q_{O_2}, i.e., μl. of oxygen taken up per milligram of dry weight of tissue per hour, and in the presence of glucose as $Q_{O_2}{}^{G}$.

(c) *Amino Acid Transport.* Transport of amino acids was studied using sacs of ileum stripped of the muscular layer and then inverted. The sacs were incubated at 37.5° C. in Krebs-Ringer phosphate medium which was placed both inside and outside the sac. The amino acid under study was placed on the mucosal side of the sac and serial samples were removed from the serosal side by means of a fine catheter placed inside the sac. The serial samples were placed on Eastman thin layer chromatograms, using ethanol-acetic acid as solvent. The amino acids were developed with Ninhydrin spray (Sigma). This series of experiments was carried out on 34 dogs fed normal food, 9 of which were controls. Five were assayed one hour following retransfusion, 5 at 18 hours follow-

ing retransfusion, and 15 were 3-day survivors. Sixteen dogs fed the elemental diet were assayed, with 10 being control; while two were assayed one hour after retransfusion, and four were 3-day survivors.

Results and Comments

The Morbid State of the Intestinal Epithelium as a Primary Factor in Shock. Necrosis of the ileal and colonic epithelium not only exceeds in magnitude but precedes in time of appearance the pathologic lesions in distal organs.

Massive antemortem necrosis of the epithelium and the tips of the villi has been recognized for sometime in dogs dying in the early hours of normovolemic shock. Immediately after retransfusion, the metabolism of these cells is already greatly reduced long before similar changes are detectable in other organs.[7] This necrobiotic process does not necessarily assume the spectacular hemorrhagic features and may not be appreciated on direct macroscopic observation of the mucosal surface. Dogs which survive severe shock show either fragmentation and vacuolization of the mucosal epithelial cells, or these elements are actually shed into the lumen to be replaced several hours later by new flat, undifferentiated cells. Two to three days after injury, focal necrosis appears in the kidney, heart, and mid-brain, but again the intestinal lesion precedes in time and exceeds in magnitude that of the other organs.

For those reasons we suspected that intestinal epithelial necrosis *per se* could be a factor in extraintestinal involvement or death. In order to avoid generalized ischemia in other organs, such as occurs in a shock preparation, we produced a local intestinal ischemia by clamping the mesenteric arteries for only 90 minutes. Seventeen dogs constituted the control group on the normal kennel ration (Group III). Five acute deaths occurred but 12 survived to be sacrificed and studied at 3 or 7 days (Table 5).

Blood pressure did not change following removal of the clamps from the mesenteric arteries; blood analysis did not show a systemic anaerobic effect (Table 6); blood volume remained within control limits. Yet in every dog which developed necrosis of the epithelial mucosa of the ileum, a series of extraintestinal lesions developed. These dogs also showed, one hour after declamping, an average 25% fall in cardiac output. These lesions reproduced to a startling degree the organic changes previously seen in dogs surviving acute hemorrhagic shock. We, therefore, became convinced that necrosis of the superficial mucosal structures of the intestinal lining was indeed a primary factor capable of inducing via the circulation characteristic and severe systemic effects. The hemorrhagic infarction related to the action of tryptic ferments is only a complication and not an inevitable consequence.

The same must be said for congestion and pooling of blood in the intestinal vascular bed. This phenomenon occurs sometimes, especially when hemorrhagic infarction is present, or in the very early phase of shock after too rapid retransfusion; it is neither essential to the development of the intestinal necrosis nor is it at all related to the outcome of shock. Dogs that do survive shock without any anatomical or functional complication may show at sacrifice hyperemia and pooling; animals with severe lesions may often lack any signs of congestion or splanchnic pooling. The common denominator appears thus to be the necrosis or morbid state of the epithelial mucosal lining of the ileum. This need not be extensive to be of significance; it may involve no more than the tips of the villi.

Prophylactic Effect of the Elemental Diet. This essential role of the intestinal mucosa prompted us to study the factors responsible for the greater vulnerability of this particular tissue. The implication was

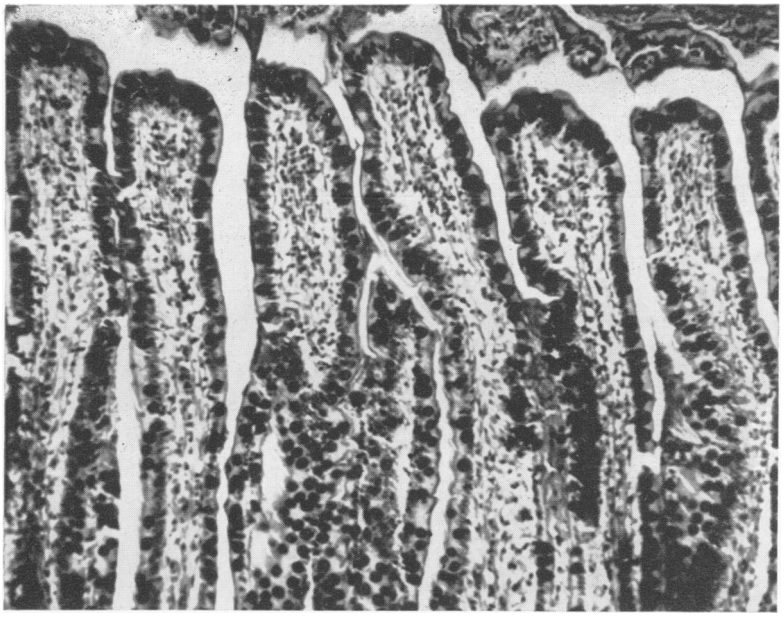

FIG. 7. Typical ileum (P.A.S.) of a dog on elemental diet, 3 days after shock, showing normal morphology.

that if one could prevent or control intestinal necrosis the overall outcome of shock might be influenced favorably. Previously published work has shown that pancreatic proteolytic enzymes in the lumen were indeed involved in the pathogenesis of the hemorrhagic dissolution of the mucosal surface following necrosis of the epithelial lining.[7] The role of pancreatic proteolytic enzymes in the pathogenesis of necrotic hemorrhagic enteritis has since been confirmed by Tiberio,[30] Hiatt,[18] and Smith.[27] Furthermore, previously published data had shown that, in dogs with ileostomies, the distal defunctioned half of the intestine, excluded for 2 to 3 days from the fecal transit, failed after shock to develop necrosis of the mucosal epithelium of the same magnitude as that seen in the proximal half.[6]

The shunting of normal food products from entire gut in the present study does indeed protect the mucosa from necrosis subsequent to a standard hemorrhagic shock or intestinal ischemia (Tables 1, 3, 5). From the analysis of these tables, it is clear that as the incidence of necrosis of the intestinal epithelium is greatly reduced in the diet groups, so is the frequency of extraintestinal complications. As shown in Table 1 (Group I), the hemorrhagic shock procedure in 18 dogs on normal food results in a 50% mortality during the early hours following retransfusion of blood. The survivors sacrificed on the third day showed extensive necrosis of the ileal and colonic epithelium with varying degrees of extraintestinal lesions. Only one dog (6630) appeared normal at autopsy; significantly, the ileal and colonic mucosa remained intact during and after shock. By contrast, the experimental group of 15 dogs on the "elemental" diet (Table 3, Group II), suffered no mortality as a result of a controlled and identical hemorrhagic shock procedure. These 15 survivors at the time of sacrifice on the third day, showed either no pathologic lesions at all or a mild degree of fatty infiltration (Dogs 6562, 6592, 6604, 6614, 6627). Areas of focal necrosis in extraintestinal areas were not visible on either gross or microscopic study. The intestinal mucosa of both the ileum and colon was normal (Fig. 7).

TABLE 1. *Hemodynamic Data and Pathology in Group I (Control Series, Hemorrhagic Shock)*

Dog No.	Max. Blood Volume cc./Kg.	Per Cent Uptake	Autopsy	Histology
6560		25%	Killed on third day	
			Heart: no gross lesions	Small focal infarcts in left ventricle
			Kidney: area of cortical pallor and medullary congestion	Numerous areas of tubular cortical necrosis
			Liver: normal	Numerous areas of cellular necrosis
			Ileum: normal	Tips of villi, fragmented cells, the rest columnar cells, no PAS positive material
			Lungs: normal	
6563			Died 20 hours later	
			Heart: full thickness miocardial infarcts. Papillary muscles involved in both ventricles. Infarcts on right ventrical wall	Fatty infiltration in many areas of right ventricles, focal infarcts
			Kidney: slight cortico-medullary congestion, cortical pallor	Focal tubular necrosis, tubular glomer reflux
			Ileum: areas of hemorrhagic necrosis	
				Liver: large areas of infarcts
			Lungs: moderate congestion	
6575	38	5%	Killed on third day	
			Heart: subendocardial hemorrhages; fatty infiltration in both ventricles; small focal infarct in the papillary muscles of left ventricle	Fatty degeneration; small infarct
			Kidney: mild congestion in medulla; cortical pallor	Cortical tubular necrosis, glomerular tubular reflux
			Ileum: few small areas of redness	Flat cells covering almost all villi
			Liver: normal	Diffuse cellular vacuolization
				Colon: erosion and superficial necrosis
6578	36	16%	Killed on third day	
			Heart: subendocardial hemorrhages, focal infarcts in papillary muscles	Focal infarcts
			Kidney: cortical pallor, medullary congestion	Cortical tubular necrosis, glomerular tubular reflux
			Liver: normal	Congestion and diffuse cellular vacuolization
			Ileum: moderate herringbone type redness	Flat cells covering tip of villi, fusion of adjacent villus surfaces
				Colon: superficial necrosis
6593	31	29%	Died 8–12 hours later	
			Heart: no appreciable miocardial lesions, subendocardial hemorrhages	Subendocardial hemorrhages
			Ileum and Colon: massive hemorrhagic necrosis	Ileum: massive hemorrhagic necrosis with no sign of regeneration

TABLE 1.—(*Continued*)

Dog No.	Max. Blood Volume cc./Kg.	Per Cent Uptake	Autopsy	Histology
6602	50	35%	Died 8–12 hours later	
			Heart: subendocardial hemorrhages	
			Lung: bilateral congestion few atelectatic areas	
			Liver: multiple necrotic areas	
			Kidney: medullary congestion, cortical pallor	Cortical tubular necrosis
			Ileum: mild redness of mucosa in some areas	Severe epithelial necrosis
6605	17	70%	Died about 8 hours later	
			Heart: subendocardial hemorrhage	Subendocardial hemorrhage
			Kidney: mild tubular necrosis	Tubular cell necrosis
			Liver: necrotic areas	
			Ileum: diffuse hemorrhagic necrosis	
6613	46	33%	Died 48 hours later	
			Heart: diffuse subendocardial fatty infiltration, focal infarcts in papillary muscles of left ventricle. Right ventricle wall fatty infiltration	Fatty infiltration, focal infarcts
			Kidney: cortical pallor, medullary congestion	Tubular cell necrosis, interstial hemorrhages
			Liver: multiple small infarcts	Pericentrolobular cell, vacuolization, interstial congestion
			Ileum: small areas of herringbone type redness, no hemorrhage	Massive necrosis of the villi, particularly epithelial cells
			Colon: few red areas	Diffuse superficial necrosis
6617	39	25%	Killed fourth day	
			Heart: subendocardial infarcts on papillary muscles of right ventricle. Subendocardial hemorrhages and one small infarct on left ventricle	Infarcts in the papillary muscles
			Kidney: medullary congestion area of cortical pallor	Focal tubular necrosis, glomerular tubular reflux
			Ileum: normal	Columnar cells with total loss of mucin
6626	38	30%	Killed on third day	
			Heart: one focal ventricular infarct	Focal infarcts
			Kidney: cortical pallor, medullary congestion	Tubular necrosis, numerous alive casts, congestion
			Ileum: normal	Columnar cells with loss of mucin
				Colon: superficial necrosis
6630	46	38%	Killed on third day	
			Heart: normal	Normal
			Kidney: normal	Normal
			Liver: normal	Severe congestion and cell vacuolization
			Ileum: normal	Normal
				Colon: normal

TABLE 1.—(*Continued*)

Dog No.	Max. Blood Volume cc./Kg.	Per Cent Uptake	Autopsy	Histology
6641	56	17%	Died 36 hours later	
			Heart: small infarcts on right and left ventricles	Miocardial infarcts
			Kidney: cortical pallor	Cortical tubular necrosis
			Liver: normal	Pericentrolobular cellular vacuolization, congestion
			Ileum: normal	Necrosis of mucosal epithelium
				Colon: superficial necrosis
6645	41	19%	Killed on third day	
			Heart: subendocardial hemorrhages; small miocardial infarcts and fatty infiltration	Focal small infarcts
			Kidney: medullary congestion	Tubular necrosis; glomular tubular reflux
			Liver: normal	Diffuse cellular vacuolization, interstitial hemorrhage
			Lungs: normal	
			Ileum: mild herringbone redness	Some villi with columnar cells; no mucin, other necrotic or flat cells
				Colon: superficial necrosis
6646	44	20%	Killed on third day	
			Heart: subendocardial hemorrhage; infarcts on papillary muscles; scattered fatty infiltrates	Numerous focal infarcts
			Kidney: medullary congestion, cortical pallor	Tubular cortical necrosis, interstitial hemorrhages
			Ileum: mild redness in some areas, no hemorrhages	Cellular necrosis
				Liver: diffuse cellular vacuolization, congestion
6647	44	28%	Died 36 hours later	
			Heart: subendocardial hemorrhages; infarcts in right ventricle wall and left ventricle papillary muscles	Intramiocardial hemorrhages, areas of accumulation of poli
			Kidney: cortical pallor and medullary congestion	Tubular cortical necrosis glomerular tubular reflux
			Lung: normal	
			Liver: congestion	Congestion
			Ileum: mild herringbone type redness	Mucosal necrosis
				Colon: superficial necrosis
6648	44	26%	Died 24 hours later	
			Heart: subendocardial hemorrhages, small infarct on papillary muscles	Focal infarcts
			Liver: congestion	Cellular vacuolization and congestion
			Kidney: cortical pallor, medullary congestion	Tubular cortical necrosis
			Ileum: moderate herringbone necrosis	Hemorrhagic necrosis
				Colon: superficial necrosis
6704	44	25%	Died overnight	
			Heart: subendocardial infarcts	
			Ileum: massive necrosis of the epithelium and tips of villi with some hemorrhagic areas	

TABLE 1.—(*Continued*)

Dog No.	Max. Blood Volume cc./Kg.	Per Cent Uptake	Autopsy	Histology
6705	50	5%	Killed on third day	
			Heart: focal miocardial necrosis	Small necrosis
			Kidney: medullary congestion, cortical pallor	Tubular focal necrosis, interstitial hemorrhages
			Ileum: normal appearance	Ileum and colon: superficial epithelium appears fragmented and cells vacuolized
Average:	41.5	26%		

In the series submitted to mesenteric artery clamping, the trend was similar. Table 5 (Group III) illustrates the extent, location, and characteristics of intestinal and extraintestinal lesions in survivors of the control group on normal food. The early mortality was rather low (5 of 17 animals). However, most of the animals, killed on the third or seventh day, showed characteristic anatomic changes involving first of all the epithelium of small and large bowel. These alterations took the form of fragmentation, vacuolization of the epithelial cells or actual substitution of these with new flat elements covering the previously denuded villi.

The extraintestinal pathology following mesenteric arterial occlusion is similar to that seen following hemorrhagic shock and may be summarized as follows. In the heart, one finds diffuse or patchy fatty infiltration with eventually focal necrosis near the subendocardial aspect, particularly of the major papillary muscles of the left ventricle, and patchy subendocardial hemorrhages, sometimes extending into the myocardium. In the kidney, large areas of cortical tubular necrosis are seen with sometimes glomerular tubular reflux, medullary congestion or hemorrhages. The liver shows centrolobular hepatocellular vacuolization and fatty infiltration. The brain may show small focal hemorrhages in the basal ganglia without pathological alteration of the neurons. The changes observed in the lungs in the form of patchy atelectasis with hemorrhages appear not related to the severity of concomitant complications in other organs. Furthermore, no signs of failure in pulmonary function have been detected following these injuries in a previously healthy dog. The vascular lesions are rather characteristic, fragmentation of the lamina elastica in small arterioles in the heart and basal ganglia of the brain, no signs of thrombosis in *in vitro* biopsies or immediately postmortem. It is interesting to observe that the arteries and arterioles of the intestinal submucosa appear normal.

In the group on the elemental diet with mesenteric artery clamping, Group 4, all 15 dogs survived. At sacrifice on the third day, the autopsy and histologic examination of the standard areas was negative in most animals. Only two dogs (6544 and 6488) showed anatomic signs of minor intestinal epithelial change with low cuboidal cells and reduced mucus. This was interpreted as a sign of an attenuated generation of cells, there being no indication of a full-blown necrotizing lesion. Otherwise, no organ lesions whatever were seen; and accordingly, we have dispensed with the corresponding table to record the results of this group.

TABLE 2. *Blood Analysis in Group 1 (Control Series, Hemorrhagic Shock)*

Dog No.	Lact./Pyruv. Bef.	Lact./Pyruv. Aft.	pH Bef.	pH Aft.	PO_2 Bef.	PO_2 Aft.	PCO_2 Bef.	PCO_2 Aft.	Na Bef.	Na Aft.	Na 3 Day	K Bef.	K Aft.	K 3 Day	Total Protein Bef.	Total Protein Aft.	Total Protein 3 Day	LDH Cont.	LDH 1st Day	LDH 3rd Day	SGOT Cont.	SGOT 1st Day	SGOT 3rd Day
6560	4.1/0.84	23.5/2	7.300	7.140	84	97	32	30	146	144		3.7	4.8		6.4	5.1							
6563	5.3/1.24	40/3.86	7.320	7.080	66	90	46	28.5	145	138		3.9	7.6		6.9	6.3							
6576	6.5/1.40	35.2/2.97	7.370	7.250	86	104	37	33	143	156	144	3.8	3.9	7	5	4.2	4.7	150	190	160	17	31	27
6578	4.7/0.88	37/3.18	7.285	7.225	63	101	49	29	150	155	149	4.7	4.9	5	5.3	4.9	5.2	290	700	590	28	121	110
6593	9.6/1.25	27.2/2.3	7.260	7.160	63	71	42	22	143	138		3.2	4.3		5.5	5.1		150	610		29	120	
6602	9.6/0.9	90/3.84	7.355	7.130	64	91	48.5	34.5	152	152		3.9	5		7.4	6.6			1250			1760	
6605	9.6/1.40	55.5/2.7	7.395	7.205	85	121	31.5	20	137	134		5.5	5.7						1000			163	
6613	4.8/1.15	25.8/2.7	7.380	7.275	88	91	37	22.5	152	152		3.3	5		6.3	5.6			850			228	
6617	3.5/1.25	33.6/4.2	7.290	7.230	74	113	54	22	164	149		3.2	2.9	3.2	6	4.8	7.3		210	210		42	210
6626	4.7/1.20	68.7/5	7.330	7.010	70	131	42	17.5	154	150	130	3.6	6.6	4.2	7.3	7.7	7.3	110	1500	210	23	1340	310
6630	5.9/0.95	18.8/6.55	7.335	7.090	97	141	38.5	36	154	162	140	3.6	4.2	3	5.8	5.2	5.9				18	64	50
6641	5.9/1.80	54.6/2.62	7.300	7.060	93.5	111	40	28	147	144		3.2	5.2		6.3	4.8		80	160		27	143	
6645	3.5/1.35	12.3/3.6	7.275	7.155	86	94	32	22	148	154	146	3.5	4.1	4	6.1	6	5.8	40	440	170	28	68	61
6646	3.5/1.05	27/4.5	7.345	7.115	77	99	44.5	32	155	155	147	4.8	6	4.2	6.2	5.6	6.4	80	1284	90	36	184	56
6647	8.2/1.50	40/3.60	7.290	7.155	81	112	45	25.5	145	155		5.1	5.2		6	6.5		130	630		30	260	
6648	10/1.67	34.1/1.85	7.405	7.215	79	94	37	36	156	149		5.5	6.1		6	5.6		110	860		34	105	
6704	8/2	37/3.82	7.405	7.280																			
6705	6.8/1.05	28.8/2.3	7.400	7.310																			
Average	6.3/1.28	38.2/3.4	7.335	7.171	78.5	103.8	41.0	27.4	149.4	149.2	142.7	4.0	5.1	4.4	6.2	5.6	6.1	126.7	766	238.3	27	330.6	117.7

TABLE 3. *Hemodynamic Data and Pathology in Group 2 (Diet Series, Hemorrhagic Shock)*

Dog No.	Max. Blood Volume cc./Kg.	Per Cent Uptake	Autopsy	Histology
6561			Killed on third day	
			Heart: normal	Normal
			Kidney: normal	Normal
			Ileum: normal	Normal
			Colon: normal	Normal
				Liver: congestion and slight hemorrhage
6562			Killed on fourth day	
			Heart: left ventricle small areas of fatty infiltration in both papillary muscles, scattered areas of infiltration near the subepicardial aspect; no infarcts, right ventricle: normal	Areas of fatty infiltration
			Liver: normal	Normal
			Kidney: normal	Normal
			Ileum: normal	Normal
			Colon: normal	Normal
6572	52	0	Killed on third day	
			Heart: subendocardial hemorrhages; small areas of fatty infiltration on right ventricle; no infarcts	Areas of fatty infiltration no infarcts
			Kidney: medullary congestion	Normal
			Liver: normal	Congestion
			Ileum: normal	Normal
			Colon: normal	Normal
6576	41	0	Killed on third day	
			Heart: normal	Normal
			Kidney: normal	Normal
			Liver: normal	Congestion
			Ileum: normal	Normal
6579	70	18%	Heart, Kidney, Liver, and Ileum: normal	Normal
			Lung: pneumonitis	Pneumonitis
6592	44	0	Killed on third day	
			Heart: small areas of fatty infiltration on left ventricular papillary muscles; no infarcts	Fatty infiltration; no infarcts
			Kidney: medullary congestion	Normal
			Liver: normal	Normal
			Ileum: normal	Normal
6601	50	8%	Killed on third day	
			Heart: subendocardial hemorrhages	Normal
			Kidney, Liver, Ileum: normal	Normal
6604	29	35%	Killed on third day	
			Heart: left ventricle, subendocardial hemorrhages	Normal
			Kidney, Liver, Ileum: normal	Liver: fatty infiltration Kidney, Ileum: normal

TABLE 3.—(*Continued*)

Dog No.	Max. Blood Volume cc./Kg.	Per Cent Uptake	Autopsy	Histology
6614	60	0	Killed on third day	
			Heart: left ventricle one area of 1–3 mm. of fatty infiltration on left papillary muscle, subendocardial hemorrhages; no infarcts	Areas of fatty infiltration; no infarcts
			Ileum: few patchy areas of red color	Normal
			Kidney: medullary congestion	Normal
			Colon: normal	Normal
			Lung: normal	Normal
6616	39	10%	Killed on third day	
			Heart: subendocardial hemorrhages	Normal
			Kidney: medullary congestion	Normal
			Ileum, Liver, Colon: normal	Normal
6627	58	22%	Killed on third day	
			Heart: subendocardial hemorrhages. Very small areas of fatty infiltration in subendocardium	Small areas of fat infiltration; no infarcts
			Kidney: medullary congestion	Normal
			Lung: normal	Normal
			Ileum: very mild herringbone redness	Normal
			Liver: normal	Congestion and slight cellular vacuolization
			Colon: normal	Normal
6629	45	13%	Killed on fourth day	
			Liver: normal	Slight cellular vacuolization and congestion
			Heart, Kidney, Ileum, and Colon: normal	Normal
6642	55	0	Killed on third day	
			Heart: left ventricle subendocardial hemorrhages	Normal
			Kidney, Liver, Ileum and Colon: normal	Normal
6718	37	14%	Killed on third day	
			Heart, Kidney, Ileum, Colon, and Brain: normal	Negative
6719	48	22%	Killed on third day	
			Heart, Kidney, Ileum, and Colon, Brain: normal	Negative
Average:	48	11%		

The Validity of the Experimental Preparation in Assessing the Effect of the Diet. It was necessary to ascertain that both groups of dogs submitted to hemorrhagic shock were indeed exposed to the same degree of hypoperfusion during the 4½-hour period of hypovolemia. All animals were maintained for the same length of time at the same level of hypotension as measured by the aortic blood pressure. However, other measurements provided confirmation that a comparable degree of hemodynamic injury was inflicted on both groups. For example, the maximum bled blood volume in ml./Kg. was even somewhat higher (average 48 ml./Kg.) in the

TABLE 4. *Blood Analysis in Group 2 (Diet Series, Hemorrhagic Shock)*

Dog No.	Lact./Pyruv. Bef.	Lact./Pyruv. Aft.	pH Bef.	pH Aft.	PO_2 Bef.	PO_2 Aft.	PCO_2 Bef.	PCO_2 Aft.	Na Bef.	Na Aft.	Na 3 Day	K Bef.	K Aft.	K 3 Day	Total Protein Bef.	Total Protein Aft.	Total Protein 3 Day	LDH Cont.	LDH 1st Day	LDH 3rd Day	SGOT Cont.	SGOT 1st Day	SGOT 3rd Day	CPK
6558	7.6 / 1.60	54 / 3.87	7.310	7.285	79	109	47	12	150	150		4.8	4		5	5.8								
6561	15.9 / 2.76	30 / 2.46	7.240	7.230	73.5	104	43.5	23.5	148	139		4	4		6.1	5.3								
6562	4.7 / 0.96	24.1 / 4.09	7.275	7.140	62	81	46	39	147	146		3.4	3.8		8.3	6.7								
6572	7.6 / 1.12	64 / 4.80	7.275	7.030	80	111	48.5	40	153	147	154	3.8	4	3.6	5.6	5.4	5.7	150	220	150	15	77	120	5.83
6576	4.7 / 1.20	22.9 / 2.40	7.310	7.260	87	101	37	25.5	148	148	150	4.3	4.4	3.9	5	4.2	5.9	170	390	170	15	42	18	3.29
6579	5.9 / 1.29	34.1 / 3.21	7.230	7.225	60	102	48	17	151	166		3.5	8.4		6.6	7.8		150	920		19	124		
6592	7.7 / 0.10	61 / 5.45	7.340	7.200	79	99	35.5	32	143	141	145	3.7	4.4	4.2	4.9	4.2	4.7	270	700	550	26	175	80	
6601	8.5 / 1.20	60.9 / 2.25	7.395	7.140	85	100	34	27.5	163	165	164	4.8	4.6	4.9	7.3	6.1	8		700	1080		108	342	
6604	10.7 / 1.35	41.1 / 2.92	7.395	7.205	80	111	32.5	23	148	141	149	3.4	5.9	4.2	6.3	6.4	7.1		1040	230		348	53	7.74
6614	5.3 / 1.20	16.9 / 3.10	7.390	7.350	79	94	35	20.5	154	150		3.6	4.5		5.9	5		100	280		18	43		
6616	2.7 / 1.50	39.6 / 4.35	7.355	7.250	101	111	37.5	22	161	148		4.2	5		6.7	6.4			940			308		
6627	7 / 1.27	29.4 / 4.20	7.315	7.115	84	121	42	24.5	154	153		4	6.2		6.3	5.7	7.9	90	1440	150	43	800	240	6.4
6629	3.5 / 1.35	14.7 / 3.45	7.365	7.130	99	112	36.5	34.5	157	162	156	3	4.8	4.4	6.1	5.8	6.2	120	330	250	20	46	30	
6642	3.5 / 1.10	24.1 / 3.90	7.300	7.060	96	111	44	28	139	140	138	3	3.6	4	5.5	4.9	6.9	40	230	170	33	68	270	3.7
6718	2 / 1.20	47 / 3.45	7.310	6.971	74	87	45	58																
6719	6.56 / 1.4	43.48 / 3.35	7.385	7.225	79	83.5	40.5	35																
Average:	6.4 / 1.28	38 / 3.5	7.324	7.176	81.0	101.7	40.7	28.8	151	150	150.8	3.8	4.8	4.1	6.1	5.6	6.5	136.2	658	343.7	23.6	194.4	144.1	

TABLE 5. *Pathology in Group 3 (Mesenteric Arteries Occlusion for 90 Minutes, Control—Survivors Killed on Third Day)*

Dog No.	Autopsy	Histology
6349	Killed on third day	
	Heart: normal	Infarcts with small vessel damage
	Kidney: congestion and cortical ischemia	Focal infarct, tubular necrosis and tubular reflux
	Small bowel: moderate herringbone congestion	Flat cells covering villi and marked reduction in goblet cells
	Liver: Mild congestion	Central vein congested. Centrilobular hepatic necrosis
	Brain: grossly normal	Minimal vascular changes with perivascular hemorrhage in midbrain
6356	Killed on third day	
	Heart: focal infarcts in both ventricles	Multiple myocardial infarcts
	Kidney: severe cortico-medullary congestion and cortical pallor	Tubular necrosis, tubular reflux
	Small bowel: moderate herringbone congestion	Flat cells
	Brain: grossly normal	Liver: central vein congestion and cellular necrosis
6357	Died two days	
	Heart: fatty infiltration	Micro infarcts and fatty infiltration
	Kidney: cortico-medullary congestion and cortical pallor	Tubular necrosis, tubular reflux, and micro hemorrhages
	Small bowel: marked herringbone congestion	Flat cells and reduced mucin production
	Liver: mildly congested	Congestion and hepatocyte necrosis
	Brain: grossly normal	
6363	Killed on fourth day	
	Heart: multiple focal infarcts	Numerous micro infarcts
	Kidney: severe cortico-medullary congestion and cortical pallor	Tubular necrosis and reflux
	Liver: mild congestion	Centrilobular hepatic necrosis
	Small bowel: severe herringbone congestion	Flat cells with marked reductions in mucin production
		Brain: small vessel damage in thalamus
6364	Killed on seventh day	
	Kidney: moderate cortico-medullary congestion and cortical pallor	Tubular necrosis and reflux
	Small bowel: moderate submucosal herringbone congestion	Flat cells and reduced mucin production
	Liver: mild congestion	Centrilobular hepatic necrosis
	Brain: grossly normal	Small vessel changes in midbrain and basal ganglia
6365	Killed on third day	
	Heart: normal	Occasional micro infarct
	Kidney: mild cortico-medullary congestion and cortical pallor	Cloudy swelling of proximal tubules
	Small bowel: mild herringbone congestion	Reduced mucin production. Columnar cells intact
	Liver: normal	Cloudy swelling of centrilobular hepatocytes

Dogs No. 6349 to 6366 included had 100,000 units of Trasylol injected into the duodenum 20 minutes prior to clamping.

TABLE 5.—(*Continued*)

Dog No.	Autopsy	Histology
6366	Died on declamping	
	Heart: normal	Occasional focal lymphocytic infiltrate
	Kidney: moderate cortico-medullary congestion and cortical pallor	Cloudy swelling of proximal tubules
	Small bowel: moderate herringbone congestion	Diminished mucin production
	Liver: normal	Questionable cloudy swelling of centrilobular hepatocytes
6373	Died on first day	
	Heart: normal	Occasional focal lymphocytic infiltrates. No micro infarcts per se
	Kidney: mild cortico-medullary congestion and cortical pallor	Cloudy swelling of proximal tubules
	Small bowel: mild herringbone congestion	Signs of denudation of epithelium and reduced mucin production
	Liver: normal	Cloudy swelling of centrilobular hepatocytes
6374	Killed on fifth day	
	Heart: several focal infarcts. Subendocardial hemorrhage	Numerous focal microscopic infarcts
	Kidney: moderate cortico-medullary congestion and cortical pallor	Tubular necrosis and reflux
	Small bowel: moderate herringbone congestion	Flat cells and diminished mucin production
	Liver: mild congestion	Cloudy swelling and necrosis of centrilobular hepatocytes
	Brain: grossly normal	Small vessel damage in midbrain and basal ganglia
6380	Killed on third day	
	Heart: multiple focal infarcts	Numerous microscopic infarcts
	Kidney: focal infarcts. Severe cortico-medullary congestion and cortical pallor	Several focal infarcts. Tubular necrosis and reflux
	Small bowel: severe herringbone congestion	Flat cells and diminished mucin production
	Liver: moderate congestion	Congestion of central vein. Centrilobular necrosis
	Brain: grossly normal	Focal hemorrhages in brain stem and basal ganglia
6381	Killed on third day	
	Heart: multiple focal infarcts	Numerous microscopic infarcts
	Kidney: Moderate cortico-medullary congestion and cortical pallor	Focal hemorrhages. Tubular necrosis and tubular reflux
	Small bowel: severe ileal herringbone congestion	Flat cells. Marked diminution in mucin production
	Liver: mild congestion	Central vein congestion. Necrosis of centrilobular hepatocytes
6387	Killed on third day	
	Heart: normal	Normal
	Kidney: mild cortico-medullary congestion	Capillary congestion. Essentially normal
	Small bowel: mild herringbone congestion	Mucin production down
	Liver: normal	Mild central venous congestion
	Brain: grossly normal	Small hemorrhages in basal ganglia and brain stem

TABLE 5.—(*Continued*)

Dog No.	Autopsy	Histology
6388	Died 30 hours postoperatively	
	Heart: several small infarcts and subendocardial hemorrhages	Microscopic infarcts and small vessel damage
	Kidney: mild cortico-medullary congestion and cortical pallor	Tubular necrosis and glomerular reflux
	Small bowel: mild herringbone congestion	Denuded villi, marked reduction in mucin production
	Liver: normal	Central vein congestion. Cloudy swelling of centrilobular hepatocytes
6400	Killed on third day	
	Heart: subendocardial hemorrhages. Questionable infarcts	Multiple smal infarcts and small vessel damage
	Kidney: moderate cortico-medullary congestion and cortical pallor	Tubular necro[sis and glomerular reflux
	Small bowel: moderate herringbone congestion	Flat cell regeneration. Mucin production down
	Liver: mild congestion	Central vein congestion. Necrosis of centrilobular hepatocytes
	Brain: grossly normal	Small vessel changes and hemorrhage in basal ganglia and brain stem
6401	Killed on third day	
	Heart: grossly normal	Questionable micro infarcts with scattered cellular infiltration
	Kidney: mild cortico-medullary congestion	Cloudy swelling of proximal tubules
	Small bowel: mild herringbone congestion	Mucin production down. Necrosis of tips of villi
	Liver: normal	Mild congestion of central veins
6404	Killed on fourth day	
	Heart: normal	Normal
	Kidney: mild cortico-medullary congestion	Cloudy swelling in proximal tubules
	Small bowel: essentially normal	Mucin production down. Cells intact
6405	Died 48 hours postoperatively	
	Heart: grossly normal	Several small infarcts. Small vessel damage
	Kidney: moderate cortico-medullary congestion & cortical pallor	Tubular necrosis and glomerular reflux
	Small bowel: moderate herringbone congestion	Denuded villi. Mucin production down

diet group than in the control (41.5 ml./Kg.). Thus the blood volume loss during hypovolemia was comparable. The average lactate/pyruvate ratio was almost precisely the same in both groups before hemorrhage. The increase in the ratio in relation to hemorrhage was very similar indeed: from 4.9 to 11.2 in Group I (Table 2), and from 5 to 10.9 in Group II (Table 4). Blood pH and gases followed a similar pattern in Group I and II and the increase in serum K was also within the same range. The values for LDH and SGOT were so scattered and the variation between individual dogs was too wide to permit a statistical evaluation of any significance. The electrocardiograms performed 24 hours after shock will be reported in a separate study. The general pattern was S-T depression, appearance of pathological Q waves in some cases, and T-wave inversions. No significant difference was noticed between Group I and Group II, attesting further to the fact that the myocardial ischemia was

similar in both groups. An interesting corollary to the histologic studies was the fact that hyperemia or congestion, when observed, bore no relationship to the anatomic changes, nor to the outcome of shock.

Despite such evidence, one must concede that the actual state of the capillary perfusion cannot be precisely estimated in hemorrhagic shock. For this reason, it was decided to test further the validity of our assumption regarding the crucial role of hypoperfusion by producing a total ischemia for 90 minutes in the area which appeared to be primarily involved in the production of the shock syndrome, and of particular significance in relation to the effect of the diet, namely, the intestine itself. The results appear to be clearcut. Total occlusion of the mesenteric vascular bed produced lesions similar to those seen in hemorrhagic shock, and these lesions were prevented by the elemental diet (Groups III and IV). Finally, in order to rule out seasonal differences, each experimental animal on the elemental diet was paired with a control dog on normal food.

The Site of Action of the Elemental Diet: Metabolic Data. In this section, we shall attempt to show that the beneficial effects of the elemental diet are primarily upon the mucosa of the intestine. Although the constituents of the experimental diet reproduced the control diet in an elemental form, it remains true that some factors have been introduced that may have affected, over the 3-day period, systems and organs other than the gut and may perhaps have enhanced the general resistance of the organism. Nothing, however, has been added to the experimental diet that was not in the normal food, and may thus have entered the blood stream to provide the organism with a greater capacity to resist injury. The blood analysis of the two control groups indicates that proteins, electrolytes and blood gases are in similar concentrations as in the diet group (Tables 2, 4, 6, 7). Lactate/pyruvate ratios are almost precisely identical, and as far as these parameters reflect intermediary metabolism, no systemic effect appears to be produced by a 3-day period on the elemental diet. However, a local metabolic effect upon the mucosal cells of the lower ileum was observed at the end of this three-day period.

The incorporation of tritium labelled adenine into the ATP of the ileal mucosa and of the blood is shown in Table 8. The values obtained 2 hours after the administration of the isotope are presented while incorporation of the isotope is showing an increase in all tissues. It can be seen that the incorporation of adenine into the ATP of the ileal mucosa is increased five-fold in the dogs fed on the elemental diet over those fed on the normal diet, with a percentage extraction ratio of 163% in the former group and only 34.5% in the latter ($p < 0.001$).

This increase is not due to omission of nucleic acid products from the diet, since luminal absorption is not the normal port of entry of these materials. Rather, they are synthesized *de novo* from an array of

TABLE 6. *Average Values of Blood Analyses for the Dogs in Group 3*

Lact./ Pyruv.		pH		PO_2		PCO_2		Na			K			Total Proteins		
	1		1		1		1		1	24		1	24		1	24
B.	hr.	B.	hr.	B.	hr.	B.	hr.	B.	hr.	hr.	B.	hr.	hr.	B.	hr	hr.
7.9	13	7.325	7.241	80	75	45	55	150.3	149.2	148.7	3.55	4	4.2	6.3	6.3	6.2
0.76	0.96															

TABLE 7. *Blood Analysis in Group 4 (Diet Series, Mesenteric Arteries Clamping for 90 Minutes)*

No.	Lact./Pyruv. B.	Lact./Pyruv. 1 hr.	pH B.	pH 1 hr.	PO_2 B.	PO_2 1 hr.	PCO_2 B.	PCO_2 1 hr.	Na B.	Na 1 hr.	Na 24 hr.	K B.	K 1 hr.	K 24 hr.	Total Proteins B.	Total Proteins 1 hr.	Total Proteins 24 hr.	CPK	LDH	SGOT
6468	5.9 / 0.6	3.2 / 0.57	7.225	7.255	66	84	47.5	44.5	153	152	150	3.4	4.1	3.6	6	6	5.7		440	174
6469	7 / 0.58	43 / 2.49	7.325	7.405	77	64	35	20	143	139		2.9	3.5		4.9	4.6				
6471	9.4 / 0.41	12.3 / 0.45	7.325	7.26	88	97	42.5	46	144	143	142	3.7	4.4	3.9	5.4	5.3	5.6		250	18
6510	7 / 0.47	4.1 / 0.41	7.240	7.375	69	76	54	35	150	155	146	5.1	4.4	3.4	6.1	6.9	6		150	75
6511	6.5 / 0.61	7 / 1.08	7.360	7.365	81	82	34.5	37	147	155	147	4.1	4.8	4	6.7	6	6.1		120	40
6514	8.8 / 0.8	48.8 / 4.57	7.305	7.280	91	94	37	33.5	150	140	147	4	2.9	3.9	6	6.6	6.2		250	99
6521	9.4 / 0.27	6.5 / 0.61	7.305	7.310	66	70.5	38.5	42.7	148	144		4	4.2		6.3	5.2		5.10		
6526	6.5 / 1.31	2.4 / 0.94	7.200	7.280	65	72	49.5	46.5	148	150	150	3.8	5.2	4.4	5.9	5.1	6.4	0.53	210	25
6527	9.4 / 0.86	9.4 / 1.71							150	146		4.6	3		8.1					
6566	7.1 / 1.28	6.5 / 1.12	7.215	7.300	74	72	51.5	38	154	149	145	3.7	4.8	4.2	7.3	7.5	8.2	3.70	140	86
6534	4.1 / 0.94	4.4 / 1.41	7.240	7.285	65	81	57.5	45	147	145		3.9	4.2		6.4	6.4				
6542	15.9 / 1.34	20.6 / 1.29	7.300	7.205	77	93	44.5	53	147	148		3.5	4.2		6.3	5.8				
6543	19 / 1.10	11.8 / 1.20	7.305	7.345	80	98	46	39.5	147	148	148	3.4	4.4	4.2	6	5.5	6	0.85	150	29
6544	10 / 0.86	10 / 1.36	7.395	7.305	105	93	32.5	34.5	144	153	152	3.6	4.1	3.6	6.2	6.6	6.6	0.64	190	46
6545	12 / 1.27	7.6 / 1.12	7.365	7.395	83	75	35	32	149	157	155	3.8	4.3	4.3	6.7	6.9	7.6	2.10	160	92
Average:	9.2 / .81	13.2 / 1.35	7.293	7.310	77.6	82.3	43.3	39.1	148.1	148.3	148.2	3.8	4.2	3.9	6.3	6.0	6.4	2.1	216.0	68.4

Dog No. 6468 to 6566 included had 100,000 units of Trasylol injected into the duodenum 20 minutes prior to clamping.

TABLE 8. *Incorporation of Adenine-2,8-H³ into ATP and Nucleic Acid in Shock*

	Group I: Normal Diet		Group II: "Elemental" Diet		
	I-A Control	I-B Hemorrhagic Shock	II-A Control	II-B Hemorrhagic Shock	II-C Hemorrhagic Shock Survivor
S.A. ATP Ileum	22,135 ± 5,889[5]	3,671 ± 2,119[3]	109,130 ± 21,909[5]	53,881 ± 7,505[3]	26,845 ± 5,895[4]
S.A. ATP Blood	127,929 ± 49,800[5]	137,092 ± 4,726[3]	72,368 ± 8,193[5]	308,619 ± 55,427[3]	172,204 ± 46,046[4]
S.A. Nucleic Acid Ileum	4,229 ± 606[5]		7,073 ± 1,956[5]	3,231 ± 848[3]	2,733 ± 1,339[2]
S.A. ATP Liver	20,612 ± 4,123[5]	11,895 ± 1,154[3]	46,525 ± 5,398[5]	54,367 ± 13,747[3]	9,444 ± 4,172[4]
S.A. ATP Myocardium	24,747 ± 7,737[4]	7,453 ± 3,316	26,718 ± 2,872[5]	10,371 ± 1	13,881 ± 3,162[4]
$\frac{\text{S.A. ATP Ileum}}{\text{S.A. ATP Blood}} \times 100$	34.45 ± 12.6[5]	3.5 ± 0.998[3]	163.6 ± 40.6[5]	17.65 ± 7.74[3]	16.10 ± 3.63[4]
$\frac{\text{S.A. N.A. Ileum}}{\text{S.A. ATP Ileum}} \times 100$	15.9 ± 2.72[5]		6.2 ± 0.424[5]	5.88 ± 0.79[3]	8.55 ± 0.066[2]
$\frac{\text{S.A. ATP Liver}}{\text{S.A. ATP Blood}} \times 100$	38.41 ± 10.9[5]	8.75 ± 0.998[3]	65.9 ± 6.79[5]	17.25 ± 3.15[3]	4.99 ± 1.91[4]

All values shown as Mean ± S.E.M.?
S.A. = Specific Activity expressed as disintegrations per minute per micromole of adenine.
Number of animals averaged shown by superscripts.
Group I-A: Controls on normal diet.
Group I-B: Two and one half hours following retransfusion.
Group II-A: Controls on elemental diet.
Group II-B: Two and one half hours following retransfusion.
Group II-C: Eighteen hours following retransfusion.

TABLE 9. *Tissue Respiration in Mesenteric Arterial Occlusion*

	Group I: Normal Diet		Group II: "Elemental" Diet	
	I-A Control	I-B Post-occlusion	II-A Control	II-B Post-occlusion
Q_{O_2} Ileal Mucosa	4.56 ± 0.231[5]	3.26 ± 0.562[5]	5.38 ± 0.438[5]	4.99 ± 0.893[5]
$Q_{O_2}{}^G$ Ileal Mucosa	4.47 ± 0.332[5]	2.79 ± 0.460[5]	5.03 ± 0.397[5]	4.43 ± 0.555[5]
Q_{O_2} Liver	3.38 ± 0.122[2]	4.98 ± 0.342[4]	5.00 ± 0.404[3]	5.73 ± 0.400[5]
$Q_{O_2}{}^G$ Liver	2.65 ± 0[2]	4.59 ± 0.474[4]	5.32 ± 0.578[2]	5.16 ± 0.376[5]
$CO_2: \frac{C\text{-}6}{C\text{-}1}$	0.320 ± 0.065[5]	0.308 ± 0.012[4]	0.394 ± 0.134[3]	0.246 ± 0.056[5]

All values shown as Mean ± S.E.M.

Q_{O_2} = μl. oxygen taken up per milligram of dry weight of tissue per hour.

$Q_{O_2}{}^G$ = μl. oxygen taken up per mg. dry weight of tissue per hour in the presence of 10 mM. glucose.

$$\frac{C\text{-}6}{C\text{-}1} = \frac{\text{Total disintegrations per minute of } CO_2 \text{ formed from glucose-6-}C^{14}}{\text{Total disintegrations per minute of } CO_2 \text{ formed from glucose-1-}C^{14}}.$$

No. of animals averaged shown by superscripts.
I-B and II-B = Tissues obtained one hour after release of clamps on mesenteric vessels.

nitrogenous compounds. In some instances, the nitrogen and carbon skeletons are derived from a nutritionally essential amino acid; in others, only the nitrogen atoms need have their origin in the dietary amino acid since the remainder of the molecule can be provided from carbohydrate precursors. The capacity of the body to perform these conversions is apparent from the fact that a synthetic diet which provides nitrogen only in the form of the nutritionally essential amino acids plus the small amount of vitamins, supports maximal growth.[31] The elemental diet thus provides for all that is required for the *de novo* synthesis of nucleotides and nucleic acids.

It will also be noticed from Table 8 that the percentage of ileal mucosa ATP which is used for the synthesis of nucleic acids is altered in the animals which have been fed the elemental diet. In the normal diet dogs, 15.9% of the mucosal ATP is used in the formation of nuclei acids; whereas, in the animals fed the elemental diet, this value falls to 6.3% ($p < 0.001$).

These results implicate a greater stability of the ileal mucosa in the Group II animals on diet (Table 8); for despite the greatly increased incorporation of adenine into ATP, much less is being utilized for nucleic acid synthesis, suggesting that the omission of digestive products from the lumen of the intestine enforces a lower turnover of epithelial cells.

The incorporation of adenine into the ATP of the liver is also increased in dogs fed the elemental diet, though to a much smaller extent than that seen in the intestine. There may also be increased myocardial ATP turnover between the two groups of animals, but the results are not statistically significant.

The results obtained from the respiratory studies are presented in Table 9. It can be seen that the Q_{O_2} and the $Q_{O_2}{}^G$ values for ileal mucosa slices are similar in Groups I-A and II-A, although there is a tendency for these values to be increased in the group fed the elemental diet. The carbon dioxide production from radioactive glucose as represented by the C-6/C-1 ratio,

rises from 0.320 in the normally fed animals to 0.394 in the elemental diet animals. This indicates a relative increase in the latter group in the amount of glucose oxidized by the tricarboxylic acid cycle, although this increase is not nearly as great as would be expected from the five-fold increase in the incorporation of adenine into ATP exhibited by the dogs fed the elemental diet.

There is, however, a two-fold increase in the $Q_{O_2}{}^G$ of the liver in the dogs fed the elemental diet over those fed the normal diet, and this increased metabolism is consistent with the two-fold increase in adenine incorporation into the liver ATP.

The capacity of the intestinal mucosa to transport amino acids *in vitro* is not altered by the feeding of the elemental diet. In both groups, amino acids appear on the serosal side of the inverted sacs within 1 minute from the start of the incubation period and increase steadily in amount for the next 30 minutes.

These results suggest, therefore, that the intestinal mucosa has markedly increased the incorporation of adenine into ATP when the animals have been fed the elemental diet, but that this increase is not reflected in an increased nucleic acid synthesis; nor is there the marked alteration in respiratory activity that would be expected from the increased ATP values.

Tissue Metabolism After Shock and Intestinal Ischemia. Dogs from both dietary groups were subjected to 4½ hours of hypovolemia; and after retransfusion, similar studies were carried out.

It can be seen in Table 8 that the incorporation of labelled adenine into ATP of the ileal mucosa suffered a 90% depression in both groups of animals, which indicates the similarity of degree in ischemia injury. However, it will be noticed that although the incorporation into ATP after shock is only 10% of the value of the control dogs, the dogs in Group II-B show a five-fold increase in percentage incorporation from the blood (17.55%) after shock, compared to the 3.5% shown by the dogs on a normal diet in Group I-B. The depression of ATP synthesis is still evident 18 hours following the shock period (Group II-C). Both liver and myocardium show a 50 to 60% decrease in incorporation of adenine into ATP in both groups of animals following hemorrhagic shock, which persists in the animals allowed to survive for 18 hours.

The respiratory studies after shock and intestinal ischemia are presented in Table 9. In these experiments, respiratory studies were conducted on animals subjected to 90-minute clamping of the mesenteric arteries, and the tissue samples removed 1 hour after the release of the clamps (Groups I-B and II-B). The animals fed a normal diet (Group I-B) exhibit a depressed Q_{O_2} following occlusion, and an even more markedly depressed $Q_{O_2}{}^G$ compared to the controls in Group II-A ($p < 0.001$). No such changes are observed after the mesenteric arterial occlusion in the dogs fed the elemental diet. The Q_{O_2} and $Q_{O_2}{}^G$ for the liver increases in Group I-B with no alterations in these values being exhibited by the dogs fed the elemental diet.

The carbon dioxide production shown by the C-6/C-1 ratios shows that in the dogs fed the normal diet, there is decreased activity of the tricarboxylic acid cycle. In the dogs fed the elemental diet, depression in the C-6/C-1 ratio is seen after clamp release.

The transport of amino acids by the small intestine almost completely ceases immediately after hemorrhagic shock, whether or not the dogs had been fed the elemental diet. However, studies done 3 days following the shock procedure showed that the capacity of the mucosa to transport amino acids in dogs fed the elemental diet had returned, although at a slower rate than normal, whereas there was a continued

marked depression in the animals which had been fed normal food.

These results are interesting in the light of the functions of the small bowel mucosa. This tissue has an extremely active transport mechanism to provide for the absorption of nutrients. A second major function is to replace lost and damaged cells, normally effecting a complete renewal of the mucosal epithelium every 36 to 48 hours. Both of these major functions of the intestine require large quantities of ATP. As a result, interference with ATP synthesis would alter markedly both the capacity of the intestinal cell to transport materials as well as to replace itself. The studies with radioactive adenine have shown that the depression of ATP synthesis is reflected in a concomitant depression of nucleic acid synthesis, a vital component in the manufacture of new cells. Experiments with transport of amino acids have shown that this function also is markedly affected, although the dogs which have been fed the elemental diet recover this capacity within three days.

It must be remembered that although ATP production is depressed, it does not cease, and there is apparently enough of it being synthesized by the mucosa to take care of the endogenous metabolism. As a result, the effects of ischemia on the respiration of the mucosa are only temporary.

One could speculate, therefore, that the major metabolic difference between the two groups of dogs is the fact that dogs fed the elemental diet do not lose their epithelial cells, so that following the shock procedure, they are not required to replace these cells as are the dogs on normal food. Accordingly, the return to normal function as regards transport activity can be achieved within the time limit studied.

The changes produced by the elemental diet on the intestinal mucosa are thus indicative of profound alterations in cellular metabolism. These alterations are not seen, at least to the same extent, in the liver or in other organs studied. The changes observed in the terminal ileum may well be related to the increased tolerance of the mucosa to ischemia, although the exact mechanisms through which such tolerance is provided are still a matter of speculation.

Hypothesis on the Mechanism of Action of the Elemental Diet. The sole administration of an elemental diet for 3 days produces, as we have seen, some changes in the metabolic pattern of the epithelium of the terminal ileum which are of considerable potential importance. One might speculate that the enhanced tolerance to ischemia is at least in part due to an intrinsic modification of the cellular energy metabolism. At the same time, however, the content of the gut is modified in such a way that it would be less toxic should the intestinal barrier to intraluminal content falter. It is difficult, however, to separate the cellular and intraluminal factors since both appear in a way strictly related and probably interdependent. For example, the concept of a decreased intestinal barrier to intraluminal toxins already implies cellular changes in the mucosa, and unless the intraluminal toxins are removed once the cellular changes have already begun, one could not safely decide which of the factors are predominant in terms of extra-intestinal involvement.

The mechanism through which the diet could lead to a greater cellular resistance involves a concomitant reduction in toxic intraluminal elements. Our studies indicate that after three days of treatment the intestinal flora is not qualitatively altered although some slight quantitative reduction is observed (Figs. 8, 9). In particular, the reduction in the E. coli organisms was insignificant. Other observations [29] failed to reveal in control dogs any signs of significant bacterial invasion of the blood. The tissue specimens taken from pathologic areas were sterile. These observations on a large number of control dogs led us to assume that the intestinal bacterial factor

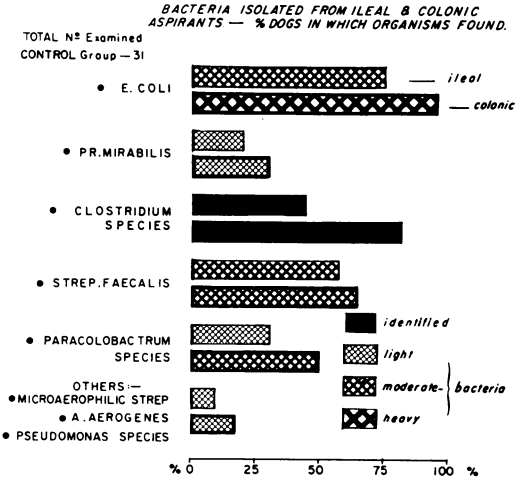

FIGURE 8.

may not play a predominant role in the pathogenesis of shock. This hypothesis is, of course, supported by the abundant literature on shock in germ-free animals.

Finally, it should be mentioned that the motility of the ileum may possibly be affected by the elemental diet. For example, the segmental contractions which occur several times a minute, apparently independent of central nervous control, have been thought to contribute to proper mixing of non-homogenous chyme. Our liquid diet is already homogenous when given orally and probably both the stimulus and need for these movements are less conspicuous. It is known that the circulation of blood to the mucosa depends to a great extent on the resistance to flow in the muscular wall of the intestine and this again relates in part to the changes in interstitial pressure during contraction. If muscular contractions were to cease in the wall, the pattern of mucosal circulation would be certainly affected. Studies by Rougereau and Thouvenot [26] have shown a decrease in oxygen consumption during *in vitro* absorption in the duodenum apparently explained by an increased tonicity of the muscular wall which accompanies the passage of chyme.

The Role of Pancreatic Proteolytic Enzymes. In previous reports, we have shown that the concentration of intraluminal trypsin was a determinant factor in the anatomical evolution of an ischemic intestine. A moderate degree of ischemia such as is produced by 2 hours of hypotension at 35 to 40 mm. Hg may result in intestinal hemorrhagic necrosis in areas with an excessively high concentration of trypsin, while 4 to 5 hours of similar ischemia are necessary to produce analogous lesions in normal dogs after an 18-hour fast. The anatomical integrity of the epithelial cells of the intestine is the result of an equilibrium of forces which one could group in a sort of equation having as the numerator the energy produced by respiration, and as denominator the hydrolytic enzymes of catabolism. If one of the factors is exceedingly great, the other must be increased if equilibrium is to be preserved. In the dogs fed the elemental diet, the pancreatic excretion is preserved as documented by the concentration of trypsin in the chyme squeezed from the upper half of the ileum after 3 days of diet. These trypsin measurements were made with the technic of Lundh [22] 18 hours after the last meal of the diet on 11 animals. The average value

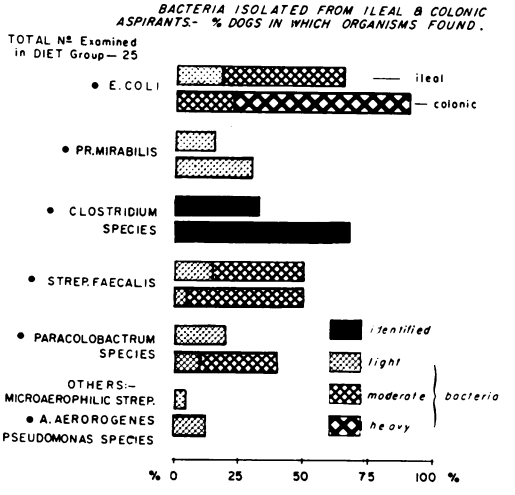

FIGURE 9.

was 424 μg./ml. (62-931). These values compare closely with 412 μg./ml. (70-1012) observed in nine control dogs 18 to 20 hours after their last regular meal. Since the lack of food proteins in the diet group would result in a greater concentration of unbound trypsin, it would appear that the total pancreatic excretion of trypsin with the diet is adjusted to a lower level so that the resultant free trypsin in the chyme remains practically unchanged. It is interesting to speculate that a feed-back control mechanism, comparable to that of gastric acid inhibition of gastrin release, may exist in the duodenum, high concentrations of free trypsin functioning as the trigger mechanism resulting in pancreatic inhibition. This may be a further example of small intestinal homeostasis designed to protect the mucosa from destructively high concentrations of proteolytic enzyes.

Despite the normal intraluminal tryptic concentrations, the intestinal epithelium survived ischemia in the diet series without the assistance of Trasylol, provided that the protocol was adhered to. However, one dog (No. 6558) originally in Group II (Table 3), showed a massive upper intestinal hemorrhagic necrosis. Similarly, two non-reported dogs of the diet series of Group IV developed severe hemorrhagic necrotizing infarcts of the duodenal and jejunal mucosa on declamping. The common characteristic in these three dogs was the fact that they accidentally ate their diet one hour before injury and presumably the pancreatic and biliary excretions were at a peak. These three dogs have been excluded from the groups as reported. Trasylol was not used in all the dogs of the diet series, since with a fasting period of 18 hours it was found that the inhibition of intestinal trypsin was not essential. Trasylol was not used in any of the dogs in Group II (Table 3) and in only a few of Group IV. However, should an elemental diet be administered for a long time to clinical cases, it would be advisable to inhibit intestinal pancreatic proteases in connection with the last meal preceding operation or injury.

Summary

Diffuse necrosis of the intestinal epithelium has been confirmed as a primary lesion in hemorrhagic shock. A similar necrosis induced by short-term clamping of the mesenteric arteries has been found to be associated with the development of lesions in heart, kidneys, and other organs similar to those which are seen after hemorrhagic shock. The very function of digestion of normal food appears to create in the intestinal mucosa a condition of relative intolerance to ischemia.

The feeding of an "elemental" diet prior to injury reduces the intracellular digestive burden of the intestinal epithelium while maintaining absorption and nutrition. Some significant changes occur in the metabolism of the epithelial cells. A 3-day period on the diet leads to an increased rate of incorporation of labelled adenine into the ATP of the mucosa. Following shock, this rate of incorporation falls proportionally in both groups of dogs, but the resultant rate in the mucosa of dogs on the elemental diet maintains a level five times that reached by dogs on normal food.

It is concluded that a period of 3 days on the elemental diet not only reduces the intraluminal toxic factors, but also appears to enhance the metabolic state of the intestinal mucosa making it more tolerant to ischemia.

In proportion to the degree of mucosal integrity, whether morphologic or metabolic, survival is improved and the extraintestinal lesions are virtually eliminated.

Acknowledgment

The authors thank Misses Louise Carpentier, Renee de Lisle and Jennifer Grove for invaluable technical assistance; Dr. D. B. Tonks, Director, Department of Clinical Chemistry for the analyses of SGOT, LDH and electrolytes; Dr. Joan de Vries, Director, and Dr. Mary Platnoff of the De-

partment of Microbiology, for the studies on their bacteriological cultures; Dr. M. H. Finlayson, Department of Neurology, for the examination of the brain lesions; and Mr. H. Artinian and Miss Mary Gzowski, for the photography and medical illustration.

References

1. Bachrach, W. H. and Thorner, M. O.: Hemorrhagic Enteropathy Complicating Myocardial Infarction. Amer. J. Cardiol., **2**:89, 1963.
2. Berger, R. L. and Byrne, J. J.: Intestinal Gangrene Associated with Heart Disease. Surg. Gynec. Obstet., **112**:529, 1961.
3. Bhagwat, A. G.: Terminal Hemorrhagic Necrotising Enteropathy. Amer. J. Gastroent., **45**:163, 1966.
4. Bloomfield, D. A. and Walters, M. N. I.: Pseudomembranous Enterocolitis. Med. J. Austral., **5**:854, 1960.
5. Bounous, G., Brown, R. A., Mulder, D. S., Hampson, L. G. and Gurd, F. N.: Abolition of Tryptic Enteritis in the Shocked Dog. Arch. Surg., **91**:371, 1965.
6. Bounous, G., Cronin, R. F. P. and Gurd, F. N.: Dietary Prevention of Experimental Shock Lesions. Arch. Surg., **94**:46, 1967.
7. Bounous, G., Hampson, L. G. and Gurd, F. N.: Cellular Nucleotides in Haemorrhagic Shock: Relationship of Intestinal Metabolic Changes to Haemorrhagic Enteritis and the Barrier Function of the Intestinal Mucosa. Ann. Surg., **160**:650, 1964.
8. Brawley, R. K., Roberts, W. C. and Morrow, A. G.: Intestinal Infarction Resulting From Non Obstructive Mesenteric Arterial Insufficiency. Arch. Surg., **92**:374, 1966.
9. Drucker, W. R., Davies, J. H., Holden, W. D. and Reagan, J. R.: Hemorrhagic Necrosis of the Intestine. Arch. Surg., **89**:42, 1964.
10. Ende, N.: Infarction of the Bowel in Cardiac Failure. New Eng. J. Med., **258**:879, 1958.
11. Fogarty, T. J. and Fletcher, W. S.: Genesis of Non Occlusive Mesenteric Ischemia. Amer. J. Surg., **111**:130, 1965.
12. Frebet, H.: Infarctus Ileal Sans Lesions Vasculaires. Mem. Acad. Chir. (Paris), **78**:661, 1952.
13. Freiman, D. G.: Hemorrhagic Necrosis of the Gastrointestinal Tract. Circulation, **32**:323, 1965.
14. Gregoire, R. and Convelaire, R.: Apoplexies Viscerales, Sereuses et Haemorrhagiques: Infarctus Visceraux. Paris, Masson and Cie, 1937.
15. Greco, A.: Sulla Probabile Natura Dell 'Infarto Intestinale Sensa Lesioni Vascolari. Giorn. Ital. Chir., **3**:687, 1947.
16. Heer, F. W., Silen, W. and French, S. W.: Intestinal Gangrene Without Apparent Vascular Occlusion. Amer. J. Surg., **110**:231, 1965.
17. Herman, B. and Hermanova, K.: Haemorrhagische Komplikationen Des Verdauungstraktes Bei Herzkrankheiten. Gastroenterologia, **104**:352, 1965.
18. Hiatt, N., Warner, N. E., Furman, G. and Merchey, M.: Nitrogen Mustard, Hyperamylasemia and Intestinal Lesions. Surgery, **61**:590, 1967.
19. Hunter, J.: On the Digestion of the Stomach After Death. *In* The Works of John Hunter, F.R.S. Vol. IV. Edited by J. F. Palmer, London, Longmans, 1835, p. 11.
20. Klemperer, P., Penner, A. and Berheim, A. I.: The Gastrointestinal Manifestations of Shock. Amer. J. Digest. Disease, **7**:410, 1940.
21. Luna, G. A. and Tinelli, J. C.: Infarto Intestino Mesenterico Inexplicado. Prensa Medica Argentina, **43**:669, 1956.
22. Lundh, G.: Determination of Trypsin and Chymotrypsin in Human Intestinal Content. Scand. J. Clin. Lab. Invest., **9**:229, 1957.
23. Mallory, T. B.: Systemic Pathology Consequent to Traumatic Shock. J. Mount Sinai Hospital, **16**:137, 1949.
24. Ming, S. C. and Levitan, R.: Acute Hemorrhagic Necrosis of the Gastrointestinal Tract. New England J. Med., **263**:59, 1960.
25. Penner, A. and Berheim, A. I.: Acute Postoperative Enterocolitis. Arch. Path., **27**:966, 1939.
26. Rougereau, A. and Thouvenot, J.: Consommation D'Oxygene du Duodenum Isole de Rat. Ses Divers Ordres de Variations. Comptes Rendus Soc. Biol., **160**:845, 1966.
27. Smith, E. E.: Effect of Pancreatectomy on Intestinal Fluid Loss in Hemorrhagic Hypotension. Fed. Proc., **26**:267, 1967.
28. Straub, N.: Shock and Intestinal Infarction Without Mesenteric Thrombosis. Geneesk. Gids., **28**:155, 1950.
29. Sutherland, N. G., Bounous, G. and Gurd, F. N.: Necrosis of Intestinal Epithelium as a Primary Factor in the Genesis of Extraintestinal Lesions Following Haemorrhagic Shock and Mesenteric Artery Occlusion. (To be published.)
30. Tiberio, G., Gagliani, P., Parmeggiani, A., Nava, S. and Raffaglio, E.: Sens de la Prevention de l'Enterite Necrotique Hemorrhagique Par Le Choc Hypovolémique Irreversible Experimental. Proceedings of the 2nd Congress of the European Society of Experimental Surgery. To be published in "Forum Chirurgicum" Louvain (Belgium) 1967.
31. White, A., Handler, P. and Smith, E. L.: Principles of Biochemistry, New York, McGraw Hill Book Company, 1964, p. 506.
32. Wyatt, G. R.: *In* The Nucleic Acids, Vol. I. Edited by E. Chargaff and I. N. Davidson. New York, Academic Press, 1955, p. 250.