Gastric Mucosal Energy Metabolism and "Stress Ulceration"

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Acute gastric erosions following hemorrhagic shock (stress ulceration) have been attributed to gastric hyperacidity, altered gastric secretion of mucus and an abnormal permeability of the gastric mucosa to H^+. This report aims at presenting evidence supporting an alternate hypothesis: the event linking shock-induced gastric mucosal ischemia to mucosal necrosis is a deficit in gastric mucosal energy metabolism. Our experimental procedure consisted of harvesting the stomachs of rats and rabbits by "stop-freeze" (liquid N_2) at different intervals after the induction of hemorrhagic shock. Levels of adenosine-phosphates and of glycolytic intermediates in gastric *mucosa* were measured. We studied the changes in the levels of these substrates produced by shock as well as by factors capable, *when combined with shock*, of rendering the gastric mucosa more vulnerable to stress ulceration. The influence of shock and of these modifying factors were evaluated by comparison with data from appropriately designed control experiments. In parallel experiments we examined the frequency of stress ulceration (gross and microscopic) under these same standard conditions. There have emerged from these studies a number of observations all based upon data with the highest statistical significance. The data are consonant with the hypothesis stated above: an energy deficit severe enough to cause cellular necrosis is the event linking shock-induced gastric mucosal ischemia and stress ulceration.

IN MAN, severe stress in the form of a operation[9] (particularly when complicated by hemorrhage)[14] trauma or thermal burns is sometimes followed by the development of "stress ulcers." It has been noted that the incidence of "stress ulceration" is greater when these situations are complicated by sepsis and/or pulmonary insufficiency.[27] Although the terms "stress ulcer" and "stress ulceration" have become widely used, it should be noted that the lesions usually consist of multiple, superficial *gastric* mucosal erosions rarely extending beyond the muscularis mucosae. Characteristically, these lesions tend to cluster in the mucosa of the corpus and the fundus and respect the antrum.[10,14,26,28] In severe cases the process of mucosal necrosis may extend to the small intestine and colon. Lesions similar in all respects to those observed in patients under the circumstances described above, can be induced by hemorrhagic shock in several animal species and serve as a convenient animal model for the study of this phenomenon. It has also been found that hemorrhagic gastric erosions develop in rodents subjected to physical restraint; lesions to which the term of "stress ulcer" has also been applied.[4,13,24] Although there is no evidence for or against the view that mucosal lesions precipitated by shock have a different etiology from those caused by restraint, we prefer to reserve the term of "restraint ulcers" for the latter and would caution against applying any experimental data derived from the study of this phenomenon to the explanation of the former and vice versa.

The nature of the event or events linking shock or trauma with gastric erosions remains unknown. Stress-induced gastric hyperacidity has been invoked but (except in some instances of cranial injury) has never been substantiated by the demonstration of a consistent pattern of hyperacidity in association with trauma or burns.[16,22,27] On the contrary, the available data indicate that in man as well as in animals, trauma and shock reduce basal gastric acid output.

Others have invoked an alteration in the quantity and the biochemical composition of gastric mucus on the basis of studies showing that ACTH[7] and cortisone[20] reduce gastric mucous secretion. However, this theory

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suffers from a lack of information concerning the possible mechanisms, if any, by which mucus might "protect" the underlying epithelium. It has also been postulated that stress-induced gastric mucosal injury might result from a reduction in the rate of renewal of the surface epithelial layer, a change which might be expected to affect adversely the integrity of the gastric epithelium. This theory was derived from experimental data showing a reduction in the cell turnover rate in the gastric epithelium of animals receiving ACTH or cortisone.[18] Although these changes may play a role in the phenomenon of stress ulceration, we do not believe that they constitute the initial event leading to epithelial breakdown.

In recent years considerable attention has been focused on the possibility that stress-induced mucosal injury may result from back-diffusion of acid through a mucosal membrane rendered more permeable to hydrogen ion by some factor or factors, such as ischemia, associated with the stressful event.[15] Having gained access to the mucosal tissue, hydrogen ion would trigger a chain of events, prominent among which would be hemorrhage leading to focal mucosal necrosis. This theory is based upon the studies of Skillman *et al.*[27-29] who found an increased back-diffusion of acid in the stomach of rabbits 3 hours after the induction of hemorrhagic shock. They made similar observations in critically ill patients and postulated that the gastric hypoacidity often found under these conditions may result from a loss of acid via back-diffusion rather than from an absolute decrease in gastric secretory activity. This line of inquiry was inspired by the classical studies of Davenport[5] on the gastric mucosal barrier. Others[21] have been unable to demonstrate acid back-diffusion in shocked animals.

The studies forming the basis for this report were undertaken to evaluate the validity of an alternate explanation for stress ulceration: *stress-induced gastric mucosal injury results from a mucosal energy deficit severe enough to cause cellular necrosis.* To test this hypothesis we have carried out a series of experiments designed to find evidence to reject it. Our data will show that we have been unable to reject this theory.

I. Is Experimental Stress Ulceration Associated with a Significant Gastric Mucosal Energy Deficit?

Because shock can be expected to produce an energy deficit in most tissues of the body, the hypothesis under study would be tenable only if such a deficit were peculiarly severe in the gastric mucosa.

Materials and Methods

In this first phase of our studies we designed an animal model of shock-induced stress ulceration and examined both the time-course of anatomic gastric mucosal injury and the time-course of changes in gastric mucosal energy metabolism produced by hemorrhagic shock and compared the latter changes with those taking place in other tissues of the same animal.

a) Hemorrhagic shock was induced in 300 g rats by removing 20.0 ml/kg of blood from the vena cava in 2 minutes under light urethane anesthesia. Exactly 15, 30, 45 or 60 minutes later the stomach was removed and studied for erosions and hemorrhage prior to fixation in 10% formalin. Sections from the glandular mucosa were stained with H&E and examined under light microscopy. Eight rats were used for each time interval. Stomachs removed from 6 non-bled rats subjected to 60 minutes of urethane anesthesia served as controls.

b) Rats were subjected to hypovolemic shock as described in the previous paragraph. Exactly 15, 30, 45 or 60 minutes after bleeding, the experiment was terminated by cooling to the temperature of liquid nitrogen, the stomach and wafer-thin slices of liver and skeletal muscle. Identical tissue sampling was done in non-bled rats subjected to the same intervals of light urethane anesthesia. Rats were assigned randomly to the different test and control groups. Levels of ATP, ADP and AMP, of creatine-P (muscle only), glucose-6-P, pyruvate and lactate and glycogen in gastric glandular *mucosa,* and in liver and skeletal muscle tissue (rectus abdominis) were estimated according to standard[1] methods.

Results

a) Gross. The glandular mucosa of stomachs removed 15 or 30 minutes after bleeding appeared normal. Half of the stomachs removed at 45 minutes and all of those examined at 60 minutes showed multiple hemorrhagic foci in the glandular mucosa of the corpus (not in the antrum).

Microscopic. Changes consisting of focal, superficial epithelial necrosis were present in all of the stomachs removed 15 minutes after bleeding (Fig. 1). At 60 minutes these changes had progressed to focal mucosal hemorrhage and superficial erosions (Fig. 2) in all of the stomachs.

b) Changes in levels of adenine nucleotides taking place in gastric mucosa and liver under the influence of hypovolemic shock (approximate 30% reduction in blood volume) are summarized in Fig. 3. In gastric mucosa a 75% drop in ATP levels and a 47% drop in total adenosine phosphates occurred within 15 minutes. Changes in hepatic tissue were significantly less severe and recovery was more rapid. In muscle, a slight but significant drop in levels of phosphocreatine was the only manifestation of enery deficit. In addition, we noted that glycogen levels, normally very low in gastric mucosal

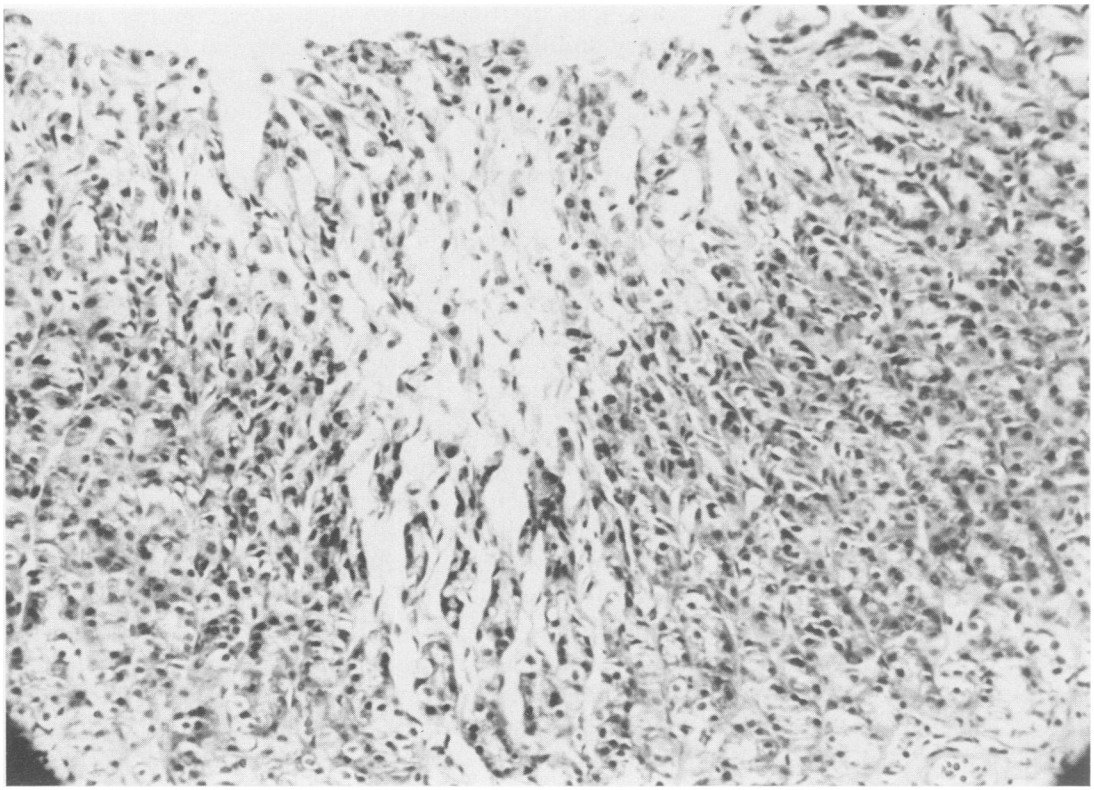

FIG. 1. Section from fundic mucosa of a rat shocked by removal of blood (20.0 ml/kg). Fifteen minutes later the stomach was removed and fixed in 10% formalin. Note the presence of focal mucosal necrosis. (H&E, approx. ×200)

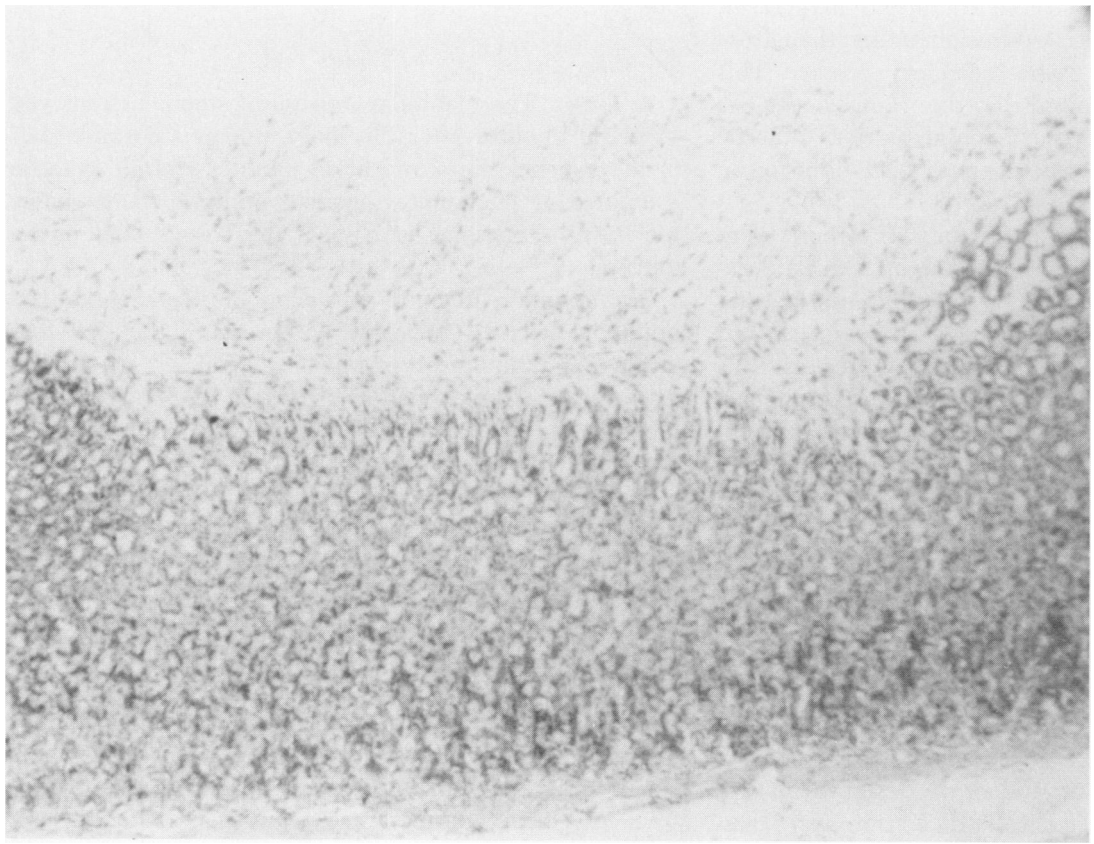

FIG. 2. Section from fundic mucosa of a rat stomach removed 60 minutes after induction of hemorrhagic shock. Section taken through one of multiple mucosal erosions. Note the extensive, superficial mucosal necrosis. (H&E, approx. ×25)

tissue, were almost completely depleted after 15 minutes of shock. Liver glycogen was less severely affected and muscle glycogen remained unchanged. Increases in[lactate]/[pyruvate] were significantly less marked in gastric mucosa than in liver or muscle.

Comment

The energy deficit observed in gastric mucosal and hepatic tissues of shocked rats may be attributed to ischemia and reduced oxidative phosphorylation. The greater severity of the energy deficit in mucosa by comparison with liver and muscle could result from a more severe regional ischemia in this tissue or from a greater vulnerability of gastric mucosal energy metabolism to ischemia. The following experiment was designed to answer this question.

II. Is Gastric Mucosal Energy Metabolism Peculiarly Vulnerable to Ischemia?

We believed an answer to this question might be provided by subjecting gastric mucosa, liver and muscle tissue to identical periods of *complete* ischemia which, by converting these tissues into closed systems and eliminating the factor of differences in input of oxygen and substrates, would limit energy-generating metabolic sequences to the tissue's intrinsic metabolic equipment.

Materials and Methods

Gastric mucosal, hepatic and skeletal muscle tissues were rendered completely ischemic in the following fashion. A silk ligature was placed around the esophagus immediately above the stomach. At the appropriate moment the stomach was lifted from its bed by traction on the ligature and was swiftly and completely severed from all its connections. It was then left *in situ* for 30 or 60 seconds and then frozen to the temperature of liquid N_2. Wedges of liver and rectus abdominis muscle were excised with a single sweep of a scalpel, left *in situ* for 30 or 60 seconds and similarly frozen. Frozen, non-ischemic tissues served as controls. Only one tissue sample was taken from an individual animal and this was done in random order.

Results

Changes in tissue levels of adenine nucleotides during complete ischemia are summarized in Fig. 4. After 60 seconds of ischemia the drop in ATP and rise in AMP were significantly greater in gastric mucosa than in hepatic tissue. Levels in skeletal muscle did not change. In addition, we noted at 60 seconds a 60% depletion of gastric mucosal glycogen by contrast with a 16% drop in hepatic tissue and no change in muscle. [Lactate]/[pyruvate] increased significantly only in liver and muscle.

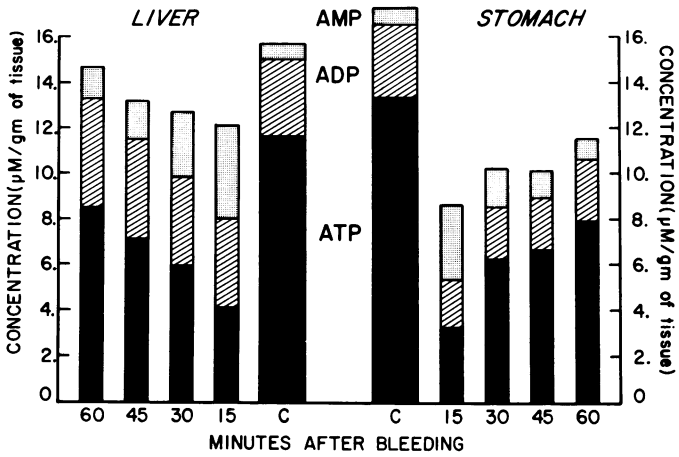

FIG. 3. Influence of hemorrhagic shock on adenosine phosphate levels in gastric mucosa and liver of rats. Bars represent absolute, mean levels (micromoles/gram of tissue, dry weight) of adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP). C = control experiments (9). There were 8 experiments at each time interval. All test ATP levels differ ($p < .001$) from control values; changes in [ATP + ADP + AMP] levels in mucosa and liver (−47% and −22%, −38% and −19%, −39% and −16%, −31% and −7% at 15, 30, 45 and 60 minutes respectively) also differ significantly ($p < .001$).

Comment

The data indicate that gastric mucosal energy metabolism is peculiarly vulnerable to ischemia and that the appearance of shock-induced gastric mucosal injury is accompanied by a marked mucosal energy deficit. Although these observations agree with the hypothesis un-

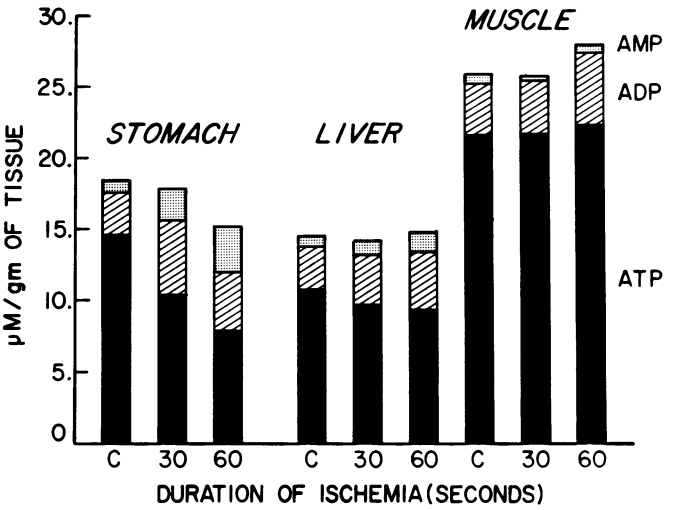

FIG. 4. Influence of *complete* ischemia on adenosine phosphate levels in gastric mucosa, liver and muscle of rats. Bars represent absolute, mean (of eight experiments for each tissue) levels of ATP, ADP and AMP. Changes in these levels in mucosa were significantly different ($p < .001$) from control values (c) at 30 and 60 secs but not in liver and muscle.

der study and do not allow us to reject the theory, they do *not* prove it because we do not know what minimal tissue levels of ATP are essential for cellular survival. Clearly, further experimental testing of the hypothesis is needed. To this end we used an interesting feature of stress ulceration, i.e., the tendency of this phenomenon to involve mainly the corpus and fundus and respect the mucosa of the antum.[10,14,26,28] We reasoned that if the energy deficit developing in the antral mucosa of shocked animals were identical to, or greater, than that taking place in fundic or corpus mucosa, the energy-deficit hypothesis of stress ulceration would not be tenable.

III. Is the Energy Metabolism of Antral Mucosa More or less Vulnerable to Shock Than That of Corpus or Fundic Mucosa?

Materials and Methods

a) Male albino rabbits were maintained on rabbit chow until 6:00 PM of the evening before the experiment when their food was removed and their drinking water was replaced with 500 ml of a 5% sucrose solution. At 8:00 AM the following morning the nutrient solution was removed and the experiment was started at 10:00 AM. Animals were anesthetized with nembutal (30 mg/kg). Artificial ventilation was maintained with room air via tracheostomy. A femoral artery was cannulated and heparin (10 mg/kg) was administered. The plastic arterial cannula was connected via a disposable plastic stop-cock to a pressure transducer and arterial blood pressure was recorded continuously. Hemorrhagic shock was induced by withdrawing, over a period of 5 minutes, an amount of blood sufficient to lower the arterial blood pressure to a mean level of 30 mm Hg where it was maintained by withdrawing appropriate volumes of blood. After 15 or 30 minutes of hypotension, the entire stomach was crushed between 2 large aluminum paddles pre-cooled to the temperature of liquid N_2. Tissue extruding beyond the paddles was severed and the entire sample was dropped into liquid N_2. The entire sample was then lyophilized. Samples of *antral, corpus* and *fundic* mucosa were then subjected to the same analytical procedures as described above. Values obtained from tissues of non-shocked rabbits subjected to the same surgical manipulations and 30 minutes of anesthesia served as controls.

b) Rabbits were prepared for the experiment as in the previous paragraph with the omission of arterial cannulation, heparinization and bleeding. At a given moment (always the same with respect to the induction of anesthesia) the stomach was completely severed from all of its connections. It was left *in situ* for 60, 120 or 180 seconds and cooled to the temperature of liquid N_2. Controls were obtained by freezing the stomach without a preliminary period of ischemia. Frozen stomachs were lyophilized. Dry tissues were opened and samples of antral, corpus and fundic mucosa were taken for biochemical analysis.

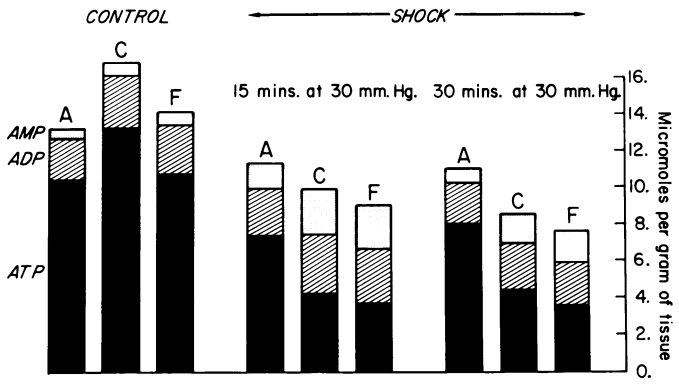

FIG. 5. Influence of hemorrhagic shock on adenosine phosphate levels in mucosa of antrum (A) corpus (C) and fundus (F) of rabbit stomachs. Bars represent absolute, mean (of 11 control experiments and 8 test experiments at 15 and 30 minutes after bleeding) levels of ATP, ADP and AMP. Both at 15 and at 30 mins. after bleeding, ATP levels in antral mucosa were significantly higher than in corpus and fundic mucosae ($p < .01$).

Results

a) The data are summarized in Fig. 5. They show that levels of ATP, normally significantly lower in the antral mucosa than in corpus mucosa, remained significantly higher than in corpus and fundic mucosa during up to 30 minutes of hemorrhagic hypotension. An analysis of the data provided by changes in levels of free glucose, glucose-6-P, lactate and pyruvate in these 3 regions of the gastric mucosa during hemorrhagic shock indicated that the more rapid breakdown of high-energy phosphate in corpus and fundic mucosa during shock was accompanied by an accelerated glycolytic flux.

b) Data provided by experiments in which the entire stomach of rabbits was subjected to complete warm ischemia lasting up to 180 seconds showed that dephosphorylation of adenosine phosphates occurred at a twofold *greater rate* in corpus and fundus mucosa by comparison with antral mucosa. As with the shock experiments, the more rapid breakdown of high-energy phosphates in the mucosa of the fundus and corpus was accompanied by a marked acceleration of glyoclytic flux by comparison with antral mucosa.

Comment

These experiments show that a greater energy deficit occurs in the mucosa of the corpus and fundus during hemorrhagic shock. Since stress ulceration produced by experimental shock characteristically affects these regions of the gastric mucosa, the data are consonant with

the hypothesis under study, i.e., that shock-induced gastric mucosal necrosis results from a profound mucosal energy deficit. Our data also suggest that the more rapid breakdown of adenosine phosphates in corpus and fundic mucosa during shock does *not* result from regional ischemia (more marked for corpus and fundus than for antrum) since the same differences between antral mucosa on one hand and corpus and fundic mucosa on the other, were found in the mucosa of stomachs subjected to complete ischemia.

In these experiments the animals were *not* fasted and received supplemental carbohydrate before the experiment. Under these conditions the more rapid breakdown of high-energy phosphates in the mucosa of the corpus and fundus was accompanied by an accelerated glycolytic flux, event which suggested that the inability of these regions of the gastric mucosa to maintain the same energy levels as the antral mucosa during shock (or complete ischemia) was *not* due to less efficient anaerobic glycolysis in the parietal cell mucosa but to greater energy requirements in this area of the mucosa. This led us to theorize that the energy deficit in the parietal cell mucosa might be increased by reducing the amount of substrate available for anaerobic glycolysis. If the hypothesis under study is correct and if other conditions (severity of hypotension) remain equal, this greater energy deficit should be accompanied by an increased incidence of stress ulceration. These questions formed the basis for another series of experiments.

IV. Is an Increased Gastric Mucosal Energy Dificit Accompanied by an Increased Incidence of Stress Ulceration?

Materials and Methods

Rabbits were subjected to hemorrhagic shock according to the procedure described in paragraph (a) of Materials and Methods in the preceding series of experiments. After 15 minutes of hypotension the stomach was frozen in situ or the shed blood was returned to the animal and the stomach removed 3 hours later for evaluation of the severity of stress ulceration. These experiments were performed in 2 groups of test animals: 1) rabbits fasted for 24 hours prior to the experiment; 2) and rabbits fed as usual until 6:00 PM of the evening preceding the experiment when their food was removed and replaced by a 5% sucrose solution. Test data were compared with pooled values obtained from fasted and non-fasted rabbits subjected to the same procedure with the exception of bleeding.

Results

a) Influence of Fasting on Shock-induced Changes in Gastric Mucosal Energy Metabolism. Gastric mucosal energy deficit as estimated by a reduction in tissue levels of ATP and of ATP + ADP + AMP was significantly more severe in all regions of the gastric mucosa of the fasted animals. Average percentage changes in ATP levels from control values of antral, corpus and fundic mucosa of non-fasted and fasted animals were −31% and −62% ($p < .01$), − 69% and −86% ($p < .001$), −65% and 83% ($p < .05$) respectively. Corresponding values for ATP + ADP + AMP were −14% and −40% ($p < .001$), −41% and −64% ($p < .01$), −36% and −56% ($p < .05$).

In parallel studies we found that the marked hyperglycemia occurring in the non-fasted and shocked rabbits was absent in the fasted animals subjected to the same degree of hemorrhagic shock. Moreover, blood lactate levels were significantly less elevated in the latter than in the former.

b) Influence of Fasting on the Incidence of Stress Ulceration. The data are summarized in Table 1. None of the non-fasted rabbits had gross erosions and only one had mild microscopic evidence of mucosal injury. All but one of the fasted rabbits had very severe erosive, hemorrhagic gastritis in the corpus and fundic mucosa (no antral lesions) when the stomach was examined 3 hours after a 15-minute period of hypotension.

Comment

If we had found that a more rapid breakdown of high-energy phosphate in gastric mucosa was not accompanied by a higher incidence of stress ulceration, the hypothesis under study would not be tenable. Our findings, which show that a greater mucosal energy deficit is accompanied by more severe mucosal injury, are consonant with the hypothesis but do not, of course, prove its validity. Because anaerobic glycolysis present during hemorrhagic shock requires glucose as energy substrate, it is reasonable to assume that the lower blood lactate levels and the absence of hyperglycemia in the fasted rabbits was caused by a rapid depletion of inadequate carbohydrate reserves. The reduced glycolytic flux should impair the capacity of tissues, particularly those with low glycogen levels such as the gastric mucosa, to generate ATP during ischemia. These findings are in agreement with the interesting experiments of Bounous *et al.*[2] who showed that ischemic necrosis of the intestinal mucosa could be prevented by introduc-

TABLE 1. *Incidence of Stress Ulceration*
(Rabbit, 3 hrs. after 15 mins. of Shock)

Control		Fast	
Gross	Micro	Gross	Micro
0/6	1/6	5/6	6/6

ing carbohydrate substrate into the lumen of the intestine.

In pursuing this line of investigation, the thought occurred to us that the energy-deficit hypothesis would be strengthened if it could be shown that an agency, known to render the gastric mucosa more vulnerable to stress ulceration, has an adverse effect on gastric mucosal energy metabolism. We elected to study the action of bile acids whose role in this phenomenon is particularly important since they are naturally occurring substances.

V. Do Bile Salts Reduce the Efficiency of Gastric Mucosal Energy Metabolism?

Several studies have shown that when bile or bile salts are in the lumen of the stomach during hemorrhagic shock, the incidence of stress ulceration is increased.[3,6,12,26] Conversely, stress ulceration in shocked animals is prevented by prior ligation of the common bile duct or of the pylorus.[3,11] Because gastric reflux of bile in man is a well-documented phenomenon which has been incriminated in the pathogenesis of chronic gastric disease, these interesting observations suggest that bile salts may play an important role in the pathogenesis of stress ulceration in man.

Materials and Methods

a) *In vivo* experiments were carried out in rabbits according to the procedure described in paragraph III

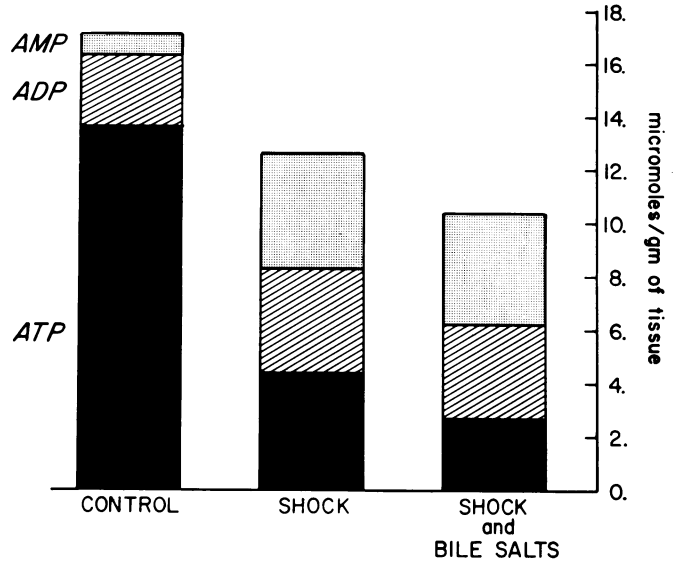

FIG. 6. Influence of Na Taurocholate on oxidation of succinate by mitochondria from corpus mucosa of rabbit stomach. Rabbit liver mitochondria (M) were diluted with an isotonic buffer containing mannitol (45 mM), sucrose (15 mM), EDTA (.02 mM) KCl (40 mM), $MgCl_2$–$6H_2O$ (20 mM), K–PO_4 buffer (20 mM) pH 7.4. Succinate (S) and ADP were added as indicated on the graphs to give final concentrations of 15 mM and .30 mM respectively. Na Taurocholate (B.S.) was added to give final concentrations indicated on the figure.

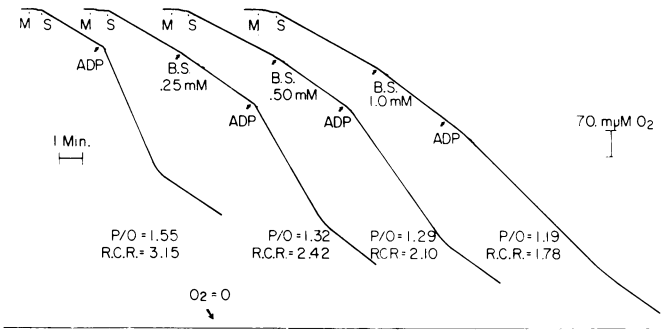

FIG. 7. Influence of bile salts on gastric mucosal energy deficit produced by a 15 min period of hemorrhagic hypotension (30 mm Hg). Bars represent absolute, mean (of 8 control experiments; of 9 test experiments without instillation of Na Taurocholate into the stomach; of 12 test experiments with inragastric instillation of Na Taurocholate at concentration of 30 mM) levels of ATP, ADP and AMP in corpus mucosa of rabbit stomach. ATP levels were significantly ($p < .01$) lower when intragastric instillation of bile salts was superimposed upon shock.

with the following modifications. Prior to the induction of shock, the pylorus was ligated and the stomach was lavaged with warm 0.9% NaCl until returned fluid was clear. Then 50.0 ml of a solution (H^+,80mEq/l; NA^+, 50 mEq/l; K^+, 10 mEq/l; Cl^-, 140 mEq/l) with or without Na Taurocholate (30 mM) was instilled into the stomach. Twenty minutes later hemorrhagic shock to a level of 30 mm Hg was induced as described previously. Fifteen minutes later the stomach was frozen and fundic and corpus mucosa was subjected to biochemical analysis. (The antral mucosa was not studied in this experiment.) Control animals were subjected to the same procedure but were not bled.

b) The influence of Na Taurocholate on oxidative phosphorylation in vitro was studied with the Clark Oxygen electrode[8] on mitochondria obtained from rabbit corpus mucosa.

c) $(Na^+ + K^+)$ −ATPase activity in homogenates prepared from rabbit gastric corpus mucosa was assayed according to standard methods[23] and the influence of different concentrations of Taurocholate on enzyme activity was studied.

Results

a) The data provided by *in vivo* experiments with rabbits are summarized in part in Fig. 6. Average ATP levels in corpus mucosa after 15 minutes of shock were 2.745 μM/g and 4.403 μM/g in the presence and absence of bile salts in the gastric lumen respectively. Corresponding values for fundic mucosa were 2.597 and 4.253. These values differ significantly from each other ($p < .01$ and $p < .01$) as well as from the average control level ($p < .001$).

b) The influence of different concentrations of Na Taurocholate on mitochondrial oxidation of succinate is

illustrated in Fig. 7. At low concentrations (.250 mM–1.0 mM) Taurocholate had the characteristic effects of an uncoupler of oxidative phosphorylation: increased state IV respiration and reduced P:O ratio and respiratory control ratio.

c) As can be seen from Fig. 8, Taurocholate in a concentration of 8.0 mM completely inhibited (Na^+ + K^+)-ATPase activity of homogenates of corpus mucosa (rabbit).

Comment

Our data clearly indicate that Taurocholate has an adverse effect on gastric mucosal energy metabolism. When this bile acid is in the gastric lumen during a short period of hemorrhagic shock, the energy deficit measured in the parietal cell mucosa is greater than when shock is induced in the absence of bile salts from the stomach. This may be explained by the uncoupling effect of Taurocholate on oxidative phosphorylation which we found and which can be expected to reduce the efficiency of respiratory-chain synthesis of ATP. Moreover, the severity of the energy deficit occurring in the gastric mucosa of shocked rabbits in the presence of bile salt may be even greater than the low levels of ATP would indicate since we found that Taurocholate has the added characteristic of inhibiting gastric mucosal (Na^+ + K^+)-ATPase, i.e. the utilization of ATP.

Discussion

Although none of the experimental data described in this report has provided any evidence that would lead us to reject the hypothesis under study, it should also be made clear that they cannot be accepted as proof of its validity. Because we do not know what are the minimal levels of ATP required for maintenance of cellular integrity *in vivo,* we cannot draw any conclusions regarding the possible impact upon gastric mucosal cellular function of the energy deficits of the magnitude described in this report. We can only *intuitively* postulate that there must be some critically low level of intracellular energy reserves at which the ion pump mechanism should fail with intra-cellular shifts of Na^+ and H_2O. There *must* be a critically low level of cellular energy where anaerobic glycolysis is arrested at the phosphofructokinase step for want of ATP. And so on! But until one is able to correlate certain vital cellular functions with ATP levels (or better yet, turnover) the energy-deficit hypothesis of shock-induced tissue injury must remain conjectural.

The assumption that impaired tissue energy metabolism may play a role in some of the manifestations of shock has been examined experimentally beginning with the pioneering work of McShan.[19] Some studies have suffered from the incorrect (we believe) experimental

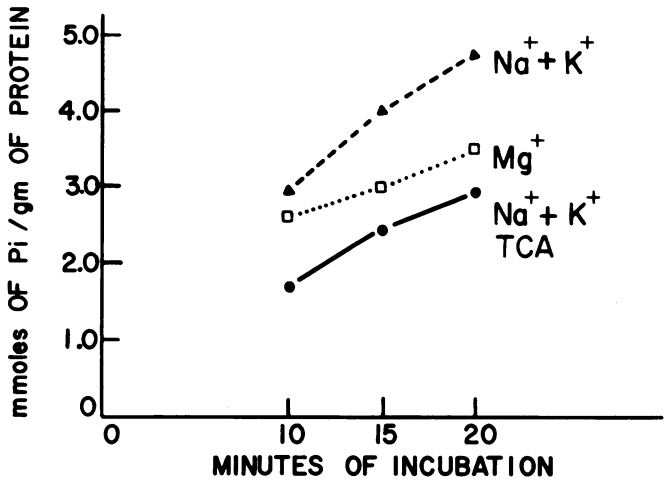

FIG. 8. Influence of Taurocholate (TCA) on adenosine triphosphatase activity (ATPase) of homogenate of rabbit gastric mucosa (corpus). Initial concentrations were 3 mM ATP (Tris salt), 5 mM $MgCl_2$, 100 mM NaCl, (when appropriate), 30 mM KCl (when appropriate), 30 mM Tris (pH 7.4), 8.0 mM Taurocholate (Tris salt) and 0.1 ml of mucosal homogenate in 1.0 ml reaction volume. Reaction was terminated by bringing the mixture to .5M $HClO_4$.

design of attempting to correlate energy deficits in one tissue, such as the liver, with the severity of the general shock syndrome as estimated by animal survival. For instance, the fact that Rosenbaum *et al.*[25] found no correlation between hepatic energy deficits and survival of shocked dogs has been used as an argument against the thesis that such deficits play an important role in the events leading to shock-related death. It may be more rewarding to attempt, as we have, to find an association between one type of shock-induced tissue injury and that tissue's peculiar ability to adjust to the altered environment brought about by the rheologic and metabolic derangements associated with hypovolemic shock.

Summary

Shock-induced acute gastric mucosal lesions (stress ulceration) have been attributed to several factors including gastric hyperacidity, impaired gastric secretion of mucus and an abnormal gastric mucosal permeability to hydrogen ion. The purpose of this report is to present evidence for the theory that a deficit in gastric mucosal energy metabolism may be the event linking shock-induced gastric mucosal ischemia to mucosal necrosis. Levels of adenosine-phosphates and of intermediates of glycolysis were measured in the gastric mucosa of rats and rabbits under different experimental conditions. The salient findings were as follows: 1) The appearance of shock-induced gastric mucosal lesions coincides with a severe mucosal energy deficit. 2) Antral mucosal energy metabolism is less affected by ischemia than that of parietal cell mucosa. This results, not from a more ef-

ficient anaerobic energy metabolism in antral mucosa, but from lower energy requirements in this tissue. This observation may explain why stress ulceration characteristically spares the antrum. 3) When the availability of glucose substrate to the gastric mucosa is reduced by a preliminary period of fasting, both the severity of the gastric mucosal energy deficit and the incidence of stress ulceration in response to a standard state of shock increase markedly. 4) We found that Taurocholate has an uncoupling effect on oxydative phosphorylation of mitochondria obtained from the gastric mucosa. Moreover, we found that when Taurocholate is in the gastric lumen during shock, the measured mucosal energy deficit is significantly greater than that produced by the same degree of shock alone. We also found that Taurocholate, *in vitro*, inhibits $(Na^+ + K^+)$-ATPhase activity of gastric mucosal homogenate. These observations could explain the well-documented fact that the presence of bile salts in the stomach during shock renders the mucosa more vulnerable to stress ulceration.

These observations are consonant with the hypothesis linking shock-induced acute gastric mucosal necrosis to a severe mucosal energy deficit.

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Discussion

Dr. Alexander J. Walt (Detroit): I would like to relate the clinical story of a patient who was admitted to hospital, dehydrated, deeply jaundiced and weak with a pulse of 140, and who was given 7½ L of fluid over the first 24 hours, operated upon the next day, and had a stone removed from the common duct. Four days later, the patient was nauseous and began to