Stress Ulcers during Live Escherichia coli Sepsis

The Role of Acid and Bile

MYRDDIN REES, M.B., F.R.C.S., JOHN C. BOWEN, M.D., F.A.C.S.

This study was designed to define the conditions that will consistently produce stress ulcers following the systemic infusion of live *E. coli* ($1.0–1.6 \times 10^{10}$ organisms/kg/hr). Using gold-filled oxygen microelectrodes and the *in vivo* gastric chamber model in dogs, the authors found that the intracellular oxygen tension of the superficial gastric epithelium declined during sepsis despite maintenance of total gastric blood flow. This hypoxia persisted for the three-hour experiment when normal saline bathed the gastric surface (n = 6). Adding 1-mM taurocholate (Tc) (n = 6) or 80-mM hydrochloric acid (HCl) (n = 6) to the gastric chamber improved the cellular hypoxia induced by sepsis, and no ulcers were produced. However, addition of physiologic concentrations of bile in acid (1-mM Tc in 80-mM HCl) produced widespread ulceration of the mucosa within 30 minutes in nine of ten dogs. These experiments demonstrate that epithelial hypoxia induced by sepsis predisposes the gastric mucosa to ulcerate in the presence of physiologic concentrations of topical acid and bile.

From the Department of Surgery, Ochsner Medical Institutions, New Orleans, Louisiana

ACUTE ULCERATION OF THE STOMACH with subsequent hemorrhage is a well recognized and hazardous complication of severe sepsis.[1,2,3] Though the ulcerogenic potential of topical bile salts in an acid medium has been well documented during hemorrhagic shock[4,5] or vasopressin-induced ischemia,[6] the precise etiologic factors involved in the development of stress ulcers during septicemia remain undetermined. The fact that septic patients appear to be the most refractory to prophylaxis and treatment of stress ulcers[3,7] gives further impetus to researchers to investigate the problem under controlled conditions.

Clinical studies have shown that stress ulcers develop during generalized or localized sepsis in the absence of late septic shock,[8] thereby excluding hypotension and gross organ ischemia as likely etiologic factors. This laboratory has recently demonstrated the reproducibility of a septic shock model utilizing the systemic infusion of known quantities of live *Escherichia coli* organisms,[9] which has enabled the authors to investigate the etiology of stress ulcers in the absence of gross organ ischemia. Using gold-filled microelectrodes to determine the intracellular oxygen tension of gastric surface epithelium, they have previously found that septicemia induces a profound hypoxia of surface cells, despite maintenance of total gastric blood flow.[9] To test the significance of the mucosal hypoxia induced by sepsis, this investigation was designed to record mucosal oxygen tension of the canine stomach while it was exposed to known concentrations of acid and bile during *E. coli* sepsis, and to see whether stress ulcers could be produced with concentrations of bile in acid that are well within physiologic range.[10,11]

Methods and Materials

The experimental model and methods have been recently described in detail[9,12] and will be summarized briefly. Thirty-two mongrel dogs of both sexes, each weighing approximately 20 kg and previously determined to be free of microfilaria and parasites, were not fed for 24 hours but allowed water *ad libitum*. They were anesthetized with intravenous pentobarbital (30 mg/kg) following premedication with intramuscular ketamine (4 mg/kg), and ventilated through a cuffed endotracheal tube with room air at a volume of 120 ml/kg/min. The right jugular vein was cannulated with a Swan-Ganz thermodilution catheter (model 93-131-7F); the tip was positioned in a branch of the pulmonary artery. Both pulmonary artery pressure and right atrial pressure were then measured continuously using a strain

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Reprint requests: Dr. John C. Bowen, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, LA 70121.

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gauge transducer, and cardiac output was calculated every 15 minutes by a cardiac output computer (Edwards Laboratories, model 9520) utilizing the thermodilution technique. Both femoral arteries were cannulated. The right artery was connected to a strain gauge transducer for continuous monitoring of arterial blood pressure and heart rate. Blood samples were drawn from the left artery at 30-minute intervals for measurement of arterial p_{O_2}, p_{CO_2}, and pH using a pH/blood gas analyzer (Corning pH Blood Gas Analyzer Model 165/2). This insured that normal oxygenation of the arterial blood was being maintained. The left femoral vein was cannulated and used to infuse normal saline at a rate of 5 ml/kg/hr throughout the experimental period and to give supplemental anesthetic if required. All dogs were kept warm with an electric heating blanket.

Through a midline abdominal incision, the spleen was removed, and a flap of stomach from the greater curvature of the fundus, pedicled on the splenic vessels, was secured between the rings of a lucite chamber (area 20.3 cm^2) to which 50 ml of normal saline were then added. An electromagnetic blood flow transducer (internal diameter 2.5 mm) was placed around the distal splenic artery, just proximal to the gastric branches. An electromagnetic square wave flow amplifier (Zepeda, model SWF-4RD), previously calibrated with a pulsatile roller pump and canine blood, was then used to determine blood flow to the exteriorized flap of stomach.

Gold-filled microelectrodes with a tip diameter of 1–2 μ were used to measure the intracellular oxygen tension (ICP_{O_2}) and transmembrane potential difference (TMPD) of the surface epithelium in the gastric chamber (Fig. 1). These electrodes, which are constructed and calibrated in this laboratory, have a rapid response time (less than 1 sec), draw very little current (about 5×10^{-12} amp), have a low measured resistance (10–15 Mohms), and are stable over several hours at the same locus. An Ag–AgCl reference electrode was placed against the exposed gastric mucosa. Using a micromanipulator, the calibrated microelectrode was advanced into the mucosa until the electrical potential increased abruptly to greater than −45 mV. To determine intracellular p_{O_2}, a predetermined potential was applied through a potentiometer, and the current generated by reduction of oxygen ions at the electrode tip was measured. The magnitude of the current observed is therefore directly proportional to the quantity of oxygen available within the cell. Alternating the electronic switches permits measurement of both the ICP_{O_2} and TMPD during the experimental period. Occasionally, electrodes were broken during the experimental period and were replaced by new electrodes.

Sepsis was induced by a systemic infusion of live pathogenic *E. coli* type BO26 prepared as follows. Lyophylized *E. coli* were grown in soy broth for 24 hours and then inoculated onto soy agar slants for four hours. The live bacteria were suspended in sterile normal saline and adjusted to give a 40% T on a Coleman linear-absorbance spectrophotometer at a wavelength of 550 nm. This predetermined density provided approximately 0.5×10^{10} *E. coli* organisms/ml. The actual bacterial count infused was calculated each time by culture of a known dilution of the bacteria for 24 hours and counting the individual colonies.

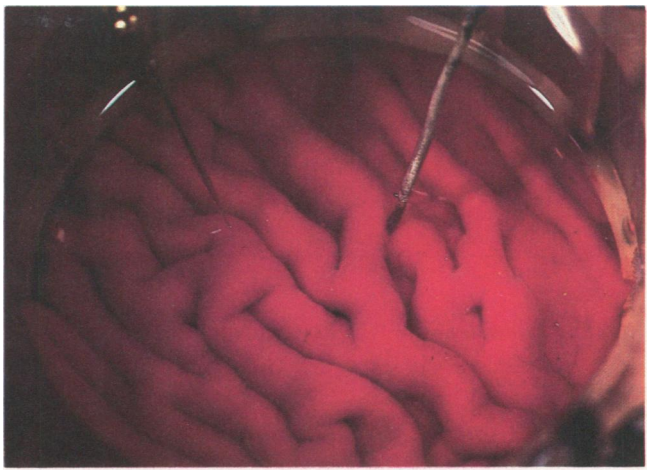

FIG. 1. Oxygen microelectrode and reference electrode *in situ*.

Experimental Design

After a stabilization period of one hour following surgery, baseline measurements were taken during a control period of 30 minutes. Septicemia was then induced in all dogs by the systemic infusion of live *E. coli* ($1.0–1.6 \times 10^{10}$ organisms/kg) during a one-hour period, and the effects observed for a further two hours. In control dogs (n = 6), the gastric chamber was bathed in normal saline at pH 7.2 throughout the experimental period. In the three experimental groups, the saline bathing solution was changed 30 minutes after the bacterial infusion to one of the following: 1-mM, 3-mM, or 5-mM Tc in saline (n = 10) (pH range 5.3–6.8); 80-mM HCl (n = 6) (pH 1.1); or 1-mM Tc in 80-mM HCl (n = 10) (pH 1.1). No further changes were made in the bathing solution during the remaining 90 minutes of the experimental period.

At the end of the experimental period, the mucosa was assessed morphologically by naked eye and photographed to obtain a lesion score based on a numeric scoring of 0 to 5 (Table 1). In addition, a full-thickness biopsy specimen of the gastric mucosa was taken and immediately fixed in formalin. Histologic sections were prepared with hematoxylin–eosin stains and examined

TABLE 1. *Lesion Index*

Score	Mucosal Appearance
0	Normal
1	Edema
2	Multiple punctate erosions <1mm or one ulcer <3mm
3	Up to 10 ulcers >1mm but <3mm
4	Up to 10 ulcers >3mm
5	Widespread ulceration

by light microscopy by an experienced pathologist with no knowledge of the experimental groups.

Calculations and Statistical Analyses

Cardiac output (liters/min) was normalized for dog size by dividing it by the surface area and was expressed as the cardiac index. Total peripheral resistance (dyne sec/cm^5) was calculated as follows: (mean arterial blood pressure − right atrial pressure) × 80, divided by the cardiac index. Data taken from the written record at 15-minute intervals throughout the experiments were analyzed by analysis of variance, including repeated measures. Where statistical difference was shown, the Student's t-test was used to determine the precise points of significant difference. In all analyses, the 95% confidence level was considered significant. Values given for each group are expressed as the mean ± SEM.

Results

Systemic Effects

Each of the dogs followed a similar pattern following infusion of live bacteria. To preserve clarity of presentation, the hemodynamic data are reported as a direct comparison between ulcerated and nonulcerated dogs. This was transcribed to a comparison of septic dogs with both acid and bile added to the stomach *versus* the three other groups. Where statistical significance is shown, an individual group comparison is shown to help define the importance of the changes.

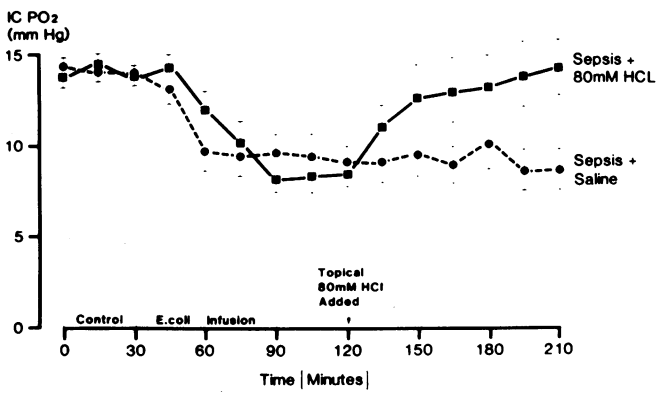

FIG. 2. Epithelial hypoxia induced by sepsis was reversed by 80 mM HCl ($p < 0.001$).

There were no significant changes in mean arterial blood pressure between ulcerated and nonulcerated dogs. Mean arterial blood pressure at the start of the bacterial infusion was 86 ± 4 and 91 ± 4 mmHg, respectively. Bacterial infusion induced a profound hypotension, which persisted for the remainder of the experiment, within 30 minutes. Actual values for ulcerated dogs taken at the end of the infusion period and at the end of the experiment were 54 ± 4 and 51 ± 7 mmHg, respectively. Corresponding readings for nonulcerated dogs were 57 ± 4 and 68 ± 6 mmHg.

Although the pattern for cardiac index differed between ulcerated and nonulcerated groups ($p < 0.05$), there was no significant difference during the time that topical agents were added; furthermore, there was no significant difference between individual groups. At the time of changing the bathing solution, the mean cardiac index in ulcerated dogs was 1.5 ± 0.2, compared with 1.5 ± 0.1 in nonulcerated dogs. By the end of the experiment, these values were 1.4 ± 0.1 and 1.4 ± 0.1, respectively.

Similarly, there were no significant differences in total peripheral resistance between the groups. Despite an initial delay, the dogs that were ulcerated became as vasodilated as the nonulcerated dogs by the end of the infusion period. TPR in dyne sec/cm^5 at the time the bathing solution was changed was 3538 ± 1003 in ulcerated dogs, compared with 3655 ± 378 in nonulcerated dogs. Corresponding values by the end of the experiment were 4072 ± 347 and 4129 ± 505, respectively.

Infusion of live bacteria induced a profound systemic acidosis in all the groups. Arterial pH for the ulcerated dogs at the beginning of the experiment, 30 minutes after the bacterial infusion, and at the end of the experiment was 7.48 ± 0.04, 7.34 ± 0.03, and 7.29 ± 0.03, respectively. There was no statistical significance between the ulcerated and nonulcerated dogs, the corresponding values for the latter being 7.46 ± 0.03, 7.30 ± 0.03, and 7.21 ± 0.05.

Total blood flow to the gastric chamber was no different in ulcerated and nonulcerated dogs. At the beginning of the bacterial infusion, total gastric blood flow in ml/100 gm/min was 71 ± 8 in the ulcerated group and 81 ± 11 in the other dogs. Corresponding values 30 minutes after the bacterial infusion were 44 ± 3 and 52 ± 7, whereas by the end of the experiment, flow had increased to 65 ± 9 and 60 ± 8, respectively.

Tissue Effects

Electrode data were obtained in dogs that did not ulcerate. The extensive tissue damage in the group that

ulcerated invariably broke the electrodes and prevented collection of meaningful data. Intracellular oxygen tension was 14 ± 1 mmHg in the control saline group, 14 ± 1 mmHg in the 1-mM Tc group, and 14 ± 1 mmHg in the 80-mM HCl group. The degree of mucosal hypoxia induced by sepsis was similar in all groups and the ICP_{O_2} just prior to changing the bathing solution was 9 ± 1, 9 ± 2, and 8 ± 1, respectively.

The ICP_{O_2} remained low when saline bathed the gastric epithelium, the final reading being 9 ± 1 mmHg. The addition of 1-mM Tc improved the ICP_{O_2} in four of six dogs, there being no improvement in two dogs. The mean ICP_{O_2} at the end of the experiment was 12 ± 3 mmHg in the 1-mM Tc group, which just failed to reach statistical significance. The addition of 3-mM Tc and 5-mM Tc in four dogs did not improve epithelial oxygenation; however, no ulcers were produced. Adding 80-mM HCl alone during sepsis improved tissue oxygenation fairly rapidly in all six dogs (Fig. 2), the final value being 14 ± 1 mmHg ($p < 0.01$).

The transmembrane potential showed changes similar to those of ICP_{O_2} in the three groups observed. The TMPD at the start of the experiment was −51 ± 2 mV in the control group, −52 ± 3 mV in the acid group, and −47 ± 3 mV in the 1-mM Tc group. Thirty minutes after the bacterial infusion, and prior to changing the bathing solution, the TMPD had fallen to −35 ± 4, −33 ± 4 and −32 ± 4 mV, respectively. The addition of 1-mM Tc produced an immediate improvement to −42 ± 5 mV, which was maintained for the remainder of the experiment. These changes were significant ($p < 0.001$) compared with the saline control group in which the TMPD remained low, the final reading being −33 ± 4 mV (Fig. 3). Similarly, adding 80-mM HCl improved TMPD to −43 ± 7 mV, which was maintained for the remaining 90 minutes of the experiment ($p < 0.01$) (Fig. 4).

Morphology and Histology

The infusion of live *E. coli* induced a noticeable, increased secretion of gastric mucus and, usually, the gradual onset of mucosal edema. No erosions or frank ulcers were seen in the control saline group. Similarly, the addition of 1-mM, 3-mM, or 5-mM Tc solutions in saline or of 80-mM HCl alone did not produce any further visible changes in the gastric epithelium. In marked contrast, the addition of 1-mM Tc in 80-mM HCl produced widespread gross ulceration in nine of ten dogs (Fig. 5). Within minutes of addition of the acid/bile solution, widespread pale areas and white streaks appeared along the crests of the gastric rugae. These then progressed to form frank stress ulcers, usually within 30 minutes of addition of bile in acid. The lesion index was recorded as 1 in one dog, 3 in another

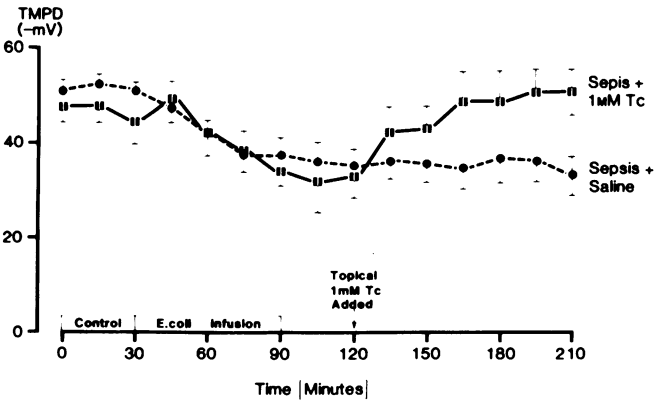

FIG. 3. Fall in TMPD induced by sepsis was ameliorated by 1-mM Tc ($p < 0.001$).

dog, 4 in three dogs, and 5 in five dogs, making a mean lesion score of 4.1 ± 0.4. In marked contrast, the mean lesion index in the saline group, the Tc group, and the acid group was 0.5 ± 0.2, 0.8 ± 0.2, and 0.5 ± 0.2 respectively, that is, no ulcers appeared (Fig. 6).

Histologic examination confirmed the appearance of subepithelial edema in all the groups studied. When saline, 80-mM HCl, or Tc (1, 3, or 5 mM) bathed the mucosa, no further microscopic changes were observed. However, adding 1-mM Tc in 80-mM HCl produced extensive mucosal edema and focal necrosis involving the mucosa. These necrotic changes were most severe in surface epithelium, but extended to involve cells down to but not beyond the muscularis mucosa. There were no acute inflammatory cells seen in any of the sections.

Discussion

This study confirms the susceptibility of the gastric mucosa during sepsis and documents those conditions that will consistently produce stress ulcers. Exposure of the gastric lining to physiologic concentrations of bile and acid following infusion of live bacteria induced

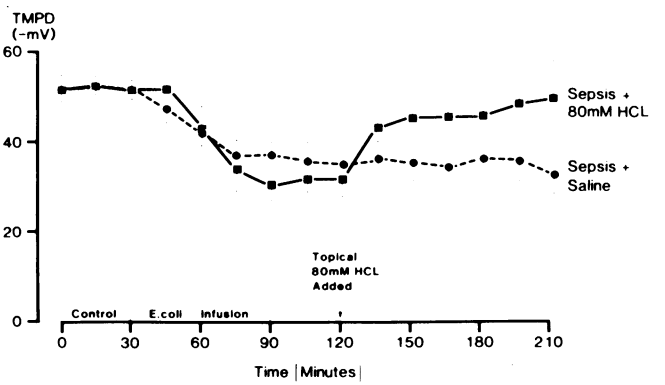

FIG. 4. TMPD declined following sepsis, but improved with topical 80-mM HCl ($p < 0.001$).

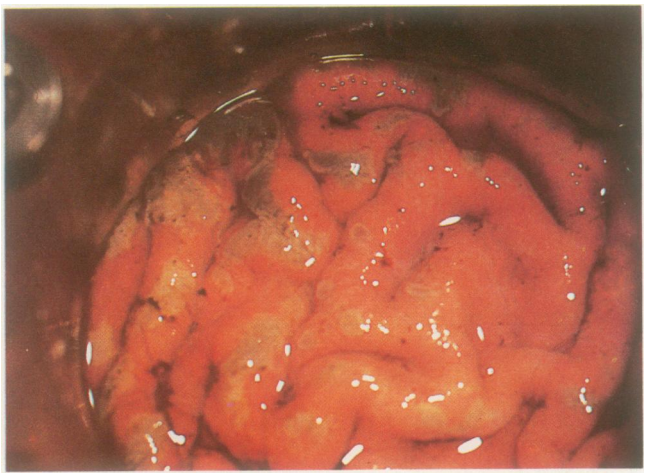

FIG. 5. Typical gross appearance of stress ulcers.

widespread ulceration. The underlying defect in mucosal defense appears to be hypoxia of the surface epithelium, which occurs during sepsis despite maintenance of total blood flow to the stomach.

The nature of the hypoxic injury that occurs during septicemia remains unclear. The most likely cause of epithelial hypoxia is decreased oxygen delivery. In the absence of a decrease in total blood flow[9,13] or anatomic arteriovenous shunts,[12-15] more subtle rearrangements of flow in the mucosal microcirculation seem to be the best explanation for the cellular hypoxia. Previous work in this laboratory suggests a redistribution of nutrient blood flow away from the surface epithelium.[5,16] Functional or pathophysiologic shunting would deny the surface cells the benefit of such nutrient substrates as glucose and oxygen, which are needed for oxidative phosphorylation. Energy-consuming events involved in maintaining the gastric mucosal barrier include mucus release[17,18] and bicarbonate secretion.[19,20] Interruption of both of these defense mechanisms may predispose to mucosal injury.[17]

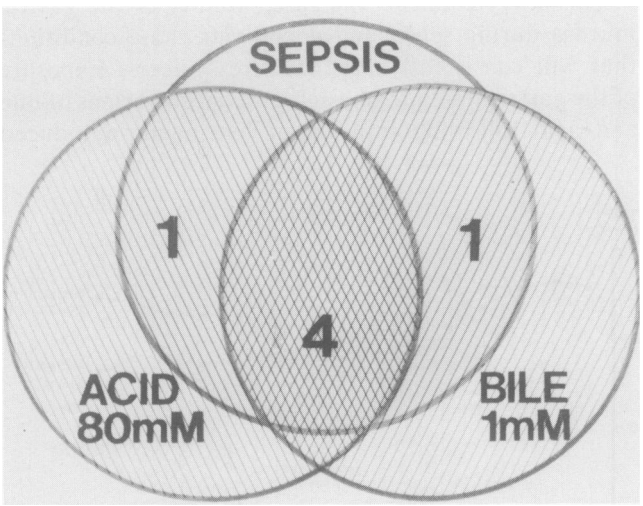

FIG. 6. Summary of the mean lesion score in the three groups. The triad of sepsis, bile, and acid (represented by the overlapping circles) generated ulcers in nine of ten dogs making a mean lesion score of 4.

Adequate nutrient flow is important in maintaining bicarbonate ion delivery to the surface mucus cell. Bicarbonate ions are essential for neutralizing back-diffusing hydrogen ions. The ratio between back-diffusing hydrogen ions and buffering capacity of the gastric mucosa is an important key to mucosal integrity.[22] When nutrient flow and cellular energy supply are intact, the gastric mucosa is capable of handling high concentrations of back-diffusing hydrogen ions.[22] However, when the mucosal buffering power is compromised by ischemic hypoxia, hydrogen ions may be allowed to accumulate in the surface mucus cells, with subsequent deterioration in cellular function.[24] Furthermore, the systemic acidosis that developed in our septic dogs would be expected to augment mucosal acidosis, as was first demonstrated in the pioneering work of Cummins, Grossman, and Ivy.[25]

Transmembrane potential difference is a good indicator of mucosal cell metabolism. In previous experiments during hemorrhagic shock, TMPD declined secondarily to intracellular oxygen tension,[21] the critical oxygen tension being approximately 9 mmHg.[12] In contrast, sepsis induced simultaneous fall in both ICP_{O_2} and TMPD, which suggests that during sepsis the underlying ischemic hypoxia is augmented by a direct toxic effect of endotoxin on cellular metabolism.[9] This provides one explanation for the increased susceptibility of the gastric mucosa to ulcerate during sepsis as compared with during ischemia alone.

Disruption of the gastric mucosal barrier by bile salts is now well established,[4,6,23] though the exact mechanism remains controversial. Experimental evidence has shown that bile salts are capable of making the surface bilipid membrane soluble by their detergent action.[26] Alternatively, in acidic solutions they may become lypophilic and enter the mucosa,[27] thereby directly interfering with cellular metabolism.[28,29] Bile salts increase the net forward diffusion of Na^+ and net back diffusion of H^+.[6,30] Therefore, when bile salts are present the gastric epithelium has to dispose of greater concentrations of hydrogen ions, which would highlight and exacerbate any underlying injury to mucosal defense mechanisms.

The amelioration of epithelial hypoxia by bile or acid alone contrasts sharply with the synergistic potential of bile and acid to produce ulcers. Sepsis concomitant with topical acid and bile is highly ulcerogenic, and the three factors constitute an etiologic triad, which, now that it has been identified, will form a logical basis for

development of new prophylactic maneuvers. Prevention of tissue hypoxia during sepsis will provide a benchmark as to the efficacy of the various cytoprotective agents and will, it is hoped, add another piece to the intriguing jigsaw puzzle of stress ulceration.

Acknowledgments

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Discussion

Dr. Wallace P. Ritchie, Jr. (Charlottesville, Virginia): First, the methodology for assessing intracellular Po_2 and transmembrane potential difference is exacting, elegant, and superb.

Second, the model of hyperdynamic sepsis which Dr. Bowen has developed over the past year—again, with great effort— is not only reproducible, but is also extremely relevant to the clinical circumstance.

Third, the questions that are being addressed with this kind of study are on the very cutting edge of our attempts to understand how it is that the gastric muscosa resists autodigestion; that is to say, can cytoprotect itself. They are, again, particularly relevant to the distressing problem of stress ulceration clinically.

Finally, the potential for evaluating the possible efficacy of so-called cytoprotective drugs, such as the prostaglandins, is very real and very exciting.

(slide) In my opinion, there are several barriers which might contribute to cytoprotection, and I have listed them in the order in which I think they are recruited, as the magnitude of the insult increases.

For the past several years, Dr. Bowen has focused on the interrelationship of the last two, a physiologically intact monolayer of surface cells and mucosal blood flow, and he has been the foremost proponent of the thesis that physiologic injury results from a rearrangement of mucosal perfusion away from the surface cell layer. He has demonstrated that with hemorrhagic shock, tourniquet ischemia, and now with sepsis.

(slide) I have one word of warning for you, Dr. Bowen, concerning your preparation. I, too, have been interested in those last two factors. I go to such things as scanning electron microscopy. This is a scanning