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

The authors are extremely grateful for the expert technical assistance of Mr. J. C. LeDoux, MA, and to Dr. B Willis for grading the histologic sections.

References

1. Altemeier WA, Fuller WD, McDonough JJ. Sepsis and gastrointestinal bleeding. Ann Surg 1972; 175:759-770.
2. Priebe MJ, Skillman JJ, Bushnell LS, et al. Antacid versus cimetidine in preventing acute gastrointestinal bleeding. N Engl J Med 1980; 302:426-430.
3. Martin LF, Mose MH, Polk HC Jr. Failure of gastric pH control by antacids or cimitidine in the critically ill: a valid sign of sepsis. Surgery 1980; 88:59-68.
4. Hamza KN, DenBesten L. Bile salts producing stress ulcers during experimental shock. Surgery 1972; 71:161-167.
5. Bowen JC, LeDoux JC, Harkin GV. Evidence for pathophysiologic arteriovenous shunting in the pathogenesis of acute gastric mucosal ulceration. Adv Shock Res 1979; 1:35-42.
6. Ritchie WP. Acute gastric mucosal damage induced by bile salts, acid and ischemia. Gastroenterology 1975; 68:699-707.
7. Ritchie WP. Stress ulcer and erosive gastritis—introduction. World J Surg 1981; 5:135-137.
8. LeGall JR, Mignon FC, Rapin M, et al. Acute gastroduodenal lesions related to severe sepsis. Surg Gynecol Obstet 1976; 142:377-380.
9. Payne JG, Bowen JC. Hypoxia of canine gastric mucosa caused by *Escherichia coli* sepsis and prevented with methylprednisolone therapy. Gastroenterology 1981; 80:84-93.
10. Grossman MI. Regulation of gastric acid secretion. In: Johnson L, ed. Physiology of the Gastrointestinal Tract. New York: Raven Press, 1981; 659-572.
11. Ritchie WP, Shearburn EW. Acute gastric mucosal ulcerogenesis is dependent on the concentration of bile salts. Surgery 1981; 80:98-105.
12. Bowen JC, Garg DK. Effects of graded mechanical ischemia on oxygen tension and electrical potential in the canine gastric mucosa. Gastroenterology 1977; 73:84-88.
13. Rees M, Payne JG, Bowen JC. Naloxone reverses tissue effects of live *Escherichia coli* sepsis. Surgery 1982; 91:81-86.
14. Guth PH. The gastric microcirculation and gastric mucosal blood flow under natural and pathological conditions. In: Glass GBJ, ed. Progress in Gastroenterology. New York: Grune and Stratton, 1977; 3:323-347.
15. Delaney JP. The paucity of arteriovenous anastamoses in the stomach. Surgery 1975; 78:411.
16. Bowen JC, Garg DK, Salvato PD, Jacobsen ED. Differential oxygen utilization in the stomach during vasopressin and tourniquet ischemia. J Surg Res 1978; 25:15-20.
17. Allen A, Garner A. Mucus and bicarbonate secretion in the stomach and their possible role in mucosal protection. Gut 1980; 21:249-262.
18. Zalewsky CA, Moody FG. Mechanisms of mucus release in exposed canine gastric mucosa. Gastroenterology 1979; 77:719-729.
19. Flemstrom G, Sacchs G. Ion transport by amphibian antrum *in vitro*. I. General characteristics. Am J Physiol 1975; 228:1188-1198.
20. Kivilaasko E, Barzilai A, Schiessel R, et al. Ulceration of isolated amphibian mucosa. Gastroenterology 1979; 77:31-37.
21. Bowen JC. Persistent gastric mucosal hypoxia and interstitial edema after hemorrhagic shock: prevention with steroid therapy. Surgery 1979; 85:268-274.
22. Silen W, Kivilaasko E, Schiessel R, Merhav A. The cytoprotective effects of bicarbonate. In: Harmon JW, ed. Basic Mechanisms of Gastrointestinal Mucosal Cell Injury and Protection. Baltimore/London: Williams and Wilkins, 1981; 265-273.
23. Ritchie WP, Cherry KJ. Influence of hydrogen ion concentration on bile acid-induced acute gastric mucosal ulcerogenesis. Ann Surg 1979; 189:637-642.
24. Martin LF, Ratcliffe DJ, Fry DE. The effects of acidosis on mitochondrial function and microsomal ATPase activity. Circ Shock 1981; 8:211.
25. Cummins GM, Grossman MI, Ivy AC. An experimental study of the acid factor in ulceration of the gastrointestinal tract in dogs. Gastroenterology 1948; 10:714-726.
26. Duane WC, Wiegand DM. Mechanism by which bile salt disrupts the gastric mucosal barrier in the dog. J Clin Invest 1980; 66:1044-1049.
27. Davenport HW. Absorption of taurocholate-24-^{14}C through the canine gastric mucosa. Proc Soc Exp Biol Med 1967; 125:670-673.
28. Menguy R, Masters YF. Mechanism of stress ulcer. Influence of sodium taurocholate on gastric mucosal energy metabolism during hemorrhagic shock and on mitochondrial respiration and ATPase in gastric mucosa. Am J Dig Dis 1976; 21:1001-1007.
29. Kuo KY, Shanbour LL. Inhibition of ion transport by bile salts in canine gastric mucosa. Am J Physiol 1976; 231:1433-1437.
30. Davenport HW, Warner HA, Code CF. Functional significance of gastric mucosal barrier to sodium. Gastroenterology 1964; 47:142-152.

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

electron micrograph of surface mucosa of the dog exposed to a luminal solution of pH 7.5. The entire surface is carpeted with a lovely arrangement of surface cells, which are morphologically intact and adjacent to one another. Here's a gastric pit, and there's another one, and surface cells extend right down into the pits.

(slide) On the other hand, if you expose surface epithelial cells to a combination of physiologic concentrations of bile and acid, this is what you see. Here is a gastric pit, again, and here, intact— at least, morphologically—surface cells, but here an advancing ridge of desquamating, dying, obviously dead surface cells, and over here they've sloughed to reveal the underlying lamina propria.

In other words, the morphologic insult is not homogenous, and it's amazing to me that your data are so uniform, given the relative blindness with which you must be inserting the probe into the surface epithelium.

I would like to ask three brief questions. In a previous study, you demonstrated very convincingly that in septic mucosa the alterations in intracellular P_{O_2} and transmembrane potential difference induced by sepsis alone could be reversed by steroids. Have you had the opportunity to look at other cytoprotective agents in this model, particularly the prostaglandins?

Second, isn't it possible that the decrease in intracellular P_{O_2} is the result not of decreased oxygen delivery, but of increased oxygen consumption? I realize that the transmembrane potential difference speaks against that, but perhaps, if you uncouple oxidative phosphorylation, you might see exactly that combination of circumstances.

I'm wondering if you have an explanation for the remarkable ability of 1 mM taurocholate and 80 mM hydrochloric acid to increase intracellular P_{O_2} in the septic state. In a previous study, 1 mM taurocholate had no effect in the nonseptic mucusa on the same parameters, and I wonder if you could explain that discrepancy.

Finally, in view of the relative primacy of intraluminal acid which you have demonstrated in your model, is there a clue in your data to help us understand why it is that cimetidine, despite very high blood levels and a prolonged half-life in the septic patient, is relatively inefficacious in a prophylactic setting?

DR. LEWIS M. FLINT, JR. (Louisville, Kentucky): Dr. Bowen's postulate—that is, a subtle redistribution of microcirculatory flow, being an important contributor to the stress ulcer phenomenon—is consistent with experimental observations that we have made in other organs within the peritoneal cavity during the course of experimental peritonitis. I coauthored with my associates Dr. Rink and Dr. Fry, a paper presented some three years ago which measured surface oxygen tension in the liver, using a multielectrode probe, our findings indicated hypoxia during the course of experimental peritonitis and are similar to the observations reported this morning by Dr. Bowen.

In the clinical arena, we've also been interested in prophylaxis of this phenomenon. Dr. Martin Max and Dr. Louis Martin reported from our unit some several months ago the consistent failure of cimetidine, and sometimes antacids, to adequately prevent a very low intragastric pH in patients who had on-going sepsis.

The parallels that exist in other organs, such as the liver and the lung, would indicate that the gastric muscosa has taken its rightful place as an organ which can fail during sepsis.

I think the future of cytoprotection is perhaps more in the area of better detection and better control of sepsis than in better protection and better control of the gastric mucosa. We find in our clinical observations, for instance, that these patients, who are desperately ill, and who have septic sites at more than one location in the body, pose challenges which are very difficult. It is particularly difficult to make a specific diagnosis in which one might plan an operation which would control the infection.

We do believe in, however, and continue to practice, the attitude of aggressive abdominal re-exploration in these patients, feeling that even though the patients have multiple sites of infection, we are rewarded with a debridable or drainable focus of sepsis in about 50% of the cases.

DR. JOHN C. BOWEN (Closing discussion): Dr. Ritchie asked several important questions, I'll try to answer them.

The first question concerned the effects of sepsis on P_{O_2} and PD alone. Have we done anything with steroids, or anything else, to try to prevent these effects?

We have not tested steroids as an antiulcer agent. However, we have tested steroids against the deleterious effects of sepsis on P_{O_2} and PD. We have shown in previously published studies that treatment with methylprednisolone 30 minutes after the start of the bacterial infusion ameliorated mucosal hypoxia and restored PD to normal; furthermore, methylprednisolone prevented the development of focal and confluent interstitial edema with dilated capillaries in the lamina propria near the apices of the faveoli. We have been working for the last year on the role of the endogenous endorphin opiates in the production of acute gastric ulcers and we will shortly have a paper coming out that reports the effectiveness of naloxone in preventing these ulcers.

The second question was about the cause of the falling P_{O_2}, can it be due to something besides redistribution of blood flow or inhibition of oxygen delivery? You've already mentioned what I think is the main thing, and that's the PD, Dr. Ritchie. If the PD doesn't change, or goes down, I think that's very good evidence that the metabolic machinery is not increased enough to cause a decline in P_{O_2} as a result of increased oxygen consumption.

The other, indirect evidence is that in other studies we have measured total oxygen consumption to the stomach, and it does not go up. I have pointed out in previous publications, as you know, that there's a dissociation at times between the P_{O_2} in the mucosa versus the oxygen consumption by the total organ; but that's an indirect piece of evidence.

Why does 1 mM taurocholate and 80 mM hydrochloric acid seem to help? I think the key here, and one of the points I have been trying to make all along, is that it matters what concentrations of the various solutions are used. If they are well within physiologic range, the stomach is capable of handling them, and in general there are mechanisms that help the stomach under physiologic conditions, just as in any organ. And I think that the increase in epithelial P_{O_2} reflects an increase in mucosal blood flow that is a response to the application of a physiologic concentration of acid or bile.

Now, if you further increase that concentration, eventually you'll get to the point where you've produced a battering ram effect against the mucosal barrier. They are then corrosive agents and the mucosa cannot resist. That's my theory, at least.

Another important question concerned the apparent disparity between the uniform distribution of our electrode data and the focal nature of the ulcerations seen not only in our model but in the corresponding clinical disease. We feel that the alterations in epithelial P_{O_2} and PD reflect the specific microcirculatory and cellular changes that predispose the epithelial membrane to ulceration. However, as this study demonstrates, other factors, namely topical acid and bile when physiologic concentrations are used, are necessary to induce visible injury. As in all biologic systems, injury must begin at a focus where the tissue is weakest—hence the focal nature of visible injury. You may call this the "weakest link" explanation of focal ulcerogenesis.

The last question, which was alluded to also by Dr. Flint, I think is an important one, about cimetidine, and why it is inefficacious against acute mucosal erosions in some patients, usually septic patients, in whom cimetidine just does not work. If you can reduce acid production with cimetidine, why is this so?

I think that under septic conditions cimetidine simply can't lower acid production enough to prevent ulceration from occurring. As we have shown in this study, it doesn't require much acid to produce frank ulceration under septic conditions. It's going to be virtually impossible to completely rid the mucosa of acid, and so you're always going to have that potential, until we attack the underlying problem that enhances the susceptibility of the tissue to ulcerate in the presence of modest concentrations of acid and bile; and that's to begin to dissociate the sepsis from the tissue effects by pharmacologic means or to get rid of the septic focus, as Dr. Flint has indicated.