10. Smith MD, Couhig E, Miller JJ, Salaman JR. Cimetidine and the immune response. Lancet 1979; 1:1406.
11. Jorizzo JL, Sams WM, Jegasothy BV, Olansky AJ. Cimetidine as an immunomodulator; chronic mucocutaneous candidiasis as a model. Ann Int Med 1980; 92:192–195.
12. Gifford RRM, Schmidtke JR, Ferguson RM. Cimetidine modulation of lymphocytes from renal allograft recipients. Transp Proc 1981; 13:663–667.
13. Stuart FP, Reckard CR, Ketel BL, Schulak JA. Effect of splenectomy on first cadaver kidney transplants. Ann Surg 1980; 192:553–561.
14. Colton T. Statistics in Medicine. Boston, Little, Brown & Co., 1974. pp. 248–250. 15. Menguy R. The prophylaxis of stress ulceration. N Engl J Med 1980; 302:461.
16. Priebe HJ, Skillman JJ, Bushnell LS, et al. Antacid versus cimetidine in preventing acute gastrointestinal bleeding. N Engl J Med 1980; 302:426–430.
17. Basso N, Bagarani M, Materia A, et al. Cimetidine and antacid prophylaxis of acute upper gastrointestinal bleeding in high risk patients. Am J Surg 1981; 141:339–341.
18. Halloran LG, Zfass AM, Gayle WE, et al. Prevention of acute gastrointestinal complications after severe head injury: a controlled trial of cimetidine prophylaxis. Am J Surg 1980; 139:44–48.
19. Martin LF, Stalock DK, Simonowitz DA, et al. Failure of cimetidine prophylaxis in the critically ill. Arch Surg 1979; 114:492–496.
20. Levine B, Sirinek K, McLeod C, et al. The role of cimetidine in the prevention of stress induced gastric mucosal injury. Surg Gynecol Obstet 1979; 148:399.
21. Goldberg EH, Goodwin JS, Orritt SE, Williams RC. Prolongation of male skin graft survival by female mice treated with cimetidine. Transplantation 1979; 28:432–433.
22. Jones RH, Rudge CJ, Bewick M, et al. Cimetidine: prophylaxis against upper gastrointestinal hemorrhage after renal transplantation. Br Med J 1978; 1:398–400.
23. Charpentier B, Fries D. Cimetidine and renal allograft rejection. Lancet 1978; 1:1265.
24. Hussey JL, Belzer FO. Cimetidine in renal transplant recipients. Lancet 1979; 1:1089.

Discussion

Dr. Olga Jonasson (Chicago, Illinois): Upper gastrointestinal bleeding in the transplant recipient is unusual in the absence of sepsis, rejection, or both. The ulceration that occurs during the septic episode is most commonly of the erosive gastritis type, not at all unlike the stress ulceration seen in patients with postoperative sepsis due to a variety of factors. The value of cimetidine has been questioned in patients with stress ulceration in association with sepsis, and antacids have been more reliably effective.

The upper gastrointestinal hemorrhage seen in patients with rejection may also include more typical peptic ulcer disease, complicated by periodic anticoagulation and by uremia. In these patients, especially those with a history of peptic ulcer disease, cimetidine may, in fact, be the optimal prophylactic therapy.

Therefore, I would ask Dr. Stuart if he believes that the reduction in upper gastrointestinal bleeding episodes he has observed in recent years can really be attributed to cimetidine prophylaxis, or, instead, may it be credited to an overall reduction in the incidence of post-transplant sepsis, as we have become more knowledgeable in the management of the transplant recipient, both before and after operation.

Dr. Stuart, if you were to do a prospective, randomized study today comparing antacids and cimetidine as the only means of prophylaxis of upper gastrointestinal bleeding, what would you predict the outcome of such a study would be?

Dr. Arnold G. Diethelm (Birmingham, Alabama): This is a particularly important subject, since the morbidity and mortality rates of patients with upper gastrointestinal bleeding are well known to those involved in renal transplantation.

As noticed by Dr. Stuart, it is essential that early, aggressive diagnostic measures be initiated in the course of bleeding, including endoscopy and gastrointestinal contrast studies.

Having reviewed the manuscript, I agree with his thesis that approximately 4 units of bleeding in the first 24 hours is an indication for surgical intervention, and if, in fact, gastroduodenal ulceration is present, then I favor pyloroplasty and vagotomy.

However, the most serious sequence of events involves patients with severely impaired renal function after transplantation caused by rejection or acute tubular necrosis and with sepsis. This group has a particularly high mortality, and requires early operation and, in many instances, prompt removal of the allograft and discontinuation of immunosuppressive therapy.

My early experience, from 1968 to 1975, was similar to that reported today. However, in the past two calendar years, I have had a consecutive series of 207 patients, and only one patient had gastroduodenal ulceration. This patient had a gastric ulcer, and probably had the lesion before transplantation.

My associates and I have not used cimetidine. We have used the usual antacid protocol, and therefore upper gastrointestinal bleeding in our current experience appears to be a minimal issue.

The central question raised by Dr. Stuart relates to whether or not cimetidine is of value in decreasing complications of gastroduodenal ulceration in the early posttransplant course. If it is, then this would be of considerable importance. However, the question is whether or not the use of cimetidine is truly cause and effect in regard to his findings.

I too, like Dr. Jonasson, wonder if a randomized, prospective study would be of help in solving the problem.

I think the most important contribution in the prevention of this problem has been limiting the total dose of steroids, early graft removal, and avoid sepsis if at all possible.

Dr. Richard E. Wilson (Boston, Massachusetts): Gastroduodenal complications occur in patients not only with kidney transplants, but in a whole variety of immunosuppressed individuals. For the surgeon, however, the transplant patient presents an ideal model to investigate the possibility of controlling these problems, since he or she has an opportunity to see these patients and manage them before they receive their drug therapy, this is not so with many other conditions.

Chronic uremia per se is associated with increased gastrin levels and abnormal clotting capabilities. Corticosteroids affect protective mucus production and the gastric mucosal barrier of parietal cells, while antimetabolites interfere with the repair process of any mucosal injury. It is no wonder that gastrointestinal bleeding and ulceration should occur more frequently in these patients. Patients with a known ulcer diathesis are even at higher risk, as Dr. Stuart pointed out.

Dr. Stuart has demonstrated the value of a vigorous prophylactic approach to this predictable problem, as have surgeons in most other groups. In 1972, we began doing vagotomy and pyloroplasty for all patients with known ulcer history, and it, too, produced a remarkable reduction in gastrointestinal complications.

It is clear that cimetidine plus antacids with vagotomy produced the best results for short- and long-term control in patients with known ulcer history. However, as the other two discussers have pointed out, is cimetidine added to antacids for people without ulcer history better than antacids alone, and is cimetidine plus antacids with vagotomy necessary for persons who have a known ulcer history? Dr. Stuart has not really proved that.

Fortunately, Dr. Stuart has shown no harmful effects from this drug, but I think that widespread and long-term use of cimetidine, or other agents which might come along, could be dangerous.

Would Dr. Stuart be interested in initiating such a randomized trial? Also, does he do for patients who have sepsis or rejection after the one-month period. Does he automatically start cimetidine and antacids in those patients, and does he do any prophylactic surgical procedure for special categories of patients?

DR. WILLIAM SILEN (Boston, Massachusetts): I am in complete agreement with Dr. Stuart's efforts to institute prophylactic measures in this high-risk group.

I emphasize that control of gastric luminal pH is essential in the seriously ill patient. Obviously, this is not pragmatic in the ordinary transplant patient who is doing well. However, in the eight patients in this series who bled within 30 days while receiving antacids only, five had sepsis, and the other three underwent rejection.

Perhaps the message is that once sepsis or rejection occurs in the transplant patient, monitoring of gastric pH should begin immediately.

My associates and I have not had to operate on a single patient within the last 12 years for stress bleeding, just as long as the luminal pH was kept at 3.5 or above.

Whether one accomplishes this with antacids alone, or with a combination of antacids and cimetidine, does not matter. However, the surgeon should be certain that whatever method is used is efficacious. Patient acceptability may make cimetidine more useful in long-term transplant patients. There is some evidence that in seriously ill patients cimetidine may not be quite as effective in increasing luminal pH as it is in normal individuals. For that reason, monitoring of luminal pH is mandatory in seriously ill patients.

Because the risk factors for stress bleeding have been identified in general surgical patients, that is, patients in a state of severe shock, or with sepsis and peritonitis, especially when respiratory and renal failure are superimposed, we can select patients who require stringent prophylaxis.

In addition, the experience of Dr. Stuart and that of the Minnesota transplant group suggests that stress not only produces the typical superficial erosive process that we have come to recognize as stress ulceration, but that it also may activate a preexistent chronic lesion, a lesson we can translate to the general surgical population.

DR. FOLKERT O. BELZER (Madison, Wisconsin): The authors have shown two things: that cimetidine and antacids can prevent upper gastrointestinal problems, and that cimetidine does not appear to evoke rejection. I believe that the authors asked me to comment because a paper was published several years ago from our group suggesting that cimetidine, perhaps, would stimulate immune rejection. Our material was completely anecdotal, but we thought that cimetidine perhaps could influence the rejection process. I believe that the authors have shown to my satisfaction that cimetidine does not produce or aggravate renal allograft rejection. My question, like some of the other discussers is, how often is cimetidine necessary? Since I arrived in Madison we have done close to 500 renal transplants and we have had to operate on only three patients because of upper gastrointestinal problems. One was a patient with a peptic ulcer, one was a patient with Mallory-Weiss Syndrome, and one was a patient with diffuse gastritis. In addition, we do not practice prophylactic acid-reducing operations unless the transplant recipient has an active ulcer on appropriate medical management. We do transplants on patients with previous duodenal ulcer without performing a prophylactic vagotomy and pyloroplasty, and with active antacids therapy we seem to get away with it. My question again, to the author is, which patient do you think needs the cimetidine in addition to the antacids? We are, however, in debt to you, in proving that cimetidine at least is not harmful.

DR. JOHN S. NAJARIAN (Minneapolis, Minnesota): In 1970, my associates and I began doing prophylactic vagotomies and pyloroplasties for any patient who had evidence of a duodenal ulcer, or who had a previously documented duodenal ulcer. We did this because of David Hume's experience at the Medical College of Virginia, and our own, which showed that if patients bleed after kidney transplantation, the mortality rate can be as high as 50–70%.

In 1974 our group published a paper documenting the efficacy of prophylactic vagotomy and pyloroplasty in preventing this complication. Since beginning this approach in 1970, we have performed 1500 kidney transplants, and we have not had to operate for upper gastrointestinal bleeding when a vagotomy and pyloroplasty had been performed. We believe this is an effective modality, and one that should be used whenever there is evidence of active ulcer or a history of ulcer disease.

We have changed our technique in the past two years, however. We no longer combine vagotomy and pyloroplasty, but, rather, do a highly selective vagotomy, which I feel is a better prophylactic procedure. When a gastric vagotomy is done, the gastrointestinal tract is not entered in these patients, who have poor healing because of steroids and their uremia. Our experience in 25 highly selective vagotomies indicates the protective effect is as good as vagotomy and pyloroplasty and eliminates the need for pyloroplasty.

I do not think that cimetidine is needed here. Antacids, used prophylactically in patients on high doses of steroids, that is, in excess of what are considered physiologic doses, are effective in preventing bleeding or stress ulceration. We have used cimetidine when necessary on patients who have hiatus hernias or problems of gastric reflux and esophagitis.

I do caution, however, that although this paper does not show that cimetidine will cause rejection, the fact remains that *in vitro* cimetidine is an immunostimulant. *In vivo* studies from several groups, including Dr. Robert Gifford from our own group and Fritz Bach and others, have prevented experimental tumor inoculation in animals taking cimetidine. Thus, I feel it is an immunostimulant, and should be used with caution in the transplant patient. I am curious to see what a randomized trial will show.

DR. GEORGE D. ZUIDEMA (Baltimore, Maryland): We recently completed a randomized, prospective study in our intensive care area, randomizing into three groups, one receiving antacids only, one a control group, and one receiving cimetidine in doses of 300 mg every six hours.

We found that when more than two of nine risk factors indicating organ failure were present, antacids offered statistically significantly superior protection against stress ulceration; that with fewer than two risk factors present, cimetidine and antacids were equally effective. When seven or more risk factors were present, neither cimetidine nor antacids were beneficial. We therefore have abandoned the use of cimetidine and have adopted Maalox as our antacid of choice for prophylaxis.

DR. FRANK P. STUART (Closing discussion): I do not have any evidence that cimetidine has added anything to our patients, either those without a history of ulcer disease in the past or with a history of it.

We do want to stress that at least there seems not to have been any rejection stimulation. We agree with Dr. Najarian about the papers showing *in vitro* stimulation of the immune system. However, there are two well-controlled studies in the rat skin graft model in which cimetidine actually prolonged skin graft survival.

Dr. Jonasson, a prospective study would be a good idea. I am not so sure I would be interested in one that just compared antacids with cimetidine. Perhaps, rather, one that compared antacids alone with antacids and cimetidine would be better, since most seem to agree that there is little or no morbidity with antacids, and they are inexpensive.

Dr. Wilson, when the patient comes in with a septic problem or rejection, we usually do resume giving antacids, and have resumed giving cimetidine too, and usually the patients stop taking both within a few months after the transplant.

This may be the appropriate time, Dr. Silen, as you suggest, to monitor the pH and be sure that it is kept at 3.5 or higher. Certainly your studies show that it is worth doing in other kinds of patients at high risk.

Dr. Belzer, we have not proved that cimetidine is necessary at all, and we would certainly be interested in entering into prospective studies with other transplant centers.